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JOCEAH 39 (25) 3619–3804 (1974)
ISSN 0022-3263

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VOLUME 39, NUMBER 25 DECEMBER 13, 1974

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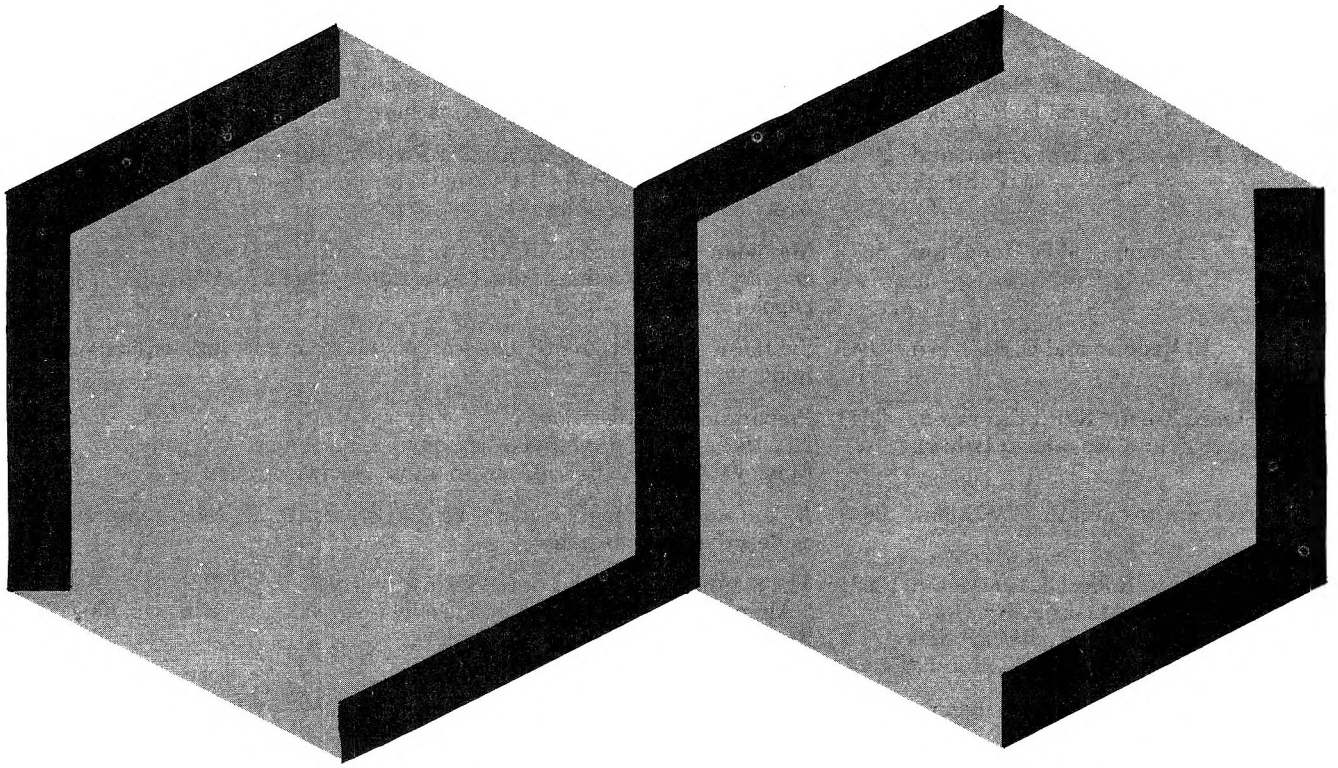

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THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 25

DECEMBER 13, 1974

Mesoionic Compounds. XXX. Cycloaddition Reactions of the *anhydro*-2-Aryl-5-hydroxy-3-methylthiazolium Hydroxide System[1]

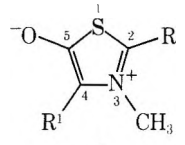
K. T. Potts,* J. Baum,[1d] E. Houghton, D. N. Roy, and U. P. Singh

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

Received April 19, 1974

The title mesoionic ring system underwent cycloaddition of dimethyl acetylenedicarboxylate with elimination of carbonyl sulfide from the initial 1:1 adduct forming substituted pyrroles. *N*-Thiobenzoylsarcosine, the precursor to this mesoionic system, acetic anhydride, and dimethyl acetylenedicarboxylate also gave the substituted pyrrole, and this convenient procedure has been extended to the precursors to the mesoionic oxazole and sydnone systems. *N*-Phenylmaleimide and dimethyl fumarate readily gave 1:1 adducts and the endo isomer of the former product was readily isomerized to the exo isomer. Complex reaction mixtures were obtained from other olefinic dipolarophiles. With tetracyanoethylene no cycloadduct was formed but rather an "ene"-type product was isolated, in which substitution had occurred at the 4 position of the thiazole nucleus. With phenyl isothiocyanate at elevated temperatures, *anhydro*-2-aryl-4-mercapto-1-methyl-3-phenylimidazolium hydroxide and its 1:1 adduct with the heterocumulene were formed, whereas with phenyl isocyanate, 1:1 adducts of the heterocumulene with the thiazole and imidazole mesoionic systems were isolated. Activated isocyanates readily reacted at room temperature giving stable 1:1 cycloadducts.

In the thiazole ring system two isomeric mesoionic systems,[2] represented by the *anhydro*-2,4-disubstituted 5-hydroxy-3-methylthiazolium hydroxide (**1**) and the *anhydro*-2,3,5-trisubstituted 4-hydroxythiazolium hydroxide (**2**) are possible. The number of potential products is increased by possible variation of the exocyclic substituent between oxygen, sulfur, and nitrogen and, as has been shown recently in the *s*-triazole system,[3] with carbon substituents containing electron-delocalizing groups. In this publication we describe the cycloaddition reactions of **1** and its conversion into mesoionic imidazole derivatives and, in those following, the synthesis of **2** and its reactions with a wide variety of dipolarophiles.



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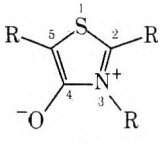

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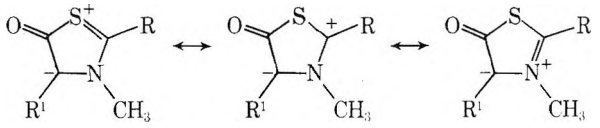


3a **3b** **3c**

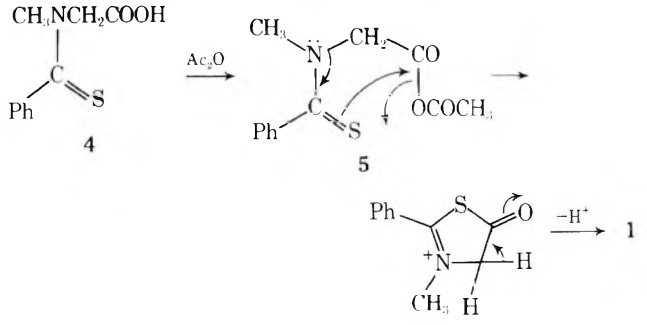
Inherent in the mesoionic concept[2b] are contributions to **1** from dipolar forms **3a–c**. This "masked" 1,3-dipole is an azomethine ylide stabilized by the sulfur atom and **1** would be expected to undergo analogous 1,3-dipolar cycloaddition reactions[4] to those observed with the mesoionic 1,2,3-oxadiazole (sydnone) system,[5] the 1,3,4-oxadiazole system,[5a] and the oxazole system.[6] In this present system it was anticipated that COS would be eliminated from cycloadducts with acetylenic dipolarophiles giving pyrroles and that the adducts with olefinic dipolarophiles would be sufficiently stable for isolation. This present system is particularly interesting as it completes the series oxazole, thiazole, and imidazole in which the azomethine ylide is stabilized by adjacent oxygen, sulfur, and nitrogen atoms, respectively.

Synthesis. The mesoionic system **1** was first synthesized[7] in 1957 as its acetyl derivative (**1**; R = Ph; R^1 = $COCH_3$) from *N*-thiobenzoylsarcosine (**4**) and hot acetic anhydride. However, a cold mixture of acetic anhydride and triethylamine resulted[8] in the formation of *anhydro*-5-hydroxy-3-methyl-2-phenylthiazolium hydroxide (**1**; R = Ph; R^1 = H), and *N*-phenyl-*N*-thiobenzoylglycine gave the corresponding 2,3-diphenyl product. Variation of this latter procedure was found to be excellent for the preparation in greater than 80% yield of the derivatives of **1** (R = Ph, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$; R^1 = H) used in this study. These were all stable, pale-yellow, crystalline products which partially decomposed after storing over several months. The corresponding acetyl compounds (**1**; R^1 = $COCH_3$) were quite stable, a property reflected in their being completely unreactive in cycloaddition reactions, and were prepared from **1** and hot acetic anhydride.

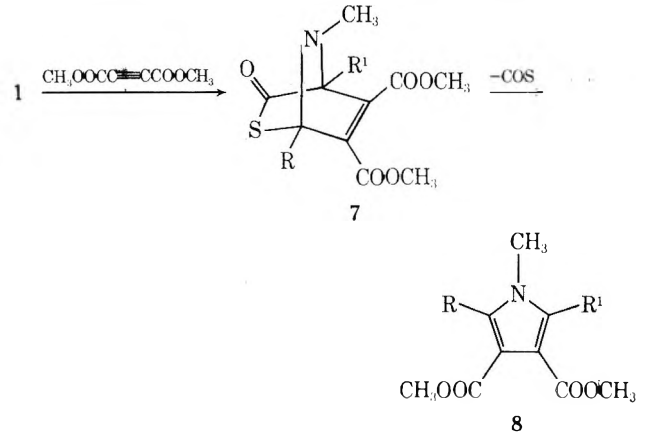
The Ac_2O/Et_3N cyclization mixture is also effective in similar ring closures to other mesoionic systems where acetylation or other reactions occur in the absence of Et_3N.[9] It is thought that an initial mixed anhydride **5** undergoes ring closure to **6** with subsequent removal of a proton by acetate ion. The latter would be a slow and relatively unfavorable process and, accordingly, these cyclizations with Ac_2O require moderately high temperatures and under these reaction conditions acetylation of **1** readily occurs. However, in the presence of Et_3N (pK_a = 11.4), removal of the proton from **6** would be fast and this is reflected in the

extremely mild conditions required for cyclization with the mixed reagent. Pyridine (pK_a = 5.2) was ineffective in the cyclization mixture, the acetyl product (**1**; R^1 = $COCH_3$) only being obtained in poor yield.

anhydro-2,4-Disubstituted 5-hydroxy-3-methyloxazolium hydroxide has also recently been converted into **1** and its exocyclic sulfur derivative[6b] by reaction with carbonyl sulfide and carbon disulfide, respectively.



Cycloaddition Reactions with Acetylenic Dipolarophiles. The *anhydro*-2-aryl-5-hydroxy-3-methylthiazolium hydroxides (**1**; R = Ph, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$; R^1 = H) underwent ready cycloaddition of dimethyl acetylenedicarboxylate in hot benzene. Elimination of carbonyl sulfide from the initial 1:1 adduct **7** occurred with formation of a substituted pyrrole **8** (R = Ph, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$; R^1 = H) with yields in excess of 80%. This is the first instance in which carbonyl sulfide was eliminated from a primary 1:1 adduct, although later experiments have shown that a variety of fragments may be eliminated from initial cycloadducts in reactions with mesoionic systems.

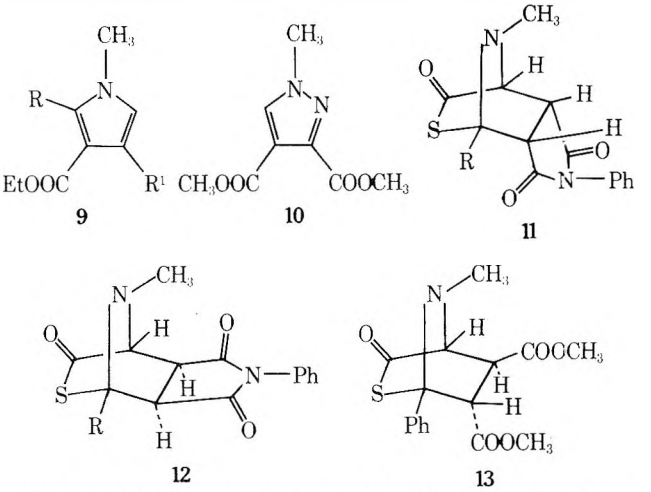


Cycloadditions Utilizing Precursors to the Mesoionic System 1. A modification of the above procedure provides an attractive route to the preparation of various derivatives of **8**, and it may be extended to the synthesis of other five-membered heterocycles.[10] The precursor to the mesoionic system **1**, *N*-thiobenzoylsarcosine (**4**), when heated with Ac_2O and dimethyl acetylenedicarboxylate gave, as the final product, the pyrrole (**8**; R = Ph; R^1 = H) in 78% yield. Carbonyl sulfide was identified as the effluent gas, indicating that cyclization to the mesoionic system (**1**; R = Ph, R^1 = H) had occurred. These reaction conditions are analogous to those under which the acetyl derivatives of **1** (R^1 = $COCH_3$) were obtained and the 1,3-dipolar addition of the dipolarophile must have occurred considerably faster than any acetylation of the nucleus. The presence of Et_3N had no effect on the overall yield of the reaction product.

This *in situ* cycloaddition procedure avoids the need for isolating the mesoionic ring system which may, in some instances, present experimental difficulties.

A variety of acetylenic dipolarophiles, such as ethyl propiolate and ethyl phenylpropiolate, gave the pyrroles **9** (R = Ph, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$; R^1 = H) and **9** (R = Ph, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$; R^1 = Ph), respectively. The same pyrroles may also be obtained in comparable yields by utilizing the *N*-benzoylsarcosine precursors to the corresponding oxazolium mesoionic systems[10a] (Experimental Section).

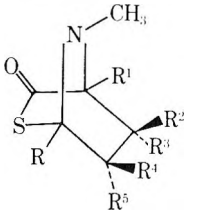
Similarly, *N*-nitrososarcosine, the precursor to *N*-methylsydnone, underwent reaction with dimethyl acetylenedicarboxylate under analogous conditions forming dimethyl 1-methylpyrazole-3,4-dicarboxylate (**10**) in good yield.



Cycloaddition Reactions with Olefinic Dipolarophiles. The reaction of **1** (R = Ph; R^1 = H) with *N*-phenylmaleimide in benzene proceeded smoothly at room temperature with the precipitation of a colorless solid, which was isolated and characterized as the 1:1 primary cycloadduct, N,6-diphenyl-2-oxo-3,4,5,6-tetrahydro-3α,6α-epi-*N*-methylimino-2*H*-thiapyran-4β,5β-dicarboximide[10b] (**11**; R = Ph), on the basis of the following evidence. Carbonyl absorptions were observed under a broad band centered at 1730 cm^{-1} in the infrared spectrum and no ultraviolet absorption maxima occurred above 203 nm. Besides the aromatic protons at δ 7.08–7.58, a doublet of doublets ($J_{4,5}$ = 1.5 Hz, $J_{5,6}$ = 5.5 Hz) at δ 4.30 was assigned to H-5. A doublet containing the small coupling at δ 3.87 was assigned to the bridgehead proton H-4, and H-6 occurred as a cis-coupled doublet at δ 3.83. The bridgehead *N*-methyl protons resonated at δ 2.28 (Table I). These data indicate that the endo configuration **11** is more plausible, in analogy with cycloadducts of the 4-hydroxythiazolium system[11] and the isomeric adduct described below. Rapid decomposition of **11** was observed in the mass spectrometer indicative of thermal instability and a marked tendency for expulsion of COS from the molecule.

In an attempt to oxidize **11** with *m*-chloroperbenzoic acid, a product was obtained from normal work-up (Experimental Section) whose analytical data corresponded to that of an isomeric product. The mass spectrum of this compound showed a fragment ion M − 60 at *m/e* 304 (7%), which indicated that the COS bridge remained intact in this product. The nmr spectrum showed three aliphatic multiplets (Table I) with the same coupling patterns as in the endo adduct **11**. The resonance at δ 4.35 (d, J = 0.5 Hz) may be assigned to the bridgehead proton H-4, the doublet at δ 3.93 (J = 7.5 Hz) to H-6, and the doublet of doublets at δ 3.38 to H-5. The most likely structure for this product is **12**, the exo adduct, formed possibly by acid-catalyzed rearrangement of **11**. Any dissociation–reassociation process would appear to be excluded by the known instability of the initial mesoionic structure **1** to hydrolytic conditions.

Table I
Nmr Spectral Data of Cycloadducts of *anhydro*-2-Aryl-5-hydroxy-3-methylthiazolium Hydroxide and Olefinic Dipolarophiles



Compd[a]	Chemical shift (δ)[b] R¹	R²	R³	R⁴	R⁵	N–CH₃
11, R = Ph R¹ = R² = R⁴ = H R³ = R⁵ = CONPhCO	3.87, d $J_{1,2}$ = 1.5; $J_{2,4}$ = 5.5 Hz	4.30, dd		3.83, d		*2.28*,[c] s
12, R = Ph R¹ = R³ = R⁵ = H R² = R⁴ = CONPhCO	4.35, d $J_{1,3}$ = 0.5; $J_{3,5}$ = 7.5 Hz		3.38, dd		3.93, d	*2.40*, s
11, R = *p*-ClC₆H₄ R¹ = R² = R⁴ = H R³ = R⁵ = CONPhCO	3.83, d $J_{1,2}$ = 2.0; $J_{2,4}$ = 4.0 Hz	4.30, dd		3.80, d		*2.32*, s
12, R = *p*-ClC₆H₄ R¹ = R³ = R⁵ = H R² = R⁴ = CONPhCO	4.33, bs $J_{1,3}$ = ~0–0.5; $J_{3,5}$ = 7.5 Hz		3.40, bd		3.92, d	*2.37*, s
13, Ar = Ph R¹ = R³ = R⁴ = H R² = R⁵ = $COOCH_3$[b]	4.20, d $J_{1,3}$ = 0.0; $J_{3,4}$ = 5.25 Hz	*3.74*, s	3.90, dd	4.11, d	*3.15*, s	*2.34*, s

[a] Spectra determined in $CDCl_3$ at 100 MHz. [b] Aromatic protons usually occurred in the range δ 7.1–7.5. [c] Methyl resonances in italics.

In comparing the nmr data for **11** and **12**, it is seen that the H-4 proton is deshielded in the exo adduct **12** due to the effects of the imide carbonyl group. Similarly H-5 was found at higher field in **12** relative to **11** due to either a greater deshielding effect of the *N*-methylimino bridge or a shielding effect of the β-carbonyl group. Although the coupling constants do not compare exactly with the stereochemical assignments in the 4-hydroxythiazolium cycloadducts, this may be due to a slightly different geometry within the bicyclic ring system.[11]

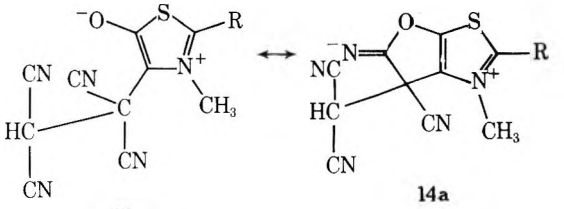
With dimethyl fumarate and **1** (R = Ph; R¹ = H) in benzene at room temperature an adduct represented by **13** was isolated, showing three carbonyl absorptions at 1740, 1730, and 1710 cm^{-1} within a broad band. Absorption maxima were observed at 313 nm (log ε 3.51) and 248 (3.63) in the ultraviolet spectrum and nmr data (Table I) showed three coupled aliphatic protons at δ 4.20 (d, J = 6.0 Hz), δ 4.11 (d, J = 5.3 Hz), and δ 3.90 (dd) assigned to H-4, H-6, and H-5, respectively. Methyl resonances were observed at δ 3.74, 3.15, and 2.34 assigned to the C-5 $COOCH_3$, C-6 $COOCH_3$, and the N–CH_3 protons respectively. The 4-5 coupling (J = 6.0 Hz) is quite large and may be indicative of a bridgehead-endo coupling in comparison with the cycloadducts from the 4-hydroxythiazolium system.[11] The major fragmentation of the molecular ion of **13** involved the formation of an M − 60 ion, corresponding to the elimination of COS.

The mesoionic compound **1** (R = *p*-ClC_6H_4; R¹ = H) similarly underwent cycloaddition with *N*-phenylmaleimide yielding a primary cycloadduct **11** (R = *p*-ClC_6H_4) similar in properties to the adduct **11** (R = Ph) described above. Also in an analogous fashion, treatment of **11** (R = *p*-ClC_6H_4) with *m*-chloroperbenzoic acid afforded an isomeric product given the exo structure **12** (R = *p*-ClC_6H_4). The nmr data for these compounds are listed in Table I. This formation of 1:1 adducts with these olefinic systems is in direct contrast to the reactions of the analogous oxazolium systems where the primary adducts break down with loss of CO_2.

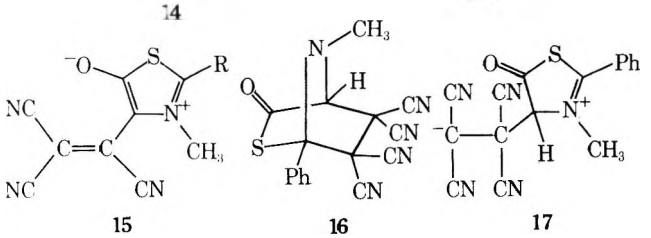
It should be noted that the reactions of **1** with the dipolarophiles, methyl vinyl ketone, *trans*-dibenzoylethylene, and fumaronitrile gave complex reaction mixtures from which no solid derivatives could be isolated.

Tetracyanoethylene was also found to undergo reaction with the thiazolium system **1** on gentle warming in benzene solution. In one instance from **1** (R = Ph; R¹ = H), two products were isolated from an initial deep-red mass which separated from the reaction mixture after a few minutes.

The following considerations led to the assignment of structures **14** and **15**, respectively, to these two products.



14 **14a**



15 **16** **17**

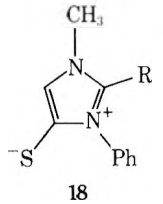
Analytical and mass spectral data showed the products differed from each other by the elements of HCN. The first product was apparently a simple 1:1 adduct of **1** and tetracyanoethylene but representation of this as a 1,3-dipolar cycloadduct in the manner of those described above may be disregarded. Such an adduct would not be expected to have a visible absorption spectrum and also it would not lose

HCN, as the double bond would then be introduced at the bridgehead unless some accompanying ring opening occurred. Thermal ring opening of the mesoionic oxazolium system has been shown[6d] to yield a transient ketene and, if such a valence bond isomerization were occurring with **1**, the anticipated product would be a tetracyanocyclobutanone. This is excluded on the basis of the carbonyl absorption of the product (ν_{CO} 1560 cm^{-1}). Though this value for the carbonyl absorption is *ca.* 50 cm^{-1} lower than anticipated, it may indicate some interaction of the oxygen atom with an adjacent cyano group as in **14a**, so that some contribution from a C=N absorption is actually being observed as well.

The second product had a ν_{CO} 1610 cm^{-1}, comparable to that of **1** (R = Ph; R^1 = H), and there as an increase in intensity of the ν_{CN} absorption at 2200 cm^{-1} compared to that in **14** (ν_{CN} 2205 cm^{-1}). These data are consistent with structure **15**.

Under the above reaction conditions **1** (R = *p*-ClC_6H_4; R^1 = H) and tetracyanoethylene gave only the product corresponding to **15**. Similar products have been observed with other mesoionic ring systems and tetracyanoethylene,[12,13] and several possible ways of forming products of type **15** are feasible but no data are available which allow a distinction to be made between an intermediate such as the "normal" 1:1 adduct **16** or whether an "ene" type process involving **17** is operative. The opportunity for stabilizing the negative charge by the cyano groups in **17** tends to favor a dipolar process which would be consistent with the ionic character of numerous tetracyanoethylene cycloadditions.[14]

Cycloaddition Reactions with Heterocumulenes. An alternative procedure to the direct synthesis of a mesoionic ring system by a cyclodehydration route is a cycloaddition reaction with a heterocumulene. Phenyl isothiocyanate is particularly effective in this respect and, on reaction with **1** (R = Ph, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$; R^1 = H) in hot benzene, the corresponding *anhydro*-2-aryl-4-mercapto-1-methyl-3-phenylimidazolium hydroxide (**18**) was obtained. In the absence of solvent, in addition to **18**, the cycloaddition product **19** of **18** with phenyl isothiocyanate was also isolated. These structures were assigned on the basis of analytical data and the chemical and spectral evidence described below.



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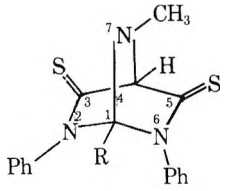
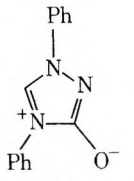


19

N-Phenylsydnone underwent[15] reaction with phenyl isocyanate in the absence of solvent to give *anhydro*-1,4-diphenyl-3-hydroxy-*s*-triazolium hydroxide (**20**), rather than the anticipated *anhydro*-1,3-diphenyl-4-hydroxy-1,2,3-triazolium hydroxide (**21**). A similar, reverse mode of addition can be excluded for the thiazolium system on the basis of the nmr spectrum of the *anhydro*-2-aryl-4-mercapto-1-methyl-3-phenylimidazolium hydroxide (**18**). A singlet proton resonating at δ 6.91 is more consistent with structure **18** than with structure **22**, the product from the reverse mode of addition. In the latter, the single proton at position 2 is of the formamidinium type and, in compounds related to **20**, this proton has been observed at δ 10.41–9.51, depending on the solvent.[16]

The imidazolium mesoionic derivatives readily formed methiodides and, in these salts, the 5 proton was observed at δ 8.0, consistent with the formulation of the salts as **23**. These salts also enable addition across the C=S of phenyl isothiocyanate to be excluded as such an addition, contrary to the usual mode of reaction of phenyl isothiocyanate,[17] would give *anhydro*-2-aryl-3-methyl-5-phenyliminothiazolium hydroxides (**24**). These, on reaction with methyl iodide, would form the thiazolium salts **25**. The chemical



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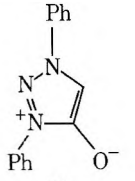

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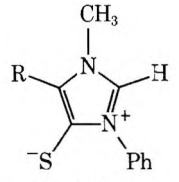

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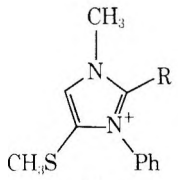

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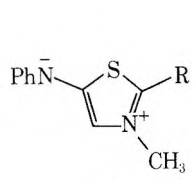

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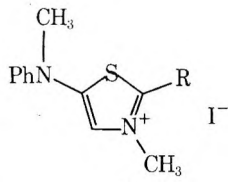

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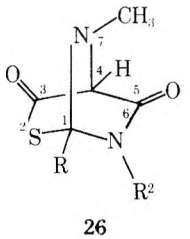
shifts of the added methyl groups in these salts were δ 2.5–2.4, clearly establishing them as SCH_3 groups rather than NCH_3 groups.[18]

Reaction of *anhydro*-2-aryl-4-mercapto-1-methyl-3-phenylimidazolium hydroxide (**18**) with phenyl isothiocyanate gave the same product **19** that was isolated from the reaction of **1** with phenyl isothiocyanate. Similar considerations regarding the mode of addition of phenyl isothiocyanate to **18** as were discussed for its addition to **1** need to be taken into account. Poor solubility precluded definitive nmr data but a consideration of the products obtained with phenyl isocyanate strongly support structure **19** (see below).

A more highly substituted member of this imidazolium system **18** has also been obtained from the reaction of *anhydro*-4-mercapto-3-methyl-2,4-diphenyloxazolium hydroxide with phenyl isothiocyanate.[19] However, in this case the additional phenyl substituent in the 5 position apparently deactivates the nucleus as no 1:1 adduct with phenyl isothiocyanate was observed. In this connection it is also of interest to note that the exocyclic sulfur system corresponding to **1** has greatly reduced 1,3-dipolar addition characteristics, a thiophenetetracarboxylic ester being obtained on prolonged reaction with dimethyl acetylenedicarboxylate.[6b]

Reaction of **1** (R = Ph; R^1 = H) with phenyl isocyanate gave two products, the primary 1:1 adduct of **1** and phenyl isocyanate represented by **26** (R = R^2 = Ph), and the 1:1 adduct **28** (R = Ph) formed from *anhydro*-2,3-diphenyl-4-hydroxy-1-methylimidazolium hydroxide (**27**) and phenyl isocyanate. Elimination of carbonyl sulfide from **26** (R = R^2 = Ph) most likely accounts for the formation of **27** in the reaction medium. It is not surprising that **27** itself was not isolated from the reaction as it has been shown that this is an extremely reactive ring system[12] and that the 5 position is one of high electron density.[20] Structures **26** (R



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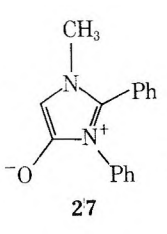

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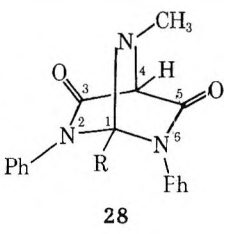

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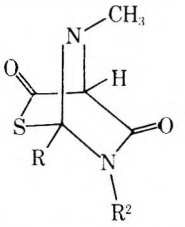
Table II
1:1 Primary Cycloadducts Derived from *anhydro*-2-Aryl-5-hydroxy-3-methylthiazolium Hydroxides (1) and Activated Isocyanates



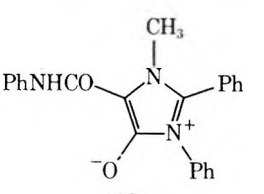
R	R^2	Mp, °C, dec	Yield, %	Crystal habit	Spectral data[c] ν_{CO}, cm^{-1}	λ_{max}, nm (log ε)	M·⁺	Nmr data[b]
Ph	*p*-$CH_3C_6H_4SO_2$	200–204	79	Colorless prisms[c]	1675, 1600	344 (4.08) 275 (4.04) 228 (4.27)	388 (8)	δ 11.55 (bs, 1, C_4-H, D_2O exchanged), 7.18–8.12 (m, 9, aromatic), 4.08 (s, 3, NCH_3), 2.45 (s, 3, CCH_3)
p-ClC_6H_4	*p*-$CH_3C_6H_4SO_2$	215–218	78	Yellow prisms[c]	1660, 1600	350 (4.09) 273 (4.08) 226 (4.27)		δ 11.43 (bs, 1, C_4-H, D_2O exchanged), 7.13–8.10 (m, 8, aromatic), 4.07 (s, 3, NCH_3), 2.43 (s, 3, CCH_3)
Ph	COPh	165–167	82	Light-yellow needles[c]	1730, 1680, 1610	348 (4.29) 290 (3.92) 241 (4.49)	338 (6)	δ 12.37 (bs, 1, C_4-H, D_2O exchanged), 7.38–8.13 (m, 10, aromatic), 4.25 (s, 3, NCH_3)
p-ClC_6H_4	COPh	238–240	72	Yellow needles[d]	1730, 1675, 1620	352 (4.21) 288 sh (3.80) 242 (4.37)	372 (40)	δ 12.28 (bs, 1, C_4-H, D_2O exchanged), 7.08–8.25 (m, 9, aromatic), 4.23 (s, 3, NCH_3)
Ph	*p*-ClC_6H_4CO	232–235	80	Light-yellow needles[d]	1725, 1680, 1610	348 (4.26) 293 (3.83) 247 (4.47)	372 (35)	δ 12.35 (bs, 1, C_4-H, D_2O exchanged), 7.27–8.10 (m, 9, aromatic), 4.25 (s, 3, NCH_3)
p-ClC_6H_4	*p*-ClC_6H_4CO	250–253	77	Light-yellow needles[d]	1720, 1680, 1620	353 (4.30) 292 sh (3.86) 249 (4.52)	406 (23)	δ 7.47–8.13 (m, aromatic), 4.33 (s, 3, NCH_3)

[a] Ir (KBr), uv (CH_3OH). [b] All $CDCl_3$ except R = *p*-ClC_6H_4, R^1 = *p*-ClC_6H_4CO. [c] Solvent: 1,2-dichloroethane–ether. [d] Solvent: 1,2-dichloroethane. [e] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table: Ed.

= R^2 = Ph) and **28** (R = Ph) were assigned on the basis of analytical and spectral data and because of a striking consistency in their physical characteristics with those of analogous products obtained from related mesoionic systems.

The molecular formula of **26** (R = R^2 = Ph) was established from mass spectral data, with a strong molecular ion at *m/e* 310 (28%). The proton at the 4 position in **26** was observed at δ 10.64, this extremely low value being attributed to the proton being in the deshielding zones of the adjacent carbonyl groups in the 3 and 5 positions. Carbonyl absorptions in the infrared spectrum at 1660 and 1600 cm^{-1}, and the absence of any OH or NH absorptions, exclude structures containing an OH or NH group, a structural feature usually associated with such a low chemical shift. Moreover, the formation of **28** *via* **27** cannot be readily explained unless an intermediate **26** is involved in the reaction.

Similarly **28**, the adduct from **27** and phenyl isocyanate, gave a strong molecular ion, *m/e* 369 (30%), in its mass spectrum. The corresponding 4 proton was observed at δ 10.58 and again, carbonyl absorption at 1670 and 1640 cm^{-1} and the absence of any OH or NH absorption favor a 1:1 adduct of this type. Structures such as **29** and **30** to



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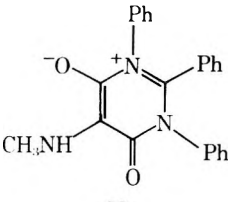

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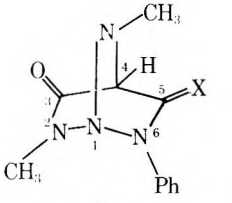

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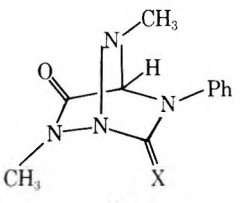
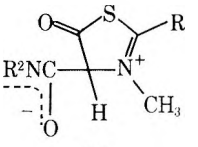


32

which rational transformations from the initial reactants may be devised are not consistent with the above spectral data.

This low-field chemical shift of the 4 proton in these 1:1 adducts has also been observed in the 1:1 adducts formed from the isomeric *anhydro*-2,3-diaryl-4-hydroxythiazolium hydroxide and phenyl isocyanate and phenyl isothiocyanate.[9] Analogous to the present system are the adducts formed from *anhydro*-1,3-dimethyl-4-hydroxy-1,2,3-triazolium hydroxide and these heterocumulenes.[21] Represented by structures **31** (X = O and S, respectively), the 4 proton was observed at δ 10.23 in the former and at δ 12.5 in the latter. The downfield shift of the 4 proton in the latter was attributed to the known extra deshielding of the thiocarbonyl group in the 5 position of **31** (X = S) and eliminates from consideration the isomeric product (**32**) formed by addition of phenyl isothiocyanate in the reverse manner. Similar arguments apply to the structures discussed above.

A similar series of cycloadducts were obtained from **1** (R = Ph, *p*-ClC_6H_4; R^1 = H) and the activated isocyanates, *p*-toluenesulfonyl, benzoyl, and *p*-chlorobenzoyl isocyanate. These all reacted readily at room temperature in contrast to the high reaction temperatures involved in the above reactions, and the adducts were isolated in excellent yields. In all cases 1:1 adducts were obtained and elimination of COS was not observed under the reaction conditions (Table II). In analogy with the reactions described above, the bicyclic structure **26** is preferred for these cycloadducts although the ylide structure **33** cannot be rigorously excluded with the present data.[22a]



33

The properties of these compounds proved uncharacteristic of ylides. For example, **26** (R = Ph; R^2 = *p*-$CH_3C_6H_4SO_2$), the adduct derived from **1** (R = Ph; R^1 = H) and *p*-toluenesulfonyl isocyanate, did not form a salt with perchloric and picric acid, methyl iodide, Meerwein's reagent, methyl *p*-toluenesulfonate, and acetyl chloride, and was stable to hot 10% NaOH. Refluxing **26** with isopropenyl acetate gave a complex reaction mixture from which no homogeneous compound could be isolated. The other cycloadducts within this series behaved in an analogous fashion.

Spectral characteristics, however, are ambiguous. The proton assigned C-4 in all compounds [excepting **26** (R = Ph, R = *p*-ClC_6H_4; R^2 = *p*-ClC_6H_4CO), only soluble in CF_3COOD] resonated in a chemical shift range of δ 9.80–12.37, and was exchanged with D_2O, although at varying rates depending on the solubility of the compounds in $CDCl_3$. This low-field resonance suggests either an NH, an aldehydic type proton, or an α-proton in a β-diketone. The first is excluded on the basis of the infrared spectra, and the other two from the observance in the mass spectrometer of a retro Diels–Alder reaction into the respective mesoionic and isocyanate fragment ions. However, in the mass spectrum of **26** (R = Ph; R^2 = *p*-$CH_3C_6H_4SO_2$), besides the retro Diels–Alder reaction, a rearrangement was observed with the formation of an [M − 107] ion at *m/e* 281. The intensity of the isotope peak at *m/e* 283 (5.4%) strongly suggests the presence of sulfur with the ^{34}S isotope contributing *ca.* 4.5% to this ion intensity. Formation of *m/e* 281 requires the loss of *p*-$CH_3C_6H_4O\cdot$, a process well documented for arylsulfonamides,[22b] and though more conveniently accommodated by structure **33**, it is conceivable that **33** is formed in the primary ionization process. This behavior can only arise from an initial simple association of the mesoionic compound and the appropriate isocyanates, also precluding any rearrangement to an aldehyde moiety. The chemical shift of the N–CH_3 protons in the isolated products was noted between δ 4.07–4.27 ($CDCl_3$) and in one instance δ 4.33 for **26** (R = *p*-ClC_6H_4; R^2 = *p*-ClC_6H_4CO) in CF_3COOD, consistent with a methyl group bonded to a quaternary nitrogen.

Experimental Section[23]

N-*p*-**Methoxythiobenzoylsarcosine.** *p*-Methoxythiobenzoylthioglycollic acid[24] (2.5 g) and sarcosine (0.9 g) were dissolved in 10% NaOH solution and the pH adjusted to 8–9. After 4 days at room temperature the deep pink color of the dithioglycollic acid had disappeared and, on addition of dilute HCl, a solid product (2.3 g) separated. It crystallized from chloroform–petroleum ether (bp 35–60°) as pale yellow needles: mp 132–133°; $M^{\cdot+}$ 239.

Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.23; H, 5.44; N, 5.85. Found: C, 55.01; H, 5.51; N, 6.07.

anhydro-**5-Hydroxy-2-*p*-methoxyphenyl-3-methylthiazolium Hydroxide (1; R = *p*-$CH_3OC_6H_4$; R^1 = H).** *N*-*p*-Methoxythiobenzoylsarcosine[24] when treated at room temperature for several hours with a 1:3 mixture of Ac_2O/Et_3N gave the above product which crystallized from dry acetone as yellow needles: mp 155–156° dec.; 80%; ir (KBr) 1615 cm^{-1} (CO); λ_{max} (CH_3OH) 215 nm sh (log ϵ 4.12), 255 (3.67), 272 (3.65), 357 (3.97); nmr ($CDCl_3$) δ 3.73 (s, 3, OCH_3), 3.88 (s, 3, NCH_3), 6.23 (s, 1, 4-H), 6.91, 7.07 (ABd, 2, J = 9.0 Hz, aromatic), 7.31, 7.47 (ABd, 2, J = 9.0 Hz, aromatic); $M^{\cdot+}$ 221 (100).

Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.73; H, 4.93; N, 6.33. Found: C, 59.67; H, 5.03; N, 6.35.

The physical characteristic of *anhydro*-5-hydroxy-3-methyl-2-phenyl- (and 2-*p*-chlorophenyl-) thiazolium hydroxide have been described previously.[1b]

Dimethyl 1-Methyl-2-*p*-methoxyphenylpyrrole-3,4-dicarboxylate (8; R = *p*-$CH_3OC_6H_4$; R^1 = H). *anhydro*-5-Hydroxy-2-*p*-methoxyphenyl-3-methylthiazolium hydroxide and excess dimethyl acetylenedicarboxylate were heated under reflux in anhydrous benzene for 15 hr. After chromatography on neutral alumina using benzene as eluent, the product crystallized from benzene–petroleum ether (bp 35–60°) as pale yellow needles: mp 155–156°; 80%; ir (Nujol) 1710 cm^{-1} (CO); λ_{max} (CH_3OH) 226 nm (log ϵ 4.46), 265 (4.20); nmr ($CDCl_3$) δ 3.47 (s, 3, 4-$COOCH_3$), 3.68 (s, 3, 3-$COOCH_3$), 3.81 (s, 3, OCH_3), 3.85 (s, 3, NCH_3), 6.87, 7.01 (ABd, 2, J = 9.0 Hz, aromatic), 7.22, 7.37 (ABd, 2, J = 9.0 Hz, aromatic), 7.25 (s, 1, 5-H); $M^{\cdot+}$ 303 (75).

Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.37; H, 5.61; N, 4.61. Found: C, 63.51; H, 5.74; N, 4.55.

The corresponding 2-phenyl and 2-*p*-chlorophenyl products have been characterized previously.[1b]

Cycloaddition Reactions Utilizing Precursors to Mesoionic Compounds. Preparation. A. Dimethyl 1-Methyl-2-phenylpyrrole-3,4-dicarboxylate (8; R = Ph; R^1 = H). *N*-Benzoylsarcosine[25] (1.93 g) in acetic anhydride (20 ml) was treated with dimethyl acetylenedicarboxylate (1.42 g) and, after the initial exothermic reaction had subsided, the reaction mixture was warmed at 125–130° for 1 hr. It was poured into cold water and the product extracted with chloroform which was then washed with $NaHCO_3$ solution (10%), water, and dried (anhydrous Na_2SO_4). After evaporation of the chloroform, the residue was chromatographed on neutral alumina using benzene as eluent. The pyrrole crystallized from benzene–petroleum ether (bp 35–60°) as colorless needles: 1.9 g (65%); mp 118–119°. Its spectral characteristics have been described previously.[1b]

When *N*-thiobenzoylsarcosine[24] was used in this reaction, the pyrrole was obtained in 78% yield and the corresponding *N*-*p*-chlorothiobenzoylsarcosine[24] and *N*-*p*-methoxythiobenzoylsarcosine[24] resulted in an 88 and 75% yield of the corresponding pyrroles, respectively.

B. Ethyl 1-Methyl-2-phenylpyrrole-3-carboxylate (9; R = Ph; R^1 = H). *N*-Benzoylsarcosine (0.96 g), acetic anhydride (10 ml), and ethyl propiolate (0.49 g) reacted together as above and, after reaction workup, the product was obtained as a colorless oil which, on distillation, bp 105–110° (0.02 mm), crystallized. It

formed colorless plates from benzene–petroleum ether (bp 35–60°): 0.36 g (30%); mp 49–50°; ir (Nujol) 1710 cm^{-1} (CO); λ_{max} (CH_3OH) 220 nm (log ϵ 4.07), 273 (3.79); nmr ($CDCl_3$) δ 0.98, 1.10, 1.22 (t, 3, J = 7.0 Hz, CH_2CH_3), 3.35 (s, 3, NCH_3), 3.95, 4.07, 4.18, 4.30 (qt, 2, J = 7.0 Hz, CH_2CH_3), 6.61, 6.66 (ABd, 1, J = 2.25 Hz, 4-H), 6.70, 6.75 (ABd, 1, J = 2.25 Hz, 5-H), 7.41 (s, 5, phenyl); $M^{\cdot+}$ 229 (33).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55; N, 6.11. Found: C, 73.53; H, 6.53; N, 6.09.

Use of *N*-thiobenzoylsarcosine in the above reaction gave the pyrrole in 38% yield.

C. Ethyl 2,4-Diphenyl-1-methylpyrrole-3-carboxylate (9; R = R^1 = Ph). *N*-Benzoylsarcosine (1.92 g), acetic anhydride (20 ml), and ethyl phenylpropiolate (1.74 g) were heated at 130° for 1 hr as above. Chromatography of the residue, obtained from evaporation of the chloroform extract, on neutral alumina using benzene as eluent gave the pyrrole as a pale yellow oil. After distillation [bp 155–160° (0.2 mm)] it crystallized as colorless needles: 0.96 g (31%); mp 84–85°; ir (Nujol) 1700 cm^{-1} (CO); λ_{max} (CH_3OH) 222 nm (log ϵ 5.34), 280 (3.98); nmr ($CDCl_3$) δ 0.73, 0.85, 0.97 (t, 3, J = 7.0 Hz, CH_2CH_3), 3.43 (s, 3, NCH_3), 3.78, 3.89, 4.01, 4.14 (qt, 2, J = 7.0 Hz, CH_2CH_3), 6.66 (s, 1, 5-H), 7.40 (s, 10, phenyl); $M^{\cdot+}$ 305 (100).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.70; H, 6.23; N, 4.60. Found: C, 78.51; H, 6.33; N, 4.43.

This was also the sole product (33%) when *N*-thiobenzoylsarcosine was used in the above reaction.

Dimethyl 1-Methylpyrazole-3,4-dicarboxylate (10). *N*-Nitrososarcosine[26] (2.36 g), dimethyl acetylenedicarboxylate (2.84 g), and acetic anhydride (20 ml) reacted together as above. After chromatography of the crude product on neutral alumina using benzene–petroleum ether (bp 35–60°) (1:2), the pyrazole was obtained as colorless crystals. It separated from benzene–petroleum ether as colorless needles: 2.30 g (60%); mp 68–69°; ir (Nujol) 1745 cm^{-1} (CO); λ_{max} (CH_3OH) 224 nm (log ϵ 4.06); nmr ($CDCl_3$) δ 3.87 (s, 3, NCH_3), 3.97 (s, 3, 4-$COOCH_3$), 4.00 (s, 3, 3-$COOCH_3$), 7.91 (s, 1, 5-H); $M^{\cdot+}$ 198 (90).

Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.40. Found: C, 48.27; H, 4.96; N, 13.87.

Reaction of *anhydro*-5-Hydroxy-3-methyl-2-phenylthiazolium Hydroxide with *N*-Phenylmaleimide. The mesoionic compound 1 (R = Ph; R^1 = H) (1.3 g, 0.0068 mol), *N*-phenylmaleimide (1.2 g, 0.0068 mol), and dry benzene (30 ml) were stirred together at room temperature. Filtration of the precipitated solid and recrystallization from ethanol gave the endo isomer, *N*,6-diphenyl-2-oxo-3,4,5,6-tetrahydro-3α,6α-epi-*N*-methylimino-2*H*-thiapyran-4β,5β-dicarboximide (**11**; R = Ph) as colorless needles: 1.45 g (58.5%), mp 146–148° dec (with gas evolution); ir (KBr) 1730 (broad, CO) cm^{-1}.

Anal. Calcd for $C_{20}H_{16}N_2O_3S$: C, 65.91; H, 4.43; N, 7.69. Found: C, 65.79; H, 4.48; N, 7.67.

Isomerization of 11 (R = Ph). To 11 (R = Ph) (0.5 g, 0.0014 mol) in methylene chloride (20 ml) was added in small portions *m*-chloroperbenzoic acid (0.28 g, 0.0014 mol) with stirring for 1 hr at room temperature. Extraction of the CH_2Cl_2 layer with 10% sodium bicarbonate, water, drying over sodium sulfate, and evaporation of the solvent *in vacuo*, followed by recrystallization of the residue from ethanol afforded the exo isomer, *N*,6-diphenyl-2-oxo-3,4,5,6-tetrahydro-3α,6α-epi-*N*-methylimino-2*H*-thiapyran-4α,5α-dicarboximide (**12**; R = Ph) as yellow needles: 0.2 g (38%); mp 151–153° dec (with gas evolution); ir (KBr) 1720 (broad, CO) cm^{-1}; mass spectrum *m/e* (rel intensity) ($M^{\cdot+}$ − COS) 304 (7), 184 (18), 157 (22), 156 (31), 60 (100), 45 (10), 42 (13), 32 (33).

Anal. Calcd for $C_{20}H_{16}N_2O_3S$: C, 65.91; H, 4.43; N, 7.69. Found: C, 65.92; H, 4.45; N, 7.58.

Reaction of *anhydro*-5-Hydroxy-3-methyl-2-phenylthiazolium Hydroxide with Dimethyl Fumarate. The mesoionic compound 1 (R = Ph; R^1 = H) (1.3 g, 0.0068 mol), dimethyl fumarate (0.98 g, 0.0068 mol), and dry benzene (30 ml) were stirred together at room temperature overnight. Solvent was removed under reduced pressure and the residue was chromatographed on preparative Silica gel (chloroform) followed by recrystallization from ethanol affording dimethyl 6-phenyl-2-oxo-3,4,5,6-tetrahydro-3α,6α-epi-*N*-methylimino-2*H*-thiapyran-4α,5β-dicarboxylate (**13**) as colorless prisms: 1.05 g (46%); mp 129–131° dec (with gas evolution); ir (KBr) 3000, 2950 (CH), 1740, 1730, 1710 (CO) cm^{-1}; λ_{max} (CH_3OH) 248 nm (log ϵ 3.63), 313 (3.51); $M^{\cdot+}$ 335 (2).

Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18. Found: C, 57.57; H, 5.23; N, 3.99.

Reaction of *anhydro*-2-*p*-Chlorophenyl-5-hydroxy-3-methylthiazolium Hydroxide with *N*-Phenylmaleimide. Equimolar amounts of the mesoionic compound 1 (R = *p*-ClC_6H_4; R^1 = H) and *N*-phenylmaleimide in dry benzene were stirred together at room temperature. The endo adduct, 6-*p*-chlorophenyl-2-oxo-*N*-phenyl-3,4,5,6-tetrahydro-3α,6α-epi-*N*-methylimino-2*H*-thiapyran-4β,5β-dicarboximide (**11**, R = *p*-ClC_6H_4) was isolated as small, colorless needles from ethanol: yield 68%; mp 134–136° dec (with gas evolution); ir (KBr) 1710 (broad, CO) cm^{-1}; λ_{max} (CH_3OH) 222 nm (log ϵ 4.30); mass spectrum *m/e* (rel intensity) (M − COS) 338 (1), 60 (49), 46 (96), 45 (50), 43 (43), 32 (54), 31 (100).

Anal. Calcd for $C_{20}H_{15}N_2ClO_3S$: C, 60.22; H, 3.79; N, 7.02. Found: C, 60.48; H, 3.92; N, 6.89.

Isomerization of 11 (R = *p*-ClC_6H_4). Treatment with an equimolar amount of *m*-chloroperbenzoic acid in methylene chloride at room temperature yielded, after extraction in the usual manner, the exo isomer 6-*p*-chlorophenyl-2-oxo-*N*-phenyl-3,4,5,6-tetrahydro-3α,6α-epi-*N*-methylimino-2*H*-thiapyran-4α,5α-dicarboximide (**12**, R = *p*-ClC_6H_4) as cream prisms from acetonitrile: yield 20%; mp 161–164° dec (with gas evolution); ir (KBr) 1710 (broad, CO) cm^{-1}; λ_{max} (CH_3OH) 223 nm (log ϵ 4.38), 341 (3.51); mass spectrum (rel intensity) *m/e* 350 (4), 60 (100).

Anal. Calcd for $C_{20}H_{15}N_2ClO_3S$: C, 60.22; H, 3.79; N, 7.02. Found: C, 60.37; H, 3.93; N, 7.11.

Reaction of *anhydro*-5-Hydroxy-3-methyl-2-phenylthiazolium Hydroxide with Tetracyanoethylene. The above mesoionic compound (1, R = Ph; R^1 = H) (0.57 g, 0.003 mol) in dry benzene (30 ml) was treated with tetracyanoethylene (0.38 g, 0.003 mol) and a deep red solution was formed immediately. After warming on the water bath for a few min, a deep red product separated. After 1 hr at room temperature the product was collected (0.5 g, 53%) and was then boiled with methanol and the insoluble product **14** (R = Ph) filtered and washed with dry ether: mp 230–232°; ir (Nujol) 2205 (CN), 1560 (CO) cm^{-1}; λ_{max} (CH_3OH) 201 nm (log ϵ 4.37), 297 (3.83), 488 (4.24); $M^{\cdot+}$ 320.

Anal. Calcd for $C_{16}H_9N_5OS$; C, 60.19; H, 2.84; N, 21.94. Found: C, 60.41; H, 2.83; N, 21.71.

The above methanolic filtrate was diluted with dry ether and, on standing, a bright red crystalline product separated: 0.05 g, mp 275–277°; ir (Nujol) 2200 (CN), 1612 (CO) cm^{-1}; λ_{max} (CH_3OH) 293 nm (log ϵ 3.94), 346 (3.34), 485 (4.35); $M^{\cdot+}$ 292 (32).

Anal. Calcd for $C_{15}H_8N_4OS$: C, 61.81; H, 2.74; N, 19.23. Found: C, 61.34; H, 2.62; N, 19.13.

The structure of this product was established as *anhydro*-5-hydroxy-3-methyl-2-phenyl-4-tricyanoethenylthiazolium hydroxide (**15**, R = Ph).

Similarly from *anhydro*-2-*p*-chlorophenyl-5-hydroxy-3-methylthiazolium hydroxide (1; R = *p*-ClC_6H_4; R^1 = H) (0.45 g, 0.002 mol) and tetracyanoethylene (0.26 g, 0.002 mol) a deep red solid was obtained (0.49 g, 94%), mp 210–215°. This methanol-insoluble product was chromatographed on silica gel and eluted with a chloroform–ethanol (9.5:0.5) mixture. The deep red band was collected and the product recrystallized from methanol, separating as bright red flakes of *anhydro*-2-*p*-chlorophenyl-5-hydroxy-3-methyl-4-tricyanoethenylthiazolium hydroxide (**15**, R = *p*-ClC_6H_4): mp 283–285°; ir (Nujol) 2205 (CN), 1695 (CO) cm^{-1}; λ_{max} (CH_3OH) 222 nm (log ϵ 4.08), 237 (4.01), 298 (3.74), 480 (3.97); $M^{\cdot+}$ 326 (15).

Anal. Calcd for $C_{15}H_7N_4ClOS$: C, 55.08; H, 2.14; N, 17.14. Found: C, 55.08; H, 2.14; N, 16.49.

Reaction of *anhydro*-5-Hydroxy-3-methyl-2-phenylthiazolium Hydroxide with Phenyl Isothiocyanate. The above mesoionic compound (1, R = Ph; R^1 = H) (1.9 g) and phenyl isothiocyanate (4 ml) were warmed at 80° for 30 min in a nitrogen atmosphere. On cooling the reaction mixture solidified. Anhydrous ether was added; the product was collected and then chromatographed on Kieselgel g using chloroform as eluent. 7-Methyl-1,2,6-triphenyl-2,6,7-triazabicyclo[2.2.1]heptane-3,5-dithione (**19**; R = Ph) was eluted first using chloroform. It crystallized from chloroform–ether as yellow needles: 0.5 g (12%); mp 266–268°; ir (KBr) 1640 (w), 1600 (w), 1560 (w), 1500, 1360, 770, 700 cm^{-1}; λ_{max} (CH_3OH) 233 nm (log ϵ 4.53), 325 (4.18), 378 (4.21); nmr ($CHCl_3$) δ 4.2 (s, 3, N–CH_3), 14.6 (s, 1, 4-H), 7.9-7.2 (m, 15, aromatic); $M^{\cdot+}$ 401 (28).

Anal. Calcd for $C_{23}H_{19}N_3S_2$: C, 68.81; H, 4.77; N, 10.47. Found: C, 68.67; H, 4.77; N, 10.40.

Further development of the column with chloroform–10% methanol gave *anhydro*-2,3-diphenyl-4-mercapto-1-methylimidazolium hydroxide (**18**, R = Ph) which crystallized from chloroform–ether as yellow flakes; 1.7 g (64%), mp 231–232°. The physical characteristics of this product have been reported previously.[1b]

Reaction of *anhydro*-2,3-Diphenyl-4-mercapto-1-methylimidazolium Hydroxide (18, R = Ph) with Phenyl Isothiocyanate. The mesoionic compound (0.5 g) and phenyl isothiocyanate (2 ml) were heated at 100° under nitrogen for 5 hr. On cooling anhydrous ether was added, and the yellow solid which separated was then chromatographed on Kieselgel g using chloroform as eluent. The adduct (**19**, R = Ph) crystallized from chloroform–ether as yellow needles, mp 266–268°. This product was identical in all respects with that isolated above.[27]

Further development of the column with chloroform–10% methanol gave the mesoionic compound **18** (0.4 g).

In a similar fashion 2,6-diphenyl-1-*p*-methoxyphenyl-7-methyl-2,6,7-triazabicyclo[2.2.1]heptane-3,5-dithione (**19**, R = *p*-$CH_3OC_8H_4$) was obtained from *anhydro*-5-hydroxy-2-*p*-methoxyphenyl-3-methylthiazolium hydroxide (**1**, R = *p*-$CH_3OC_6H_4$; R^1 = H) (2.4 g) and phenyl isothiocyanate (5 ml). It crystallized from chloroform–ether as yellow needles: 1.4 g (30%); mp 250°; λ_{max} (CH_3OH) 225 nm sh (log ϵ 4.34), 265 (4.23), 323 (4.13), 377 (4.20).

Anal. Calcd for $C_{24}H_{21}N_3OS_2$: C, 66.81; H, 4.91; N, 9.74. Found: C, 66.60; H, 5.06; N, 9.47.

Further development of the column with chloroform–10% methanol gave *anhydro*-4-mercapto-2-*p*-methoxyphenyl-1-methyl-3-phenylimidazolium hydroxide (**18**, R = *p*-$CH_3OC_6H_4$) as pale yellow needles from chloroform–ether: 1.3 g (38%); mp 204–206°; ir (KBr) 1610, 1580, 1510, 1260, 1200, 845, 765, 710 cm^{-1}; λ_{max} (CH_3OH) 246 nm (log ϵ 4.18), 320 (3.91); nmr ($CDCl_3$) δ 3.63 (s, 3, NCH_3), 3.77 (s, 3, OCH_3), 6.83 (ABd, 2, J = 9.0 Hz, aromatic), 6.91 (s, 1, 5-H), 7.12 (ABd, 2, J = 9.0 Hz, aromatic), 7.33 (s, 5, aromatic); $M^{\cdot+}$ 296 (4). This product decomposed on standing and was characterized as its methiodide (**23**, R = *p*-$CH_3OC_6H_4$). This crystallized from ethanol as colorless prisms: mp 210–212°; ir (KBr) 1610, 1500, 1480, 1310, 1290, 1200, 850, 765, 710 cm^{-1}; λ_{max} (CH_3OH) 208 nm (log ϵ 4.48), 268 (4.09); nmr ($CDCl_3$) δ 2.40 (s, 3, SCH_3), 3.79 (s, 3, NCH_3), 4.00 (s, 3, OCH_3), 6.90 (ABd, 2, J = 9.0 Hz, aromatic), 7.5 (broad, s, 5, aromatic), 7.63 (ABd, 2, J = 9.0 Hz, aromatic), 7.99 (s, 1, 5-H).

Anal. Calcd for $C_{18}H_{19}IN_2OS$: C, 49.33; H, 4.37; N, 6.40. Found: C, 49.31; H, 4.39; N, 6.27.

The corresponding 2,3-diphenyl-1-methyl-4-methylthioimidazolium iodide (**23**, R = Ph) and 2-*p*-chlorophenyl-1-methyl-4-methylthio-3-phenylimidazolium iodide (**23**, R = *p*-ClC_6H_4) were prepared in a similar fashion and their physical characteristics have been described earlier.[1b]

Reaction of *anhydro*-5-Hydroxy-3-methyl-2-phenylthiazolium Hydroxide with Phenyl Isocyanate. The above mesoionic compound (**1**, R = Ph; R^1 = H) (1.91 g) and phenyl isocyanate (3.0 g) were stirred at 100° in an atmosphere of nitrogen for 5 min. On cooling the reaction mixture solidified to a yellow, crystalline mass which was triturated with dry ether and collected. It was chromatographed on Kieselgel g using chloroform–10% ethyl acetate as eluent, 1,6-diphenyl-7-methyl-6,7-diaza-2-thiabicyclo[2.2.1]heptane-3,5-dione (**26**, R = R^2 = Ph) being eluted first. It crystallized from chloroform as pale yellow needles: mp 158–159°, 11%; ir (KBr) 1660, 1600, 1550 cm^{-1}; λ_{max} (CH_3OH) 238 nm (log ϵ 4.16), 283 (4.14), 354 (4.21); nmr ($CDCl_3$) δ 4.17 (s, 3, NCH_3), 7.7–6.9 (m, 10, aromatic), 10.64 (s, 1, 4-H); $M^{\cdot+}$ 310 (28).

Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.80; H, 4.55; N, 9.03. Found: C, 66.00; H, 4.57; N, 9.11.

Further development of the chromatogram with chloroform–10% ethyl acetate gave 7-methyl-1,2,6-triphenyl-2,6,7-triazabicyclo[2.2.1]heptane-3,5-dione (**28**, R = Ph) which crystallized from chloroform–ether as colorless needles: mp 249–250°; 48%; ir (KBr) 1670, 1640, 1590, 1550, 1500 cm^{-1}; λ_{max} (CH_3OH) 222 nm sh (log ϵ 4.37), 320 (4.46); nmr ($CDCl_3$) δ 4.03 (s, 3, NCH_3), 7.8–6.9 (m, 15, aromatic), 10.58 (s, 1, 4-H); $M^{\cdot+}$ 369 (30).

Anal. Calcd for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.38. Found: C, 74.89; H, 5.28; N, 11.35.

In a similar fashion, *anhydro*-5-hydroxy-2-*p*-methoxyphenyl-3-methylthiazolium hydroxide (**1**, R = *p*-$CH_3OC_6H_4$; R^1 = H) and phenyl isocyanate gave rise to 1-*p*-methoxyphenyl-7-methyl-6-phenyl-6,7-diaza-2-thiabicyclo[2.2.1]heptane-3,5-dione (**26**, R = *p*-$CH_3OC_6H_4$; R^2 = Ph) which crystallized from chloroform–ether as yellow needles: mp 190–191°; 12%; ir (KBr) 1650, 1600, 1570, 1550, 1520 cm^{-1}; λ_{max} (CH_3OH) 222 nm (log ϵ 4.14), 243 (4.05), 286 (4.24), 357 (4.32); nmr ($CDCl_3$) δ 3.89 (s, 3, OCH_3), 4.24 (s, 3, NCH_3), 7.8–6.9 (m, 9, aromatic), 10.66 (s, 1, 4-H); $M^{\cdot+}$ 340 (52).

Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.80; H, 4.61; N, 8.32.

2,6-Diphenyl-1-*p*-methoxyphenyl-7-methyl-2,6,7-triazabicyclo[2.2.1]heptane-3,5-dione (28; R = *p*-$CH_3OC_6H_4$) was likewise eluted as the second fraction and it crystallized from chloroform–ether as colorless prisms: mp 255–256°; 50%; ir (KBr) 1670, 1640, 1610, 1590, 1550 cm^{-1}; λ_{max} (CH_3OH) 248 nm (log ϵ 4.17), 320 (4.46); nmr ($CDCl_3$) δ 3.75 (s, 3, OCH_3), 4.02 (s, 3, NCH_3), 7.8–6.7 (m, 14, aromatic), 10.54 (s, 1, 4-H); $M^{\cdot+}$ 399 (42).

Anal. Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52 Found: C, 72.39; H, 5.26; N, 10.58.

General Procedure for the Reaction of 1 with Activated Isocyanates. Reaction with *p*-Toluenesulfonyl Isocyanate. To the mesoionic compound 1 (R = Ph; R^1 = H) (1.0 g, 0.0052 mol) in dry benzene (30 ml) was added dropwise a solution of *p*-toluenesulfonyl isocyanate (1.1 g, 0.0056 mol) in dry benzene (5 ml) at room temperature with stirring for 6 hr. Addition of anhydrous ether precipitated a colorless solid that crystallized from 1,2-dichloroethane–ether as colorless prisms of 7-methyl-1-phenyl-6-*p*-toluenesulfonyl-2-thia-6,7-diazabicyclo[2.2.1]heptan-5-dione (**26**, R = Ph; R^2 = *p*-$CH_3C_6H_4SO_2$): 1.6 g (79%), mp 200–204° dec (with gas evolution) (Table II).

Registry No.—**1** (R = *p*-$CH_3OC_6H_4$, R^1 = H), 40727-16-0; **1** (R = Ph, R^1 = H), 52052-19-4; **1** (R = *p*-ClC_6H_4, R^1 = H), 51787-62-3; **8** (R = *p*-$CH_3OC_6H_4$, R^1 = H), 52705-21-2; **8** (R = Ph, R^1 = H), 19611-52-0; **9** (R = Ph, R^1 = H), 22050-30-2; **9** (R = R^1 = Ph), 22050-79-9; **10**, 22050-80-2; **11** (R = Ph), 52705-22-3; **11** (R = *p*-ClC_6H_4), 52705-23-4; **12** (R = Ph), 52745-41-2; **12** (R = *p*-ClC_6H_4), 52745-42-3; **13**, 52705-24-5; **14** (R = Ph), 52705-25-6; **15** (R = Ph), 52705-26-7; **15** (R = *p*-ClC_6H_4), 52705-27-8; **18** (R = Ph), 19950-84-6; **18** (R = *p*-$CH_3OC_6H_4$), 52705-28-9; **19** (R = Ph), 52705-29-0; **19** (R = *p*-$CH_3OC_6H_4$), 52705-30-3; **23** (R = *p*-$CH_3OC_6H_4$), 52705-31-4; **26** (R = R^2 = Ph), 52705-32-5; **26** (R = *p*-$CH_3OC_6H_4$, R^2 = Ph), 52705-33-6; **26** (R = Ph, R^2-*p*-$CH_3C_6H_4SO_2$), 52705-34-7; **26** (R = *p*-ClC_6H_4, R^2 = *p*-$CH_3C_6H_4SO_2$), 52748-19-3; **26** (R = Ph, R^2 = COPh), 52705-35-8; **26** (R = *p*-ClC_6H_4, R^2 = COPh), 52705-36-9; **26** (R = Ph, R^2-*p*-ClC_6H_4CO), 52705-37-0; **26** (R = *p*-ClC_6H_4, R^2 = *p*-ClC_6H_4CO), 52705-38-1; **28** (R = Ph), 52705-39-2; **28** (R = *p*-$CH_3OC_6H_4$), 52705-40-5; *N*-*p*-methoxythiobenzoylsarcosine, 52705-41-6; *p*-methoxythiobenzoylthioglycollic acid, 52705-42-7; dimethylacetylenedicarboxylate, 762-42-5; *N*-benzoylsarcosine, 2568-34-5; ethyl propiolate, 623-47-2; ethyl phenylpropiolate, 2216-94-6; *N*-nitrososarcosine, 13256-22-9; *N*-phenylmaleimide, 941-69-5; dimethyl fumarate, 624-49-7; tetracyanoethylene, 670-54-2; phenyl isocyanate, 103-71-9; phenyl isothiocyanate, 103-72-0; *p*-toluenesulfonylisocyanate, 4083-64-1; benzoyl isocyanate, 4461-33-0; *p*-chlorobenzoyl isocyanate, 4461-36-3; sarcosine, 107-97-1.

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Mesoionic Compounds. XXXI. The Preparation and Cycloaddition Reactions of the *anhydro*-4-Hydroxythiazolium Hydroxide System with Acetylenic Dipolarophiles[1]

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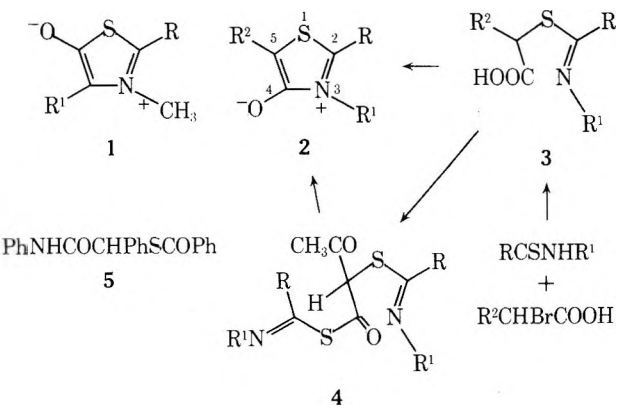
Received April 19, 1974

anhydro-2,3-Diphenyl-4-hydroxythiazolium hydroxide has been prepared by Ac_2O/Et_3N cyclization of the condensation product of thiobenzanilide and bromoacetic acid, and the product previously assigned this structure identified as 2-mercapto-1-thioacetoacetic acid, anhydrosulfide with *N*-phenylthiobenzimidic acid, *N*-phenylbenzimidate. Other derivatives of this mesoionic thiazolium system were prepared from the appropriate thiobenzanilide with bromoacetic acid (or α-bromophenylacetic acid). Dimethyl acetylenedicarboxylate, dibenzoylacetylene, dicyanoacetylene, and hexafluoro-2-butyne underwent ready cycloaddition to this thiazolium system, the final product depending on the substitution pattern of the nucleus. With 2,3-diaryl substituents, pyridones were formed with extrusion of sulfur from the initial adduct. With 2,3,5-triphenyl substituents, phenyl isocyanate was eliminated from the initial adduct with the formation of the substituted thiophene in more than 90% yield.

In the preceding publication[2] in our studies of mesoionic ring systems[3] the cycloaddition reactions of the *anhydro*-5-hydroxythiazolium hydroxide system **1**, one of the two[4] possible mesoionic ring systems based on the thiazole nucleus, were described. We now report the synthesis and cycloaddition reactions with acetylenic dipolarophiles of the isomeric *anhydro*-4-hydroxythiazolium hydroxide system **2**, which has an added interest in that there is no opportunity for elimination of carbonyl sulfide from an initial cycloadduct; rather sulfur must be extruded or a retro-Diels–Alder type reaction occur with elimination of phenyl isocyanate.

A synthesis of the mesoionic system **1** had been described[5] earlier, but its reported physical characteristics were inconsistent with those expected for a heterocycle containing a thiocarbonyl ylide structure. Repetition of the Ac_2O/Et_3N cyclization of the intermediate acid (**3**, R = R^1 = Ph; R^2 = H) obtained from thiobenzanilide and bromoacetic acid resulted in the isolation of the product described previously as colorless needles, mp 195–196°. In our preliminary communication this product was shown to have structure **4**. This most likely arises from the reaction of thiobenzanilide with the mixed anhydride derived from the intermediate acid **3** and acetic anhydride, followed by acetylation and, as such, is described as 2-mercapto-1-thioacetoacetic acid, anhydrosulfide with *N*-phenylthiobenzimidic acid, *N*-phenylbenzimidate (**4**, R = R^1 = Ph).



Reaction of thiobenz-*p*-chloroanilide with bromoacetic acid under these conditions gave an analogous product **4** (R = Ph; R^1 = *p*-ClC_6H_4). This product was likewise converted in good yield into the acetyl derivative of **2** (R = Ph; R^1 = *p*-ClC_6H_4; R^2 = $COCH_3$) with hot acetic anhydride.

Minor variation in the proportions of the reactants did not alter appreciably the outcome of the reaction. However, it was possible to have ring closure of the acid **3** to the me-

soionic system **2** favored over its condensation with thiobenzanilide by altering the reaction conditions to increase considerably the amount of Et_3N present while, at the same time, increasing the concentration of the reactants in the cyclization medium.

Treatment of the crude acid **3** (R = R^1 = Ph; R^2 = H), obtained from thiobenzanilide and bromoacetic acid, with the minimum volume for solution to occur of a 1:3 mixture of Ac_2O/Et_3N for 5 min and then inducing the product to crystallize by rapid scratching of the walls of the reaction vessel resulted in the formation of **2** (R = R^1 = Ph; R^2 = H). The intermediate acids **3** obtained from thiobenz-*p*-chloroanilide and also *p*-chlorothiobenzanilide also underwent cyclization to the corresponding substituted derivative of **2**. No acetylation of **2** was observed under these cyclization conditions which were critical,[6] slight variations resulting in decomposition products of **2**. However, the intermediate acid **3** (R = R^1 = R^2 = Ph) formed from thiobenzanilide and α-bromophenylacetic acid underwent ready cyclization to **2** (R = R^1 = R^2 = Ph) with considerable variation in the cyclization conditions being possible. This stabilizing effect of phenyl substituents has been observed in other mesoionic systems.[7]

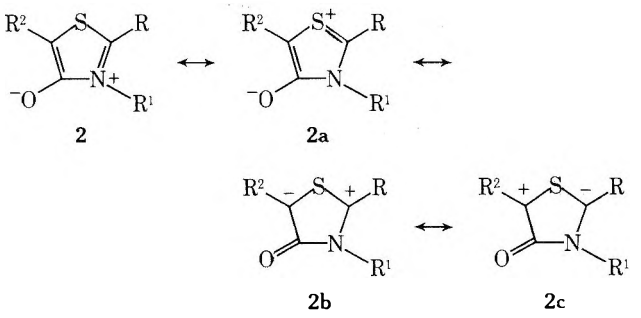
The ring system **2** unsubstituted in the 5 position is susceptible to moisture, undergoing ring opening, and it is advantageous to isolate **2** using "drybox" conditions. In the dry state, **2** is considerably more stable and may be stored without decomposition for several months, the 2-*p*-chlorophenyl analog being especially suitable in this respect.

Controlled hydrolysis of **2** (R = R^1 = Ph; R^2 = H) resulted in the acid **3** (R = R^1 = Ph; R^2 = H) being obtained in a pure state. An alternative mode of hydrolysis induced by the action of water over long periods has been observed for *anhydro*-4-hydroxy-2,3,5-triphenylthiazolium hydroxide (**2**, R = R^1 = R^2 = Ph). In this case α-(benzoylthio)phenylacetanilide (**5**) was obtained, this having been observed previously when 4-acetoxy-2,3,5-triphenylthiazolium perchlorate was treated with sodium bicarbonate.[8]

Treatment of **2** (R = R^1 = Ph; R^2 = H) with cold acetic anhydride readily gave *anhydro*-5-acetyl-2,3-diphenyl-4-hydroxythiazolium hydroxide (**2**, R = R^1 = Ph; R^2 = $COCH_3$). Analogous acetyl derivatives were obtained for the other thiazolium hydroxides used in this study.

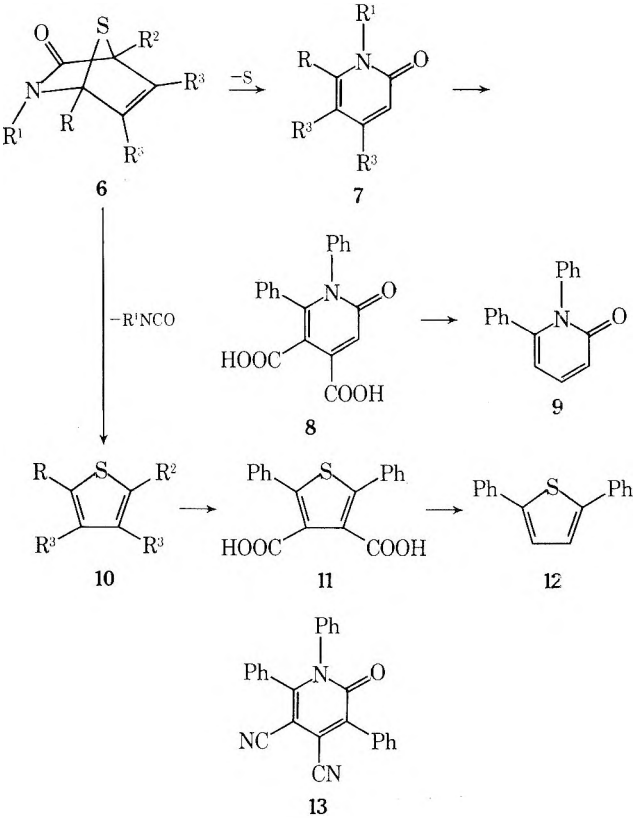
In addition to the above chemical evidence, spectral data are consistent with the assigned structure **2** for these cyclized products. An infrared carbonyl absorption at 1610 cm^{-1}, indicating some degree of single bond character, is analogous to that observed in other mesoionic systems[3,9] and is in contrast to the carbonyl absorption at 1715 cm^{-1} in Δ^2-2-phenyl-4-thiazolone.[10] Similarly the ultraviolet spectrum of **2** (R = R^1 = Ph; R^2 = H) shows a red shift to 350 nm from 330 nm for that of the 4-thiazolone. In the nmr spectrum of **2** a singlet proton was observed at δ 5.57, similar protons in other mesoionic systems usually absorbing in the region δ 8.0–5.5 depending on the nuclear heteroatoms.[2,9,11] It should be noted that this proton resonates at an appreciably higher field than does the corresponding 5-proton in thiazolium salts[12,13] (δ 8.34–7.94) and in thiazoles[13] (δ 6.87). This is most likely the result of delocalization of the exocyclic negative charge to the 5 position of the nucleus, which would be expected to be favored to some degree by interaction of the electrons at this position with the vacant d orbitals on the sulfur atom.

The mesoionic system **2** contains a masked 1,3-dipole system **2a** ↔ **2b** ↔ **2c**, which may formally be regarded as a thiocarbonyl ylide dipole stabilized to some extent by the adjacent nitrogen atom.[14a] This dipole has only very recently been studied in alicyclic systems[14b] and from the reactions of carbonyl ylide dipoles,[15] and from those of the *anhydro*-4-hydroxy-1,3-dithiolium hydroxide mesoionic system[16] and carbonyl-stabilized sulfonium ylides,[17] it was anticipated that the reactions of this ring system would be of considerable interest.



2 **2a** **2b** **2c**

The mesoionic system **2** was found to undergo ready cycloaddition with a variety of acetylenic dipolarophiles in refluxing benzene. The primary 1:1 cycloadduct was not isolated with these acetylenic dipolarophiles, the reaction product being that derived from the primary adduct by extrusion of sulfur or elimination of phenyl isocyanate. The nature of this reaction product was determined by the substituents present in **2**. Thus, *anhydro*-4-hydroxy-2,3-diphenylthiazolium hydroxide (**2**, R = R^1 = Ph; R^2 = H) and dimethyl acetylenedicarboxylate gave, *via* the intermediate **6**, dimethyl 1,6-diphenyl-2-pyridone-4,5-dicarboxylate (**7**, R = R^1 = Ph; R^3 = $COOCH_3$) in 70% yield. This ready



6 **7** **8** **9** **10** **11** **12** **13**

extrusion of sulfur during the course of the reaction is associated with the presence of the double bond in **6** and has also recently been observed in the cycloadducts from acetylenes and tetraphenylthieno[3,4-*c*]thiophene[18] and also thiophenes.[19] In the following publication[20] it will be seen that the primary 1:1 cycloadducts from **2** and olefinic dipolarophiles are quite stable, a behavior associated with bicyclic systems containing sulfur bridges which are only ex-

truded on strong heating.[21] Reaction of **2** (R = Ph, R^1 = *p*-ClC_6H_4 and R = *p*-ClC_6H_4, R^1 = Ph; R^2 = H) with dimethyl acetylenedicarboxylate gave the corresponding pyridones **7**. Similarly dibenzoylacetylene underwent cycloaddition with **2** (R = *p*-ClC_6H_4; R^1 = Ph; R^2 = H) giving **6**-*p*-chlorophenyl-4,5-dibenzoyl-1-phenyl-2-pyridone (**7**, R = *p*-ClC_6H_4; R^1 = Ph; R^3 = PhCO). The pyridone structure **7** was assigned on the basis of analytical and spectral data (Experimental Section) together with the alkaline hydrolysis of **7** (R = R^1 = Ph; R^3 = $COOCH_3$) to a product assigned the structure 1,6-diphenyl-2-pyridone-4,5-dicarboxylic acid (**8**). Subsequent decarboxylation yielded a product identified as 1,6-diphenyl-2-pyridone (**9**).

anhydro-4-Hydroxy-2,3,5-triphenylthiazolium hydroxide (**2**, R = R^1 = R^2 = Ph) also underwent cycloaddition with dimethyl acetylenedicarboxylate, though at a slower rate probably caused by the bulky phenyl substituents attached to the thiocarbonyl ylide, a factor which causes sluggish addition of olefinic dipolarophiles. However, in this case dimethyl 2,5-diphenylthiophene-3,4-dicarboxylate (**10**, R = R^2 = Ph; R^3 = $COOCH_3$), identified by spectral data, was formed in 90% yield by elimination of PhNCO (detected by glc) from the primary cycloadduct **6** (R = R^1 = R^2 = Ph; R^3 = $COOCH_3$). Alkaline hydrolysis of **10** (R = R^2 = Ph; R^3 = $COOCH_3$) gave 2,5-diphenylthiophene-3,4-dicarboxylic acid (**11**) which was decarboxylated to 2,5-diphenylthiophene (**12**), previously synthesized from cinnamic acid and sulfur.[22]

The reaction of **2** (R = R^1 = R^2 = Ph) with dibenzoylacetylene likewise gave 3,4-dibenzoyl-2,5-diphenylthiophene (**10**, R = R^2 = Ph; R^3 = COPh), although only obtained in 42% yield. Spectra and analytical data, together with its conversion into tetraphenylthieno[3,4-*c*]thiophene[18] clearly confirm the assigned structure. It has been our experience that diminished yields are often obtained in cycloadditions with dibenzoylacetylene, largely due to decomposition occurring at elevated reaction temperatures. However, it is an extremely versatile dipolarophile which allows the introduction of strategic functional groups into heteroaromatic systems.

Hexafluoro-2-butyne was also found to undergo ready reaction with **2** (R = R^1 = R^2 = Ph) giving 2,5-diphenyl-3,4-di(trifluoromethyl)thiophene (**10**, R = R^2 = Ph; R^3 = CF_3). However, the equally reactive dicyanoacetylene did not give exclusive thiophene formation with the mesoionic system **2** (R = R^1 = R^2 = Ph). In this case a mixture of 4,5-dicyano-1,3,6-triphenyl-2-pyridone (**13**) (4.4%) and 3,4-dicyano-2,5-diphenylthiophene (**10**, R = R^2 = Ph; R^3 = CN) (95.2%) was obtained.

These results suggest that the thermal decomposition of the primary 1:1 cycloadduct **6** is controlled more by steric effects than by electronic effects. Both retro-cycloadditions generate a thermodynamically stable, small fragment and a heteroaromatic system. Extrusion of sulfur from **6** (R = R^1 = R^2 = Ph) would result in a pyridone with every peripheral position substituted with bulky substituents, whereas elimination of phenyl isocyanate provides a thiophene in which this steric overcrowding is largely eliminated. Isolation of a small amount of the pyridone **13** together with the thiophene **10** (R = R^2 = Ph; R^3 = CN) from dicyanoacetylene and the mesoionic system **2** (R = R^1 = R^2 = Ph) is consistent with this rationalization. The spatial requirements of the linear cyano group are considerably less than the carbomethoxy, benzoyl, or trifluoromethyl groups and, consequently, the steric overcrowding in **13** is reduced.

In other cycloadducts analogous to **6** from which sulfur is extruded,[18,19] product formation involves aromatization to a benzene nucleus even though considerable steric overcrowding results. However, in these systems there is no alternative possibility for bond fission as exists in the case of **6**. Though it has not been realized in practice, it is conceivable to derive **6** from a thiophene and phenyl isocyanate and, as both these fragments are particularly stable, it is not surprising that the retro-Diels–Alder reaction is observed.

These cycloadditions are particularly noteworthy for the ease with which they occur and for the mild conditions under which sulfur is extruded. This is in contrast to the usual bridge-sulfur extrusion which requires more vigorous conditions.[21] They provide an extremely facile synthetic route to pyridones and thiophenes, limited only by the restraints imposed by the synthesis of **2** and the requisite acetylenic dipolarophiles. In conjunction with our study of the *anhydro*-2-aryl-4-hydroxy-1,3-dithiolium system, a variety of tri- and tetrasubstituted thiophenes are readily available. However, there are limitations to the choice of the acetylenic dipolarophile. Diphenylacetylene did not yield a well-defined product, nor did *N,N,N',N'*-tetramethyl-2-butyne-1,4-diamine, 2-methyl-1-buten-3-yne, 1-methoxy-1-buten-3-yne, and 3-hydroxy-1-hexyne. Electron-rich acetylenes such as the ynamines also resulted in intractable tarry mixtures.

Experimental Section[23]

2-Mercapto-1-thioacetoacetic Acid, Anhydrosulfide with *N*-Phenylthiobenzimidic Acid, *N*-Phenylbenzimidate (4, R = R^1 = Ph). Thiobenzanilide (10.0 g), bromoacetic acid (6.5 g), and Et_3N (19 g) were dissolved in benzene (50 ml), and the solution was stirred at room temperature for 4 hr. $Et_3N \cdot HBr$ was filtered off and the benzene and excess Et_3N were removed under vacuum yielding an unstable yellow oil which was used without further purification. This was treated with a mixture of Et_3N (15 ml) and Ac_2O (15 ml) and the solution left at room temperature for 7 days. The precipitate which separated was collected and recrystallized from chloroform–ether forming colorless needles: 4.0 g (33%); mp 192–194° (lit.[5] mp 195–196°); ir (KBr) 1725 (CO), 1680 (CO), 1590 (C=N) cm^{-1}; λ_{max} (CH_3OH) 201 nm (log ϵ 4.83), 240 sh (4.10), 267 sh (3.58); nmr ($CDCl_3$) δ 1.79 (s, 3, $COCH_3$), 4.70 (s, 1, –CH), 7.54 (m, 20, aromatic); $M \cdot^+$ 508.

Anal. Calcd for $C_{30}H_{24}N_2O_2S_2$: C, 70.85; H, 4.76; N, 5.51. Found: C, 70.67; H, 5.14; N, 5.26.

In a similar fashion *p*-chlorobenzanilide gave rise to 2-mercapto-1-thioacetoacetic acid, anhydrosulfide with *N*-*p*-chlorophenylthiobenzimidic acid, *N*-*p*-chlorophenylbenzimidate (4, R = Ph; R^1 = *p*-ClC_6H_4) and, in this case, anhydrous ether was added to effect complete precipitation of the product which crystallized from chloroform–ether as colorless needles: 3.8 g (30%); mp 190–192° (lit.[5] mp 165–166°); ir (KBr) 1720 (CO), 1660 (CO), 1590 (C=N) cm^{-1}; λ_{max} (CH_3OH) 202 nm (log ϵ 4.84), 246 sh (4.22); nmr ($CDCl_3$) δ 1.80 (s, 3, $COCH_3$), 4.75 (s, 1, –CH), 7.40 (m, 18, aromatic); $M \cdot^+$ 542.

Anal. Calcd for $C_{30}H_{22}Cl_2N_2O_2O_2S_2$: C, 62.40; H, 3.82; N, 4.86. Found: C, 62.40; H, 3.88; N, 4.84.

***anhydro*-4-Hydroxy-2,3-diphenylthiazolium Hydroxide (2, R = R^1 = Ph; R^2 = H).** Thiobenzanilide (10.0 g), bromoacetic acid (6 .5 g), and Et_3N (30 g) were dissolved in benzene (200 ml), and the solution was stirred at room temperature for 4 hr. After filtration of the $Et_3N \cdot HBr$, the excess Et_3N, and benzene were evaporated, and the residual, unstable yellow oil was then treated with a mixture of Et_3N (9 ml) and Ac_2O (3 ml) using a drybox. Upon scratching the walls of the flask a yellow precipitate formed in a few minutes. After addition of anhydrous ether the product was collected and washed with ether. The product was extremely sensitive to moisture and undergoes decomposition on standing in the atmosphere. It was obtained as orange-yellow needles: 4.5 g (38%); mp 113–115° dec; ir (KBr) 1610 (CO) cm^{-1}; λ_{max} (CH_3OH) 240 nm (log ϵ 4.27), 350 (2.62); nmr ($CDCl_3$) δ 4.57 (s, 1, 5-H), 7.28 (m, 10, aromatic); $M \cdot^+$ 235 (29).

Anal. Calcd for $C_{15}H_{11}NOS$: C, 71.14 H, 4.37. Found: C, 71.20; H, 4.66.

Using the appropriate thiobenzanilide, the following were prepared by the above general procedure.

1. *anhydro*-3-*p*-**Chlorophenyl-4-hydroxy-2-phenylthiazoli-**

um Hydroxide (2, R = Ph; R^1 = p-ClC_6H_4; R^2 = H): orange-yellow needles; 4.0 g (35%); mp 115–116° dec; ir (KBr) 1620 cm^{-1}; λ_{max} (CH_3OH) 220 nm sh (log ϵ 3.87), 242 (3.66), 385 (3.46); nmr ($CDCl_3$) δ 5.57 (s, 1, 5-H), 7.32 (m, 9, aromatic); M·+ 287 (25).

Anal. Calcd for $C_{15}H_{10}ClNOS$: C, 62.22; H, 3.48. Found: C, 62.37; H, 3.57.

2. *anhydro*-2-*p*-Chlorophenyl-4-hydroxy-3-phenylthiazolium Hydroxide (2, R = p-ClC_6H_4; R^1 = Ph; R^2 = H): orange-yellow needles; 6.5 g (52%); mp 125–130° dec; ir (KBr) 1650 (CO) cm^{-1}; nmr ($CDCl_3$) δ 5.60 (s, 1, 5-H), 7.25 (m, 9, aromatic); M·+ 287 (28).

Anal. Calcd for $C_{15}H_{10}ClNOS$: C, 62.61; H, 3.48; N, 4.87. Found: C, 62.23; H, 3.79; N, 4.71.

Reaction with Acetylenic Dipolarophiles. A. *anhydro*-2,3-Diaryl-4-hydroxythiazolium Hydroxides (2, R = R^1 = aryl; R^2 = H). The mesoionic compound 2 (R = R^1 = Ph; R^2 = H) (2.53 g, 0.01 mol) in benzene (50 ml) and redistilled dimethyl acetylenedicarboxylate (1.5 g, 0.011 mol) were mixed together and an immediate, exothermic reaction with darkening of the reaction mixture occurred. After heating at 80° for 3 hr, the benzene was evaporated and the residue chromatographed on Kieselgel g using chloroform as eluent. Dimethyl 1,6-diphenyl-2-pyridone-4,5-dicarboxylate (7, R = R^1 = Ph; R^3 = $COOCH_3$) formed colorless needles from chloroform–petroleum ether (bp 40–60°): 2.45 g (70%); mp 180–181°; ir (KBr) 1710 ($COOCH_3$), 1660 (CO–N) cm^{-1}; λ_{max} (CH_3OH) 205 nm (log ϵ 4.65), 250 (3.99), 355 (3.82); nmr ($CDCl_3$) δ 3.47 (s, 3, 4-$COOCH_3$), 3.92 (s, 3, 5-$COOCH_3$), 7.17 (m, 11, aromatic); mass M·+ 363 (100).

Anal. Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.43; H, 4.74; N, 3.84.

Similarly, dimethyl 1-*p*-chlorophenyl-6-phenyl-2-pyridone-4,5-dicarboxylate (7, R = Ph; R^1 = p-ClC_6H_4; R^3 = $COOCH_3$) was obtained from 2 (R = Ph; R^1 = p-ClC_6H_4; R^2 = H) as colorless needles from chloroform–petroleum ether; 1.95 g (70%), mp 234–235°.

Anal. Calcd for $C_{21}H_{16}ClNO_5$: C, 63.14; H, 4.02; N, 3.52. Found: C, 62.99; H, 4.09; N, 3.38.

With dibenzoylacetylene the following reaction conditions were used. The mesoionic compound 2 (R = p-ClC_6H_4; R^1 = Ph; R^2 = H) (0.7 g, 0.025 mol) in dry benzene (50 ml) was treated with dibenzoylacetylene (0.69 g, 0.025 mol) at room temperature with stirring for 18 hr. After 1 hr a product had started to separate and this was finally collected. 6-*p*-Chlorophenyl-4,5-dibenzoyl-1-phenyl-2-pyridone (7; R = p-ClC_6H_4, R^1 = Ph; R^3 = COPh) crystallized from chloroform–petroleum ether as colorless needles: 0.45 g (37%); mp 251–253°; ir (KBr) 1670 (COPh), 1610 (CON<) cm^{-1}; λ_{max} (CH_3OH) 258 nm (log ϵ 4.29), 330 (3.73); nmr ($CDCl_3$) δ 8.1–6.9 (m, aromatic); M·+ 489 (39).

Anal. Calcd for $C_{31}H_{20}ClNO_3$: C, 76.00; H, 4.11; N, 2.86. Found: C, 75.18; H, 4.07; N, 2.82.

4,5-Dibenzoyl-1,6-diphenyl-2-pyridone (7, R = R^1 = Ph; R^3 = COPh) was prepared[24] in a similar manner from 2 (R = R^1 = Ph; R^2 = H). It crystallized from ethanol as colorless, matted needles: 61%, mp 236–238°; ir (KBr) 3080, 3050 (CH), 1670 (CO) cm^{-1}; nmr ($CDCl_3$) δ 8.32–8.02 (m, 2, aromatic), 7.84–6.95 (m, 19, aromatic), M·+ 455 (92).

Anal. Calcd for $C_{31}H_{21}NO_3$: C, 81.74; H, 4.65; N, 3.08. Found: C, 82.00; H, 4.82; N, 3.15.

B. *anhydro*-4-Hydroxy-2,3,5-triphenylthiazolium Hydroxide (2, R = R^1 = R^2 = Ph). The above mesoionic compound[5] (3.3 g, 0.01 mol) in dry benzene (100 ml) and dimethyl acetylenedicarboxylate (1.5 g, 0.011 mol) were refluxed together overnight. Solution of 2 gradually occurred and the reaction color changed from deep red to yellow during this period. The benzene was evaporated and the residue chromatographed on Kieselgel g using chloroform as eluent. Dimethyl 2,5-diphenylthiophene 3,4-dicarboxylate (10; R = R^2 = Ph; R^3 = $COOCH_3$) crystallized from chloroform–petroleum ether as colorless needles: 3.10 g (90%); mp 167–168° (lit.[7b] mp 166–167.5°); ir (KBr) 1710 cm^{-1}; λ_{max} (CH_3OH) 206 nm (log ϵ 4.49), 240 (4.34), 295 (4.12); nmr ($CDCl_3$) δ 3.78 (s, 6, $COOCH_3$), 7.50 (m, 10, aromatic); M·+ 352 (100).

3,4-Dibenzoyl-2,5-diphenylthiophene (10, R = R^2 = Ph; R^3 = COPh) was prepared[24] from 2 (R = R^1 = R^2 = Ph) (2.0 g, 0.006 mol) in benzene (50 ml) and dibenzoylacetylene (1.42 g, 0.006 mol) using a 30-hr reflux period. Chromatography was on florisil using chloroform as eluent. It crystallized from 95% ethanol as cream, irregular prisms: 1.2 g (42%); mp 139–140°; ir (KBr) 1660, 1640, (CO) cm^{-1}; λ_{max} (CH_3OH) 198 nm (log ϵ 4.81), 262 (4.66); nmr ($CDCl_3$) δ 7.85–7.62 (m, 4, aromatic), 7.60–7.18 (m, 16, aromatic); M·+ 444 (100).

Anal. Calcd for $C_{30}H_{20}O_2S$: C, 81.06; H, 4.54. Found: C, 80.86; H, 4.49.

2,5-Diphenyl-3,4-di(trifluoromethyl)thiophene (10, R = R^2 = Ph; R^3 = CF_3), prepared from 2 (R = R^1 = R^2 = Ph) and hexafluoro-2-butyne formed yellow, irregular prisms sublimed at 100° (0.01 mm): 2.5 g (90%); mp 98–99°; nmr ($CDCl_3$) δ 7.43 (s, aromatic).

Anal. Calcd for $C_{18}H_{10}F_6S$: C, 58.06; H, 2.68. Found: C, 57.95; H, 2.63.

3,4-Dicyano-2,5-diphenylthiophene (10, R = R^2 = Ph; R^3 = CN). The mesoionic compound 2 (R = R^1 = R^2 = Ph) (1.0 g) and dicyanoacetylene (0.25 g) were refluxed in benzene for 3 hr. After reaction workup and chromatography as above, the thiophene was eluted from the column first and crystallized from chloroform–petroleum ether as colorless needles: 0.80 g (95.2%); mp 181–182°; ir (KBr) 2250 (CN) cm^{-1}; nmr ($CDCl_3$) δ 7.76 (m, aromatic).

Anal. Calcd for $C_{18}H_{10}N_2S$: C, 75.51; H, 3.52; N, 9.79. Found: C, 75.18; H, 3.46; N, 9.72.

The second fraction eluted from the column was 4,5-dicyano-1,3,6-triphenyl-2-pyridone (13). It crystallized from chloroform–petroleum ether as colorless needles: 0.05 g (4.4%); mp 252–254°; ir (KBr) 2290 (CN), 1700 (CO) cm^{-1}; M·+ ~500 (<1).

Anal. Calcd for $C_{25}H_{15}N_3O$: C, 80.41; H, 4.05. Found: C, 80.26; H, 4.10.

Acetylation of the Mesoionic System 2 (R = R^1 = Ph; R^2 = H). The mesoionic compound (2.0 g) in chloroform (100 ml) and Ac_2O (10 ml) was kept overnight at room temperature. After evaporation of the solvent the residue was chromatographed on Kieselgel g using $CHCl_3$: 5% EtOH as eluent. The acetyl compound (2, R = R^1 = Ph; R^2 = $COCH_3$) crystallized from chloroform–ether, and ethanol, as orange plates: 0.95 g (20%); mp 250° (lit.[5] mp 250°); ir (KBr) 1650 ($COCH_3$), 1600 (CO) cm^{-1}; λ_{max} (CH_3OH) 257 nm sh (log ϵ 3.98), 263 (4.10), 401 (4.04); nmr ($CDCl_3$) δ 2.63 (s, 3, $COCH_3$), 7.37 (m, 10, aromatic); M·+ 295 (29).

When the condensation product 4 (R = R^1 = Ph) was refluxed with Ac_2O for 10 hr and the solvent evaporated, orange plates (86%), mp 250–252° of the above acetyl compound 2 (R = R^1 = Ph; R^2 = $COCH_3$) were obtained.

***anhydro*-5-Acetyl-4-hydroxy-3-*p*-chlorophenyl-2-phenylthiazolium Hydroxide (2, R = Ph; R^1 = p-ClC_6H_4; R^2 = $COCH_3$)** was obtained from 2 (R = Ph; R^1 = p-ClC_6H_4; R^2 = H) (2.0 g) and Ac_2O as above. It crystallized from chloroform–ether as orange needles: 0.5 g (22%); mp 240–242°; ir (KBr) 1660 ($COCH_3$), 1600 (CO) cm^{-1}; λ_{max} (CH_3OH) 225 nm (log ϵ 4.14), 263 (4.02), 403 (3.92); nmr ($CDCl_3$) δ 2.65 (s, 3, $COCH_3$), 7.45 (m, 9, aromatic); M·+ 330 (20).

Anal. Calcd for $C_{17}H_{12}ClNO_2S$: C, 61.90; H, 3.64; N, 4.25. Found: C, 61.75; H, 3.86; N, 4.44.

The same acetyl derivative was obtained when the condensation product 4 (R = Ph; R^1 = p-ClC_6H_4) was refluxed with Ac_2O as above.

Hydrolysis of Dimethyl 1,6-Diphenyl-2-pyridone-4,5-dicarboxylate (7, R = R^1 = Ph; R^3 = $COOCH_3$). Dimethyl 1,6-diphenyl-2-pyridone-4,5-dicarboxylate (2.0 g) was refluxed with a 10% NaOH solution of aqueous methanol (1:1) (50 ml). The methanol was removed *in vacuo* and the aqueous solution was acidified with 2 *N* HCl. The pyridone dicarboxylic acid 8 crystallized and after filtration was obtained from aqueous ethanol as colorless prisms: 1.3 g (72%), mp 256–257°; ir (KBr) 3320 (OH), 1700 1625 (CO) cm^{-1}.

Anal. Calcd for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18. Found: C, 67.86; H, 4.01; N, 4.01.

Registry No.—**2** (R = R^1 = Ph, R^2 = H), 13288-67-0; **2** (R = Ph, R^1 = p-ClC_6H_4, R^2 = H), 26245-44-3; **2** (R = p-ClC_6H_4, R^1 = Ph, R^2 = H), 52730-97-9; **2** (R = R^1 = R^2 = Ph), 18100-80-6; **2** (R = R^1 = Ph, R^2 = $COCH_3$), 13288-62-5; **2** (R = Ph, R^1 = p-ClC_6H_4, R^2 = $COCH_3$), 52718-80-6; **4** (R = R^1 = Ph), 26245-40-9; **4** (R = Ph, R^1 = p-ClC_6H_4), 26245-42-1; **7** (R = R^1 = Ph, R^3 = $COOCH_3$), 24562-71-8; **7** (R = Ph, R^1 = p-ClC_6H_4, R^3 = $COOCH_3$), 52718-81-7; **7** (R = p-ClC_6H_4, R^1 = Ph, R^3 = COPh), 52718-82-8; **7** (R = R^1 = Ph, R^3 = COPh), 52718-83-9; **8**, 24562-72-9; **10** (R = R^2 = Ph, R^3 = $COOCH_3$), 20851-13-2; **10** (R = R^2 = Ph, R^3 = COPh), 40953-25-1; **10** (R = R^2 = Ph, R^3 = CF_3), 52718-84-0; **10** (R = R^2 = Ph, R^3 = CN), 52718-85-1; **13**, 52718-86-2; thiobenzanilide, 636-04-4; bromoacetic acid, 79-08-3; *p*-chlorobenzanilide, 6853-15-4; dimethyl acetylenedicarboxylate, 762-42-5; dibenzoylacetylene, 1087-09-8; hexafluoro-2-butyne, 692-50-2; dicyanoacetylene, 1071-98-3.

References and Notes

(1) (a) Support of this work by U.S. Public Health Service Grant CA 08495, National Cancer Institute, is gratefully acknowledged; (b) presented in part as a preliminary communication: K. T. Potts, E. Houghton, and U. P. Singh, *Chem. Commun.*, 1128, 1129 (1969).
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(23) Spectral characterizations were carried out with the following instrumentation: ir, Perkin-Elmer Model 421 and 137 infrared spectrophotometers; uv, Cary Model 14 spectrophotometer; nmr, Varian A-60 spectrometer using TMS as internal standard; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV using the direct insertion probe at a temperature of ca. 150°. Evaporations were done under reduced pressure using a rotavap apparatus and melting points were determined in capillaries. Analyses are by Galbraith Laboratories, Knoxville, Tenn., and Instranal Laboratories Inc., Rensselaer, N.Y.
(24) We thank Dr. D. McKeough for this experiment.

Mesoionic Compounds. XXXII. Cycloaddition Reactions of the *anhydro*-4-Hydroxythiazolium Hydroxide System with Olefinic Dipolarophiles[1]

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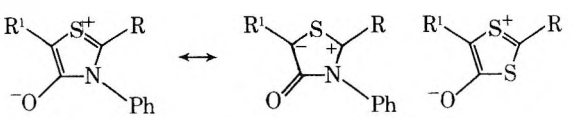
Received April 19, 1974

Di- and trisubstituted derivatives of the mesoionic *anhydro*-4-hydroxythiazolium hydroxide system underwent 1,3-dipolar cycloadditions *via* their thiocarbonyl ylide dipole giving stable 1:1 adducts of the substituted 1,2,3,4,5,6-hexahydro-3-oxo-1α,4α-epithiopyridine system with a wide variety of electron-deficient dipolarophiles. The stereochemistry of each adduct was determined by extensive nmr analysis and also by chemical methods. Several adducts lost the elements of H_2S upon treatment with sodium methoxide forming 4,5-disubstituted 1,3,6-triphenylpyrid-2-ones, and with *m*-chloroperbenzoic acid gave sulfoxide derivatives.

The title mesoionic ring system **1** has been shown[2] to undergo ready cycloaddition of acetylenic dipolarophiles to yield substituted 2-pyridones and thiophenes in good yields. The ring system contains a "masked" thiocarbonyl ylide dipole **1a** stabilized to some extent by an adjacent nitrogen atom. The same ylide is present in the *anhydro*-4-hydroxy-1,3-dithiolium hydroxide system **2** which has also



1 **1a** **2**

been shown to undergo cycloaddition of acetylenic dipolarophiles[3] to yield substituted thiophenes with elimination of carbonyl sulfide, as well as forming stable 1:1 cycloadducts with olefinic dipolarophiles.[4]

A study of the cycloaddition reactions of **1** was thus of particular interest. It would enable the effect of replacing the 3-sulfur atom in **2** with a nitrogen atom to be evaluated, as well as providing a novel series of bridged sulfur, bicyclic adducts incorporating a hexahydro-3-oxo-1α,4α-epithiopyridine system.

Electron-deficient olefins such as dimethyl maleate and fumarate, *N*-phenylmaleimide, maleic anhydride, methyl vinyl ketone, *trans*-dibenzoylethylene, ethyl acrylate, ethyl methacrylate, ethyl crotonate, acrylonitrile, and fumaronitrile all formed stable, 1:1 cycloadducts with di- and trisubstituted derivatives of **1** with relative ease. However, no major product was isolated from the reaction of **1** with norbornene, norbornadiene, tetracyanoethylene, 4-cyanopyridine, and chalcone, either in refluxing benzene or at room temperature. Similarly electron-rich olefins such as ethyl vinyl ether resulted in multi-component reaction mixtures from which no single product could be isolated.

The gross structural features of the 1:1 cycloadducts obtained from **1** and the dipolarophiles listed above were established from analytical, mass spectral, and other spectral data (Tables I–IV). All were consistent with the formation of a 1:1 adduct with the thiocarbonyl ylide dipole, and the stereochemistry of these adducts was established from their nmr spectra considered below in increasing order of complexity.

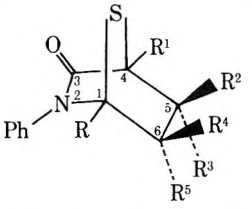
Cycloadducts from *anhydro*-2,3-Diaryl-4-hydroxythiazolium Hydroxide. *N*-Phenylmaleimide Adducts. Reaction of **1** (R = *p*-ClC_6H_4; R^1 = H) with *N*-phenyl-

Table I
Cycloadducts Derived from *anhydro*-2,3-Diaryl-4-hydroxythiazolium Hydroxide and Olefinic Dipolarophiles[a]

Compd no.	Yield, %	Mp,[b] °C	Molecular formula	M.+ (rel int)	Ir, cm^{-1}	uv max (CH_3OH), nm (log ε)
3 (R = *p*-ClC_6H_4)	35	270–273	$C_{25}H_{17}N_2ClO_3S$	460 (8)	1730, 1710 (CO)	220 sh (4.33)
3 (R = Ph)	60	265–267	$C_{25}H_{18}N_2O_3S$	426 (7)	1790, 1700 (CO)	
7 (R = *p*-ClC_6H_4)	38	225–230	$C_{31}H_{22}NClO_3S$	523 (3)	1720, 1690 (CO)	250 (4.23)
9 (R = $COCH_3$)	32	200–204	$C_{19}H_{16}NClO_2S$	357 (17)	1710, 1690 (CO)	224 (4.11)
9 (R = COOEt)	48	139–140	$C_{20}H_{18}NClO_3S$	387 (30)	1750, 1710 (CO)	224 (3.73)
13 (R = *p*-ClC_6H_4)	66	225–228	$C_{19}H_{12}NClO_4S$	385 (5)	1800, 1730 (CO)	245 sh (3.22), 223 (3.96)
15 (R = *p*-ClC_6H_4)	19	158–160	$C_{21}H_{18}NClO_5S$	431 (3)	1740, 1720 (CO)	222 (3.85)
15 (R = Ph)	70	164–165	$C_{21}H_{19}NO_5S$	397 (30)	1750, 1730, 1700 (CO)	205 (4.62)
16 (R = *p*-ClC_6H_4)	41	217–219	$C_{21}H_{18}NClO_5S$	431 (3)	1760, 1720 (CO)	222 (4.07)
16 (R = Ph)	63	219–220	$C_{21}H_{19}NO_5S$	395 (3)	1740, 1690 (CO)	240 (3.44), 206 (4.04)
17	97	235–240	$C_{25}H_{18}N_2O_4S$	442 (39)	1725 (CO), 1090 (SO)	277 (4.01)

[a] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table: Ed. [b] All melting points accompanied by decomposition.

Table II
Methine and Alkyl Group Chemical Shifts and Coupling Constants for Cycloadducts Derived from *anhydro*-2,3-Diaryl-4-hydroxythiazolium Hydroxides and Olefinic Dipolarophiles[a]

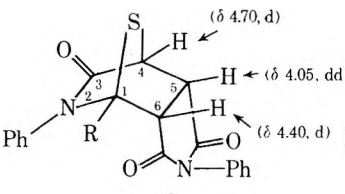


Compd no.	Chemical shifts (δ) R^1	R^2	R^3	R^4	R^5	Coupling constants, Hz $J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$
3, R = *p*-ClC_6H_4;[b] $R^3 = R^5$ = CONPhCO	4.70, d	4.05, dd		4.40, d		1.5			7.0	
3, R = Ph;[b] $R^3 = R^5$ = CONPhCO	4.69, d	4.09, dd		4.40, d		1.5			6.5	
7, R = *p*-ClC_6H_4;[b] $R^2 = R^5$ = COPh	4.43, d		4.83, t	5.80, d			4.0			4.5
9, R = *p*-ClC_6H_4;[b] $R^5 = COOCH_3$	4.27, dd	2.97, qd	2.52, qd	4.02, dd	*2.03*, s	1.0	3.5	12.5	8.0	4.5
9, R = *p*-ClC_6H_4;[c] $R^5 = COOCH_2CH_3$	4.22, dd	2.95, qd	2.71, qd	4.11, dd	3.91, q *0.97*, t	1.3	3.5	13.5	8.3	4.5
13, R = *p*-ClC_6H_4;[d] $R^3 = R^5$ = COOCO	4.97, d	4.70, dd		5.20, d		1.5			7.0	
15, R = *p*-ClC_6H_4; $R^2 = R^5$ = $COOCH_3$	4.48, d	*3.85*, s	4.08, t	4.42, d	*3.48*, s		3.8			4.3
15, R = Ph; $R^2 = R^5$ = $COOCH_3$	4.50, d	*3.83*, s	4.07, t	4.40, d	*3.42*, s		4.25			3.75
16, R = *p*-ClC_6H_4; $R^3 = R^5 = COOCH_3$	4.46, d	3.98, dd	*3.75*, s	4.37, d	*3.32*, s	1.0			9.0	
16, R = Ph; $R^3 = R^5$ = $COOCH_3$	4.51, d	4.00, dd		4.40, d		1.0			9.0	
17, R = Ph; $R^3 = R^5$ = CONPhCO	4.68, d	4.23, dd		5.17, d		1.5			9.0	

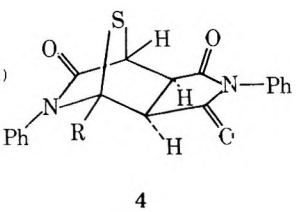
[a] Methyl resonances in italics. [b] Determined in $CDCl_3$. [c] Determined in acetone-d_6. [d] Determined in DMSO-d_6.

maleimide in refluxing anhydrous benzene gave a stable product corresponding to a 1:1 cycloadduct.

The structure of this adduct was assigned on the following basis. Infrared carbonyl absorptions were observed at 1730 and 1710 cm^{-1}, and the nmr spectrum (Table II) showed besides aromatic protons three aliphatic proton multiplets consisting of two groups of doublets (δ 4.40, 4.70) and one doublet of doublets (δ 4.05). These data are consistent with either the endo structure **3** (R = *p*-ClC_6H_4) or the exo structure **4** (R = *p*-ClC_6H_4). The stereochemistry of the 1:1 adduct is assigned the endo configuration by analogy with similar cycloadducts in the isobenzothiophene system[5] where with *N*-phenylmaleimide a mixture of endo, **5**, and exo, **6**,



3



4

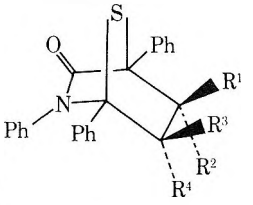
isomers was obtained. Assignments of the α-imido and bridgehead protons are as shown. It was postulated in this case that the difference in chemical shift between the protons α to the imide carbonyl from exo to endo was due to the deshielding effect of the sulfide

Table III
Cycloadducts Derived from *anhydro*-4-Hydroxy-2,3,5-triphenylthiazolium Hydroxides and Olefinic Dipolarophiles[a]

Compd no.	Yield, %	Mp, °C	Molecular formula	M·+ (rel int)	Ir, cm^{-1}	uv max (CH_3OH), nm (log ϵ)
19 (R = $COCH_3$)	17	180–182 dec	$C_{25}H_{21}NO_2S$	399 (2)	1700 (broad, CO)	
20	12.5	142–144 dec	$C_{25}H_{21}NO_2S$	399 (3)	1710 (broad, CO)	
21	17.5	148–150 dec	$C_{27}H_{25}NO_3S$	443 (21)	1750, 1720 (CO)	
22	17	170–172 dec	$C_{27}H_{25}NO_3S$	443 (6)	1740–1700 (broad, CO)	
24a	57.5	254–257 dec	$C_{25}H_{15}N_3O$	373 (100)	2240 (CN), 1680 (CO)	358 (3.83), 271 (3.82), 215 sh (4.29)
24b	87	290–293 dec	$C_{37}H_{25}NO_3$	531 (63)	1680, 1650 (CO)	340 (3.94), 254 (4.33)
24c	53.5	275–277	$C_{31}H_{20}N_2O_3$	468 (100)	1730, 1680 (CO)	362 (3.73), 287 (4.06)
24d	17	219–221 dec	$C_{27}H_{21}NO_5$	439 (100)	1745, 1670 (CO)	328 (3.74), 255 (3.64)
25a	70	198–200 dec	$C_{25}H_{17}N_3OS$	407 (4)	2250 (CN), 1720 (CO)	
25b	73	218–220 dec	$C_{37}H_{27}NO_3S$		1720, 1690, 1680 (CO)	250 (4.15)
25c	70	233–235	$C_{31}H_{22}N_2O_3S$	502 (2)	1790, 1710 (CO)	
25d	80	151–152	$C_{27}H_{23}NO_5S$	473 (5)	1735, 1725, 1700 (CO)	
25e	75	215–216	$C_{27}H_{23}NO_5S$	473 (4)	1750, 1700 (CO)	
28	84	250 dec	$C_{25}H_{17}NO_4S$	427 (2)	1780, 1710 (CO)	
29	48	240–242 dec	$C_{25}H_{19}NO_6S$		1750, 1740, 1690 (CO)	235 sh (3.59)
30	63	240–243 dec	$C_{37}H_{27}NO_4S$	581 (1)	1710, 1680 (CO), 1080 (SO)	251 (4.51)
31, 32	62	202–205	$C_{27}H_{23}NO_6S$	489 (1)	1740, 1720 (CO), 1085 (SO)	

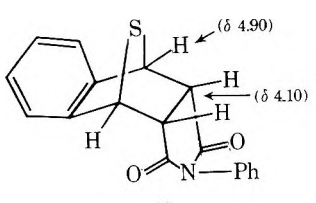
[a] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table: Ed.

Table IV
Methine and Alkyl Group Chemical Shifts and Coupling Constants for Cycloadducts Derived from *anhydro*-4-Hydroxy-2,3,5-triphenylthiazolium Hydroxides and Olefinic Dipolarophiles



Compd no.	Chemical shifts (δ) R^1	R^2	R^3	R^4	Coupling constants, Hz $J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{1,4}$	$J_{2,4}$
19, R^4 = $COCH_3$[a]	3.23, dd	2.80, dd	4.07, dd	*2.03*, s	13.5	8.5	5.0		
19, R^4 = CN[b]	3.47, dd	3.08, dd	4.76, dd		13.0	8.0	3.5		
20, R^3 = $COCH_3$[a]	3.40, dd	3.21, dd	*1.79*, s	3.88, dd	12.5			5.3	8.0
21, R^1 = CH_3;[a] R^4 = $COOCH_2CH_3$	*1.48*, d	3.52, dq	3.49, d	3.98, q[a] *0.99*, t	7.0		4.5		
22, R^3 = CH_3;[a] R^4 = $COOCH_2CH_3$	4.23, d	2.90, d	*1.70*, s	3.75, m[e] *0.77*, t	12.0				
25a, R^1 = R^4 = CN[a]		4.22, d	4.46, d				3.8		
25b, R^1 = R^4 = COPh[a]		5.18, d	5.70, d				6.0		
25c, R^2 = R^4 = CONPhCO[a]	4.17, d		4.54, d			6.5			
25e, R^2 = R^4 = $COOCH_3$[a]	4.31, d		4.52, d			9.0			
25d, R^1 = R^4 = $COOCH_3$[a]	*5.46*, s	4.29, d	4.52, d	*3.69*, s		4.5			
29, R^2 = R^4 = COOH[c]	4.47, d	12.40, s	4.78, d	12.40, s		8.5			

[a] Determined in $CDCl_3$, methyl resonance in italics. [b] Determined in acetone-d_6. [c] Determined in DMSO-d_6. [d] $J_{CH_2CH_3}$ = 7.0 Hz. [e] Non-equivalent methylene group.



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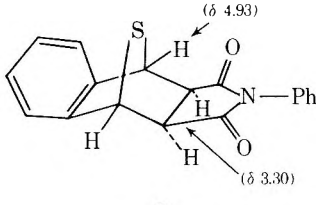

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bridge. These data are consistent with the data described above for the mesoionic *N*-phenylmaleimide adduct in an endo configuration. The coupling constant between the 4 and 5 protons in 3 (R = *p*-ClC_6H_4) was 1.5 Hz, indicating a trans coupling, and between the 5 and 6 protons it was 7.0 Hz, consistent with a cis coupling, these values being noteworthy in light of the following description of cycloadducts and their physical characteristics.

Under similar conditions 1 (R = Ph; R^1 = H) gave an analogous product whose physical constants are described in Tables I and II.

***trans*-Dibenzoylethylene Adduct.** The reaction of 1 (R = *p*-ClC_6H_4; R^1 = H) with *trans*-dibenzoylethylene gave a stable 1:1 cycloadduct, mp 225–230° dec, in moderate yield (38%), which may have either of the two possible isomeric configurations 7 or 8.

The 5-exo,6-endo configuration 7 was demonstrated by the nmr spectrum, with doublets at δ 4.43 (H_4) (J = 4.0 Hz) and δ 5.80 (H_6)

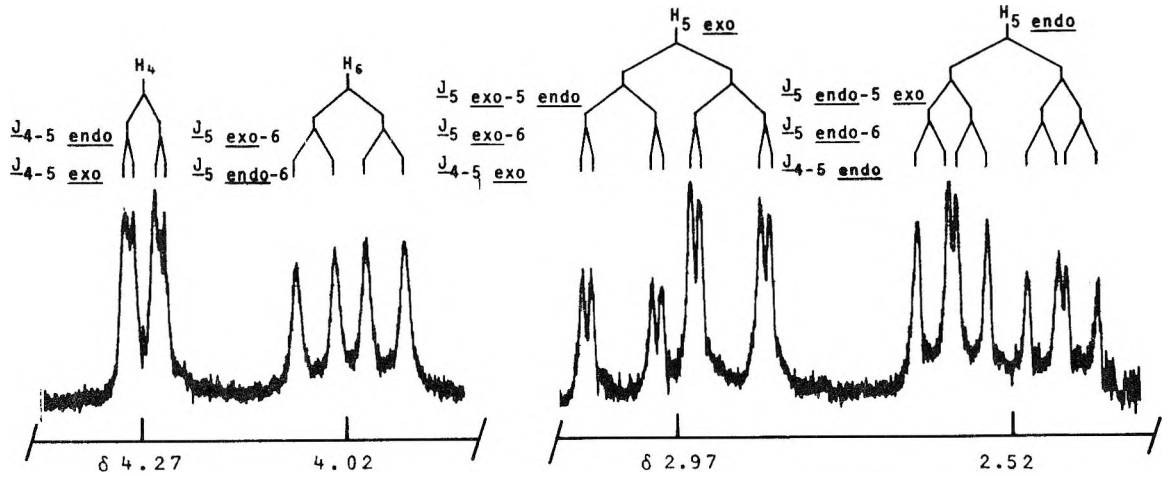
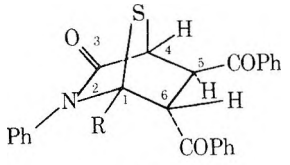


Figure 1. 100-MHz nmr spectrum of 6β-acetyl-1-*p*-chlorophenyl-1,2,3,4,5,6-hexahydro-2-phenyl-1α,4α-epithiopyrid-2-one.



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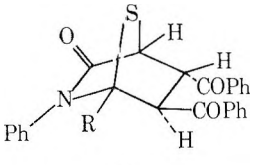

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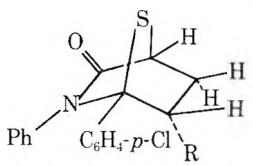
(J = 4.5 Hz) and a triplet at δ 4.83 being consistent with the trans arrangement of protons as shown. Additional evidence was provided from the nmr data of the *trans*-dibenzoylethylene adducts derived from 2,3-diphenylindenone oxide and also isobenzofuran[6] in which the 7-exo proton resonates at lower field relative to the corresponding 7-endo proton due in part to the deshielding by the oxide bridge. Since the sulfur bridge is expected to be more deshielding than an oxide bridge,[6] the 6 proton at δ 5.80 in 7 is in accord with the above results.

Methyl Vinyl Ketone Adduct. Methyl vinyl ketone allows a study of the effect of an asymmetrical olefin upon the course of the cycloaddition reaction, in particular the orientation(s) of any products isolated. The reaction of 1 (R = *p*-ClC_6H_4; R^1 = H) in refluxing methyl vinyl ketone proceeded smoothly, giving a 1:1 adduct in 32% yield with ν_{CO} at 1710 and 1690 cm^{-1} and an absorption maximum at 224 nm (log ε 4.11). The four possible configurations of the primary cycloadduct are shown below, and the 100-MHz spectrum of the adduct is shown in Figure 1.

The doublet of doublets at δ 4.27 (J = 1.0 and 3.5 Hz), a second doublet of doublets at δ 4.02 (J = 4.5 and 8.0 Hz), a quartet of doublets at δ 2.97 (J = 1.0, 8.0, and 12.5 Hz), a second quartet of doublets at δ 2.52 (J = 3.5, 4.5, and 12.5 Hz), and a singlet at δ 2.03 allow structures 11 and 12 (R = $COCH_3$) to be eliminated immediately on the basis that the two high-field multiplets (δ 2.97, 2.52) show coupling to three protons whereas structures 11 and 12



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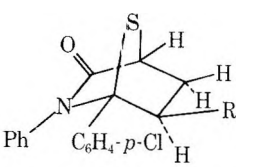

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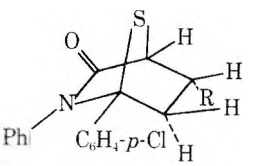

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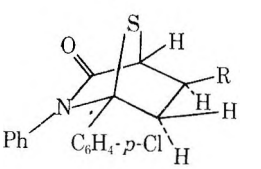

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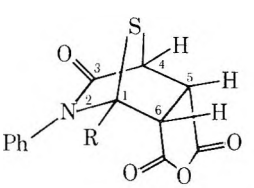
should show only one proton (H_5) coupled to three others. From this coupling information, proton 4 is assigned the multiplet at δ 4.27 since it is twice coupled in a trans fashion and falls in a chemical shift region consistent with other bridgehead protons. The δ 4.02 multiplet is assigned proton 6 since it would be anticipated to contain both a cis and trans coupling in either 9 or 10, and be deshielded by an adjacent acetyl group. The proton at δ 2.97 is assigned to $H_{5\text{-exo}}$, being deshielded by the sulfide bridge relative to $H_{5\text{-endo}}$ which is now assigned at δ 2.52. It is also clear that $H_{5\text{-exo}}$ and H_6 are cis coupled (J = 8.0 Hz) and thus proton 6 must also be in the exo position. Following these arguments, the most plausible structure for the methyl vinyl ketone adduct is 9 (R = $COCH_3$) in which the acetyl group assumes an endo configuration.

Ethyl Acrylate Adduct. The reaction of 1 (R = *p*-ClC_6H_4; R^1 = H) with ethyl acrylate produced a colorless crystalline product, mp 139–140° dec, in 48% yield with the structural possibility of four different stereoisomers **9**–**12** (R = COOEt) above. Infrared absorptions (ν_{CO} 1750, 1710 cm^{-1}) and an ultraviolet absorption maximum at 224 nm (log ε 3.73) together with the nmr data (Table II) can best be accommodated in terms of structure **9** (R = COOEt).

To obtain further information about the stereochemistry of these cycloaddition reactions, the series of cycloadducts described below which are capable of chemical interconversion was synthesized.

Maleic Anhydride Adduct. Maleic anhydride, at room temperature in dry benzene, afforded a primary cycloadduct in 66% yield with the following principal nmr characteristics.

A doublet with a cis coupling (J = 7.0 Hz) at δ 5.20 must be assigned proton 6 in either the endo **13** or exo **14** structure, and a doublet at δ 7.94 with the small trans coupling (J = 1.0 Hz) is assigned the bridgehead proton 4. Proton 5 appears as a doublet of doublets at δ 4.70. These data are consistent with the endo structure **13** (R = *p*-ClC_6H_4).



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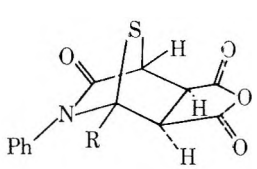

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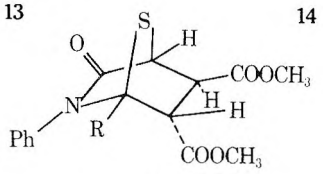


15

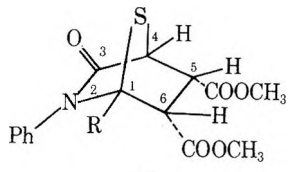
Dimethyl Fumarate Adduct. A primary 1:1 adduct, consistent with the structure **15** (R = *p*-ClC_6H_4) on the

basis of the spectral data immediately following was formed from 1 (R = *p*-ClC_6H_4; R^1 = H) and dimethyl fumarate in refluxing benzene.

Nmr multiplets at δ 4.48 (d, J = 4.3 Hz) and δ 4.42 (d, J = 3.8 Hz) can be assigned to either H_4 or H_6 and a triplet at δ 4.08 can be assigned to H_5. That the carbomethoxy groups are in the 5-exo,6-endo configuration is postulated from the expectation that the proton 4-proton 5-endo coupling should be approximately 3–4 Hz, in analogy to the *trans*-dibenzoyl adduct 7.

The analogous product obtained from *1* (R = Ph; R^1 = H) and dimethyl fumarate (Tables I and II) was assigned a stereochemistry similar to 15.

Dimethyl Maleate Adduct. Reaction of 1 (R = *p*-ClC_6H_4; R^1 = H) with diethyl maleate under reflux in dry benzene, gave a product that was identified as a 1:1 primary adduct 16 from its nmr spectrum (100 MHz).



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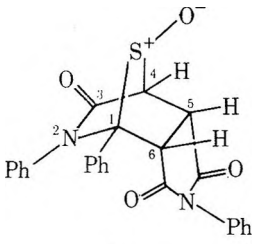

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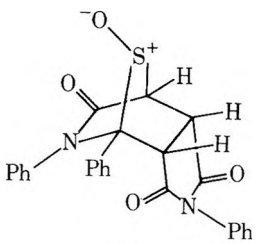

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Aliphatic resonance signals at δ 4.46 (d, J = 1.0 Hz), δ 4.37 (d, J = 9.0 Hz), δ 3.98 (dd), δ 3.75 (s), and δ 3.32 (s) were assigned to protons 4, 6, 5, and the two methoxycarbonyl methyl groups at carbons 5 and 6, respectively. These data support a structure 16 with an endo arrangement of methoxycarbonyl groups with respect to the sulfide bridge.

Reaction of dimethyl maleate with 1 (R = Ph; R^1 = H) resulted in a product analogous to 16 (Tables I and II).

Conversion of the Maleic Anhydride Adducts 13 into the Dimethyl Maleate Adduct 16. If the functional groups of the adducts 13 and 16 described above are similarly oriented, then opening of the anhydride moiety in 13 under suitable methylation conditions should give rise to an alternative synthesis of the dimethyl ester 16. Diazomethane effected the interconversion of the cycloadducts in 98% yield, with the isolation of a product identical in all respects[7] with 16. Thus the assigned endo stereochemistry is consistent within these two adducts and this stereochemistry most likely occurs in other cycloadducts of this type.

The significant deshielding effect by a sulfoxide group on syn protons has been applied to configurational assignment in suitable pairs of stereoisomeric sulfoxides[8] and, conversely, formation of a sulfoxide by oxidation of a sulfide linkage should yield stereochemical information concerning proximinal protons in these cycloadducts. The proximity of a proton to a sulfoxide oxygen atom results[9] in a downfield shift in the nmr spectrum, as *e.g.*, with the β proton in thietane *S*-oxides.[10] When 3 (R = Ph) was treated with an equimolar amount of *m*-chloroperbenzoic acid in methylene chloride at room temperature, a colorless, crystalline oxidation product was isolated. A strong band at 1090 cm^{-1} in the infrared spectrum indicated a sulfoxide and two possible diasteromeric sulfoxide structures may be proposed, 17 where the S–O bond is syn to the *N*-phenylmaleimide moiety, and 18 in which the sulfoxide is oriented anti. The structure of the sulfoxide was established from nmr data shown below.

Structure	Chemical shift (δ) H_4	H_5	H_6	Coupling constants, Hz $J_{4,5}$	$J_{5,6}$
3 (R = Ph)	4.73	4.32	4.90	1.5	7.0
17	4.68	4.23	5.17	1.5	9.0

The significant downfield shift noted for H_6 indicating the proximity of the sulfoxide oxygen suggests that the structure of the oxidation product is 17. The formation of this product is also consistent with steric considerations.

Oxidation of 15 (R = Ph) under similar conditions, however, gave a mixture of isomeric sulfoxides which were inseparable by recrystallization or chromatographic methods. The nmr data obtained from the mixture were consistent with the structural assignments above.

Cycloadditions with *anhydro*-4-Hydroxy-2,3,5-triphenylthiazolium Hydroxide (1, R = R^1 = Ph). In order to evaluate the effect of an additional substituent on the 1,3-dipolar activity of this mesoionic ring system, a series of cycloaddition reactions of (1, R = R^1 = Ph) with olefinic dipolarophiles was carried out.

trans-Dibenzoylethylene, *N*-phenylmaleimide, ethyl crotonate, dimethyl maleate, dimethyl fumarate, and maleic anhydride all gave stable 1:1 adducts, obtained in one stereochemical form. Methyl vinyl ketone, however, gave both exo and endo 1:1 adducts whereas acrylonitrile and ethyl methacrylate gave predominantly one isomer, a second isomer being observed by tlc. Fumaronitrile, on the other hand, gave a 1:1 adduct together with its H_2S elimination product 2-oxo-1,3,6-triphenylpyridine-4,5-dicarbonitrile (24a), the relative proportions of these two products being dependent on the reaction time.

Introduction of a phenyl substituent into the 5 position of 1 (R = R^1 = Ph) significantly reduced the rate of reaction with *N*-phenylmaleimide, 3 days being required for its complete reaction, though the major portion of 1 (R = R^1 = Ph) had reacted in 15 hr. However, the stereochemical pattern of adduct formation did not alter the endo adduct 25c (R^1 = R^3 = H; R^2 = R^4 = CONPhCO) being obtained exclusively. The chemical shifts of the ring junction protons (H_5, H_6) at δ 4.54 and 4.17 ($J_{5,6}$ = 6.5 Hz) (Table IV) can only be rationalized with protons in an exo configuration. This same stereochemistry can also be assigned to the other adducts described in Tables III and IV obtained with 1 (R = R^1 = Ph) in view of the consistency of the chemical shifts of the 5 and 6 protons.

This assumption is supported further by considering the exo and endo adducts obtained with methyl vinyl ketone. When 1 (R = R^1 = Ph) was refluxed in methyl vinyl ketone, the bright red color of the initial solution was discharged within 30 min and removal of excess dipolarophile *in vacuo* afforded a residue which contained two major components (tlc). Their separation was effected by preparative thin-layer chromatography and the two products isolated both corresponded to 1:1 primary cycloadducts. The structures of these adducts are assigned the endo configuration 19 (R = $COCH_3$) and the exo configuration 20 on the basis of spectral data. From the first fraction (R_f 0.5) isolated from chromatography, a colorless product, mp 180–182°, was obtained with carbonyl absorptions under a wide band centered at 1700 cm^{-1} and no absorption maxima above 203 nm. The nmr spectrum of this compound (Figure 2) clearly shows three proton multiplets. The doublet of doublets centered at δ 4.07 contains a trans coupling (J = 5.0 Hz) and a cis coupling (J = 8.5 Hz) and thus is assigned

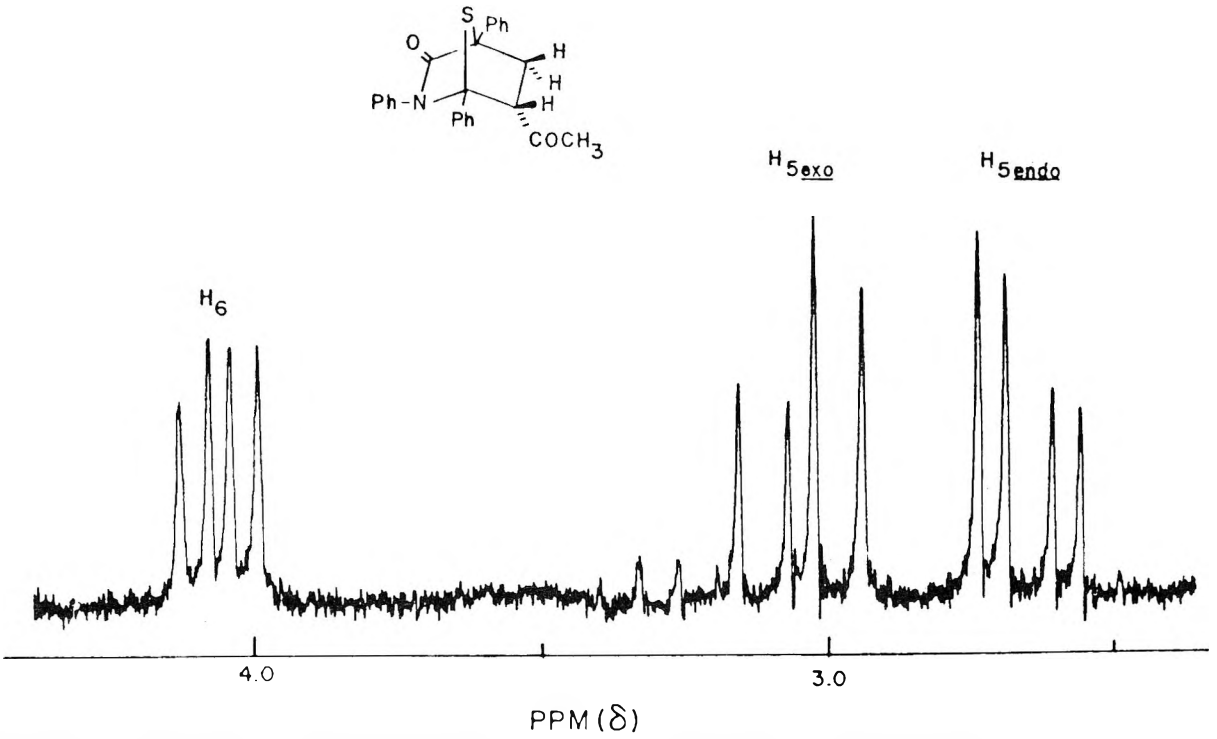


Figure 2. 100-MHz nmr spectrum of 6β-acetyl-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one.

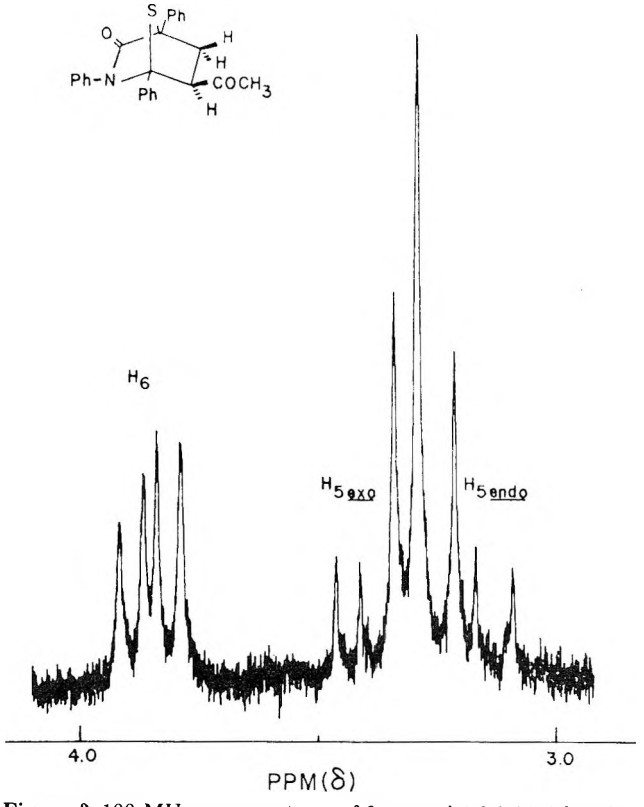


Figure 3. 100-MHz nmr spectrum of 6α-acetyl-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one.

the 6 proton. The doublet of doublets at δ 3.23 contains the cis coupling above, and a geminal coupling (J = 13.5 Hz). The third multiplet at δ 2.80 is both trans and geminally coupled. The δ 3.23 resonance multiplet is assigned the 5-exo proton since it would be expected to be further deshielded by the sulfide bridge than the 5-endo proton at δ 2.80. For the 6 proton to be cis coupled to $H_{5\text{-exo}}$ requires an endo acetyl group at carbon 6 and thus the assigned configuration is **19** (R = $COCH_3$).

The second isolated product (R_f 0.6) was obtained as colorless prisms, mp 142–144°, with an infrared spectrum very similar to **19** (R = $COCH_3$). The assignment of an exo configuration **20** for this compound was made on the basis of the nmr spectrum (Figure 3).

The data obtained (Table IV) shows that the furthest downfield multiplet at δ 3.88 (H-6) contains a trans (J = 5.3 Hz) and a cis (J = 8.0 Hz) coupling, the trans coupling being associated with the furthest downfield geminally coupled multiplet at δ 3.40 assigned to $H_{5\text{-exo}}$, and the cis coupling corresponding to the doublet of doublets at δ 3.21, $H_{5\text{-endo}}$. These data substantiate an exo arrangement of the acetyl group and thus the proposed structure is demonstrated to be **20**. It must be emphasized that the orientation of the adducts **19** (R = $COCH_3$) and **20** is based solely upon analogy to the corresponding methyl vinyl ketone adduct **9** described above.

The adducts obtained from ethyl crotonate and ethyl methacrylate (Tables III and IV) differed from each other in the position of the methyl substituent. However, this resulted in a significant and interesting change in their nmr spectra. In the 1:1 adduct from ethyl crotonate, ethyl 1,2,3,4,5,6-hexahydro-5α-methyl-1,2,4-triphenyl-1α,4α-epithiopyridine-6β-carboxylate (**21**), the ethoxycarbonyl group appeared as a quartet (δ 3.98) and a triplet (δ 0.99), these values being noteworthy in regard to the ethyl methacrylate cycloadduct described below. In the latter, ethyl 1,2,3,4,5,6-hexahydro-6α-methyl-3-oxo-1,2,4-triphenyl-1α,4α-epithiopyridine-6β-carboxylate (**22**), the ethoxycarbonyl methyl group was observed as a triplet at δ 0.77 and the adjacent methylene group did not appear as a normal quartet but rather as a complex 14-line pattern understandable in terms of the nonequivalency of these protons (Figure 4). The phenomenom of proton nonequivalency has been reported[11] in a variety of systems having the methylene group directly attached to an asymmetric center, such as in 2-chloro-4-ethyl-3-phenylcyclobut-2-enone (**23**), or in ethoxy groups attached at an asymmetric center, such as in cyclopropylmethylcarbinyl ethyl ether. The nonequivalence of the methylene protons in these cases is due to the asymmetric center of attachment which acts to favor one of the possible rotational conformations about the *O*-methy-

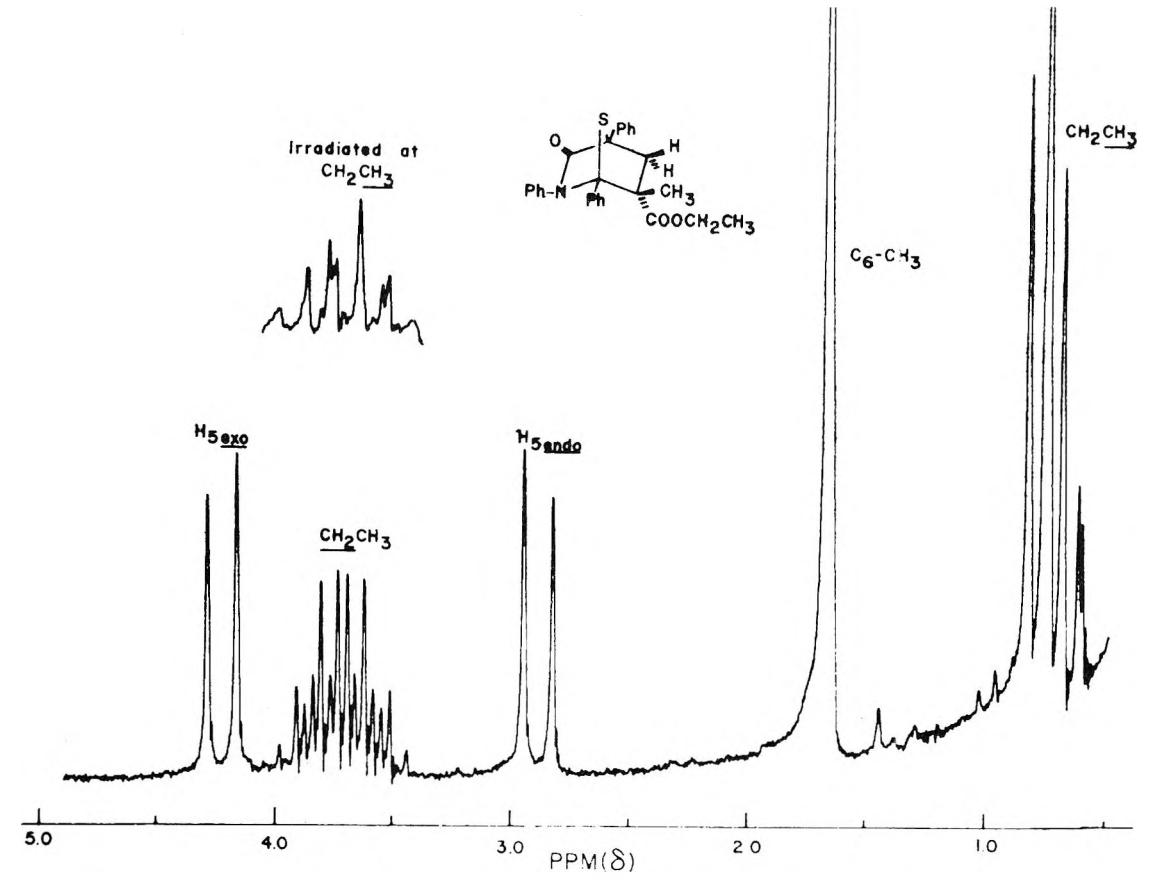
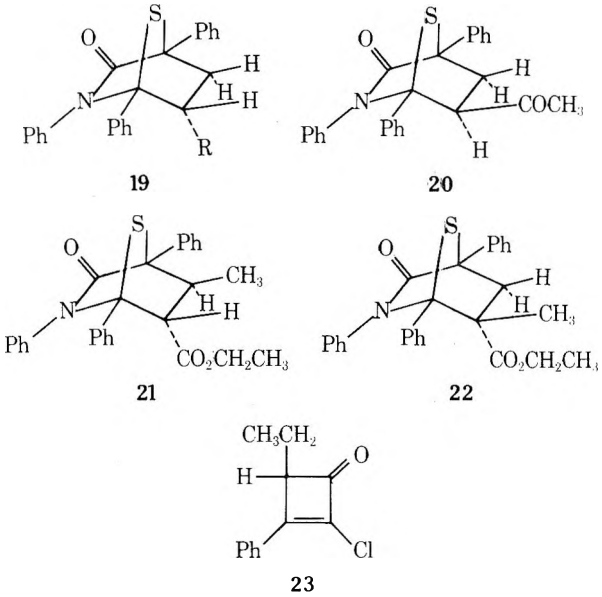


Figure 4. 100-MHz nmr spectrum of ethyl 1,2,3,4,5,6-hexahydro-6α-methyl-3-oxo-1,2,4-triphenyl-1α,4α-epithiopyridine-6β-carboxylate.



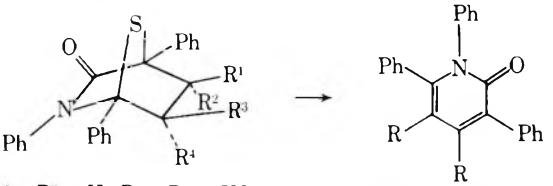
19 20

21 22

23

lene bond. In the case of the cycloadduct **22,** the asymmetric center at C-6, the bulkiness of the methyl group, and the rigidity inherent in the bicyclic ring system prevent free rotation about the O–CH_2 bond and thus an ABX_3-type pattern consisting essentially of a doublet of quadruplets arises. Theoretically a 16-line pattern is expected but overlapping of resonances reduces this to the observed 14-line multiplet. The exo methyl group at C-6 is apparently necessary for nonequivalence to occur since in the isomeric ethyl crotonate adduct **21,** a normal quartet–triplet ethyl pattern was observed. The ethoxycarbonyl methyl protons resonating as a triplet must be indicative of equal proton coupling between the methyl protons and the nonequivalent methylene protons. The result of a concentrated effort to decouple the methylene protons by irradiating at the center of the methyl resonance is shown in Figure 4, with the complex multiplet collapsing to the extent that a partial doublet of doublets was obtained.

Another interesting facet in these cycloaddition reactions was revealed in the reaction of fumaronitrile with **1** (R = R^1 = Ph) in refluxing benzene until the color of the reaction mixture had been discharged completely (89 hr). Removal of solvent and recrystallization of the crystalline residue did not afford a 1:1 primary adduct but rather 2-oxo-1,3,6-triphenylpyridine-4,5-dicarbonitrile (**24a**), a compound accountable in terms of loss of H_2S from an intermediate 1:1 primary cycloadduct **25a.** The pyridone **24a**

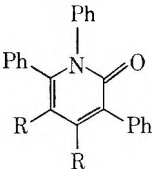


25a, $R^2 = R^3 = H$; $R^1 = R^4 = CN$
b, $R^2 = R^3 = H$; $R^1 = R^4 = COPh$
c, $R^1 = R^3 = H$; $R^2 = R^4 = CONPhCO$
d, $R^2 = R^3 = H$; $R^1 = R^4 = COOCH_3$
e, $R^1 = R^3 = H$; $R^2 = R^4 = COOCH_3$

24a, R = CN
b, R = COPh
c, R = CONPhCO
d, R = $COOCH_3$

has been prepared[12] by reaction of **1** (R = R^1 = Ph) with dicyanoacetylene in 0.5% yield, together with a 95.5% yield of 3,4-dicyano-2,5-diphenylthiophene. This excludes an initial oxidation step in the above reaction. A more plausible route may involve an initial base-catalyzed proton removal and opening of the sulfide bridge followed by a β elimination of H_2S to give **24.** Such a process has been observed with *N,N'*-diisopropyl-*N,N'*-diphenyl-2,4-thio-

Table V
4,5-Disubstituted Pyridones Derived from *anhydro*-4-Hydroxy-2,3,5-triphenylthiazolium Hydroxide Cycloadducts and Sodium Methoxide[a]



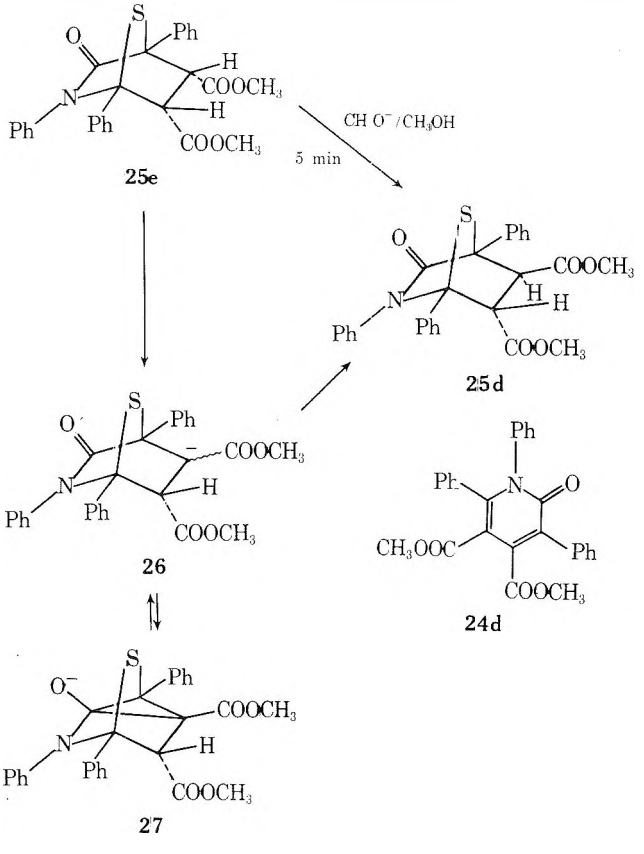
Compd no.	R	Yield, %	Mp, °C	Crystal habit and color[b]	Ir, cm^{-1}	uv max, nm (log ε)	M.+	Molecular formula
24a	CN	58	254–257dec	A	ν_{CN} 2240, ν_{CO} 1680	358 (3.83) 271 (3.82), 215 sh (4.29)	373 (100)	$C_{25}H_{15}N_3O$
24b	COPh	87	290–293dec	B	ν_{CO} 1650 (broad)	340 (3.94), 254 (4.33)	531 (63)	$C_{37}H_{25}NO_3$
24c	CONPhCO	54	275–277	B	ν_{CO} 1730, 1680	362 (3.73), 287 (4.06)	468 (100)	$C_{31}H_{20}N_2O_3$
24d	$COOCH_3$	17	219–221	C	ν_{CO} 1745, 1670	328 (3.74), 255 (3.64)	439 (100)	$C_{27}H_{21}NO_5$

[a] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table: Ed. [b] A = colorless needles (benzene). [c] B = yellow needles (ethanol). [d] C = colorless needles (ethanol).

phenediamine and acrylonitrile in which the intermediate thiol was actually trapped by a second molecule of acrylonitrile.[13a] This mechanistic pathway cannot, however, be distinguished from an initial loss of elemental sulfur from **25a** followed by sulfur dehydrogenation of the intermediate. In limiting the reaction period to 26 hr, it was possible to isolate the intermediate **25a** (Tables III and IV) along with **24a** being observed in the filtrate.

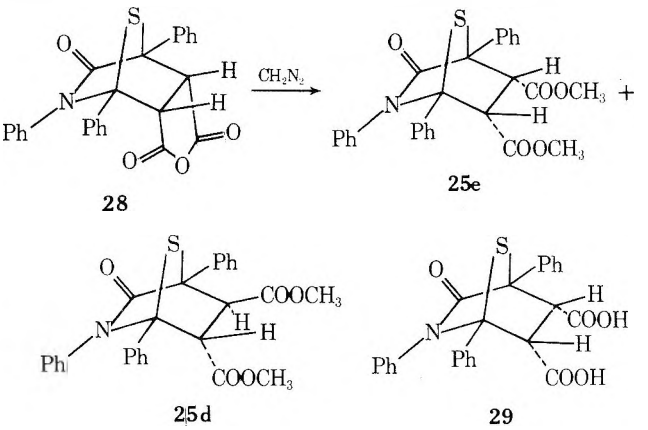
The elimination of H_2S was also observed when certain of these 1:1 adducts were treated with sodium methoxide yielding a series of 4,5-disubstituted 1,3,6-triphenylpyridones (Table V). Similar eliminations have been reported[13b] from maleic anhydride adducts of various substituted isobenzothiophenes using sodium hydroxide.

Treatment of the cis diester, dimethyl 1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyridine-5β,6β-dicarboxylate (**25e**) with sodium methoxide, however, followed a different reaction pathway. Quenching the reaction after 5 min with water deposited a solid which was identical in every respect with the trans diester **25d,** synthesized in an alternative way by reaction of **1** (R = R^1 = Ph) with dimethyl fumarate (Table III). The epimerization was thought to occur at carbon 5 due to the expected acidity of the 5 proton.



A contribution from a transannular interaction of the carbanion at C-5 with the β carbonyl group, illustrated by **26** ⇄ **27,** may be significant but no data are available to substantiate this interaction. The filtrate of this reaction gave the 4,5-dicarbomethoxypyridone **24d** identical with an authentic sample but its isolation is not definitive as it could have been formed from either the cis or trans diesters or by electron rearrangement of the immediate carbanion **26.**

The stereochemical relationship between cycloadducts derived from **1** (R = R^1 = Ph) was determined by the reaction of the maleic anhydride adduct **28** with diazomethane. Treatment of **28** with an alcoholic–ethereal solution of diazomethane deposited crystals which were identical with an authentic sample of dimethyl 1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyridine-5β,6β-dicarboxylate (**25e**). From the filtrate of the reaction mixture was isolated a second crop of crystals whose behavior on Tlc and spectral data (ir, nmr) corresponded to a mixture of *cis-* and *trans-* dicarbomethoxy ester cycloadducts, **25e** and **25d,** respectively. The formation of the trans diester **25d** can be attributed to reaction of **25e** with an excess of diazomethane, which may give rise to methoxide ion, and thus epimerize C-5 of the cycloadduct. That the cis diester is



formed reconfirms that a consistency of stereochemistry exists within cycloadducts of this mesoionic ring system.

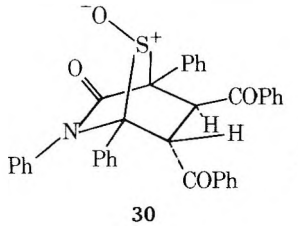
The ring opening of the maleic anhydride adduct **28** could also be achieved by base hydrolysis using sodium hydroxide, and resultant acidification of the reaction mixture produced 1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyridine-5β,6β-dicarboxylic acid (**29**) in 48% yield. Spectral data for this compound were consistent for the cis diacid structure **29** shown. Acidic protons were observed at δ 12.40 in the nmr spectrum and were exchanged with D_2O, and the 5,6-exo protons resonated at δ 4.47 and δ 4.78 (J = 8.5 Hz), respectively. Similar treatment of **29** with diazomethane afforded the cis diester **25e** identical with an authentic sample, but in this case no trans diester **25d** could be detected in the reaction mixture.

Oxidation to the corresponding sulfoxides also gave information regarding the stereochemistry of the cycloadducts. When the cycloadducts **25b** and **25d** were treated with *m*-chloroperbenzoic acid in methylene chloride, products were isolated which corresponded to oxidation of the sulfide bridge. Using the arguments advanced earlier, the orientation of the sulfoxide group was obtained from the nmr spectra. For the *trans*-dibenzoyl sulfoxide, **30**, and upfield shift of H_5 to δ 4.73, and a slight downfield shift for H_6 is consistent with the orientation of the S–O bond illustrated in **30**. This orientation might be expected on the basis of steric restraints imposed by the 5-benzoyl group. Further evidence for sulfoxide formation was obtained in the mass spectrum of **30** which had a very low intensity molecular ion (~1%) but the first fragmentation corresponded to a loss of SO.

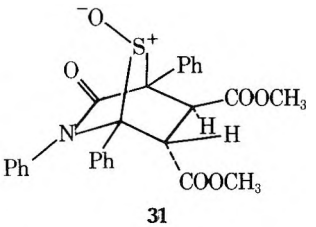
When the trans diester **25d** was oxidized, a compound homogenous on thin-layer chromatography was obtained but which corresponded to a mixture of diastereomeric sulfoxides **31** and **32** in the nmr spectrum. The resonances for the 5 and 6 protons in **25d, 31,** and **32** are listed below. The

	Chemical shift (δ)		Coupling constant, Hz
Structure	H_5	H_6	$J_{5,6}$
25d	4.29	4.52	4.5
31	4.27	4.63	5.0
32	4.60	4.98	4.5

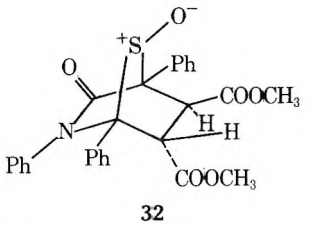
data show that a downfield shift was observed in sulfoxide **32**, the minor component in the nmr spectrum, for both H_5



30



31



32

and H_6 indicating that the sulfoxide group is proximinal to these protons, whereas a less intense effect can be observed with the major component, **31**. The mass spectral fragmentation is also indicative of sulfoxide formation, the molecular ion fragmenting with an initial loss of SO.

Experimental Section[14]

General Procedure for the Reaction of *anhydro*-4-Hydroxy-2,3-diarylthiazolium Hydroxide (1) with Olefinic Dipolarophiles. The Reaction of *anhydro*-2-*p*-Chlorophenyl-4-hydroxy-3-phenylthiazolium Hydroxide (1, R = *p*-ClC$_6$H$_4$; R^1 = H) with *N*-Phenylmaleimide. The mesoionic compound (1.4 g, 0.005 mol), *N*-phenylmaleimide (0.9 g, 0.005 mol), and dry benzene (50 ml) were refluxed overnight. The solvent was removed *in vacuo* and the residue crystallized from chloroform–petroleum ether (bp 60–80°) as colorless, irregular prisms of 1-*p*-chlorophenyl-*N*,2-diphenyl-1,2,3,4,5,6-hexahydro-3-oxo-1α,4α-epithiopyridine-5β,6β-dicarboximide (**3**, R = *p*-ClC$_6$H$_4$); 0.8 g (35%), mp 270–273° dec (Table I).

Variations of this procedure for a particular dipolarophile are shown in Table VI.

Reaction of 1-*p*-Chlorophenyl-1,2,3,4,5,6-hexahydro-3-oxo-2-phenyl-1α,4α-epithiopyridine-5β,6β-dicarboxylic Acid Anhydride (13; R = *p*-ClC$_6$H$_4$) with Diazomethane. The adduct (0.4 g, 0.01 mol) in anhydrous methanol (25 ml) was treated with an excess of an ethereal–ethanolic solution of diazomethane with stirring at room temperature. An initial exothermic reaction ensued and within 10 min a colorless solid separated which was filtered after stirring overnight. The isolated compound was identical[7] in all respects with **16** (R = *p*-ClC$_6$H$_4$); 0.42 g (97%), mp 216–217°.

Oxidation of 3 (R = Ph) with *m*-Chloroperbenzoic Acid. Equivalent amounts of the *N*-phenylmaleimide adduct **3** (R = Ph), and *m*-chloroperbenzoic acid in methylene chloride afforded the sulfoxide, 1,2,3,4,5,6-hexahydro-3-oxo-*N*,1,2-triphenyl-1α,4α-epithiopyridine-5β,6β-dicarboximide 7-oxide (**17**) as small, colorless needles from acetonitrile: yield 97%; mp 235–240° dec; ir (KBr) 1725 (CO), 1090 (SO) cm^{-1}; λ_{max} (CH_3OH) 277 nm (log ϵ 4.01); M·$^+$ 442 (39).

Anal. Calcd for $C_{25}H_{18}N_2O_4S$: C, 67.86; H, 4.10; N, 6.33. Found: C, 67.81; H, 4.17; N, 6.26.

Oxidation of 15 (R = Ph) with *m*-Chloroperbenzoic Acid. Equivalent amounts of the trans diester **15** (R = Ph) and *m*-chloroperbenzoic acid in methylene chloride at room temperature gave, after extraction of the two-component mixture with 10% $NaHCO_3$, chromatography on preparative silica gel (chloroform–ethyl acetate 80:20), and recrystallization from ethanol, a mixture of the diastereomeric sulfoxides, 5α,6β-di(methoxycarbonyl)-1,2-diphenyl-1,2,3,4,5,6-hexahydro-1α,4α-epithiopyrid-2-one 7-oxides as colorless, prismatic needles: yield 78%; mp 180–181° dec (with gas evolution); ir (KBr) 3010, 2950 (CH), 1720 (broad, CO), 1085 (SO) cm^{-1}; λ_{max} (CH_3OH) none; nmr ($CDCl_3$, HA-100) major component δ 6.70–7.50 (m, 10, aromatic), 4.58 (d, 1, C_4-H, $J_{4,5}$ = 5.0 Hz), 4.33 (d, 1, C_6-H, $J_{5,6}$ = 3.8 Hz), 3.73 (dd, 1, C_5-H), 3.84 (s, 3, C_5-$COOCH_3$), 3.48 (s, 3, C_6-$COOCH_3$); minor component δ 4.74 (d, 1, C_6-H, $J_{5,6}$ = 4.0 Hz), 4.64 (d, 1, C_4-H, $J_{4,5}$ = 6.5 Hz), 4.35 (dd, 1, C_5-H), 3.88 (s, 3, C_5-$COOCH_3$), 3.50 (s, 3, C_6-$COOCH_3$); M·$^+$ 413 (6).

Anal. Calcd for $C_{21}H_{19}NO_6S$: C, 61.00; H, 4.63; N, 3.39. Found: C, 60.90; H, 4.68; N, 3.36.

General Procedure for the Reaction of *anhydro*-2-Aryl-4-hydroxy-3,5-diphenylthiazolium Hydroxide 1 (R = Ph or *p*-ClC$_6$H$_4$; R^1 = Ph) with Olefinic Dipolarophiles. *trans*-Dibenzoylethylene. The mesoionic compound[12] (3.0 g, 0.009 mol), *trans*-dibenzoylethylene (2.1 g, 0.009 mol), and dry benzene (100 ml) were stirred and refluxed for 24 hr. Removal of the solvent *in vacuo* and repeated crystallization of the residue from benzene afforded 5α,6β-dibenzoyl-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one (**25b**, R^2 = R^3 = H; R^1 = R^4 = COPh) as colorless needles; 3.7 g (73%), mp 218–220° dec (Table III). Variation of this procedure with several dipolarophiles is shown in Table VII and below.

Reaction of *anhydro*-4-Hydroxy-2,3,5-triphenylthiazolium Hydroxide (1, R = R^1 = Ph) with Methyl Vinyl Ketone. The mesoionic compound (1.5 g, 0.0045 mol) was refluxed in methyl vinyl ketone (30 ml) for 1 hr during which time the reaction mixture changed from a dark red to a light yellow color. Removal of excess methyl vinyl ketone under reduced pressure and crystallization of the resultant residue from chloroform–anhydrous ether afforded cream, irregular prisms. Chromatography by preparative tlc (5 × 1 mm plates, silica gel PF) using chloroform–ethyl acetate (9:1) as the developing solvent, isolation of the major band (R_f 0.5), and recrystallization from chloroform–anhydrous ether afforded the endo adduct 6β-acetyl-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-

Table VI
Reaction Conditions for the Cycloaddition of 1 (R = Aryl; R^1 = H) and Various Dipolarophiles[a]

Dipolarophile	Solvent	Reaction time, hr	Reaction temp	Crystallization solvent
trans-Dibenzoylethylene	Benzene	3	Reflux	Chloroform–petroleum ether (bp 60–80°)
Methyl vinyl ketone	XS reagent	17	Reflux	Benzene
Ethyl acrylate	XS reagent	14	Reflux	Benzene
Maleic anhydride[b]	Benzene	16	Room temp	Benzene
Dimethyl fumarate	Benzene	2	Reflux	Chloroform–ether
Dimethyl maleate[b]	Benzene	5.5	Reflux	Chloroform

[a] Reaction work-up involved concentration of the reaction mixture *in vacuo* and crystallization of the residue from the solvent shown except in *b* where the product crystallized. [b] Product crystallized.

Table VII
Reaction Conditions for the Cycloaddition of 1 (R = Aryl, R^1 = Ph) and Various Dipolarophiles

Dipolarophile	Solvent	Reaction time, hr	Reaction temp	Crystallization solvent
N-Phenylmaleimide (R = Ph)	Benzene	72	Reflux	Evaporation; chloroform–ether
Dimethyl maleate (R = Ph)	Benzene	24	Reflux	Chromatography, Kieselgel g; benzene–petroleum ether
Dimethyl fumarate (R = Ph)	Benzene	15	Reflux	Evaporation; chloroform–petroleum ether
Maleic anhydride (R = Ph)	Benzene	3	Reflux	Evaporation; ethanol
Ethyl crotonate (R = *p*-ClC_6H_4)	XS reagent	10	Reflux	Evaporation; chloroform–ether

1α,4α-epithiopyrid-2-one (**19**, R = $COCH_3$), as colorless, irregular prisms; 0.3 g (17%), mp 180–182° dec (Table III).

The filtrate from the initial crystallization of the endo isomer was evaporated *in vacuo* and the oily residue chromatographed on preparative tlc (5 × 1 mm plates, silica gel PF) using chloroform–ethyl acetate (9:1) as the developing solvent. The top, major band (R_f 0.6) was isolated, and trituration of the residual oil with anhydrous ether and standing overnight, afforded the exo adduct, 6α-acetyl-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one (**20**), as colorless prisms; 0.1 g (12.5%), mp 142–144° (Table III).

Reaction of *anhydro*-4-Hydroxy-2,3,5-triphenylthiazolium Hydroxide (1, R = R^1 = Ph) with Acrylonitrile. The mesoionic compound (2.0 g, 0.0063 mol) was refluxed in acrylonitrile (50 ml) for 3.5 hr. Excess acrylonitrile was removed under reduced pressure leaving a fluffy crystalline residue. Repeated chromatography on preparative silica gel (8 × 1 mm plates), using initially chloroform–ethyl acetate (11:1) and finally benzene–ethyl acetate (4:1) as the developing solvents, afforded the 1:1 adduct 6β-cyano-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one (**19**; R = CN) as colorless, irregular prisms from chloroform–petroleum ether (bp 60–80°); 1.3 g (22%), mp 98–102° dec (Table III).

Reaction of 1 (R = R^1 = Ph) with Ethyl Methacrylate. The mesoionic compound (1.5 g, 0.0045 mol) was stirred and refluxed in ethyl methacrylate (25 ml) for 12 hr. Evaporation of excess solvent *in vacuo*, chromatography of the residue on preparative tlc (4 × 1 mm plates, silica gel PF) using chloroform as the developing solvent, isolation of the major band (R_f 0.8), and trituration of the residual oil with anhydrous ether followed by standing overnight, yielded ethyl 1,2,3,4,5,6-hexahydro-6α-methyl-3-oxo-1,2,4-triphenyl-1α,4α-epithiopyridine-6β-carboxylate (**22**) as colorless prisms; 0.35 g (17%), mp 170–172° dec (Table III).

Reaction of 1 (R = R^1 = Ph) with Fumaronitrile. A. Isolation of the Primary Cycloadduct. The mesoionic compound 1 (R = R^1 = Ph) (1.5 g, 0.0045 mol), fumaronitrile (0.36 g, 0.0045 mol), and benzene (50 ml) were stirred under reflux for 26 hr. The solvent was removed *in vacuo* and the residue dissolved in a minimum amount of chloroform and let stand overnight. Crystals separated and were isolated by suction filtration. A second crop was obtained from the filtrate. The combined solids recrystallized from chloroform–anhydrous ether affording the 1:1 adduct 5α,6β-dicyano-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one (**25a**) as colorless, irregular prisms (tlc showed 4,5-dicyano-1,3,6-triphenylpyrid-2-one (**24a**) to be present in the initial filtrate); 1.3 g (70%), mp 198–200° dec (Table III).

B. Formation of 4,5-Dicyano-1,3,6-triphenylpyrid-2-one (24a). The mesoionic compound (1.0 g, 0.003 mol), fumaronitrile (0.24 g, 0.003 mol), and dry benzene (50 ml) were stirred and refluxed for 89 hr. The solvent was removed under reduced pressure, and the residue crystallized from chloroform–anhydrous ether as light brown, irregular prisms. Recrystallization from benzene gave 4,5-dicyano-1,3,6-triphenylpyrid-2-one (**24a**) as cream needles; 0.65 g (57.5%), mp 254–257° dec (Table V).

H_2S Elimination from the 1:1 Adduct, 5α,6β-Dicyano-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one (25a). Treatment of the 1:1 fumaronitrile adduct **25a** with an excess of sodium methoxide–methanol solution at room temperature afforded a colorless solid identical[7] in all respects with 4,5-dicyano-1,3,6-triphenylpyrid-2-one (**24a**); yield 89%, mp 254–256°.

Treatment of 25b with Sodium Methoxide. The *trans*-dibenzoyl adduct **25b** (1.0 g, 0.007 mol) was suspended in dry methanol (20 ml) and an excess of sodium was added with stirring. All solid dissolved and the reaction mixture turned a light orange. Solvent was removed *in vacuo*, the residue triturated with ethanol, and filtered. Recrystallization from methanol gave 4,5-dibenzoyl-1,3,6-triphenylpyrid-2-one (**24b**) as light yellow needles; 0.82 g (87%), mp *ca.* 290–293° dec (Table V).

Application of this procedure to the 1:1 adducts **25c–e** resulted in the pyridones **24c–d** (Table V).

Treatment of 28 with Diazomethane. To a stirring suspension of the maleic anhydride adduct **28** (0.2 g) in dry methanol (20 ml) was added at room temperature an excess of an alcoholic–ethereal solution of diazomethane. A colorless solid began to separate after 0.5 hr. After stirring overnight the reaction mixture was filtered yielding authentic[7] cis diester **25e** (30 mg). The filtrate when concentrated deposited a second crop of crystals shown by infrared, tlc, and nmr data to be a mixture of cis-**25e** and *trans*-**26d** diesters. The total yield of diester was 0.1 g (45%) of which the ratio between cis–trans was approximately 3:1.

Hydrolysis of 1,2,3,4,5,6-Hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one-5β,6β-dicarboxylic Acid Anhydride (28). The maleic anhydride adduct **28** (1.0 g, 0.0024 mol) was treated with sodium hydroxide (0.8 g) in water (25 ml) and heated on a steam bath for 15 min. The cooled reaction mixture was acidified with 3 *N* HCl causing a colorless solid to separate. Isolation and recrystallization from ethanol afforded 1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one-5β,6β-dicarboxylic acid (**29**) as colorless, clustered needles; 0.5 g (48%), mp 240–242° dec (Table III).

Treatment of 29 with Diazomethane. To a stirring suspension

of the cis diacid **29** (0.2 g, 0.005 mol) in methanol (20 ml) was added an excess of an alcoholic–ethereal solution of diazomethane. A colorless solid began to separate after 10 min. After stirring overnight, filtration yielded a colorless solid (0.15 g, 46%) identical[7] in all respects with authentic cis diester **25e**. No trans diester **25d** could be detected by tlc of the isolated solid or of its filtrate.

Oxidation of 25b with *m*-Chloroperbenzoic Acid. The 1:1 cycloadduct **25b** (1.0 g, 0.0018 mol), 85% *m*-chloroperbenzoic acid (0.36 g, 0.0018 mol), and methylene chloride (40 ml) were stirred together overnight at room temperature. Extraction with 10% sodium bicarbonate, water, separation of the methylene chloride layer, drying over sodium sulfate, evaporation under reduced pressure, and recrystallization of the residue from acetonitrile gave 5α,6β-dibenzoyl-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one 7-oxide (**30**) as colorless prisms; 0.65 g (63%), mp 240–243° (Table III).

Oxidation of 25d with *m*-Chloroperbenzoic Acid. The trans diester **25d** (0.78 g, 0.0016 mol), 85% *m*-chloroperbenzoic acid (0.33 g, 0.0016 mol), and methylene chloride were stirred overnight at room temperature. Extraction in the usual manner and recrystallization of the resultant residue afforded a mixture of 5α,6β-di(methoxycarbonyl)-1,2,3,4,5,6-hexahydro-1,2,4-triphenyl-1α,4α-epithiopyrid-2-one 7-oxides (**31** and **32**) as colorless needles from ethanol; 0.5 g (62%), mp 202–205° (Table III).

Hydrolysis of *anhydro*-4-Hydroxy-2,3,5-triphenylthiazolium Hydroxide 1 (R = R¹ = Ph). From the reaction of the mesoionic compound with maleic acid in refluxing benzene was isolated after evaporation of the solvent, chromatography on preparative silica gel (chloroform), and recrystallization from ethanol, *S*-(*N*-phenylbenzimidoyl)mercaptophenylacetic acid as colorless needles: yield 25%; mp 165–167°; ir (KBr) 3280, 3050, 1660 cm^{-1}; λ_{max} (CH_3OH) 245 nm (log ε 4.38); nmr ($CDCl_3$) δ 7.03–8.33 (m, 15, aromatic), 5.60 (s, 1, CH).

Anal. Calcd for $C_{21}H_{17}NO_2S$: C, 72.59; H, 4.93; N, 4.03. Found: C, 72.39; H, 4.82; N, 3.93.

Registry No.—1 (R = *p*-ClC_6H_4, R^1 = H), 52730-97-9; **1** (R = R^1 = Ph), 18100-80-6; 1 (R = *p*-ClC_6H_4, R^1 = Ph), 52730-98-0; **3** (R = *p*-ClC_6H_4), 52730-99-1; 3 (R = Ph), 52731-00-7; 7 (R = *p*-ClC_6H_4), 52731-01-8; **9** (R = $COCH_3$), 52731-04-1; **9** (R = COOEt), 52731-05-2; **13** (R = *p*-ClC_6H_4), 52731-06-3; **15** (R = Ph), 52746-61-9; **15** (R = *p*-ClC_6H_4), 52795-10-5; **16** (R = *p*-ClC_6H_4), 52731-03-0; **16** (R = Ph), 52731-02-9; **17**, 52731-07-4; **19** (R = $COCH_3$), 52731-08-5; **19** (R = CN), 52731-09-6; **20**, 52731-10-9; **21**, 52731-11-0; **22**, 52748-26-2; **24a**, 52718-86-2; **24b**, 52731-12-1; **24c**, 52731-13-2; **24d**, 52731-14-3; **25a**, 52731-15-4; **25b**, 52748-27-3; **25c**, 52731-18-7; **25d**, 52731-16-5; **25e**, 52746-62-0; **28**, 52731-19-8; **29**, 52731-17-6; **30**, 52731-20-1; **31**, 52731-21-2; **32**, 52746-63-1; *N*-phenylmaleimide, 941-69-5; *trans*-dibenzoylethylene, 959-28-4; methyl vinyl ketone, 78-94-4; ethyl acrylate, 140-88-5; maleic anhydride, 108-31-6; dimethyl fumarate, 624-49-7; dimethyl maleate, 624-48-6; diazomethane, 334-88-3; *m*-chloroperbenzoic acid, 937-14-4; 5α,6β-di(methoxycarbonyl)-1,2-diphenyl-1,2,3,4,5,6-hexahydro-1α,4α-epithiopyrid-2-one 7-*syn*-oxide, 52731-22-3; 5α,6β-di(methoxycarbonyl)-1,2-diphenyl-1,2,3,4,5,6-hexahydro-1α,4α-epithiopyrid-2-one 7-*anti*-oxide, 52746-64-2; ethyl crotonate, 10544-63-5; acrylonitrile, 107-13-1; ethyl methacrylate, 97-63-2; fumaronitrile, 764-42-1; *S*-(*N*-phenylbenzimidoyl)mercaptophenylacetic acid, 52731-23-4.

References and Notes

(1) (a) Support of this work by U.S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged; (b) NSF Predoctoral Trainee. Abstracted in part from the Ph.D. thesis of J.B. submitted to the Graduate School, Rensselaer Polytechnic Institute, Aug 1973

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Synthesis of Olefins from Thionocarbonates by an Alkylation–Reduction Sequence

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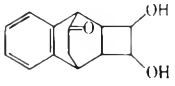
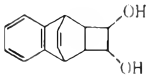
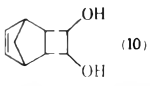
Received May 28, 1974

Thionocarbonates are alkylated at sulfur with concomitant ring cleavage by iodide to give vicinal iodo thiocarbonates. The latter are reductively cleaved to olefins by zinc dust reduction. Alkylation with methyl iodide at 90° gives the highest yields of thionocarbonate cleavage products. The method is well suited for preparation of cyclobutenes from the thionocarbonates. Stereochemistry of the starting diol is lost during the two-step procedure. Thus, either *meso*- or *dl*-hydrobenzoin thionocarbonates afford predominantly *trans*-stilbene, and either *cis*- or *trans*-cyclooctanediol thionocarbonates give only *cis*-cyclooctene.

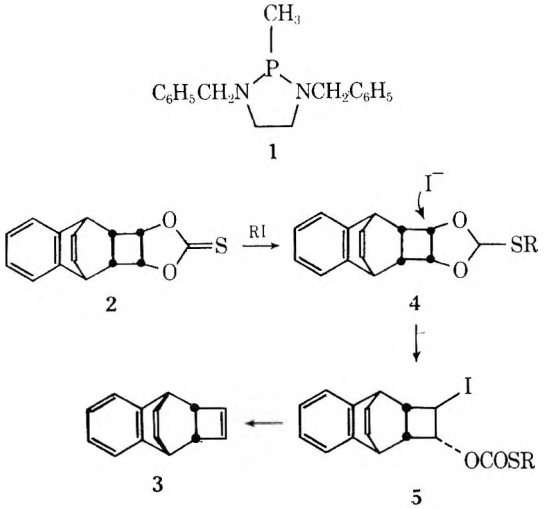
Vicinal diol thionocarbonates are useful synthetic precursors to olefins. The procedure developed by Corey, *et al.*,[1] for thionocarbonate fragmentation with trivalent phosphorus reagents has been used successfully to generate highly strained alkenes including *trans*-cycloheptene,[1a] bicyclo[3.2.1]oct-1-ene,[2a] cyclobutene derivatives,[2b,c] as well as more routine olefins.[2d,f,g] The most common variation employs trialkyl phosphite at 110–160°, but lower reaction temperatures are feasible using 1,3-dibenzyl-2-methyl-1,3-diazaphospholidine (**1**) for desulfurization.[1b] Thionocarbonate decomposition can also be accomplished with zerovalent nickel and iron complexes.[3]

Table I
Olefins from Thionocarbonates and Isopropyl Iodide

Thionocarbonate derived from	Yield of olefin after alkylation, %	Total yield of olefin after Mg–Hg reduction, %
meso-Hydrobenzoin	86 (*trans*-stilbene)	
dl-Hydrobenzoin	80 (*trans*-stilbene)	
cis-1,2-Dihydroxycyclooctane	32	42 (*cis*-cyclooctene)
trans-1,2-Dihydroxycyclooctane	28	54 (*cis*-cyclooctene)
1-Methyl-*trans*-1,2-dihydroxycyclohexane	20	30
1-Methyl-*cis*-1,2-dihydroxycyclohexane	27	28
	0	84[a]
	0	60[a]
 (10)	0	54[a]

[a] Zinc dust was used to reduce the iodo thiocarbonate.

As part of a synthetic project,[4] we had planned to prepare the cyclobutene **3** from the thionocarbonate **2**. The reaction with triethyl phosphite proved to be hopelessly slow in this sterically demanding case, and no trace of alkene was found even after 4 days at 120°. The desired conversion did occur when **2** was treated with the diazaphospholidine **1**, but the reaction was still very slow at 155° (84 hr, 57% yield). Also, we experienced considerable difficulty in handling the air-sensitive diazaphospholidine since conversion to the oxide occurred with exceptional ease. It proved necessary to manipulate **1** under argon and to carry out the thionocarbonate reaction under argon in a sealed tube.



In the hope of finding a more practical alternative route from **2** to **3**, we considered a two-step method for thionocarbonate fragntation. By analogy to the high nucleophilic reactivity of thio amides compared to their oxygen counterparts, it seemed probable that thionocarbonates would be alkylated at sulfur by methyl iodide. Subsequent nucleophilic attack by iodide would then convert the intermediate **4** into **5** which would be reduced easily to the olefin by zinc dust.

Table II
Olefins from Thionocarbonates and Methyl Iodide

Thionocarbonate derived from	Overall yield of olefin after zinc reduction, %
meso-Hydrobenzoin	90 (*trans*-stilbene)
dl-Hydrobenzoin	92 (*trans*-stilbene)
cis-1,2-Dihydroxycyclooctane	72 (*cis*-cyclooctene)
10	84

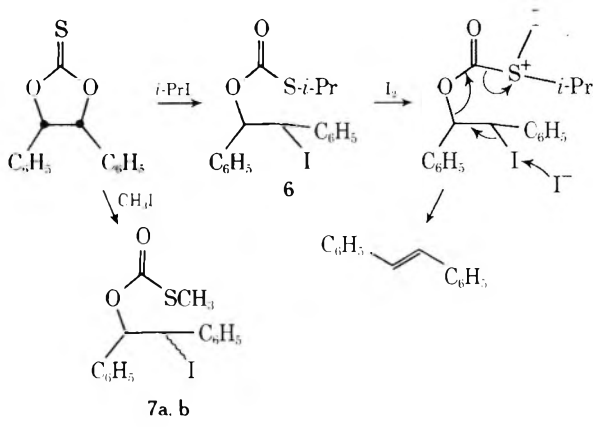


Figure 1.

Methyl iodide proved unreactive at its boiling point, but commercial isopropyl iodide reacted smoothly at 90° (5 hr) to afford an excellent yield of the reasonably stable adduct **5** (characterized by spectral data, see Experimental Section). After reductive elimination using zinc dust in ethanol, **3** was obtained in 60% overall yield from **2**. Although the yield was comparable to that obtained with the diazaphospholidine reagent, the isopropyl iodide method proved more convenient since the reaction is not air-sensitive, the conditions are milder, and the reagent is readily available.

The alkylation–reduction sequence is general, and gives satisfactory yields of cyclobutenes in the three cases studied (Table I). Simple olefins can also be prepared, although the yields are lower due to the sensitivity of the iodo thiocarbonate intermediates. Curiously, the initial alkylation step appears to be catalyzed by some impurity in commercial isopropyl iodide, probably iodine. Isopropyl iodide distilled from sodium thiosulfate does not react with thionocarbonates under the same conditions.

Subsequent experiments established that thionocarbonate alkylation with methyl iodide at 90° (sealed tube) in dimethoxyethane (DME) is faster, gives higher overall yields, and is not influenced by the purity of methyl iodide (Table II). A further difference between the methyl iodide and isopropyl iodide reactions is that the latter gives substantial yields of olefins directly from the alkylation step in cases where the olefin is unstrained.

Thus, reaction of *meso*-hydrobenzoin thionocarbonate with isopropyl iodide gives *trans*-stilbene in 86% yield without a zinc reduction step. Stilbene is probably derived from an intermediate **6** by iodide ion induced E2 elimination.[5] We suggest that iodine formed by decomposition of isopropyl iodide catalyzes the process as shown in Figure 1.

The above rationale is supported by the results of methyl iodide alkylations. Starting with the *meso*-hydrobenzoin thionocarbonate (DME, CH_3I, 90°) an intermediate **7** hav-

ing an SCH_3 singlet at δ 2.35 ppm is formed initially. The alkylation is complete after 14 hr, but a new SCH_3 singlet appears slowly at δ 2.18 ppm as the reaction proceeds. Starting with *dl*-hydrobenzoin thionocarbonate, the initial alkylation product has the δ 2.18 ppm singlet and the δ 2.35 ppm singlet appears more slowly. Stilbene is not present in the crude alkylation products from either *meso*- or *dl*-thionocarbonates. However, stilbene is formed in 85% yield if iodine is added to the methyl iodide reaction. The mixture of **7a,b** also gives stilbene upon treatment with iodine in DME, as does the parent thionocarbonate (75%). From this circumstancial evidence it appears that direct olefin formation is not possible unless a source of iodine is present in the alkylation step.

Reduction of different mixtures of **7a,b** with magnesium amalgam gives the same mixture of stilbenes (*ca.* 95% trans). Thus, even though the thionocarbonate ring cleavage by iodide is at least partly stereoselective,[6] the reductive elimination is not. Similar results are obtained with *cis*- or *trans*-1,2-cyclooctanediol thionocarbonates, either of which gives only the more stable *cis*-cyclooctene after reduction. Thus, the Corey procedure remains the method of choice for stereoselective olefin syntheses. However, the alkylation–reduction sequence should be considered where stereochemistry is not an issue, or where the lower reaction temperature may be advantageous. In particular, the alkylation method can be recommended for the preparation of cyclobutenes since the precursor thionocarbonates are more reactive toward alkyl iodides and the intermediate iodo thiocarbonates are comparatively stable.

Experimental Section

Preparations of Thionocarbonates. General Procedure for Preparing Thionocarbonates from Vicinal Diols. (a) A suspension of the vicinal diol (1 mmol) and *N,N'*-thiocarbonylbisimidazole (1.1 mmol) in dry toluene (6 ml) was refluxed (under nitrogen) for 1–2 hr. Toluene was removed under reduced pressure, and ether (20–30 ml) was added to the residue. The ether solution was washed with water and saturated brine solution, and dried (Na_2SO_4). Evaporation of the solvent usually afforded the corresponding thionocarbonate as yellow crystals. The thionocarbonates were purified by recrystallization from methanol, or by filtration chromatography over silica gel.

(b) Thionocarbonates were also prepared by reaction of the vicinal diol, *N,N'*-thiocarbonylbisimidazole, and a small amount of pyridine in toluene at room temperature for *ca.* 2 hr. Work-up was the same as in (a).

The Thionocarbonate[1a] of *meso*-Hydrobenzoin. Using method (b), *meso*-hydrobenzoin afforded the thionocarbonate in 92% yield: mp 157–158° (methanol); ir ($CHCl_3$) 1355, 1320, 1300, and 1270 cm^{-1} (s, C=S); nmr ($CDCl_3$, δ): 7.30–6.80 (10 H, m), 6.12 (2 H, s); *m/e* 256 (M^+).

The Thionocarbonate[1a] of *dl*-Hydrobenzoin. Method (a): 91% yield, mp 98–99° (methanol); ir ($CHCl_3$) 1320, 1310, 1300, and 1255 cm^{-1} (s); nmr ($CDCl_3$, δ) 7.60–7.18 (10 H, m), 5.50 (2 H, s); *m/e* 256 (M^+).

The Thionocarbonate[1a] of *cis*-1,2-Cyclooctanediol. Method (a): 81% yield, mp 140–141°; ir ($CHCl_3$) 1325 and 1280 cm^{-1} (s, C=S); nmr δ 5.02 (2 H, t, J = 4 Hz), 2.4–0.8 (12 H, m); *m/e* 186 (M^+).

The Thionocarbonate[1a] of *trans*-1,2-Cyclooctanediol. Method (a): 81% yield, mp 108–110°; ir ($CHCl_3$) 1335 and 1270 cm^{-1} (s, C=S); nmr ($CDCl_3$, δ) 4.94 (2 H, t, J = 4 Hz), 2.65–0.8 (12 H, m); *m/e* 186 (M^+).

The Thionocarbonate from 1-Methyl-*trans*-1,2-dihydroxycyclohexane.[7] Method (a): 80% yield, mp 107–108° (methanol); ir ($CHCl_3$) 1320, 1300, and 1290 cm^{-1} (s, C=S); nmr ($CDCl_3$, δ) 4.22 (1 H, dd, J = 12, 4 Hz), 2.40–1.20 (8 H, m), 1.37 (3 H, s); exact mass determination 172.055900 (calcd for $C_8H_{12}O_2S$, 172.055800).

The Thionocarbonate from 1-Methyl-*cis*-1,2-dihydroxycyclohexane.[7] Method (a): a liquid (71% yield); ir 1340 and 1340 cm^{-1} (s, C=S); nmr ($CDCl_3$, δ) 4.57 (1 H, t, J = 4 Hz), 2.40–1.20 (8 H, m), 1.55 (3 H, s); exact mass determination 172.05595 (calcd for $C_8H_{12}O_2S$, 172.05580).

***endo*-Tricyclo[4.2.1.$0^{2,5}$]non-7-ene-*endo*-3,4-diol.** *endo*-3,4-Bis(trimethylsiloxy)tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene[8] (3.14 g, 10.66 mmol) was stirred with absolute ethanol (10 ml) at room temperature (under nitrogen). After 2 hr, it was completely hydrolyzed to the corresponding acyloin: ir (neat) 3600 and 3450 (s, OH), 1770 cm^{-1} (s, C=O); nmr ($CDCl_3$, δ) 6.12 (2 H, bs), 4.50 (1 H, m, C*H*OH), 3.97 (1 H, br, OH), 3.75–2.50 (4 H, m), 1.77 and 1.53 (2 H, J = 9 Hz, AB quartet) after removal of solvent.

Sodium borohydride (1.5 g) was added to the crude ethanol solution of acyloin from above at −78°, and the resulting mixture was warmed to 0° for 2 hr and then to room temperature (2 hr). Work-up with 5% sodium potassium tartrate and ether extraction produced white crystals (1.2 g, 74%). The diol crystallized from ethanol–hexane as white prisms: mp 135–136°; ir ($CHCl_3$) 3520 and 3400 cm^{-1} (s, OH); nmr ($CDCl_3$, δ) 6.40 (2 H, t, J = 1.7 Hz), 4.35 (2 H, bs), 3.05 (4 H, m), 2.25 (2 H, m, OH), 1.45 and 1.08 (2 H, AB quartet, J = 9 Hz); exact mass determination 134.07294 ($M^+ - H_2O$, calcd for $C_9H_{10}O$, 134.07312).

The Thionocarbonate. Method (a) from the diol (92% yield): mp 89–91°; ir ($CDCl_3$) 1322, 1310, 1270, and 1255 cm^{-1}; nmr ($CDCl_3$, δ) 6.30 (2 H, bs), 5.22 (2 H, t, J = 3 Hz), 3.12 (4 H, bs), 1.60 and 1.16 (2 H, AB quartet, J = 2 Hz); exact mass determination 194.04065 (calcd for $C_{10}H_{10}O_2S$, 194.04018).

Thionocarbonate Reactions with Isopropyl Iodide. Thionocarbonate of *meso*-Hydrobenzoin. A solution of the thionocarbonate (51 mg, 0.2 mmol) in isopropyl iodide (2 ml, commercial sample from Aldrich) was gently heated under reflux for 24 hr. The resulting solution was evaporated, diluted with $CHCl_3$ (5 ml), stirred with a few crystals of $Na_2S_2O_3$, and filtered. The filtrate was concentrated and purified by tlc over silica gel using hexane as eluent. *trans*-Stilbene (31 mg, 86%) was obtained, R_f 0.14.

A solution of the thionocarbonate (26 mg) in purified isopropyl iodide (distilled from $Na_2S_2O_3$) was refluxed for 12 hr. Evaporation of isopropyl iodide afforded starting material (22 mg). If the reaction was continued (2–4 days), evaporation of isopropyl iodide afforded a mixture of starting material, *trans*-stilbene, and uncharacterized labile products containing isopropyl methyls. Upon attempted chromatography, the latter decomposed with liberation of iodine.

When sodium iodide was added to the reaction mixture, the rate of reaction was unchanged.

Reaction of *meso*-Hydrobenzoin Thionocarbonate with Iodine. The thionocarbonate (52 mg, 0.2 mmol), iodine (29 mg, 0.11 mm), and glyme (2 ml) were heated for 20 hr, and the solvent was evaporated. The residue was purified by tlc (hexane), giving *trans*-stilbene (27 mg, 75%; no cis isomer was detected by nmr) and an unidentified product (5.5 mg, yellow crystals, R_f 0.9). When 0.22 mmol of iodine was used, *trans*-stilbene was isolated in 60% yield.

Reactions of the Thionocarbonate of *dl*-Hydrobenzoin with *i*-PrI and Iodine. A solution of thionocarbonate (25 mg, 0.1 mmol) in isopropyl iodide (1 ml) was refluxed for 24 hr. The usual work-up gave *trans*-stilbene (14 mg, 80%).

The reaction was also carried out by using purified isopropyl iodide and stopped after 2–4 days. Removal of isopropyl iodide gave a complex mixture of starting material, *trans*-stilbene, and uncharacterized labile products containing the isopropyl group.

A solution of thionocarbonate (51 mg, 0.2 mmol), iodine (56 mg, 0.22 mmol), and glyme (2 ml) was heated at 90° for 16 hr. The usual work-up (tlc) yielded *trans*-stilbene (19 mg, 52%).

Reaction of the Thionocarbonate of *cis*-1,2-Cyclooctanediol. A solution of thionocarbonate (44 mg, 0.23 mmol) and *i*-PrI (0.5 ml) in a sealed tube was heated at 90° for 19 hr. The total mixture was analyzed by vpc (0.25 in. × 10 ft 10% Carbowax on Chromosorb P 60–80 mesh using 4-methylcyclohexene as internal standard). *cis*-Cyclooctene was formed in 32% yield.

Upon evaporation of the solvent and any olefin formed under vacuum, a residue (70 mg) was obtained: nmr ($CDCl_3$, δ) 5.5 (1 H, m), 4.6 (1 H, m), 3.65 (1 H, m), 1.42 (6 H, d), 1.0–2.4 (10 H, m). The residue was sealed in a glass tube with Mg(Hg) (prepared from 0.2 g of Mg and 0.3 g of $HgCl_2$ in 10 ml of THF and stirred for 15 min at room temperature) in THF (2 ml), and the mixture was stirred at room temperature overnight. The reduction mixture was analyzed by vpc (0.25 in. × 10 ft 20% TCEP on Chromosorb P 60–80 mesh; standard was 1-methylcyclohexene). *cis*-Cyclooctene was produced in 10% yield from this reduction step. Total yield was 42%. No *trans*-cyclooctene was observed in either step.

Reaction of the Thionocarbonate of *trans*-1,2-Cyclooctanediol. A solution of thionocarbonate (30 mg, 0.16 mmol) and *i*-PrI (0.4 ml) in a sealed tube was heated at 90° for 19 hr. It gave *cis*-cyclooctene in 28% yield (0.25 in. × 10 ft 20% TCEP column on

Chromosorb P, 4-methylcyclohexene as standard). Evaporation of the solvent produced a residue. The nonvolatile residue contained the expected iodo thiocarbonate and unknown side products (nmr analysis). Reduction of the residue was carried out as described above to afford *cis*-cyclooctene in 26% yield or 54% combined yield over both steps. *trans*-Cyclooctene was not observed in either step.

Reaction of the Thionocarbonate of 1-Methyl-*trans*-1,2-dihydroxycyclohexenediol. The thionocarbonate was heated at 90° with *i*-PrI for 24 hr and gave 1-methylcyclohexene in 20% yield (0.25 in. × 10 ft 20% TCEP–Chromosorb P, *cis*-cyclooctene as standard). Evaporation of *i*-PrI afforded a residue with a very complicated nmr spectrum. 1-Methylcyclohexane was obtained in 10% yield (20% TCEP, *cis*-cyclooctene as standard), when the residue was reacted with Mg(Hg) by the usual procedure.

Reactions of the Thionocarbonate of 1-Methyl-*cis*-1,2-dihydroxycyclohexane. By the method described above for reaction of the trans diol, 1-methylcyclohexene was obtained in 27% yield directly from the reaction with *i*-PrI. Reduction of the residue with Mg(Hg) as usual gave only 1% 1-methylcyclohexene.

Reaction of the Thionocarbonate of *endo*-Tricyclo[4.2.1.0^{2,5}]non-7-ene-*endo*-3,4-diol. When a solution of the thionocarbonate (58 mg, 0.3 mmol) and *i*-PrI (2 ml) was refluxed for 30 hr the corresponding iodo thiocarbonate was obtained as an oil (112 mg): ir ($CHCl_3$) 1700 cm^{-1} (s, C=O); nmr ($CDCl_3$, δ) 6.33 (1 H, m), 6.20 (1 H, m), 5.15 (1 H, dd, J = 8.6 Hz, CHO), 4.00 (1 H, dd, J = 6 and 4 Hz, CHI), 3.52 (1 H, quintet, CHS), 3.07 (4 H, bs), 1.36 (6 H, d, J = 8 Hz), 1.53 and 1.14 (2 H, AB quartet). Reduction with zinc dust (0.4 g) in refluxing ethanol (1.5 ml) and water (0.15 ml) for 24 hr, afforded *endo*-tricyclo[4.2.1.0^{2,5}]nona-3,7-diene in 54% yield. The olefin was identified by comparison of its retention time with that of the corresponding exo isomer (20% TCEP, 1-methylcycloheptene as standard).

When purified isopropyl iodide was used, the starting thionocarbonate was recovered. Addition of sodium iodide did not accelerate the reaction.

Reactions with Methyl Iodide. Reaction of *meso*-Hydrobenzoin Thionocarbonate. A mixture of the thionocarbonate (75 mg, 0.3 mmol), purified methyl iodide (0.8 ml), and dry glyme (0.8 ml) in a sealed tube was heated at 90° for 6 hr. White crystals (110 mg) were obtained after evaporation of methyl iodide and glyme. The nmr spectrum of the crystals indicated a mixture of starting thionocarbonate (20%) and the iodo thiocarbonate **7**: nmr δ 7.15 (bs, 10 H), 6.22 (1 H, d, J = 10 Hz, CHO), 5.32 (1 H, d, J = 10 Hz, CHI), 2.35 (3 H, s, CH_3).

A solution of the thionocarbonate (28 mg, 0.11 mmol), methyl iodide (0.5 ml), and glyme (0.5 ml) in a sealed tube was heated for 14 hr. A mixture of **7a,b** was obtained (no starting material was detected by tlc) as evidenced by a major methyl singlet at δ 2.35 ppm and a minor singlet at δ 2.18 ppm.

The mixture of **7a,b** was then treated with iodine (18 mg, 0.07 mmol) in glyme (1 ml) and heated at 90° for 6 hr. The reaction mixture was stirred with crystalline sodium thiosulfate to remove excess of iodine, filtered, and passed through Na_2SO_4. Evaporation of the solvent gave yellow prisms (20 mg, 95%). The product was further purified by filtration through a short silica gel column (eluted with hexane) to afford *trans*-stilbene as white prisms (15 mg, 70%).

A mixture of **7a,b** (26 mg, 0.1 mmol) was stirred with Mg(Hg)/THF (2 ml) (prepared from 0.4 g of Mg and 0.4 g of $HgCl_2$ in 10 ml of THF, stirred for 15 min) for 1 hr at room temperature. The total mixture was passed through a short silica gel column and eluted with hexane to give stilbene containing *ca.* 5% of *cis*-stilbene (nmr analysis) in 90% yield (16.2 mg).

A solution of the *meso* thionocarbonate (25 mg, 0.1 mmol), methyl iodide (0.5 ml), glyme (0.5 ml), and iodine (17 mg, 0.067 mmol) was heated for 6 hr. The usual work-up yielded *trans*-stilbene (85%).

Reaction of *dl*-Hydrobenzoin Thionocarbonate. A solution of the thionocarbonate (26 mg, 0.1 mmol), methyl iodide (0.5 ml), and glyme (0.5 ml) in a sealed tube was heated at 90° for 6 hr. The mixture contained starting thionocarbonate and **7a,b** (2:1 in favor of the δ 2.18 ppm methyl singlet relative to the δ 2.35 methyl singlet).

If the reaction was heated for 12 hr, it gave a mixture of equal amounts of **7a** and **7b**. The reaction intermediate was then treated with Mg(Hg)/THF (2 ml), prepared as usual, for 1 hr at room temperature. The reduced mixture was worked up as before to produce stilbene (*ca.* 5% cis) (16.5 mg, 92%).

Reaction of *cis*-1,2-Cyclooctanediol Thionocarbonate. The thionocarbonate (32 mg, 172 mmol) in glyme (0.5 ml) with CH_3I (0.5 ml) at 90° for 8 hr gave the corresponding iodo thiocarbonate: ir ($CHCl_3$) 1700 cm^{-1}; nmr ($CDCl_3$, δ) 5.35 (1 H, m, CHO), 4.50 (1 H, m, CHI), 2.36 (3 H, s, CH_3), 1.0–2.4 (10 H, m). Reduction of the iodo thiocarbonate with Mg(Hg)/THF (2 ml) (prepared from 0.4 g of Mg and 0.4 g of $HgCl_2$ in 10 ml of THF, stirred for 15 min) gave cyclooctene (72%) (10% Carbowax, 1-methylcycloheptene as standard).

Reaction of the Thionocarbonate of Tricyclo[4.2.1.0^{2,5}]non-7-ene-*endo*-3,4-diol. A solution of the thionocarbonate (58 mg, 0.3 mmol), glyme (0.6 ml), and methyl iodide (0.6 m) (at 90° for 12 hr) afforded the iodo thiocarbonate (100 mg): ir ($CHCl_3$) 1700 (s, C=O), 1140 cm^{-1} (s); nmr ($CDCl_3$, δ) 6.32 (1 H, m), 6.15 (1 H, m), 5.17 (1 H, dd, J = 9 and 6 Hz, CHO), 4.00 (1 H, dd, J = 6 and 4 Hz, CHI), 3.05 (4 H, m), 2.31 (3 H, s, CH_3), 1.50 and 1.10 (2 H, two doublets, J = 9 Hz, AB quartet). A mixture of the iodo thiocarbonate, zinc (0.4 g), ethanol (1.5 ml), and water (0.15 ml) in a sealed tube was heated at 85° for 24 hr. It gave the corresponding olefin in 84% yield (20% TCEP, 1-methylcycloheptene as standard).

1,3-Dibenzyl-2-methyl-1,3-diazaphospholidine. A mixture of *N,N'*-tetramethylmethylphosphonous diamide (7.5 g, 39.4 mmol) and *N,N'*-dibenzylethylenediamine (9.3 g, 38.5 mmol) in a 50-ml flask, which was attached to a distillation apparatus, was stirred and heated at 110–120° in the presence of nitrogen. Diethylamine (4.62 g) was distilled and was collected over a 7-hr period. Excess of the phosphonousdiamide was removed under vacuum and the diazaphospholidine was obtained (10.6 g, 96%): bp 142° (0.09 mm) (lit.[1b] 135° (0.04 mm)); nmr ($CDCl_3$) 7.28 (19 H, s), 4.02 (4 H, d, J = 9.5 Hz), 3.00 (4 H, m), 0.99 (3 H, d, J = 6 Hz).

***syn*-7,8-Benzotricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene.**[4] (a) A mixture of the olefin thionocarbonate **2**[9] (26 mg, 0.1 mmol) in trimethyl phosphite (173 mg, 1.4 mmol) and benzene-d_6 (100 μl) in a sealed nmr tube was heated at 120° and the reaction was monitored by nmr. After being heated for 4 days, it did not give any change in the spectrum except for appearance of a doublet at about δ 1.0, which was not identifiable. The phosphite was removed and the starting thionocarbonate (24 mg) recovered.

(b) A solution of the thionocarbonate **2** (40 mg, 0.156 mmol) in 1,3-dibenzyl-2-methyl-1,3-diazaphospholidine (0.5 ml or 645 mg) in a sealed tube (under argon) was stirred and heated at 155° for 84 hr. The mixture was dissolved in toluene (20 ml) and then treated with 1 N HCl dropwise until no more precipitate was found. The solid was filtered off and the filtrate, after being passed through a mixture of Na_2SO_4 (anhydrous) and K_2CO_3 (anhydrous) and evaporated, yielded a yellow liquid (143 mg). Purification of the liquid by tlc gave white needles of the hydrocarbon product (16 mg, 57%): mp 41–42°; ir (CCl_4) 3050, 2950, 2920, 1450, 1320, 1280, 680 cm^{-1}; nmr (CCl_4) δ 6.97 (4 H, s, aromatic protons), 6.50 (2 H, dd, J = 4 and 3 Hz, olefinic protons at C_9 and C_{10}), 5.78 (2 H, s, protons at C_3 and C_4), 3.74 (2 H, m, bridgehead protons), 2.72 (2 H, m, protons at C_2 and C_5); mass spectrum *m/e* (%) 47 (40), 48 (10), 49 (17), 50 (8), 51 (17), 52 (62), 63 (10), 76 (10), 83 (86), 84 (62), 85 (59), 86 (40), 87 (10), 101 (35), 127 (11), 128 (64), 129 (7), 152 (17), 165 (47), 178 (35), 179 (100), 180 (74, M^+), 181 (10, $(M+1)^+$); exact mass determination 180.093680 (calcd for $C_{14}H_{12}$, 180.093900).

(c) A solution of the thionocarbonate 2 (13 mg, 0.05 mmol) in isopropyl iodide (1 ml) was refluxed for 5 hr (under nitrogen). Evaporation of the solvent gave a reddish brown residue (22.5 mg, 105%) containing 99% of the iodo thiocarbonate **5** (R = *i*-Pr) by nmr: ir ($CHCl_3$) 2960, 2940, 2870, 1695, 1460, 1259, 1130, 1058, 1000 cm^{-1}; nmr ($CDCl_3$, δ) 7.16 (4 H, m), 6.54 (2 H, bt, J = 6 Hz), 5.11 (1 H, bt, HCO), 4.08 (2 H, m), 3.49 (1 H, m); 3.15 (1 H, t, J = 6 Hz, HCl), 2.88 (2 H, m), 1.36 (6 H, t, J = 8 Hz).

A mixture of the crude iodo thiocarbonate **2**, zinc dust (0.3 g), absolute ethanol (2 ml), and water (0.2 ml) was stirred overnight (12 hr) at room temperature and the hydrocarbon (5.5 mg, 60%) was obtained after usual work-up and tlc purification.

Conversion of the Thionocarbonate[9] of 9-Keto-*syn*-7,8-benzotricyclo[4.2.2.0^{2,5}]dec-7-ene-*cis*-3,4-diol to *syn*-7,8-Benzotricyclo[4.2.2.0^{2,5}]deca-3,7-dien-9-one. (a) A mixture of the keto thionocarbonate (27 mg, 0.01 mol) in trimethyl phosphite was refluxed for 84 hr in a sealed tube (under argon). There was no spot above the base line of the analytic tlc plate when ether was used as mobile phase.

(b) A solution of the keto thionocarbonate (20 mg, 0.073 mmol) and commercial isopropyl iodide (1.5 ml) under nitrogen was heated under reflux for 5 hr. Evaporation of the isopropyl iodide gave 38 mg (100%) of brown residue consisting of a mixture of iodo thiocarbonates: ir ($CHCl_3$) 2960, 2870, 1725 (C=O), 1700 (S—C=O), 1450, 1125, 1055; nmr ($CDCl_3$, δ) 7.32 (4 H, m), 5.32 (1 H, m,

HCO), 4.0–3.0 (6 H, m), 2.20 (2, H, m), 1.37 (6 H, overlapping doublets, J = 7 Hz, CH_3).

The crude iodo thiocarbonates were treated with zinc dust (0.3 g), absolute ethanol (2 ml), and water (0.2 ml) (under nitrogen) and the mixture was refluxed for 14 hr. The zinc was filtered off and the solution was concentrated and purified by tlc (hexane–ether 10:1), affording the cyclobutene product (12 mg, 84%) as white crystals: mp 48°; ir (CCl_4) 3060, 2920, 1725, 1297, 1138, 112 cm^{-1}; nmr (CCl_4) 7.24 (4 H, bs), 5.76 (2 H, ABX, J = 12, 2.5 Hz, olefinic protons), 3.98 (1 H, d, J = 3 Hz, CHC=O), 3.1–3.45 (3 H, m, $CHCH_2$ and C_2H and C_5H), 2.10 (2 H, bs, CH_2C=O); mass spectrum *m/e* (%) 115 (12), 128 (25), 152 (23), 153 (79), 154 (100, 155 (13), 165 (11), 167 (13), 196 (42, M^+), 197 (7, $(M + 1)^+$); exact mass determination 199.08906 (calcd for $C_{14}H_{12}O$, 196.08875).

Registry No.—**1**, 52718-74-8; **2**, 52718-70-4; **3**, 41791-25-7; **5**, 52718-71-5; *meso*-**7**, 52748-16-0; *dl*-**7**, 52730-77-5; *meso*-hydrobenzoin, 579-43-1; *meso*-hydrobenzoin thionocarbonate, 39247-13-7; *dl*-hydrobenzoin, 655-48-1; *dl*-hydrobenzoin thionocarbonate, 39247-17-1; *cis*-1,2-cyclooctanediol, 27607-33-6; *cis*-1,2-cyclooctanediol thionocarbonate, 50300-29-3; *trans*-1,2-cyclooctanediol, 42565-22-0; *trans*-1,2-cyclooctanediol thionocarbonate, 35859-00-7; 1-methyl-*trans*-1,2-dihydroxycyclohexane, 19534-08-8; 1-methyl-*trans*-1,2-dihydroxycyclohexane thionocarbonate, 52718-64-6; 1-methyl-*cis*-1,2-dihydroxycyclohexane, 52718-65-7; 1-methyl-*cis*-1,2-dihydroxycyclohexane thionocarbonate, 52718-66-8; *endo*-3,4-bis(trimethylsiloxy)tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene, 39762-43-1; *endo*-tricyclo[4.2.1.$0^{2,5}$]non-7-en-*endo*-3-ol-4-one, 52748-15-9; *endo*-tricyclo[4.2.1.$0^{2,5}$]non-7-ene-*endo*-3,4-diol, 52718-67-9; *endo*-tricyclo[4.2.1.$0^{2,5}$]non-7-ene-*endo*-3,4-diol thionocarbonate, 52718-68-0; isopropyl iodide, 75-30-9; *trans*-stilbene, 103-30-0; iodine, 7553-56-2; *cis*-cyclooctene, 931-87-3; 1-methylcyclohexane, 108-87-2; *endo*-tricyclo[4.2.1.$0^{2,5}$]non-7-ene iodo thiocarbonate, 52718-69-1; *endo*-tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene, 15564-44-0; methyl iodide, 74-88-4; *cis*-stilbene, 645-49-8; *cis*-1,2-cyclooctane iodo thiocarbonate, 52718-72-6; tricyclo-[4.2.1.$0^{2,5}$]non-7-ene iodo thiocarbonate, 52718-73-7; *N,N'*-tetramethyl methylphosphonous diamide, 14937-39-4; *N,N'*-dibenzylethylenediamine, 140-28-3; 9-keto-*syn*-7,8-benzotricyclo[4.2.2.$0^{2,5}$]dec-7-ene-*cis*-3,4-diol thionocarbonate, 52746-00-6; *syn*-7,8-benzotricyclo[4.2.2.$0^{2,5}$]deca-3,7-dien-9-one, 50849-00-8; 9-keto-*syn*-7,8-benzotricyclo[4.2.2.$0^{2,5}$]dec-7-ene iodo thiocarbonate, 52748-21-7; *N,N*-thiocarbonylbisimidazole, 52718-75-9.

References and Notes

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(6) In the case of the solvolytically unreactive cyclobutene precursors, the product of alkyl iodide thionocarbonate cleavage is clearly the *trans*-iodo thiocarbonate on the basis of nmr evidence. Ring cleavage by iodide ion undoubtedly involves an SN2 process in all cases. Subsequent loss of stereochemistry in the iodo thiocarbonate **7** may be due to SN2 attack by iodide at the carbon–iodine bond of **7**.

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Preparation and Reaction of 2-(2-Hydroxy-2,6-dimethyl-5-heptenyl)-1,3-dithiane. A Synthesis of Linaloyl Oxide (2,6,6-Trimethyl-6-vinyltetrahydropyran)

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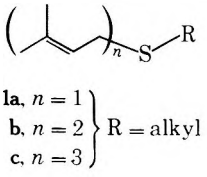
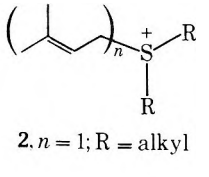
Received June 3, 1974

Preparation and reactions of 2-(2-hydroxy-2,6-dimethyl-5-heptenyl)-1,3-dithiane (**3a**) and its conversion to linaloyl oxide (**15**) are described. The alcohol **3a** was prepared in quantitative yield from the reaction of 2,6-dimethyl-1,2-epoxy-5-heptene with 2-lithio-1,3-dithiane. Selective transformations of **3a** into citral (**8**) and its key precursors **9** and **10**, and the tetrahydropyran derivative **11** were carried out. Linaloyl oxide was synthesized in 45% overall yield from 6-methyl-5-hepten-2-one by the following steps: hydrolysis of **11** yielding aldehyde **12**, reduction of **12** to alcohol **13**, and pyrolysis of the xanthate of **13**. Instead of 2-lithio-1,3-dithiane, lithio methyl methylthiomethyl sulfoxide (**16**) could be used for the preparation of linaloyl oxide.

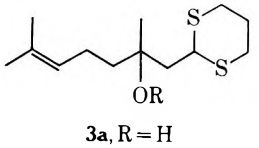
The prenyl,[1] geranyl,[2,3] and farnesyl[4,5] sulfides **1a–c** and the related sulfonium salt **2**[1] have been extensively used in syntheses of biological active terpenoids, juvenile hormones, and sex attractants. We have been interested in developing novel syntheses of terpenoids from 2-(2-hydroxy-2,6-dimethyl-5-heptenyl)-1,3-dithiane (**3a**) instead of from the sulfides and the sulfonium salt.



1a, $n = 1$
b, $n = 2$
c, $n = 3$
} R = alkyl

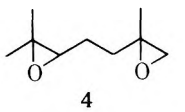


2, $n = 1$; R = alkyl



3a, R = H

In a previous communication,[6] we described a new ring closure of the diepoxide **4** with 2-lithio-1,3-dithiane pro-



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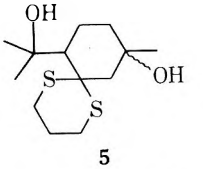

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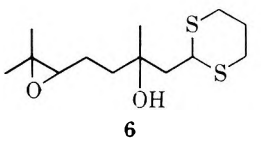

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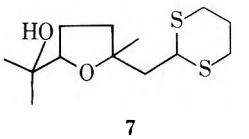
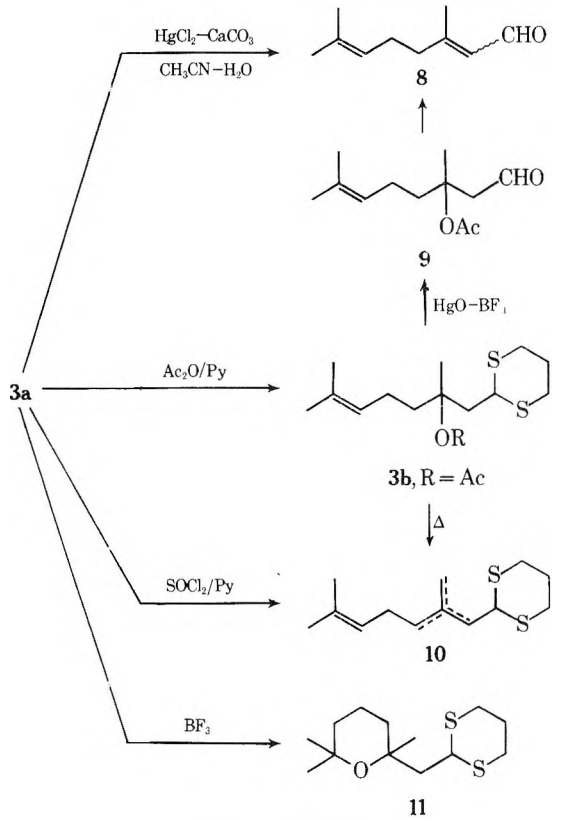


7

ducing the cyclic compounds **5** along with **6** and **7**. This paper deals with the chemistry of **3a** and its selective conversion into linaloyl oxide (**15**).

The utility of 1,3-dithiane in organic synthesis is well documented in the literature.[7] Above all, the reaction of 2-lithio-1,3-dithiane with epoxides provides a promising route to derivatives of secondary or tertiary alcohols.[8] Thus, reaction of 2,6-dimethyl-1,2-epoxy-5-heptene with 2-lithio-1,3-dithiane in dry tetrahydrofuran at −30° provided the alcohol **3a**, homogeneous by tlc, ir, and nmr, in 98% yield after chromatography on silica gel.

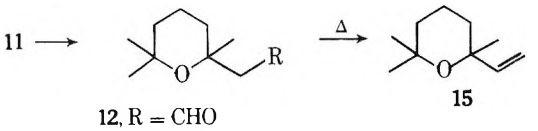
Exclusive conversion of **3a** into citral (**8**) was carried out by refluxing in aqueous 80% acetonitrile in the presence of 1 equiv of mercuric chloride and calcium carbonate, whereas hydrolysis of the acetate **3b** using mercuric oxide and boron trifluoride gave the corresponding acetate **9**[9] in 84% yield. Deacetoxylation of the acetate **9** occurred smoothly on elution over silica gel, affording citral in good yield.



Dehydration of **3a** to the dienes **10** proceeded smoothly on treatment with thionyl chloride or methanesulfonyl chloride in pyridine. Thermal deacetoxylation of **3b** also occurred at 200° to afford **10** in 95% yield. Without further purification, the dienes **10** were hydrolyzed to give citral.

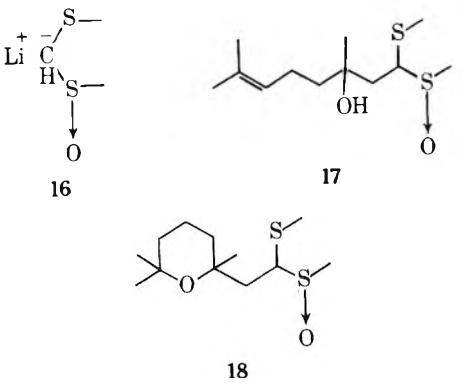
Acid-catalyzed cyclization of olefinic alcohols to cyclic ethers has been reported in the literature,[10] but few such references outline the preferred reaction conditions for selective cyclization without producing by-products. Hence, careful examination of the reaction conditions is required for obtaining satisfactory product selectivity. Indeed, reaction temperature was found to be the most critical factor influencing the yield of the cyclic ether **11**. Treatment of **3a** with 2 equiv of boron trifluoride etherate in benzene and dichloromethane (2:1) at −10° for 12 hr yielded 81% of **11**. Higher temperature (over 0°) favored the dehydration product **10**. In fact, the reaction of **3a** in benzene at 7–10° gave 10% of **10** and 60% of **11**, while on refluxing in benzene **10** was isolated as a sole product. The structural assignment of **11** was based on spectral data.

Conversion of **11** to the corresponding aldehyde **12**[11] was performed using boron trifluoride and mercuric oxide in aqueous tetrahydrofuran[12] in 84% yield. Reduction of **12** with lithium aluminum hydride furnished the alcohol **13**[13] in quantitative yield, which was converted into the corresponding xanthate **14** efficiently. Thermolysis of **14** took place instantaneously at *ca.* 320° to give linaloyl oxide (**15**)[14] as a colorless oil in 79% yield (45% overall yield from 6-methylheptenone). The spectral data (ir, nmr, and mass spectrum) of **15** were identical with those reported.[10e]



12, R = CHO
13, R = CH_2OH
14, R = $CH_2OC(S)SCH_3$

Similarly, 2,6-dimethyl-1,2-epoxy-5-heptene reacted smoothly with the lithio sulfoxide **16**[15] in tetrahydrofuran at −30° to afford **17** in excellent yield. The adduct **17** was converted to **12** by cyclization (94% yield) and hydrolysis (70% yield) in the same manner as the dithiane derivative **3a**.



Experimental Section

Boiling points were indicated by an air or an oil bath temperature without correction. Nmr spectra were recorded on a Hitachi R-24 instrument using tetramethylsilane as an internal standard. Ir spectra were taken with a Hitachi EPI-S2 instrument. Mass spectral analyses were carried out at 70 eV with a Hitachi RMS-4 mass spectrometer. Microanalysis was performed by Mr. Tsutomu Okamoto of our laboratory.

2-(2-Hydroxy-2,6-dimethyl-5-heptenyl)-1,3-dithiane (3a). Into a solution of 120 mg (1 mmol) of 1,3-dithiane and 3 ml of dry THF 2 mmol of *n*-butyllithium was added dropwise with stirring at −30° and the mixture was stirred for 1.5 hr. Following addition of 140 mg (1 mmol) of 2,6-dimethyl-1,2-epoxy-5-heptene, the mixture was stirred for 15 min at −30° and then for 12 hr at room temperature. Into the ice-cooled reaction mixture 2 ml of ether and 2 ml of saturated NH_4Cl were added. The organic layer was extracted with ether, washed twice with 2 ml of brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed over silica gel (Wakogel C-200, dichloromethane) to yield 254 mg (98%) of **3a** as a colorless oil: bp 55–60° (0.005 mm); ir (neat) 3446 (OH), 3050 (C=CH) cm^{-1}; nmr (CCl_4) δ 4.88–5.24 (m, 1 H, CH=C), 4.11 (t, J = 7 Hz, 1 H, S-CH-S), 2.73–2.98 (m, 4 H, S-CH_2), 2.40 (s, 1 H, OH), 1.30–2.26 (m, 8 H, CH_2), 1.66 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3); mass spectrum *m/e* 260 (M^+, 21), 242 (M − 18, 15), 119 (base peak).

Anal. Calcd for $C_{13}H_{24}S_2O$: C, 59.98; H, 9.29. Found: C, 59.84; H, 9.21.

2-(2,6,6-Trimethyl-2-tetrahydropyranyl)methyl-1,3-dithiane (11). Into a stirred solution of 260 mg (1 mmol) of **3a** in a mixture of 10 ml of dry benzene and 5 ml of dry dichloromethane was added dropwise 142 mg (1 mmol) of freshly distilled boron trifluoride etherate at −10° under nitrogen. The mixture was stirred at room temperature for 6 hr, treated again with 1 mmol of boron trifluoride etherate with stirring for an additional 6 hr, and quenched with 1 ml of cooled water. The organic phase was extracted with 5 ml of dichloromethane, washed twice with 2 ml of water, dried (Na_2SO_4), and concentrated *in vacuo*. The residue

was chromatographed over silica gel using a mixture of benzene and dichloromethane to yield 208 mg (81%) of **11** as a colorless oil, 2 mg (1%) of **10**, and 45 mg (17%) of the recovered **3a**. The physical data of **11** are as follows: bp 55–60° (0.005 mm); ir (neat) 1223 and 1118 (C–O) cm^{-1}; nmr (CCl_4) δ 4.09 (t, J = 6 Hz, 1 H, S–CH–S), 2.65–2.97 (m, 4H, S–CH_2), 1.80–2.14 (m, 2H, CH_2), 1.70 (d, J = 6 Hz, 2H, CH_2—C=S_2), 1.37–1.80 (m, 6 H, CH_2), 1.22 (s, 3 H, CH_3), 1.17 (s, 6 H, CH_3); mass spectrum m/e 260 (M^+, 68), 159 (base peak).

Anal. Calcd for $C_{13}H_{24}S_2O$: C, 59.98; H, 9.29. Found: C, 59.97; H, 9.10.

2,6,6-Trimethyltetrahydropyran-2-acetaldehyde (12). Into an ice-cooled mixture of 445 mg (2.1 mmol) of mercuric oxide (red) and 260.5 mg (1 mmol) of **11** in 2 ml of aqueous 85% THF solution was added dropwise 300 mg (2.1 mmol) of freshly distilled boron trifluoride etherate with stirring. The mixture was stirred for 1.5 hr at 7–10° and quenched by addition of 2 ml of ether to give a white solid, which was filtered off and rinsed three times with ether. The combined filtrates were washed with aqueous $NaHCO_3$, and twice with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Distillation of the residue under reduced pressure gave 143 mg (84%) of **12** as a colorless oil: bp 78–82° (15 mm) (lit.[11] bp 76–78° (14 mm)); ir (neat) 2748 (CHO) and 1720 (C=O) cm^{-1}; nmr (CCl_4) δ 9.76 (t, J = 3 Hz, 1 H, CHO), 2.33 (d, J = 3 Hz, 2 H, CH_2C=O), 1.30–2.20 (m, 6 H, CH_2), 1.27 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3).

2,6,6-Trimethyl-2-(2-hydroxy)ethyltetrahydropyran (13). The aldehyde **12** (170 mg, 1 mmol) was treated with 29 mg of lithium aluminum hydride in 2 ml of dry ether at room temperature. Usual work-up and distillation of the product gave 168 mg (98%) of **13** as a colorless oil: bp 90–94° (10 mm) (lit.[13] bp 62–63° (0.2 mm)); ir (neat) 3380 (OH), 1228 (C–O) cm^{-1}; nmr (CCl_4) δ 3.64 (t, J = 6 Hz, 2 H, CH_2O), 3.12 (s, 1 H, OH), 1.59 (t, J = 6 Hz, 2 H, CH_2CO), 1.36–1.80 (m, 6 H, CH_2), 1.24 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3).

2,6,6-Trimethyl-2-vinyltetrahydropyran (Linaloyl Oxide) (15). To an ice-cooled suspension of 72 mg (1.5 mmol) of sodium hydride in 3 ml of dry THF was added 172 mg (1 mmol) of **13** in 2 ml of dry THF under nitrogen. The mixture was stirred at room temperature for 3 hr, treated with 114 mg (1.5 mmol) of carbon disulfide at 0°, and further stirred at room temperature for 12 hr. Then, the ice-cooled mixture was treated with 214 mg (1.5 mmol) of methyl iodide, stirred at room temperature for 6 hr, and quenched with ice–water. The combined ether extracts were washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed over silica gel (Wakogel C-200, n-hexane–CH_2Cl_2 4:1) to yield 257 mg (98%) of **14** as a clean yellowish oil: ir (neat) 1250–1180, 1172, 1128, 1095–1040, 1011 cm^{-1}; nmr (CCl_4) δ 4.72 (t, J = 7 Hz, 2 H, CH_2O), 2.49 (s, 3 H, CH_3S), 1.91 (t, J = 7 Hz, 2 H, CH_2CO), 1.37–2.09 (m, 6 H, CH_2), 1.21 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3); mass spectrum m/e 262 (M^+, 0.8), 247 (M^+ – CH_3, 7), 69 (base peak). The xanthate **14**, without further purification, could be converted into linaloyl oxide in the following manner. To a 1-ml modified Claisen flask settled at 320° in an air bath, 80 mg (0.3 mmol) of **14** was dropped at 30-sec intervals by means of a 0.5-ml syringe. On adding **14** decomposition took place immediately to form a fumy vapor which was subsequently distilled out to give 39 mg of a colorless oil, whose vpc (neopentyl glycol, 3 m long, 4 ϕ, 90°) revealed that the oil contained 94% of **15**. The spectral data (ir, nmr, and mass spectrum) of the vpc separated sample were superimposable with those reported.[10e]

2-(2-Acetoxy-2,6-dimethyl-5-heptenyl)-1,3-dithiane (3b). The alcohol **3a** (130 mg, 0.5 mmol) was acetylated in a mixture of 1.5 ml of pyridine and 1.5 ml of acetic anhydride at 110° for 12 hr. Usual work-up and chromatography over silica gel (benzene) gave 128 mg (85%) of **3b** as a slightly yellowish oil: bp 68–72° (0.004 mm); ir (neat) 1737 (OAc) cm^{-1}; nmr ($CDCl_3$) δ 4.88–5.25 (m, 1 H, HC=C), 4.12 (t, J = 6 Hz, 1 H, S–CH–S), 2.75–3.03 (m, 4 H, CH_2S), 1.38–2.35 (m, 8 H, CH_2), 1.96 (s, 3 H, CH_3CO), 1.67 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3); mass spectrum m/e 242 (M^+ – AcOH, 8) and 119 (base peak).

Anal. Calcd for $C_{15}H_{26}S_2O_2$: C, 59.48; H, 8.67. Found: C, 59.46; H, 8.58.

Methyl 1-Methylthio-3-hydroxy-3,7-dimethyl-6-octenyl Sulfoxide (17). The sulfoxide **17** was prepared using methyl methylthiomethyl sulfoxide in a similar manner as for the preparation of **3a**. The epoxide (50 mg, 0.36 mmol) afforded 94 mg (100%) of **17** as a colorless oil after chromatographed over silica gel using chloroform–ethyl acetate (1:3): bp 76–79° (0.006 mm); ir (neat) 3376 (OH) and 1039 (S=O) cm^{-1}; nmr ($CDCl_3$) δ 4.90–5.29 (m, 1 H, HC=C), 3.67–4.12 (m, 1 H, SCHSO), 3.70–3.90 (br s, 1 H, OH), 2.71 (s, 1.5 H, $SOCH_3$), 2.58 (s, 1.5 H, $SOCH_3$), 2.30 (s, 1.5 H, CH_3S), 2.23 (s, 1.5 H, CH_3S), 1.83–2.42 (m, 4 H, CH_2), 1.68 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.34–1.77 (m, 2 H, CH_2), 1.26 (s, 3 H, CH_3); mass spectrum m/e 200 (M^+ – CH_3SOH, 4), 69 (base peak) Microanalysis for the sulfoxide **17** was not performed since it is very hygroscopic.

Methyl 1-Methylthio-2-(2,6,6-trimethyl-2-tetrahydropyranyl)ethyl Sulfoxide (18). The sulfoxide **18** was prepared in 95% yield by the same procedure as done in the preparation of **11**. Chromatography over silica gel (chloroform–ethyl acetate) and distillation gave a colorless oil: bp 70–75° (0.004 mm); ir (neat) 2923, 1447, 1378, 1223, 1119, 1054 (S=O) cm^{-1}; nmr ($CDCl_3$) δ 3.61–4.08 (m, 1 H, SCHSO), 2.56 (s, 3 H, CH_3SO), 2.35 (s, 1.5 H, CH_3S), 2.31 (s, 1.5 H, CH_3S), 1.20–2.20 (m, 8 H, CH_2), 1.18 (s, 3 H, CH_3), 1.23 (s, 6 H, CH_3); mass spectrum m/e 200 (M^+ – CH_3SOH, 4), 69 (base peak).

Anal. Calcd for $C_{12}H_{24}S_2O_2$: C, 54.53; H, 9.15. Found: C, 54.34; H, 9.32.

The Aldehyde 12 from 18. The sulfoxide **18** (50 mg, 0.19 mmol) was treated with 135 mg (0.76 mmol) of mercuric oxide (red) and 81 mg (0.57 mmol) of boron trifluoride etherate in 0.5 ml of aqueous 85% THF solution under nitrogen at 0° and the mixture was stirred for 36 hr at 15–20°. Usual work-up and distillation afforded 20 mg (70%) of **12**.

3-Acetoxy-3,7-dimethyl-6-octenal (9). The desulfurization of **3b** was carried out in the similar manner as done in the preparation of **12** from **11**. Starting from 80 mg (0.26 mmol) of **3b**, 47 mg (85%) of **9** was obtained as a colorless oil after capillary distillation: bp 58–62° (2 mm); ir (neat) 2740 (CHO), 1740 (AcO), 1730 (CHO), 1246 cm^{-1}; nmr ($CDCl_3$) δ 9.77 (t, J = 2 Hz, 1 H, CHO), 4.92–5.27 (m, 1 H, HC=C), 3.06 and 2.72 (q, J_1 = 16 Hz, J_2 = 2 Hz, 2 H, CH_2CO), 2.01 (s, 3 H, CH_3CO), 1.88–2.13 (m, 4 H, CH_2), 1.69 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3); mass spectrum m/e 152 (M^+ – AcOH, 7), 69 (base peak).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.14; H, 9.50.

The acetate **9** was eluted through silica gel column using benzene–ethyl acetate (5:1) affording citral (trans/cis = 3:1) in 80% yield.

Pyrolysis of 3b. The acetate **3b** (61 mg, 0.2 mmol) was heated at 200° for 1.5 hr and the eliminated acetic acid was removed continuously. The residue was chromatographed over silica gel using n-hexane–benzene (1:1) to afford 45 mg (93%) of an isomeric mixture **10**. The separation of the isomers was not successful by column chromatography (silica gel): ir (neat) 2921, 1647 (C=C), 1424, 1378, 1276, 908 cm^{-1}; nmr (CCl_4) δ 4.76–5.33 (m, 2 H, vinyl), 4.07 (t, 1 H, SCHS), 2.62–3.07 (m, 4 H, CH_2S), 1.80–2.62 (m, 6 H, CH_2), 1.62–1.74 (m, 9 H, CH_3); mass spectrum m/e 242 (M^+, 5), 119 (base peak).

Anal. Calcd for $C_{13}H_{22}S_2$: C, 64.44; H, 9.15. Found: 64.70; H, 9.25.

Dehydration of 3a. Into the ice-cooled solution of 50 mg (0.19 mmol) of **3a** in 0.7 ml of dry pyridine was added 42 mg (0.35 mmol) of freshly distilled thionyl chloride with stirring under nitrogen and the mixture was stirred for 2 hr at 0°. After addition of 2 ml of ether and 1 ml of cooled 5% HCl with vigorous stirring, the organic phase was extracted with ether, washed with 1 ml of 5% HCl and twice with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel using n-hexane–benzene (1:1) to afford 34 mg (74%) of an isomeric mixture of **10**, whose spectral data were quite similar with those of the mixture obtained from thermolysis of **3b**.

Conversion of 3a into Citral. A mixture of 50 mg (0.19 mmol) of **3a**, 114 mg (0.42 mmol) of mercuric chloride, and 42 mg (0.42 mmol) of calcium carbonate in 1 ml of aqueous 80% acetonitrile was stirred under nitrogen at 85–90° for 6 hr. The mixture was filtered to remove a white precipitate and the filtrate was concentrated. The residue was rinsed with ether and filtered and the slight yellow precipitate was washed twice with ether. The combined filtrates were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow oil (32 mg), which was chromatographed over silica gel using n-hexene–ethyl acetate (10:1) affording 21 mg (72%) of citral (trans/cis = 2:1).

Registry No.—**3a**, 52920-86-2; **3b**, 52920-87-3; **9**, 52920-88-4; **10** isomer a, 25094-26-2; **10** isomer b, 52920-89-5; **10** isomer c, 52920-90-8; **11**, 52920-91-9; **12**, 2259-20-3; **13**, 52920-92-0; **14**, 52920-93-1; **15**, 7392-19-0; **17**, 52977-08-9; **18**, 52920-94-2; 1,3-dithiane, 505-

23-7; 2,6-dimethyl-1,2-epoxy-5-heptene, 50340-32-4; methyl methylthiomethyl sulfoxide, 33577-16-1.

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A Convenient Means of Generating Alkyl-Substituted Isobenzofurans as Reactive Intermediates

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Received June 14, 1974

A tautomeric equilibrium is demonstrated to exist between 1-benzalphthalan and 1-benzylisobenzofuran. This equilibrium is exploited as a convenient means of generating alkyl-substituted isobenzofurans as reactive intermediates and the same principle is employed to prepare 1-*tert*-butyl-3-phenylisobenzofuran. Examples are given of the use of these isobenzofuran derivates to prepare substituted naphthalenes and a naphthol. The generation of substituted isobenzofurans by the procedure described here has the advantage that the initial reagents are readily prepared and the generation of the isobenzofuran is not accompanied by any coproduct.

The facile oxidation[1,2] of benzalphthalan, **1a**, is inconsistent with its structure. However, this reactivity suggested that an equilibrium might exist between **1a** and its tautomer 2-benzylisobenzofuran, **2a**. Subsequent reactions then proceed through this reactive[3] intermediate.

The existence of this equilibrium was established by capturing the intermediate **2a** through a Diels–Alder reaction with dimethyl acetylenedicarboxylate to provide **3a**. Attempts to observe directly this equilibrium by nmr or uv spectroscopy were unsuccessful.

In pursuit of a directly observable equilibrium, compounds containing one phenyl substituent were prepared. Thus dehydration of the hydroxyphthalan **5b** gave **1b** which in the presence of dimethyl acetylenedicarboxylate formed the Diels–Alder adduct **3b**. Unfortunately, the isobenzofuran **2b** could not be detected spectroscopically.

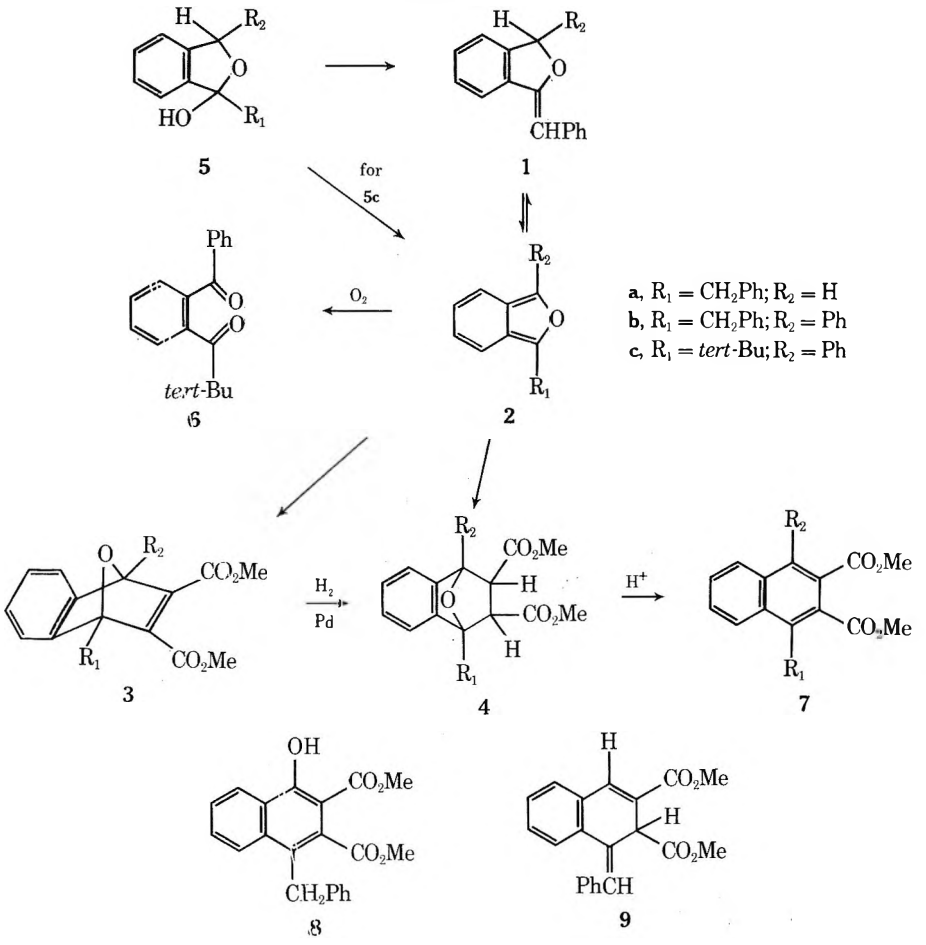
In the case of the hydroxyphthalan **5c**, dehydration of necessity produced the corresponding isobenzofuran **2c**, isolated as a reactive yellow oil with a brilliant fluorescence under uv light. The isobenzofuran structure was supported by its uv spectrum, by its easy oxidation[4] to the diketone **6**, and by the reaction of **2c** with dimethyl acetylenedicarboxylate and dimethyl maleate to produce **3c** and **4c**, respectively (maleic anhydride also reacts).

The accessibility of isobenzofurans as reactive intermediates has important synthetic consequences. Thus substituted naphthols can be formed by acid-catalyzed ring opening[5] of **3** and the reaction **3a** to **8** was effected here. Again, substituted naphthalenes[5,6] can be obtained by ring opening of compounds such as **4**, which, in turn, are prepared from **2** and dimethyl maleate (*e.g.*, **4c**) or by hydrogenation of **3** (*e.g.*, **3a** and **3b**). The ring openings are sensitive to the substituent groups present. While **4b** was transformed smoothly to **7b**, **4c** resisted conversion to the corresponding naphthalene perhaps because of the steric crowding which would arise in the product from the coplanarity of the substituent groups, the peri interactions being exaggerated by the buttressing effects of the carbomethoxy groups. On the other hand, **4a** was converted to a mixture containing **7a** as the major product and **9** as the minor product. Since **7a** and **9** are not in equilibrium, these products must arise by competitive eliminations. This suggests that the stereochemistry of **4** or the conformation of the intermediates are an important factor in this reaction.

In this regard, **4a** has the endo configuration since coupling is observed between the bridgehead hydrogen and the hydrogen α to the carbomethoxy group. It is suggested that **4b** and **4c** have the more stable exo configuration since attempts to isomerize these compounds have been unsuccessful.

The utilization of isobenzofuran[3,6b,7] as a reactive intermediate in syntheses has been reported elsewhere. These methods generally involve the initial preparation of Diels–Alder adducts which decompose photolytically or thermally to provide the desired intermediate. The approach described here has the advantage that the initial reagents are readily prepared and no coproduct is generated on forming the isobenzofuran.

Scheme I
Formation and Detection of the Isobenzofuran Derivatives



Experimental Section

Melting points are uncorrected. Spectra were recorded on Beckmann IR 10, Unicam SP-800, and Varian T-60 spectrometers. Nmr spectra were determined in $CDCl_3$ and are reported in ppm downfield from TMS as internal standard (δ scale). Infrared spectra were measured in KBr unless otherwise specified. Analyses were performed by MHW Laboratories, Garden City, Mich.

Benzalphthalan (**1**, R_2 = H) and 1-benzyl-1-hydroxyphthalan (**5a**) were prepared as described elsewhere.[2] The hydroxyphthalans **5b** and **5c** were not isolated because of their facile dehydration but were converted directly to the products **1** (R_2 = Ph) and **2c**, respectively.

Preparation of 1-Benzal-3-phenylphthalan 1 (R_2 = Ph). The Grignard reagent, prepared from 2.78 g (0.022 mol) of benzyl chloride and 0.61 g (0.025 g-atom) of magnesium in 50 ml of DEE, was added to 4.20 g (0.02 mol) of 3-phenylphthalide[8] in 50 ml of DEE. After 8 hr at 20° the mixture was hydrolyzed with aqueous NH_4Cl and the ether layer separated, dried, and evaporated. Normally, the diastereomeric alcohols[5b] were not purified but immediately dehydrated. In one instance, the material was purified by precipitation from benzene solution with hexane: nmr 3.40 and 3.47 (s, 2, $PhCH_2$), 5.72 and 6.25 (s, 1, PhCH), 7.0–7.6 (m, 14, aromatics).

Dehydration was effected by warming **5b** in benzene containing a catalytic quantity of *p*-toluenesulfonic acid (TsOH). Evaporation gave a quantitative yield of **1** (R_2 = Ph) which was sufficiently pure for subsequent use. The analytical sample was obtained by four recrystallizations from ether–pentane: mp 119° dec; nmr 6.04 (s, 1, *tert*-H), 6.58 (s, 1, vinyl H), 7–8 (m, 14, aromatic H); ir (KBr) 1650 (C=C), 1500, 810, 750, 690 (aromatic).

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.93; H, 5.63.

Preparation of 1-*tert*-Butyl-3-phenylisobenzofuran, 2c. The Grignard reagent, prepared from 2.8 g (0.03 mol) of *tert*-butyl chloride and 0.85 g (0.035 g-atom) of magnesium in 50 ml of DEE, was added to 4.20 g (0.02 mol) of 3-phenylphthalide[8] in 50 ml of DEE at 20°. After 12 hr, the mixture was hydrolyzed with aqueous NH_4Cl and the ether layer separated, dried, and concentrated.

The nmr spectrum of the product at this stage showed resonance peaks characteristic of the starting phthalide, the isobenzofuran **2c**, and a *tert*-butyl peak at 1.55 assigned to **5c**. The reaction product was dissolved in 100 ml of benzene, treated with 5 mg of TsOH, concentrated, and applied to a chromatographic column of 100 g of silica gel and elution carried out with benzene. The isobenzofuran eluted first and was readily located by its intense fluorescence under uv light (366 nm). Concentration of the eluate gave 2.2–2.6 g (44–52%) of **2c** as an oil: nmr 1.52 (s, 9, *tert*-Bu), 6.6–7.9 (m, 9, aromatic H);[9] ir (film) 2960 (aliphatic CH), 1600, 1500, 760, 740, 680, 660 (aromatic) cm^{-1}; uv (MeOH) λ (ϵ), 265 (6.5×10^3), 275 (6.4×10^3), 286 (5.8×10^3), 305 (3.8×10^3), 319 (4.9×10^3), 336 (5.3×10^3), 364 (10^4) nm.

Anal. Calcd for $C_{18}H_{18}O$: C, 86.35; H, 7.26. Found: C, 86.26; H, 7.16.

Diels–Alder Reactions. The Diels–Alder reactions were conducted in refluxing DEE containing a catalytic amount of acid with the isobenzofuran precursors (**1**, R_2 = H or Ph) or **2c** and an equivalent amount or excess of the dienophile. Washing the solution with aqueous $NaHCO_3$, evaporation, and recrystallization provided the products shown in Table I. In some cases, the product **4** in Table I were made by hydrogenation of **3**. Hydrogenation was effected in ethyl acetate using 5% Pd on charcoal as catalyst at 50 psi hydrogen pressure.

No change occurred in compounds **4b** and **4c** on refluxing in xylene for 12 hr.

Naphthalene Derivatives. The products **4** were converted to their corresponding naphthalene derivatives by refluxing in the presence of acid. The results are summarized in Table II.

Oxidation of 1-*tert*-Butyl-3-phenylisobenzofuran, 2c. Treatment of 4.26 g (0.017 mol) of **2c** with sodium dichromate in aqueous sulfuric acid gave 4.08 g of product. Distillation provided 1.95 g (43%) of **6**: bp 145–150° (0.3 mm); nmr 1.27 (s, 9), 7.2–8.0 (m, 9); ir (film) 1690 and 1660 (C = 0), 1270, 1600, 760, 700 (aromatics).

Table I
Diels-Alder Adducts and Related Compounds

Compd[a]	Yd, %	Mp, °C	Nmr, [ir]
3a	70	141–142.5	3.99 (s) and 4.02 (s) (total 6) overlaps 3.85 and 4.25 (ABq, J = 17 Hz, 2), 6.02 (s, 1) 7.0–7.6 (m, 9) [1720 (broad, C=O), 1620 (C=C), 1300 (C–O), 1500, 760, 750, 700 (aromatics)]
3b	49[b]	140–141.5	3.62 (s, 3), 3.67 (s, 3), 3.78 and 4.13 (ABq, J = 16 Hz), 7.0–7.9 (m, 14) [1720 (C=O), 1250 (C–O), 1630, 1500, 740, 700 (aromatics)]
3c	80	128–129	1.32 (s, 9), 3.56 (s, 3), 3.76 (s, 3), 7.0–8.0 (m, 9) [1730 (C=O), 1250 (C–O), 1620 (C=C), 750 and 700 (aromatics)]
4a	93[d]	110–111	3.39 (s), 3.44 (s), overlapping 3.1–3.9 (m) (total 10), 4.91 (d, J = 5 Hz, 1), 7.2–7.6 (m, 9) [1750 and 1730 (C=O), 1150 and 1210 (broad, C–O), 1500, 760, 730, 700 (aromatics)]
4b	94[d]	125.5–127 (90–92)[g]	3.47 (s, 3), 3.53 (s, 3), overlapping ABq, 3.48 and 3.77 (J = 12 Hz, and broad s), 3.77 (4) 7.2–7.9 (m, 12). [1740 (C=O), 1200 (broad, C–O), 1500, 750, 690 (aromatics)]
4c	95[d] 92[c] 75[e]	151–152	1.32 (s, 9), 3.50 (s, 6), 3.98 (s, 2), 7.2–7.8 (m, 9) [1750 and 1735 (C=O), 1200 (broad, C–O), 760, 700 (aromatics)]
f	83	147.5–148	1.39 (s, 9), 4.18 (s, 2), 6.9–8.1 (m, 9)

[a] Satisfactory analytical data were reported for all new compounds listed here. [b] Based on phenylphthalide. [c] Diels-Alder reaction using dimethyl maleate. [d] Hydrogenation of corresponding 3. [e] Reduction of 4c by zinc in refluxing concentrated HCl. [f] Diels-Alder adduct with maleic anhydride. [g] Mp obtained from EtOH–H_2O; mixture mp not depressed.

Table II
Preparation of Naphthalene Derivatives

Compd[a]	Conditions	Yd, %	Mp, °C	Nmr [ir]
7a	C_6H_6/TsOH	70[b]	101.5–102.5	3.92 (s) and 3.95 (s) (total 6), 4.50 (s, 2), 7.23 (s, 5), 7.2–8.2 (m, 4), 8.53 (s, 1, peri H) [1720 (broad, C=O), 1440, 1280, 1200, 1130, 780, 730, 700, 680]
7b	MeOH/HCl	93	157–158	3.52 (s, 3), 3.85 (s, 3), 4.68 (s, 2), 7.2–8.4 (m, 14)
7c	Xylene/TsOH	No reaction		
9	See 7a		139–140	3.65 (s, 3), 3.80 (s, 3), 5.21 (s, 1), 7.13 (s, 1), 7.3–7.9 (m, 5) [1730 and 1710 (C=O), 1200 (broad, C–O), 750 and 700 (aromatics)]

[a] Satisfactory analytical data were reported for all new compounds listed here. [b] Isolated; reaction mixture contains ~80% 7a and ~20% 9 by nmr. Both 7a and 9 are unchanged in refluxing C_6H_6/TsOH.

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.20; H, 6.86.

Preparation of 8. The Diels–Alder adduct **3a** (1.0 g, 0.0029 mol) was refluxed in a mixture of 25 ml of methanol and 10 ml of concentrated hydrochloric acid. The reaction product was isolated by ether extraction and purified by chromatography on silica gel. The initial fraction, 0.69 g (69%), was **8**, mp 113.5–115.5°. Recrystallization from ethanol–water gave the analytical sample: mp 115–116°; nmr 3.82 (s, 3), 3.93 (s, 3), 4.30 (s, 2), 7.13 (s, 5), 7.4–8.6 (m, 4), 12.45 (s, 1); ir 3450 (broad, OH), 1740 (C = 0), 1660 (C = 0), 810, 760, 710 (aromatics).

Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.22; H, 5.22.

Registry No.—1 (R_2 = Ph), 52540-37-1; **2c**, 52540-38-2; **3a**, 52540-39-3; **3b**, 52540-08-6; **3c**, 52540-09-7; **4a**, 52540-40-6; **4b**, 52540-10-0; **4c**, 52540-11-1; *cis*-**5b**, 52540-12-2; *trans*-**5b**, 52540-13-3; **5c**, 52540-14-4; **6**, 52540-15-5; **7a**, 52540-41-7; **7b**, 52540-16-6;

7c, 52540-17-7; 8, 52540-18-8; 9, 52540-42-8; 3-phenylphthalide, 5398-11-8.

References and Notes

(1) Two days at 20° suffices to destroy 1a. The stability of 3,3-dimethyl-1-benzalphthalan suggests that hydrolysis of the enol structure is not an adequate explanation of the reactivity of 1a.
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(9) The chemical shifts reported for isobenzofuran[3b,c] imply the presence of a strong diamagnetic ring current. The data reported here for 2c are consistent with these earlier reports. However, the nmr spectrum of the compound reputed to be 2,5-di-*tert*-butylisobenzofuran[10] (1.16 (*tert*-Bu), 5.60–5.11 (aromatic H)), is sufficiently different as to render the structural assignment doubtful.
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The Synthesis of 2-Substituted Derivatives of 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide. Ring Opening Reactions of 2-Azapurine Nucleosides

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Received July 18, 1974

The reaction of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**1a**) with *N*-bromoacetamide gave the corresponding 2-bromo nucleoside (**3**). The latter compound was ring closed with nitrous acid to afford 6-bromo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**5**). The bromine of **5** was displaced by various nucleophiles to give 6-substituted imidazo[4,5-*d*]-*v*-triazine nucleosides such as 6-azido-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazine-(3*H*)4-one (**6**), 6-methoxy-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**9**), 7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazine-4,6-dione (**11**), and 6-thio-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**12**). Compound **6** in the presence of hydrogen and Pd/C was reduced to corresponding 6-amino-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**7**). Compounds **7** and **9** under the influence of hydrogen and Raney Ni were ring opened to give previously unreported 2,5-diamino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**8**) and 5-amino-2-methoxy-1-β-D-ribofuranosylimidazole-4-carboxamide (**10**), respectively.

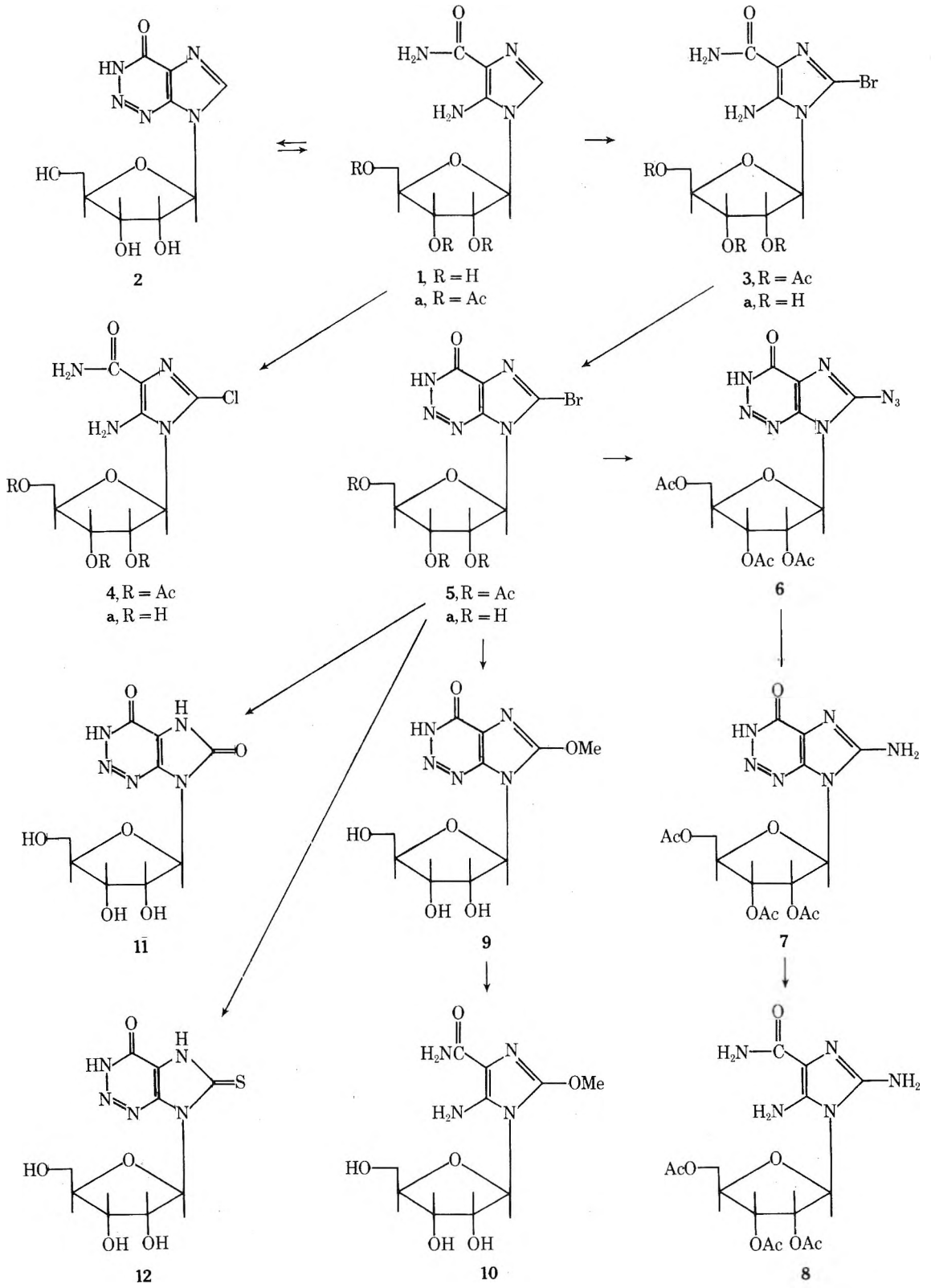
During the past few years, based on the original work of Buchanan and his colleagues,[1] there have been series of significant papers by Shaw and coworkers[2,3] on the synthesis of imidazole nucleosides related to the key intermediates in the *de novo* purine biosynthetic pathway. Relatively few studies have been made on the chemical modifications of these intermediates due to their difficult accessibility.[4] 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA riboside) (**1**) is of special interest due to its central role[1] and recent commercial availability.[5]

Several of the procedures described in the literature, for the synthesis of AICA riboside[6,7] and its derivatives[8–10] include the ring opening of purine nucleosides. Ikehara and Muneyama[11] reported the formation of a 2-methylsulfonyl AICA riboside derivative by the cleavage of the pyrimidine ring of 8-methylsulfonylguanosine with sodium *tert*-butoxide but the precise structure of the product was never determined. Thus, 2-substituted derivatives of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide are until now unknown. In the present work we describe a novel and convenient route for the synthesis of certain 2-substituted AICA riboside derivatives by (1) direct electrophilic substitution and (2) by the ring opening of substituted 2-azapurine nucleosides.

Direct attempts to brominate 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (**1**) in various solvents were discouraging, and resulted mainly in unidentified oxidation products. However, when 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide[12] (**1a**) was treated with *N*-bromoacetamide in anhydrous tetrahydrafuran at −10°, crystalline 5-amino-2-bromo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**3**) was obtained in 70% yield. Subsequent deacetylation with a catalytic amount of sodium methoxide in methanol afforded the nucleoside, 5-amino-2-bromo-1-β-D-ribofuranosylimidazole-4-carboxamide (**3a**). In a similar experiment, using *N*-chlorosuccinimide as the halogenating agent, the corresponding 5-amino-2-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**4**) and 5-amino-2-chloro-1-β-D-ribofuranosylimidazole-4-carboxamide (**4a**) were prepared.

As expected, the direct displacement of bromine atom from **3** or **3a** by various nucleophiles was unsuccessful, *e.g.*, several hours reflux of **3** with excess 2 *M* methanolic sodium methoxide showed the presence of **3a** as the only reaction product. The ease by which the bromine would be displaced in such a molecule would depend upon lowering the electron density at the C-2 position. An earlier report from this laboratory[13] described the ring annulation of AICA riboside (**1**) *via* diazotization to give 7-(β-D-ribofuranosyl)imidazo-[4,5-*d*]-*v*-triazin-4-one (**2**, 2-azainosine). We subsequently discovered that 2-azainosine could readily be ring opened and reconverted into AICA riboside by hydrogenation in the presence of Raney Ni. In a similar experiment, when Raney Ni was replaced by Pd/C (10%) the starting material was recovered unchanged. Thus it was expected that 2-bromo-AICA riboside (**3a**) could be first converted to 6-bromo-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-4-one (**5a**) which renders the bromine susceptible to nucleophilic attack. Subsequent hydrogenolysis in the presence of Raney Ni should provide the required 2-substituted derivative of AICA riboside.

Scheme I



Indeed, treatment of **3a** with nitrous acid at −25° in 6 *N* hydrochloric acid afforded **5a** in 50–60% yield. In order to simplify the isolation of the nucleoside, the protected nucleoside **3** was similarly ring closed to 6-bromo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**5**). The product **5** was isolated by extraction and purified by column chromatography. Subsequent treatment of **5** with methanolic ammonia left the bromine at the C-6 position still intact and afforded the corresponding deacetylated product, 6-bromo-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (5a) in 85% yield.

Treatment of **5** with sodium azide in Me_2SO furnished the corresponding 6-azido-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**6**). The catalytic hydrogenation studies of this molecule are of special interest. The Pd/C catalyzed hydrogenation of **6** selectively reduced the azido function to give 6-amino-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-

one (7) showing the stability of the υ-triazine ring under these conditions. In contrast, during hydrogenolysis of 7 in the presence of Raney Ni as the catalyst the υ-triazine was ring opened to give 2,5-diamino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (8). Treatment of **5** with excess methanolic sodium methoxide furnished 6-methoxy-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-υ-triazin-(3*H*)4-one (**9**). In this reaction introduction of the methoxyl and the removal of the acetyl groups were accomplished simultaneously. Catalytic hydrogenolysis of **9** in the presence of Raney Ni afforded 5-amino-2-methoxy-β-D-ribofuranosylimidazole-4-carboxamide (**10**).

The replacement of the bromine atom at C-6 of **5a** by two other nucleophiles further illustrates the versatility of this intermediate. When 6-bromo-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-υ-triazin-(3*H*)4-one was treated with aqueous sodium hydroxide it gave the desired 7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-υ-triazine-4,6-dione (**11**). In a similar experiment when sodium hydroxide was replaced by sodium hydrosulfide the corresponding 6-thio-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-υ-triazin-4-one (**12**) was obtained. In these experiments the base-catalyzed deacetylation was achieved *in situ*.

Experimental Section

The ir spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer (KBr). Nmr spectra were determined on a Hitachi Perkin-Elmer Model R-20A spectrometer using DSS as an internal standard. Where indicated by elemental analyses, hydration was confirmed by nmr spectroscopy in absolute Me_2SO-d_6 by exchange with D_2O and reintegration. Melting points were obtained on a Thomas Hoover apparatus and are uncorrected. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo. The uv spectra were recorded on a Cary 15 ultraviolet spectrometer. Baker analyzed silica gel powder (60–200 mesh) was used for column chromatography. The homogeneity of the compounds was checked by thin-layer chromatography using precoated (250 μ) ICN (Life Science Group) Woelm tlc plates (silica gel F-254). Short-wave ultraviolet light (mineralight UVS 11) was used to detect the spots. A Parr apparatus was used for hydrogenation reactions.

5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide (1). Ring Opening of 2-Azainosine. To a solution of 2-azainosine (54 mg, 0.2 mmol) in water (12 ml) was added Raney Ni (wet, 180 mg) and the mixture was hydrogenated at 44 psi for 22 hr. The catalyst was removed by filtration through a Celite pad and washed with water. The filtrate and washings were concentrated to dryness. The residue was crystallized from ethanol–water to give 28 mg (54%) of **1** as colorless needles, mp 211–212° (lit.[14] 213–214°). An authentic sample[5] and the product had the same mixture melting point (211–212°) and their uv and ir were identical in all respects.

5-Amino-2-bromo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (3). 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**1a**) (3.84 g, 10 mmol) was dissolved in dry tetrahydrofuran (THF) and treated with a solution of *N*-bromoacetamide (1.41 g, 11 mmol) (in 50 ml of dry THF) at −10°. After 30 min at −10° the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (50 ml), extracted with H_2O (4 × 100 ml), dried (Na_2SO_4), evaporated to dryness, and recrystallized from aqueous EtOH to yield 3.32 g (70%): mp 169–170°; nmr (Me_2SO-d_6) δ 6.93 (s, 2, NH_2), 5.91 (s, 2, NH_2), 4.39 (br s, 3, H-4′, H-5′); λ_{max} (MeOH) 271 mμ.

Anal. Calcd for $C_{15}H_{19}N_4O_8Br$: C, 38.89; H, 4.13; N, 12.09. Found: C, 38.89; H, 4.15; N, 12.01.

5-Amino-2-bromo-1-β-D-ribofuranosylimidazole-4-carboxamide (3a). Compound **3** (463 mg, 1 mmol) was dissolved in freshly prepared 0.01 *M* methanolic sodium methoxide. After 10-min reflux it was kept at room temperature for 2 hr and then treated with excess Amberlite IRC 50 (in H^+ form). The resin was removed by filtration and the solution was evaporated to dryness. The residue was crystallized from EtOH to yield 205 mg (61%): mp 159–161°; nmr (Me_2SO-d_6–D_2O) δ 5.69 (d, 1, $J_{1',2'}$ = 6.5 Hz, H-1′); $\lambda_{max}^{pH\ 1}$ 272 mμ (ε 19,900); $\lambda_{max}^{pH\ 11}$ 272 (19,900).

Anal. Calcd for $C_9H_{13}N_4O_5Br \cdot 0.5C_2H_5OH$: C, 33.31; H, 4.48; N, 15.25. Found: C, 33.30; H, 4.44; N, 15.09.

5-Amino-2-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (4). A solution of **1a** (1.92 g, 5 mmol) in dry THF (30 ml) at −15° was treated with *N*-chlorosuccinimide (0.75 g, 5.5 mmol). After 2 hr at room temperature the solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of EtOAc–$CHCl_3$ (4:1, 10 ml) and kept at −20° for 16 hr. Colorless crystals of succinimide deposited and were removed by filtration. The filtrate was evaporated to dryness and the residue recrystallized from boiling H_2O to yield 2.01 g (81%) of desired product: mp 189–190°; nmr (Me_2SO-d_6) δ 5.90 (d, 1, $J_{1',2'}$ = 6 Hz, H-1′), 4.35 (br s, 3, H-4′, H-5′); λ_{max} (MeOH)271 mμ.

Anal. Calcd for $C_{15}H_{19}N_4O_8Cl$: C, 42.98; H, 4.54; N, 13.74. Found: C, 42.81; H, 4.66; N, 13.52.

5-Amino-2-chloro-1-β-D-ribofuranosulimidazole-4-carboxamide (4a). Compound **4** (255 mg, 0.5 mmol) was deacetylated by refluxing it with a freshly prepared 0.01 *M* solution of methanolic sodium methoxide (10 ml) for 10 min. After 2 hr at room temperature it was treated with excess Amberlite IRC 50 (H^+ form), the resin was removed by filtration, and the solvent evaporated slowly *in vacuo* to a small volume (~1 ml). After the mixture had cooled to room temperature crystalline material deposited which was recrystallized from aqueous MeOH to yield 124 mg (84%): mp 175–176°; nmr (Me_2SO-d_6) δ 6.83 (s, NH_2), 6.37 (s, NH_2), 5.66 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1′), $\lambda_{max}^{pH\ 1}$ 272 mμ (ε 17,700); $\lambda_{max}^{pH\ 11}$ 272 (17,7000).

Anal. Calcd for $C_9H_{13}N_4O_5Cl \cdot H_2O$: C, 35.00; H, 4.85; N, 18.00. Found: C, 35.02; H, 4.89; N, 18.15.

6-Bromo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-υ-triazin-(3*H*)4-one (5). Compound **3** (4.63 g, 10 mmol) was dissolved in cold (−25°) 6 *N* HCl (50 ml). A saturated aqueous solution of $NaNO_2$ (2.1 g, 30 mmol) was added dropwise to the rapidly stirred solution over a period of ~30 min. After an additional 30 min stirring the pH of the reaction mixture was adjusted to 4.5 with concentrated NH_4OH. Up to this point the temperature was carefully kept between −22 and −25°. The product was extracted with EtOAc (4 × 100 ml) and the combined EtOAc fractions were dried (Na_2SO_4) and evaporated to dryness. The resulting light tan foam was applied to a column of silica gel (3 × 30 cm) packed in $CHCl_3$. The product was eluted with $CHCl_3$–EtOAc (8:6). The fractions containing the major product were combined and evaporated to dryness to yield amorphous, slightly yellowish material, 3.16 g (64%): nmr (Me_2SO-d_6) δ 15.66 (s, 1, 3-NH); λ_{max} (MeOH) 298 mμ.

Anal. Calcd for $C_{15}H_{16}N_5O_8Br$: C, 37.99; H, 3.40; N, 14.76. Found: C, 38.06; H, 3.33; N, 14.58.

6-Bromo-7-β-D-ribofuranosylimidazo[4,5-*d*]-υ-triazin-(3*H*)4-one (5a). Compound **5** (2.84 g, 6 mmol) was added to saturated (0°) methanolic ammonia (200 ml). It was kept at 25° for 16 hr, then evaporated to dryness. The residue was dissolved in H_2O (20 ml) and extracted with EtOAc (4 × 50 ml). The pH of the aqueous solution was adjusted with Dowex 50 (H^+ form) to 4, the resin was removed by filtration, and the solvent evaporated *in vacuo*. The product was recrystallized from boiling EtOH to yield 1.95 g (85%): mp 94–95°; nmr (D_2O) δ 6.16 (d, 1, $J_{1',2'}$ = 5.0 Hz, H-1′); $\lambda_{max}^{pH\ 1}$ 293 mμ (ε 7300); $\lambda_{max}^{pH\ 11}$ 298 (9350).

Anal. Calcd for $C_9H_{10}N_5O_5Br \cdot (C_2H_5OH)$: C, 33.21; H, 4.07; N, 17.74. Found: C, 33.30; H, 4.11; N, 17.57.

6-Azido-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-υ-triazin-(3*H*)4-one (6). Compound **5** (4.74 g, 10 mmol), NaN_3 (1.95 g, 30 mmol), and Me_2SO (20 ml) were stirred at room temperature for 3 days, in the dark. H_2O (200 ml) was added and then the solvent was removed by azeotropic vacuum distillation. The dark residue was dissolved in $CHCl_3$ (20 ml) and applied to a column of silica gel, Baker (4 × 50 cm), packed in $CHCl_3$. The desired product was eluted with $CHCl_3$–EtOAc (7:3). The uv-absorbing fractions were combined and evaporated to dryness to yield an amorphous solid, 1.62 g (37%): ir 2150 cm^{-1} (N_3); $\lambda_{max}^{pH\ 1}$ 308 mμ (ε 9000) and 264 (sh) (7200); $\lambda_{max}^{pH\ 11}$ 307 (9900) and 265 (sh) (6530).

Anal. Calcd for $C_{15}H_{16}N_8O_8$: C, 41.28; H, 3.89; N, 25.61. Found: C, 41.33; H, 4.07; N, 25.40.

6-Amino-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-υ-triazin-(3*H*)4-one (7). Compound **6** (0.436 g, 1 mmol) was dissolved in 96% EtOH (20 ml). Pd/C (10%, 100 mg) was added and the mixture hydrogenated at 25° and 1 atm of pressure. After 45 min the catalyst was removed by filtration and the filtrate evaporated to dryness. A crystalline product was obtained by recrystallization from EtOH to yield 244 mg (60%): mp 173–176°; nmr (Me_2SO-d_6) δ 7.47 (s, 2, 6-NH_2); $\lambda_{max}^{pH\ 1}$ 323 mμ (ε 8200); $\lambda_{max}^{pH\ 11}$ 310 (10,050).

Anal. Calcd for $C_{15}H_{18}N_6O_8$: C, 43.88; H, 4.38; N, 20.47. Found: C, 44.01; H, 4.29; N, 20.21.

2,5-Diamino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (8). Raney Ni (500 mg) was added to a solution of 7 (80 mg) in 50% aqueous ethanol. The mixture was shaken under 40 psi of H_2 for 1 hr at 70°. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The material was purified by preparative thin-layer chromatography (20 cm × 20 cm × 2 mm silica gel plate) using an ethyl acetate–methylene chloride–methanol (6:3:1) system. Compound **8** was obtained as hygroscopic amorphous solid: 32 mg (40%); nmr (Me_2SO-d_6) δ 7.28 (s, 2, 2-NH_2); (Me_2SO-d_6–D_2O) δ 5.94 (s, 1, $J_{1',2'}$ = 6 Hz, H-1'); $\lambda_{max}^{pH\ 1}$ 276 mμ (ε 9700); $\lambda_{max}^{pH\ 11}$ 284 (12,600).

Anal. Calcd for $C_{15}H_{21}N_5O_8$: C, 45.11; H, 5.30; N, 17.54. Found: C, 45.02; H, 5.46; N, 17.38.

6-Methoxy-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (9). Compound **5** (142 mg, 0.3 mmol) was refluxed with freshly prepared 0.35 *M* methanolic sodium methoxide (6 ml) for 2 hr. After 16 hr at room temperature it was treated with Dowex 50 (H^+ form) to remove the sodium, filtered, and evaporated to dryness to yield an amorphous product, 78 mg (62%): mp 114–116°; nmr (Me_2SO-d_6) δ 5.87 (d, 1, $J_{1',2'}$ = 6 Hz, H-1'), 4.22 (s, 3, OCH_3); $\lambda_{max}^{pH\ 1}$ 306 mμ (ε 10,500); $\lambda_{max}^{pH\ 11}$ 299 (12,200).

Anal. Calcd for $C_{10}H_{13}N_5O_6$: C, 40.07; H, 4.34; N, 23.33. Found: C, 40.16; H, 4.19; N, 23.11.

5-Amino-2-methoxy-1-β-D-ribofuranosylimidazole-4-carboxamide (10). Raney Ni (500 mg) was added to a solution of **9** (299 mg, 1 mmol) in H_2O (10 ml). It was hydrogenated at 30 psi and 25° for 40 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was triturated with EtOH, giving a crystalline product which was recrystallized from EtOH–H_2O giving 171 mg (59%) of **10**: mp 182–184°; nmr (D_2O) δ 5.66 (d, 1, $J_{1',2'}$ = 6 Hz, H-1'), 4.00 (s, 3, OCH_3); $\lambda_{max}^{pH\ 1}$ 272 mμ (ε 11,800); $\lambda_{max}^{pH\ 11}$ 281 (14,400).

Anal. Calcd for $C_{10}H_{16}N_4O_6$: C, 41.66; H, 5.59; N, 19.44. Found: C, 41.42; H, 5.79; N, 19.25.

7-β-D-Ribofuranosylimidazo[4,5-*d*]-*v*-triazine-4,6-dione (11). Compound **5a** (174 mg, 0.5 mmol) was treated with 6 ml of 3% NaOH for 16 hr at 4°, then passed through a column (1 × 15 cm) of Amberlite IRC 50 ([H^+], 100–200 mesh). The column was washed with H_2O (30 ml) and the combined eluates were evaporated to a small volume (1 ml) *in vacuo* and then applied to a column (2 × 30 cm) of microcrystalline cellulose (Avicel). The product was eluted with H_2O. A colorless, amorphous solid, 98 mg (67%), was obtained by lyophilizing the fractions containing the product: nmr (Me_2SO-d_6) δ 5.95 (d, 1, $J_{1',2'}$ = 5 Hz, H-1'); $\lambda_{max}^{pH\ 1}$ 297 mμ (ε 3560); $\lambda_{max}^{pH\ 11}$ 305 (5700).

Anal. Calcd for $C_9H_{11}N_5O_6$: C, 37.92; H, 3.86; N, 24.56. Found: C, 38.10; H, 3.77; N, 24.33.

6-Thio-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (12). Compound **5a** (348 mg, 1 mmol) was added to a freshly prepared 2 *M* aqueous solution of NaSH (5 ml), stirred at 4° for 16 hr, and then diluted with H_2O (5 ml) and MeOH (15 ml). The pH of the solution was brought to 4 with Dowex 50 (H^+ form), the resin was removed by filtration, and the filtrate was evaporated to dryness. The product was recrystallized from aqueous EtOH to yield 261 mg (75%): mp 228–231°; nmr (Me_2SO-d_6) δ 5.90 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1'); $\lambda_{max}^{pH\ 1}$ 283 mμ (ε 9600), 341 (3600); $\lambda_{max}^{pH\ 11}$ 334 (7500).

Anal. Calcd for $C_9H_{11}N_5O_5S \cdot H_2O$: C, 33.83; H, 4.08; N, 21.95. Found: C, 33.91; H, 4.08; N, 21.98.

Registry No.—**1**, 2627-69-2; **1a**, 23274-21-7; **2**, 36519-16-1; **3**, 52906-34-0; **3a**, 52906-35-1; **4**, 52906-36-2; **4a**, 52906-37-3; **5**, 52906-38-4; **5a**, 52906-39-5; **6**, 52906-40-8; **7**, 52906-41-9; **8**, 52906-42-0; **9**, 52951-30-1; **10**, 52906-43-1; **11**, 52906-44-2; **12**, 52906-45-3.

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A General Synthesis of N-Glycosides. I.[1] Synthesis of Pyrimidine Nucleosides

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Received March 29, 1974

Reaction of silylated hydroxy-, amino-, and mercaptopyrimidines as well as 6-azapyrimidines (1,2,4-triazines) with protected 1-*O*-acetyl as well as 1-*O*-methyl sugars in the presence of Friedel–Crafts catalysts gave the corresponding pyrimidine nucleosides, generally in excellent yields. The scope and limitations of this new synthetic procedure are discussed.

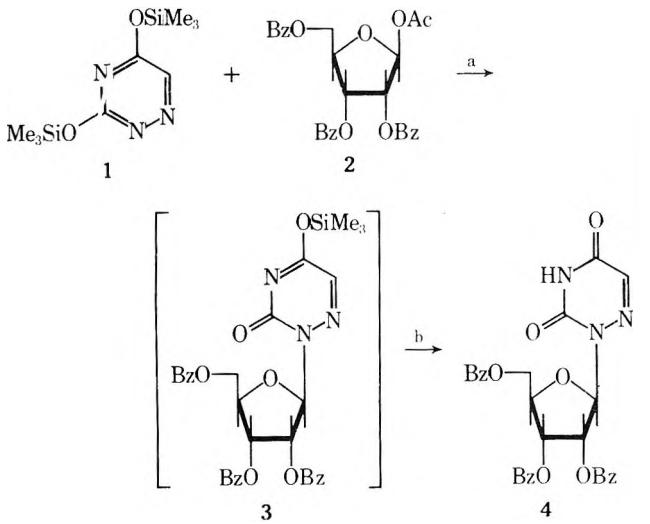
Because we wanted to prepare larger quantities of 6-azauridine, we investigated and compared the known methods for the preparation of pyrimidine nucleosides,[2] especially the silyl Hilbert–Johnson reaction.[3–8] After early synthetic studies by different groups,[9] Cristescu[10] and Wittenburg[11] had prepared 6-azauridine 2′,3′,5′-tri-*O*-benzoate in 60% yield by the benzenemercuric salt modification of the silyl Hilbert–Johnson reaction. Using this procedure we obtained varying yields of a rather impure substance which had to be purified by column chromatography. However the resulting crystalline product was still contaminated by mercuric compounds.

Since the Hilbert–Johnson reaction involves an attack of a sugar cation on the aromatic pyrimidine ring, we carried out the reaction in the presence of Friedel–Crafts catalysts, which are known[12] to convert acylated 1-acyloxy sugars into their corresponding acylated glycosyl halides.

Friedel–Crafts catalysts have been used by Baker[13] and later by Furukawa and Honjo[14] for the synthesis of purine nucleosides, but, strangely enough, the more obvious use of

Friedel–Crafts catalysts in the Hilbert–Johnson reaction had never been critically investigated.[7]

The reaction of 2,4-bis(trimethylsilyloxy)-6-azauracil (**1**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) and $SnCl_4$ in 1,2-dichloroethane gave even on a 10-kg scale, after hydrolysis of the reactive intermediate **3**, 93% recrystallized 6-azauridine 2′,3′,5′-tri-*O*-benzoate (**4**).

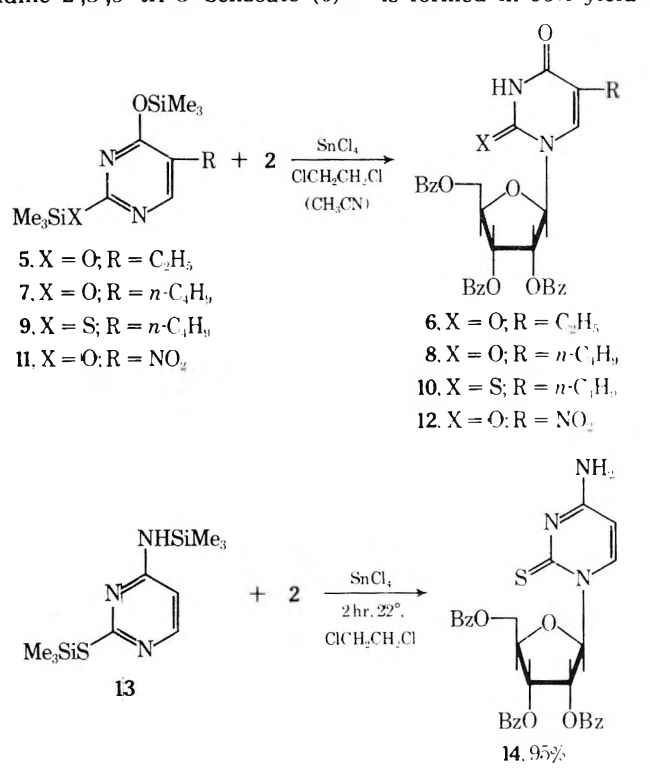


a. $SnCl_4/ClCH_2CH_2Cl$, 4 hr, 22°
b. $H_2O/NaHCO_3$

Investigation of the scope of this reaction showed that silylated uracils and cytosines as well as their silylated 2-thio[8] and 6-aza analogs react as readily as **1** with acylated sugars to form the corresponding acylated nucleosides in excellent yields.

In this reaction all silylated uracils give intermediates like **3** with a reactive 4-trimethylsilyloxy group[5] which can either be hydrolyzed to uridines or be converted by excess ammonia or primary and secondary amines into their corresponding cytidines.[15]

The following examples are typical for the Friedel–Crafts-catalyzed silyl Hilbert–Johnson reaction. 5-Ethyluridine 2′,3′,5′-tri-*O*-benzoate (**6**)[16a] is formed in 95% yield after 20 hr at 22° in 1,2-dichloroethane starting from silylated 5-ethyluracil (**5**). Silylated 5-*n*-butyluracil (**7**) reacted very slowly with **2** in 1,2-dichloroethane, but gave 5-*n*-butyluridine 2′,3′,5′-tri-*O*-benzoate (**8**)[16] in 95% yield after addition of acetonitrile and an additional amount of $SnCl_4$. The corresponding silylated 5-*n*-butyl-2-thiouracil (**9**), however, afforded the 2-thio analog **10**[16b] after 5 hr in acetonitrile in 83% yield. Surprisingly the reaction of silylated 5-nitrouracil (**11**) was complete in 0.5 hr at 22° in 1,2-dichloroethane–acetonitrile to give 5-nitrouridine 2′,3′,5′-tri-*O*-benzoate (**12**) in 98% yield.



5. X = O; R = C_2H_5
7. X = O; R = *n*-C_4H_9
9. X = S; R = *n*-C_4H_9
11. X = O; R = NO_2

6. X = O; R = C_2H_5
8. X = O; R = *n*-C_4H_9
10. X = S; R = *n*-C_4H_9
12. X = O; R = NO_2

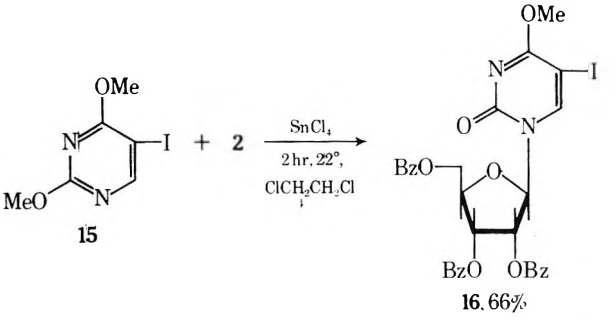
13

14, 95%

Persilylated 2-thiocytosine (**13**)[8] reacted with **2** to afford in 95% yield 2-thiocytidine 2′,3′,5′-tri-*O*-benzoate (**14**),[8,17] which gave with methanolic ammonia in excellent yield 2-thiocytidine, a rare nucleoside from t-RNA.[18]

These results indicate a complex relationship between the structure of the silylated bases and their rate of nucleoside formation in 1,2-dichloroethane and acetonitrile in the presence of $SnCl_4$ (compare also papers II and IV of this series).

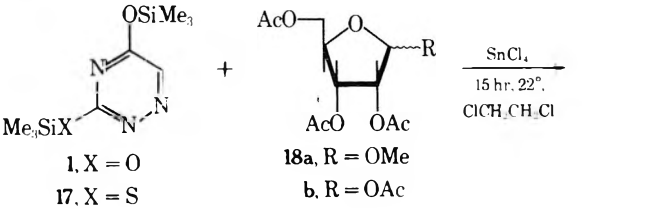
A "classical" Hilbert–Johnson reagent like 5-iodo-2,4-dimethoxypyrimidine (**15**) reacted, as expected, as the 2,4-bissilyl compound did with **2** in the presence of $SnCl_4$ to give 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-iodo-4-methoxy-1,2-dihydropyrimidin-2-one (**16**)[19] in 66% yield.



15

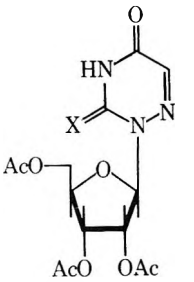
16, 66%

In the following examples we have investigated the influence of the sugar moiety on nucleoside formation in the presence of $SnCl_4$.



1, X = O
17, X = S

18a, R = OMe
b, R = OAc

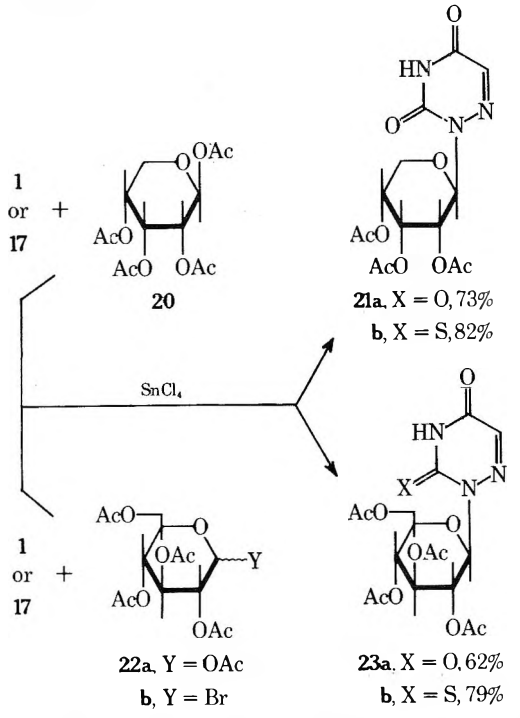


19a, X = S
b, X = O

Persilylated 2-thio-6-azauracil (**17**) reacted with syrupy, redistilled methyl 2,3,5-tri-*O*-acetyl-D-ribofuranoside (**18a**)[20] as well as with crystalline **18b**[20] to give an ~73% yield of recrystallized 2-thio-6-azauridine 2′,3′,5′-tri-*O*-acetate (**19a**). The direct conversion of **1** with **18a** or **18b** into the therapeutically important[21] 6-azauridine 2′,3′,5′-tri-*O*-acetate (**19b**) proceeds in high yields. However, crude **19b**

crystallizes poorly and very slowly even in the presence of only a small amount of impurities.

Reaction of the persilylated 6-azauracil (1) as well as the analogous 2-thio derivative (17) with 1,2,3,4-tetra-*O*-acetyl-β-D-ribopyranose (20) and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (22a) afforded the corresponding new ribopyranosides (21a and 21b) and glucopyranosides (23a and 23b) in 62–82% yields, which were saponified to the free nucleosides.



In our initial reactions with crude 20 and 22a in 1,2-dichloroethane heating to 50–60° was required to complete the reactions, but, when 1,2,3,4-tetra-*O*-acetyl-β-D-ribopyranose (20) and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (22a) were finely powdered and dried at 80° (0.001 mm) to remove traces of solvents, their reaction with 1 afforded 21a and 23a within 3 hr at 22°. The reaction of 1 with acetobromoglucose (22b) at 22° required 3 hr using 1,2-dichloroethane, but was complete in ~30 min in the more polar solvent acetonitrile (compare General Discussion).

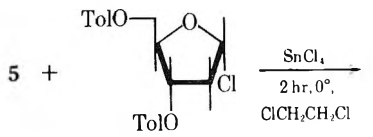
In the case of the preparation of the 2-thio analogs (21b and 23b), heating in 1,2-dichloroethane as well as acetonitrile for 3 hr at 50° or 2 hr at 80° was necessary to complete the reaction in a reasonable time.

Monitoring this reaction at 22° with tlc showed besides 23b the presence of additional products as possible intermediates which disappeared on heating the reaction mixture in either solvent with the formation of 23b. We are at present investigating the structure of these unknown products.

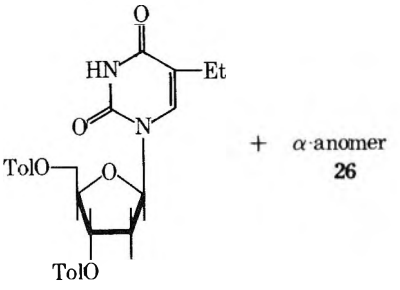
In all the examples discussed above and investigated only the β anomer of the N_1-nucleosides could be detected and isolated in the presence of a 2α-acyloxy substituent in the sugar moiety, but, as expected, in the case of acylated 2-deoxy-D-ribose as well as benzylated D-arabinose derivatives without a 2-participating group both anomeric nucleosides were formed.

Crude acylated methyl 2-deoxy-D-ribofuranoside gave with 5 a complex mixture of products[22] and was therefore converted into the commonly used crystalline 1α-chloro-2-deoxy-3,5-bis(*p*-toluoyl)-α-D-ribofuranosyl chloride (24).[23]

Reaction of the silylated pyrimidine (5) with 24 gave at 0° a 92% yield of the anomeric mixture of nucleosides from which 42% crystalline β anomer 25 could be readily separated by crystallization from the α anomer 26. In a number of experiments, we always found a nearly constant ratio of anomers α/β ≈1 which apparently could not be influenced by variation of the reaction conditions.[24]



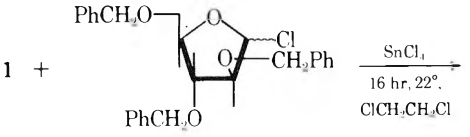
24



25

It should be emphasized here that the use of the 3,5-bis(*p*-toluoyl) sugar derivative (24) has proved quite superior to other acyl derivatives[25] in the preparation of 25 and analogs, because of the ease of separation of the β anomer during crystallization.

Reaction of persilylated 6-azauracil (1) with 2,3,5-tri-*O*-benzyl-D-arabinosyl chloride (27) gave a 74.3% overall yield of a nucleoside mixture from which the crystalline β anomer 28[26] was isolated in 42% yield.



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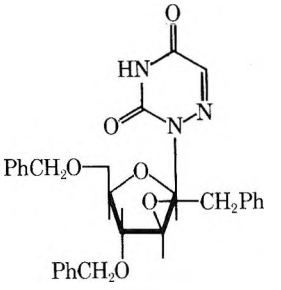


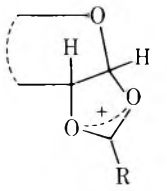
28, 42%

The β configuration of the acylated nucleosides 25 and 28 was clearly established by their nmr spectra. The $H_{1'}$ proton in 25 showed the expected triplet[27] at δ 6.31 ppm (J = 5.5 Hz) for the β anomer and the $H_{1'}$ proton in 28 the expected doublet[28] at δ 6.32 ppm (J = 6 Hz) for the cis coupling with the $H_{2\alpha'}$ proton.

The rapid reaction of 2-deoxy-3,5-bis(*p*-toluoyl)-α-D-ribofuranosyl chloride (24) with the silylated 5-ethyluracil (5) at 0° (compare formation of 6) posed the question which factors determine the rate of the nucleoside formation.

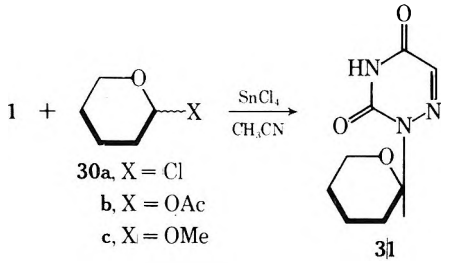
Since the reaction of silylated 6-azauracil (1) with D-glucopyranose pentaacetate (22a) as well as acetobromoglucose (22b) to give 23a proceeded at room temperature at roughly the same rate, the rather stable 1,2-α-acyloxonium salt (29)[29] formed from 2-α-acyloxy sugars seems not only to determine the exclusive formation of β anomers but consequently also to decrease the reactivity of these electrophiles.

To eliminate the influence of a 2-acyloxy group as well as of any residual substituents in the pyranose derivatives we



29

finally investigated the reaction of silylated 6-azauracil (**1**) with the tetrahydropyranyl derivatives **30** as the most simple model of such sugar pyranosides. The sensitive 2-chloro derivative **30a** as well as the more stable **30b** and **30c** gave the crystalline *dl*-pyranoside **31**[30] rapidly at 0° in yields of up to 92%.



30a, X = Cl
b, X = OAc
c, X = OMe

31

The reaction of **1** with dihydropyran in the presence of acetonitrile gave besides a 20% yield of **31** a number of additional products, which will be described in a separate publication.

In Table I the already discussed reaction of silylated 6-azauracil (**1**) with 1-*O*-acetyl-2,3,5-tribenzoyl-β-D-ribofuranose (**2**) to give 6-azauridine 2′,3′,5′-tri-*O*-benzoate (**4**) has been performed under a variety of conditions with different Friedel–Crafts catalysts and in different solvents. Most of these experiments were only done once and therefore some of the depicted yields can certainly be raised.

Table I
Variation of Reaction Conditions

Solvent	Catalyst	Amount[a]	Time, hr	*t*, °C	Yield in % Crude	Yield in % Crystalline
1,2-Dichloroethane	$SnCl_4$	0.720	4	20	97	93
Acetonitrile	$SnCl_4$	0.720	4	20	97	82.5
Dioxane	$SnCl_4$	0.720	4	101	77	72
Tetrahydrofuran	$SnCl_4$	0.720	3	65	98	75
Dimethylformamide	$SnCl_4$	0.720	4	153	77.5	68.5
Benzene	$SnCl_4$	0.720	6	80	80.5	66
Toluene	$SnCl_4$	0.720	6	111	86	66
Carbon disulfide	$SnCl_4$	0.720	4	46	87	67
Carbon tetrachloride	$SnCl_4$	0.720	4	77	93	73
1,2-Dichloroethane	$ZnCl_2$	1.440	5	84	100	83
1,2-Dichloroethane	$TiCl_4$	0.800	30	20	65	40
Chlorobenzene	$AlCl_3$	1.440	6	132	63	40
Tetrachloroethane	$FeCl_3$	1.456	5	146	44	25
Carbon disulfide	BF_3–Et_2O	1.390	6	46	70	60

[a] Mole of catalyst/mole of sugar component 2.

General Discussion

Although all Friedel–Crafts catalysts tried gave in most aprotic solvents generally good yields of 6-azauridine 2′,3′,5′-tri-*O*-benzoate (**4**), the combination 1,2-dichloroethane–$SnCl_4$ seems to be most simple and practical, since 1,2-dichloroethane is more easily purified and more stable than absolute methylene chloride or chloroform. Furthermore the use of 1,2-dichloroethane gives the opportunity to raise the reaction temperature to 83° if necessary. As catalyst, liquid $SnCl_4$ can be readily measured and administered. Fresh $SnCl_4$ can be used as such, older samples should be purified by distillation.

Besides 1,2-dichloroethane, acetonitrile as a solvent sometimes results in a more rapid reaction owing to its higher polarity and can give different products compared to 1,2-dichloroethane. In part II of this series, the reactions of silylated 6-methyluracils with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) and $SnCl_4$ are described to give strikingly varying ratios of N_1- and N_3-nucleosides when acetonitrile is used instead of 1,2-dichloroethane.

As yet no 1-acetylamino sugars could be detected as products formed by a Ritter reaction[31] between the 1-*O*-acyl sugars and acetonitrile in the presence of $SnCl_4$.

In view of the simpler purification of 1,2-dichloroethane and especially the simpler work-up after the reactions, 1,2-dichloroethane should be generally preferred to acetonitrile.

The amount of Friedel–Crafts catalysts depends on the components; *e.g.*, on using the sensitive and reactive 1-halo sugars ~0.25 equiv of catalyst is usually sufficient whereas with 1-*O*-methyl or 1-*O*-acetyl sugars 0.75 to 1.5 equiv of catalyst is necessary. If the silylated pyrimidine (or any other hydroxy N-heterocycle) has not been distilled *in vacuo*, hexamethyldisilazane (HMDS) or pyridine as a silylation solvent might still be present, which inactivate the catalyst.

The catalyst is furthermore inactivated by traces of solvents in the sugar moiety like ethanol, 2-propanol, or acetic acid (compare preparation of **21a** and **23a**). The hydrogen halide liberated by the reaction of alcohols and acetic acid with $SnCl_4$ can cleave the disaccharide linkage in reactions with peracylated cellubiose, lactose, and maltose or might lead to formation of N_3-nucleosides as well as $N_{1,3}$-bisglycosides (compare part III of this series). The liberated hydrogen halide can also destroy sensitive groups like azides. Therefore the solid acylated 1-*O*-alkyl or 1-*O*-acyl sugar derivatives should always be powdered and dried at ~50–80° (0.001 mm) or distilled under high vacuum as in the case of the liquid methyl 2,3,5-tri-*O*-acetyl-D-ribofuranoside (**18a**).

If a reaction monitored by tlc is not proceeding, either a further amount of catalyst should be added, the temperature raised, or both. Furthermore, if 1,2-dichloroethane is used as a solvent, addition of acetonitrile might accelerate the reaction as mentioned above and exemplified by the formation of **8**.

It is principally advisable to follow the reactions by tlc since the nucleoside formation can proceed rather rapidly; *e.g.*, in the case of silylated 2-mercaptopyrimidine (compare part IV of this series), a longer reaction time might lead to the destruction of already formed product.

A slight (5–10%) excess of the silylated pyrimidine is often advantageous to effect a complete conversion of the usually more precious sugar component and to simplify the reaction work-up, because the hydrolyzed pyrimidines can usually be much more easily removed than unreacted sugar derivatives.

Although normally nucleosides (N-glycosides) are formed in the presence of $SnCl_4$, O- or S-glycosides can also be isolated in certain cases (compare parts II and IV of this

series), which might be mistaken for nucleosides. Thus, when new types of silylated hydroxy or mercapto N-heterocycles are employed and doubts arise about the structure of the new products, a small scale experiment should be performed in refluxing 1,2-dichloroethane or acetonitrile–$SnCl_4$. Under these conditions the O- or S-glycosides are either rearranged[32] or decomposed, whereas the nucleosides are usually stable.

In the last years following our preliminary publication[1] a number of groups have applied successfully our standard reaction conditions (1-*O*-acetyl sugars, $SnCl_4$ or $TiCl_4$ in 1,2-dichloroethane or methylene chloride) to give acylated N_1-nucleosides in generally high yields.[16b,33-37]

It is interesting to note that Ohrui, Kuzuhara, and Emoto[33] observed that on using a very small amount of $SnCl_4$ the α-nucleoside was also formed.

Furthermore, Haynes[38] described the formation of the N_3-riboside in addition to the desired N_1-riboside by reaction of silylated uracil with 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-*O*-methyl-β-D-ribofuranose (compare part II of this series).

In paper IV of this series further applications of the Friedel–Crafts-catalyzed Hilbert–Johnson reaction to a variety of silylated hydroxy N-heterocycles are described and analogous applications by other groups reviewed.

Experimental Section

All melting points were taken on a Kofler melting point microscope and are uncorrected. The uv spectra were recorded on a Cary Model 14 spectrometer, the nmr spectra were determined on Varian A-60 and HR-100 instruments and the mass spectra on an Atlas CH4 instrument.

The thin layer chromatography was performed on Merck silica gel plates GF_{254}. For the protected nucleosides the following system was especially efficient: (A) toluene–acetic acid–H_2O (5:5:1).[8b,39]

The solvents were carefully purified: 1,2-dichloroethane was refluxed for 2 hr over P_2O_5 and distilled. Acetonitrile was refluxed for 2 hr over P_2O_5 and distilled, the procedure was repeated, and finally it was stored over 3 Å molecular sieves.

$SnCl_4$ (Riedel-deHaen) was usually redistilled at normal pressure. 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**), mp 131–132°, was prepared by a slightly modified procedure according to Recondo and Rinderknecht[40] in ~75% yield starting from D-ribose (Papierwerke Waldhof-Aschaffenburg AG). Methyl 2,3,5-tri-*O*-acetyl-D-ribofuranoside (**18a**) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**18b**), mp 82–83°, were prepared in ~95 and 50% yield according to Guthrie and Smith.[20] 1,2,3,4-Tetra-*O*-acetyl-β-D-ribopyranose (**20**), mp 110–112°, was obtained in ~70% yield according to Levene and Tipson[41] and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucose (**22a**), mp 131–132°, according to standard procedures. The crystalline peracetylated sugar derivatives were carefully powdered and dried at 70–80° (0.001 mm). Meanwhile methyl 2,3,5-tri-*O*-acetyl-D-ribofuranoside (**18a**) was distilled in a Kugelrohr apparatus at 140° (0.01 mm). Finally 1-α-chloro-2-deoxy-3,5-bis(*p*-toluoyl)-D-ribofuranose (**24**) was prepared according to Hoffer[23] and 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (**27**) according to Tejima, Glaudemans, and Fletcher.[42]

Silylation. The silylations of the corresponding uracils and cytosines were performed according to standard methods. Therefore only few silylations are described (compare the preparation of **1**). Since silylated 2-thiouracils and 2-thiocytosines are generally less stable,[8b] the distillation of these compounds should be done at the lowest temperature possible (high vacuum Kugelrohr distillation).

Work-Up. The work-up was usually performed as described for the preparation of **4**. For reactions in CH_3CN it is often advantageous to remove part of the CH_3CN *in vacuo* at 22° before dilution with 1,2-dichloroethane or methylene chloride.

3,5-Bis(trimethylsilyloxy)-1,2,4-triazine (1). 2,3,4,5-Tetrahydro-1,2,4-triazine-3,5-dione (5-azauracil)[43] (120.0 g, 1.06 mol) was suspended in hexamethyldisilazane (HMDS) (600 ml) (Dow Chemical Co.), trimethylchlorosilane (10 ml) was added, and the mixture was refluxed with exclusion of humidity. Ammonia was vigorously evolved and NH_4Cl deposited in the reflux condenser. After 2 hr the solid had dissolved and the excess HMDS was removed at ~50-mm pressure (collected for reuse after redistillation) at 90° and finally at 12-mm vacuum. The residue was distilled at 140° (0.1 mm) to give 264.4 g (97%) of **1**.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (4, 6-Azauridine Tribenzoate). To a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**, 378 g, 0.75 mol) in 1,2-dichloroethane (4.5 l) a solution of 3,5-bis(trimethylsilyloxy)-1,2,4-triazine (**1**, 204.0 g, 0.79 mol) in dichloroethane (500 ml) was added. The mixture was cooled with ice and redistilled $SnCl_4$ (63 ml, 0.54 mol) in 1,2-dichloroethane (300 ml) was added with vigorous stirring and exclusion of humidity. The yellow homogenous solution was kept for 4 hr at 22° when tlc (system A, R_f 0.5) indicated the completion of the reaction. After dilution with 1,2-dichloroethane (2.0 l.), the reaction mixture was shaken with saturated $NaHCO_3$ solution (3.0 l.) and the resulting emulsion filtered over a layer of sand–Celite. The filtering aid was carefully washed with 1,2-dichloroethane (1.0 l.); the organic phase was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The slightly yellowish crystalline residue (407.3 g) was recrystallized from acetone–ethanol to give 388.2 g (93%) of pure **4**, mp 192–194°), as colorless needles, $[\alpha]^{23}D$ −71° (*c* 0.5, $CHCl_3$).

The oily residue from the mother liquor contained mainly sugar derivatives and was discarded.

Anal. Calcd for $C_{29}H_{23}N_3O_9$: C, 62.47; H, 4.16; N, 7.54. Found: C, 62.53; H, 4.28; N, 7.55.

Methanolysis[44] gave the free nucleoside 2-[β-D-ribofuranosyl]-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (6-azauridine), mp 159–160° (lit.[9] 160°), which could be readily acetylated to the triacetate **13b**, mp 102–104° (lit.[45] 100–101°).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-ethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (6, 5-Ethyluridine Tribenzoate). To **2** (4.27 g, 8.47 mmol) in 1,2-dichloroethane (150 ml) 5-ethyl-2,4-bis(trimethylsilyloxy)pyrimidine (**5**) (3.0 g, 10.5 mmol) and $SnCl_4$ (0.71 ml, 6.0 mmol) in 1,2-dichloroethane (10 ml) were added. After 20 hr at 22° and work-up, crystallization gave 4.7 g (95%) of 6 as white prisms, mp 159–160° (lit.[16a] 154–155°), $[\alpha]^{23}D$ −96.7° (*c* 0.6, $CHCl_3$).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-butyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (8). To 5-butyl-2,4-bis(trimethylsilyloxy)pyrimidine (**7**, 22 mmol) and **2** (10.08 g, 20 mmol) in 1,2-dichloroethane (150 ml), $SnCl_4$ (1.66 ml, 14.2 mmol) in 1,2-dichloroethane (100 ml) was added. After 5 hr at 22° according to tlc only a trace of nucleoside had formed. Therefore $SnCl_4$ (2 ml, 17.1 mmol) in CH_3CN (150 ml) was added and the mixture kept for 66 hr at 22° over the weekend. After work-up crystallization (ethanol) gave 11.70 g (95.4%) of 8 with mp 157–158° (lit.[16a] 156.5–157.5°), $[\alpha]^{23}D$ −106° (*c* 1.08, $CHCl_3$).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-butyl-2-thio-1,2,3,4-tetrahydropyrimidin-4-one (10). To **2** (15.12 g, 30 mmol) in CH_3CN (200 ml) and 48 ml (30 mmol) of 5-butyl-2,4-*S,O*-bis(trimethylsilyl)pyrimidine (**9**) in CH_3CN, $SnCl_4$ (7 ml, 60 mmol) in CH_3CN (150 ml) was added. After 5 hr at 22° and work-up crystallization (ethanol) gave 15.80 g (83.7%) of **10** as white needles with mp 123–125° (lit.[16b] 122.5–124.5°), $[\alpha]^{24}D$ −88.2° (*c* 1.325, $CHCl_3$).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-nitro-1,2,3,4-tetrahydropyrimidin-2,4-dione (12, 5-Nitrouridine Tribenzoate). To **2** (2.52 g, 5 mmol) in 1,2-dichloroethane (50 ml) 5-nitro-2,4-bis(trimethylsilyloxy)pyrimidine (**11**, 7.6 mmol) in CH_3CN (10 ml) and $SnCl_4$ (0.50 ml, 4.28 mmol) in 1,2-dichloroethane (10 ml) were added. After 0.5 hr at 22° and work-up crystallization (ethanol) gave 2.94 g (97.8%) of **12**, mp 184–185° (lit.[2b] 183–184°), $[\alpha]^{23}D$ −128.8° (*c* 0.75, $CHCl_3$).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-amino-2-thio-1,2-dihydropyrimidine (14, 2-Thiocytidine Tribenzoate). To **2** (5.04 g, 10 mmol) in 1,2-dichloroethane (150 ml) a solution of 2,4-*S,N*-bis(trimethylsilyl)-2-thio-4-aminopyrimidine (**13**, 16.4 ml, 11 mmol) and $SnCl_4$ (1.68 ml, 14.4 mmol) in 1,2-dichloroethane (20 ml) was added. After 2 hr at 22° and work-up crystallization (methanol) gave 5.4 g (94.5%) of **14** as colorless crystals, mp 194–195° (lit.[17] 190–191°), $[\alpha]^{23}D$ −34.6° (*c* 1, $CHCl_3$).

For methanolysis of **14** to 2-thiocytidine compare **8b**.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-iodo-4-methoxy-1,2-dihydropyrimidin-2-one (16). To **2** (2.52 g, 5 mmol) in 1,2-dichlororethane (100 ml) 5-iodo-2,4-dimethoxypyrimidine (**15**, 1.66 g, 6.25 mmol) and $SnCl_4$ (0.84 ml, 7.2 mmol) in 1,2-dichloroethane (10 ml) were added. After 4 hr at 22° and work-up the crude **19** (3.34 g) crystallized (ethanol) to give 2.32 g (66.6%) of **16** as white needles with mp 186–187° (lit.[19] 186–187°), $[\alpha]^{23}D$ −107.7° (*c* 0.20, $CHCl_3$), nmr ($CDCl_3$) δ 6.50 (d, 1, J = 5 Hz, H_1').

Anal. Calcd for $C_{31}H_{25}IN_2O_9$ (696.46): C, 53.46; H, 3.62; N, 4.02; I, 18.22. Found: C, 53.44; H, 3.72; N, 4.03; I, 18.05.

2-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-3-thio-2,3,4,5-tetrahydro-1,2,4-triazin-5-one (19a, 2-Thio-6-azauridine Triacetate). To **18a** (7.8 g, 30 mmol) and 3,5-*S,O*-bis(trimethylsilyl)-1,2,4-triazine (**17**, 9.0 g, 33 mmol) in 1,2-dichloroethane (250 ml), $SnCl_4$ (3.7 ml, 31.2 mmol) in 1,2-dichloroethane (30 ml) was added. After 5 hr at 22° crystallization (benzene) and recrystallization (ether) gave 8.43 g (72.5%) long needles of **19a**, mp 101–104°, $[\alpha]^{23}D$ −44.8° (c 1, $CHCl_3$), nmr ($CDCl_3$) δ 7.15 (d, 1, J = 3 Hz, $H_{1'}$).

Anal. Calcd for $C_{14}H_{17}N_3O_8S$: C, 43.41; H, 4.; N, 10.85; S, 8.28. Found: C, 43.23; H, 4.71; N, 10.92; S, 8.35.

Methanolysis[8b] gave the free nucleoside with mp 201–203° which was identical with an authentic sample[8b] of 2-thio-6-azauridine and could be oxidized by alkaline H_2O_2[8b,46] to 6-azauridine.

2-(2,3,4-Tri-*O*-acetyl-β-D-ribopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (21a). To 1,2,3,4-tetra-*O*-acetylribopyranose (**20**, 1.59 g, 5 mmol) in 1,2-dichloroethane (100 ml) 5.54 ml of **1** (6.25 mmol) in benzene and $SnCl_4$ (0.42 ml, 3.6 mmol) in 1,2-dichloroethane (5 ml) were added. After 3 hr at 22° and work-up crystallization (ethanol) gave 1.36 g (73.3%) of **21a** as white needles, mp 172–173°) $[\alpha]^{23}D$ −25.7° (c 1, $CHCl_3$).

Methanolysis[44] afforded in 87.8% yield the free 2-(β-D-ribopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione, mp 221–222°, $[\alpha]^{23}D$ −60.0° (c 0.5, $C_2H_5OH + H_2O$ (1:1)).

2-(2,3,4-Tri-*O*-acetyl-β-D-ribopyranosyl)-3-thio-2,3,4,5-tetrahydro-1,2,4-triazin-5-one (21b). To **20** (9.5 g, 29.9 mmol) and **17** (10.2 g, 37.4 mmol) in 1,2-dichloroethane (300 ml) $SnCl_4$ (5.04 ml, 43.4 mmol) in 1,2-dichloroethane (500 ml) was added. After 3 hr at 50° and work-up **21b** was obtained as a slight yellowish foam, which was homogenous on tlc (system A): yield 9.46 g (81.8%); nmr ($CDCl_3$) δ 6.82 (d, 1, J = 9 Hz, $H_{1'}$), 7.63 (s, 1, H_5).

Anal. Calcd for $C_{14}H_{17}N_3O_8S$ (387.36): C, 43.41; H, 4.42; N, 10.85; S, 8.28. Found: C, 43.19; H, 4.62; N, 10.78; S, 8.36.

2-(β-D-Ribopyranosyl)-3-thio-2,3,4,5-tetrahydro-1,2,4-triazin-5-one. To **21b** (1.86 g, 4.8 mmol) in dry methanol (100 ml) a $NaOCH_3$ solution (8 ml, 7.2 mmol) was added. After 3 hr at 22°, filtration through a 1 × 20 cm column of Dowex 50 (H^+) resin and washing with 2:1, CH_3OH–H_2O the eluate was evaporated. Crystallization (methanol) gave 937 mg (74.8%) of free nucleoside with mp 239–241°, $[\alpha]^{23}D$ −37.8° [c 1.066, $CH_3OH + H_2O$ (8:2)], nmr (D_2O) δ 6.80 (d, 1, J = 9 Hz, $H_{1'}$).

Anal. Calcd for $C_8H_{11}N_3O_5S$ (261.26): C, 36.77; H, 4.24; N, 16.08; S, 12.27. Found: C, 36.69; H, 4.38, N, 16.14, S, 12.53.

2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (23a). To 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**22a**, 27.3 g, 70 mmol) in 1,2-dichloroethane (600 ml) 77.5 ml of **1** (87.5 mmol) in benzene and $SnCl_4$ (5.9 ml, 50.4 mmol) in 1,2-dichloroethane (100 ml) were added. After 5 hr at 22° and work-up crystallization (ethanol) gave 19.2 g (61.6%) white needles of **23a**, mp 208–210°, $[\alpha]^{20}D$ −53.4° (c 1, $CHCl_3$), nmr ($CDCl_3$) δ 5.93 (d, 1, J = 9 Hz, $H_{1'}$).

Anal. Calcd for $C_{17}H_{21}N_3O_{11}$ (443.37): C, 46.05; H, 4.77; N, 9.48. Found: C, 45.85; H, 4.84; N, 9.55.

Methanolysis[44] gave in 85% yield the free 2-(β-D-glucopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione with mp 210–212°, $[\alpha]^{23}D$ −44.4° [c 0.5, EtOH + H_2O (1:1)], nmr (D_2O) δ 5.75 (d, 1, J = 9 Hz, $H_{1'}$).

Anal. Calcd for $C_9H_{13}N_3O_7$ (275.22): C, 39.27; H, 4.76; N, 15.27. Found: C, 39.40; H, 5.04; N, 15.35.

2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-thio-2,3,-4,5-tetrahydro-1,2,4-triazin-5-one (23b). To **22a** (15.6 g, 40 mmol) in 1,2-dichloroethane (400 ml) **17** (12.3 g, 45 mmol) and $SnCl_4$ (6.8 ml, 57.7 mmol) in 1,2-dichloroethane (40 ml) were added. After 3 hr at 50° and work-up crystallization (ethanol) gave 14.5 g (79%) of **23b** as white needles with mp 225–226°, $[\alpha]^{20}D$ + 18.5° (c 1, pyridine), nmr ($CDCl_3$) δ 6.74 (d, 1, J = 8.5 Hz, $H_{1'}$).

Anal. Calcd for $C_{17}H_{21}N_3O_{10}S$ (459.44): C, 44.43; H, 4.61; N, 9.14; S, 6.98. Found: C, 44.41; H, 4.87; N, 9.20; S, 7.07.

Methanolysis[44] gave in 87% yield the free 2-(β-D-glucopyranosyl)-3-thio-2,3,4,5-tetrahydro-1,2,4-triazin-5-one which crystallized (ethanol–H_2O) as the monohydrate (the yellow prisms changed to a glass above 130°), $[\alpha]^{23}D$ −139.2° [c 1.135, ethanol–H_2O (1:1)], nmr (D_2O) δ 6.61 (d, 1, J = 9.5 Hz, $H_{1'}$) 7.78 (s, 1, H_6).

Anal. Calcd for $C_9H_{13}N_3O_6S \cdot H_2O$ (309.31): C, 34.95; H, 4.89; N, 13.59; S, 10.37. Found: C, 34.79; H, 5.08; N, 13.64; S, 10.66.

1-[2-Deoxy-3,5-bis-*O*-*p*-toluoyl)-β-D-ribofuranosyl]-5-ethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (25, 5-Ethyldeoxyuridine Ditoluoylate). To **24** (1.95 g, 5.0 mmol) and 5-ethyl-2,4-bis(trimethyl-silyloxy)pyrimidine (**5**, 1.78 g, 6.25 mmol) in 1,2-dichloroethane (50 ml) $SnCl_4$ (0.107 ml, 1.25 mmol) in 1,2-dichloroethane (25 ml) was added at 0°. After a few minutes the solution became clear and was kept for 2 hr at 0°. After work-up the crude nucleoside (2.8 g) gave on fractionated crystallization (ethanol) 1.41 g (57%) **25** with mp 197–198°, $[\alpha]^{23}D$ −90° (c 0.49, $CHCl_3$), nmr ($CDCl_3$) δ 6.44 (dd, 1, J = 7 + 7 Hz, $H_{1'}$).

Anal. Calcd for $C_{27}H_{28}N_2O_7$ (492.51): C, 65.84; H, 5.73; N, 5.69. Found: C, 65.59; H, 5.90; N, 5.71.

From the mother liquor the α anomer **26** was isolated as crystalls with mp 160–161°, $[\alpha]^{23}D$ −10.0° (c 1, $CHCl_3$), nmr ($CDCl_3$) δ 6.35 (dd, 1, J = 7 + 3.0 Hz, $H_{1'}$).

Methanolysis[44] of **25** gave the free 5-ethyl-2′-deoxyuridine with mp 149–151° (lit.[25] 152–153°).

2-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (28). From 2,3,5-tri-*O*-benzyl-D-arabinofuranose (4.62 g, 11 mmol) the halo sugar **27**[42] was prepared and dissolved in 1,2-dichloroethane (100 ml), then **1** (7 ml, 11 mmol) in benzene and subsequently at 0° a solution of $SnCl_4$ (0.42 ml, 3.6 mmol) in 1,2-dichloroethane (2 ml) were added with stirring. After 16 hr at 22° and work-up crystallization (CH_2Cl_2–pentane) gave 2.40 g (42%) of **28** as long white needles with mp 123–124°, nmr ($CDCl_3$) δ 6.31 (d, 1, J = 5.5 Hz, $H_{1'}$).

Anal. Calcd for $C_{29}H_{29}N_3O_6$ (515.55): C, 67.56; H, 5.67;, N, 8.15. Found: C, 67.43; H, 5.76; N, 8.07.

1-(Tetrahydro-2-pyranyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (31). A. **1** (13 ml, 20.8 mmol) in CH_3CN was diluted with CH_3CN (100 ml) and $SnCl_4$ (1.51 ml, 25 mmol) and finally 2-chlorotetrahydropyran (**30a**, 30 ml, 25 mmol) in 1,2-dichloroethane (50 ml) was added dropwise with stirring at 0° under an atmosphere of argon during 45 min. After 2 hr at 4° concentration *in vacuo* to ~30 ml, dilution with 1,2-dichloroethane (500 ml), and work-up gave crude **31** which crystallized (ethyl acetate) to give 3.6 g (92%) of **31** as colorless prisms with mp 163–164° (lit.[30] mp 160–162°).

Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.79; H, 6.00; N, 21.20.

B. Analogous reaction of **1** with **30b** and **30c** gave **31** in 85% and 72% yield, respectively.

Acknowledgment. We are indebted to Dr. G.-A. Hoyer and Dr. D. Rosenberg for the nmr spectra and Diplom-Ing. G. Huber for the analyses. We thank furthermore Dr. R. Nickolson for checking our English text.

Registry No. **1**, 17331-61-2; **2**, 6974-32-9; **4**, 1627-29-8; **5**, 31167-05-2; **6**, 25692-02-8; **7**, 40110-78-9; **8**, 40110-83-6; **9**, 40110-77-8; **10**, 40110-82-5; **11**, 52522-97-1; **12**, 23392-16-7; **13**, 52522-98-2; **14**, 20649-48-3; **15**, 52522-99-3; **16**, 2880-93-5; **17**, 33088-44-7; **18a**, 52554-28-6; **19a**, 29725-42-6; **20**, 4049-34-7; **21a**, 52523-00-9; **21a** free nucleoside, 52523-01-0; **21b**, 52523-02-1; **21b** free nucleoside, 52523-03-2; **22a**, 83-87-4; **23a**, 31356-88-4; **23a** free nucleoside, 52523-04-3; **23b**, 29725-44-8; **23b** free nucleoside, 33156-22-8; **24**, 4330-21-6; **25**, 29900-44-5; **26**, 29900-45-6; **27**, 52554-29-7; **28**, 29725-46-0; **30a**, 3136-02-5; **31**, 52554-30-0; 6-azauracil, 461-89-2.

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A General Synthesis of N-Glycosides. II.[1] Synthesis of 6-Methyluridines

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Received March 29, 1974

The reaction of silylated 6-methyl- as well as 5,6-dimethyluracil with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose gave strikingly varying yields of N_1- and N_3-glycosides depending on the use of either 1,2-dichloroethane or acetonitrile as solvents. Silylated 2-thio-6-methyl- as well as 5,6-dimethyluracil afforded only mixture of S- and N_3-glycosides. The steric as well as mechanistic implications of these results are discussed.

The synthesis of the chemically[2] as well as biologically[3] interesting 6-methyl substituted pyrimidine nucleosides has recently been investigated by different groups.[4–7]

The data obtained by the previous workers[5,7] indicate that very subtle steric as well as energetic factors seem to determine whether the thermodynamically more stable N_1 or (in the presence of a 6 substituent) the sterically and, apparently kinetically, favored N_3 product is formed. Furthermore any excess of the halo sugar seems to lead to N_1,N_3-bisglycoside formation.

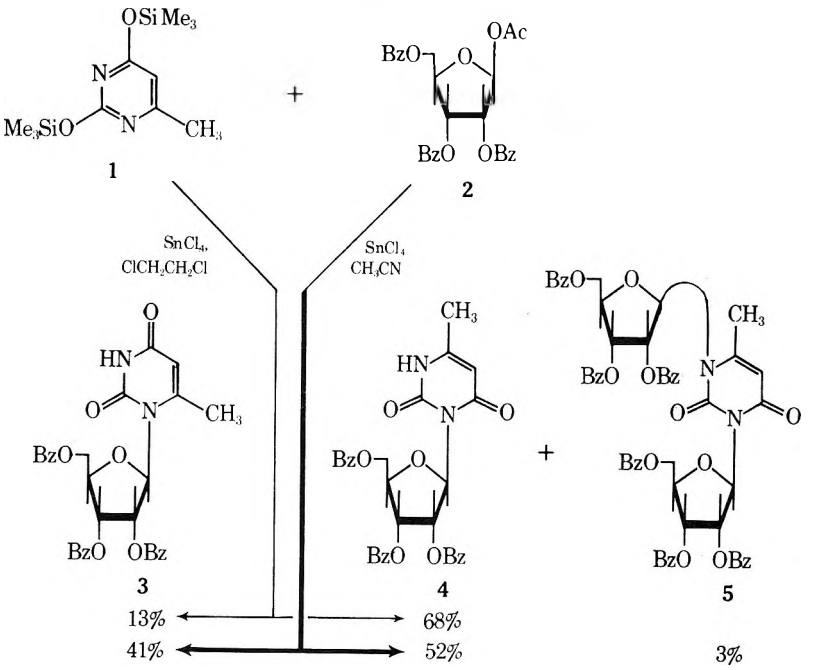
Since the Hilbert-Johnson reaction of silylated pyrimidines with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) and $SnCl_4$ had given exclusively the natural β-N_1-pyrimidine nucleosides (compare part I of this series), we were curious how silylated 6-methyl- as well as 5,6-dimethyluracil would behave under these reaction conditions.

Our first results are summarized in Scheme I. In the less polar solvent 1,2-dichloroethane 6-methyl-2,4-bis(trimethylsilyloxy)pyrimidine (**1**) reacted with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) and $SnCl_4$ to give only 13% crystalline benzoylated N_1-riboside **3** and 68% crystalline benzoylated N_3-riboside **4**, whereas in the more polar acetonitrile ~41% **3** and ~52% **4** were obtained as well as 3% benzoylated N_1,N_3-bisriboside **5**. As described earlier[5] the N_1- and N_3-nucleosides can be readily separated by column chromatography on alumina or silica gel.

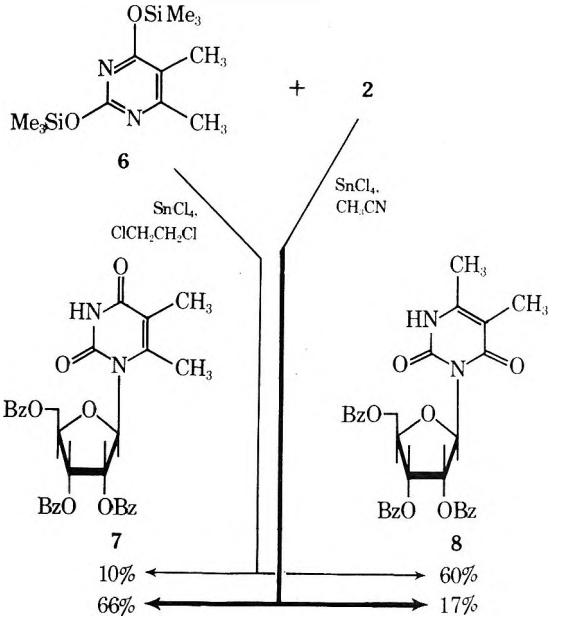
The structures of the N_1- as well as the N_3-nucleosides were established by the typical bathochromic shift of the uv spectra of the N_3-nucleosides in alkaline medium.[8] Furthermore the N_3-β-D-ribofuranosides show a characteristic downfield shift of the H-1′ proton of up to 1 ppm which is due to the two neighboring lactam carbonyls compared to the N_1-nucleosides with only one neighboring lactam carbonyl group.

The difference in yields on changing the solvents is even more striking for the reactions of 5,6-dimethyl-2,4-bis(trimethylsilyloxy)pyrimidine (**6**) (Scheme II). The yields of 10% N_1-nucleoside **7** and 60% N_3-nucleoside **8** in 1,2-di-

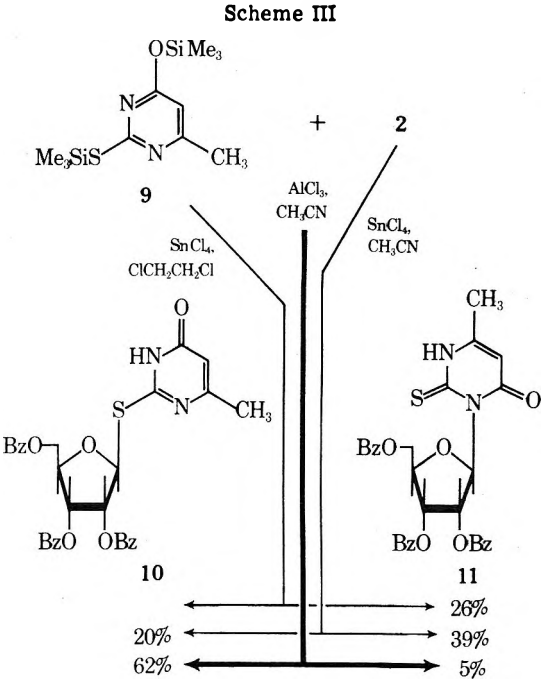
Scheme I



Scheme II



Scheme III



chloroethane were nearly reversed using acetonitrile as a solvent. There was obtained in this instance 66% **7** and 17% **8**, both of which crystallized.

Saponification of the benzoylated N_1-ribosides **3** and **7** gave the known[4,5] corresponding crystalline 6-methyl- and 5,6-dimethyluridines which were identified by their physical data. Saponification of the benzoylated N_3-ribosides **4** and **8** gave the corresponding free N_3-ribosides, which could not be obtained in crystalline form.

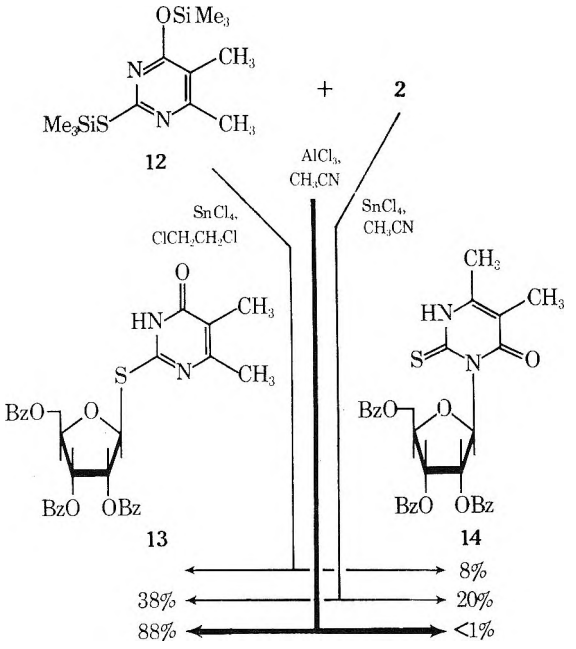
When we tried to prepare 6-methyluridine in larger amounts we encountered difficulties. It turned out that the yield of the benzoylated N_1-riboside **3** was extremely dependent on the purity of the solvents and reagents. As already emphasized in the preceding paper[1] the acetonitrile had to be distilled twice over phosphorus pentoxide, the $SnCl_4$ had to be fresh or to be redistilled, and the 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) had to be recrystallized from 2-propanol or ethanol and subsequently dried carefully in high vacuum.

Traces of acetic acid or 2-propanol in **2** or humidity in the solvents resulted in a dramatic lowering of the yield of the desired benzoylated N_1-riboside **3** and a corresponding increase of the yield of the benzoylated N_3-riboside **4** and N_1,N_3-diriboside **5**. The yield of **3** also decreased on addition of ethereal HCl to the reaction mixture. Furthermore pretreatment of $SnCl_4$ in acetonitrile with small amounts of acetic acid and subsequent addition of **1** and **2** did not give any protected N_1-nucleoside **3** but only a 80% yield of the benzoylated N_3-nucleoside **4**.

When the optimal reaction time of ~3–5 hr was exceeded, the yield of the N_1 product **3** decreased in favor of less polar products. Replacement of $SnCl_4$ by fresh $AlCl_3$ did not improve the yield of **3**. Thus products and yields are dependent on very subtle changes in the reaction conditions and care has to be exercised in order to insure that the reactions proceed optimally.

The reaction of silylated 2-thio-6-methyluracil (**9**)

Scheme IV



(Scheme III) with **2** and $SnCl_4$ or $AlCl_3$ in 1,2-dichloroethane and acetonitrile did not give any of the desired benzoylated N_1-riboside. Instead, only the crystalline benzoylated S-riboside **10** as well as the crystalline benzoylated N_3-riboside **11**[9] were obtained in varying amounts. With increasing polarity of the solvent and strength of the Friedel–Crafts catalyst surprisingly[10] more S-riboside **11** was formed.

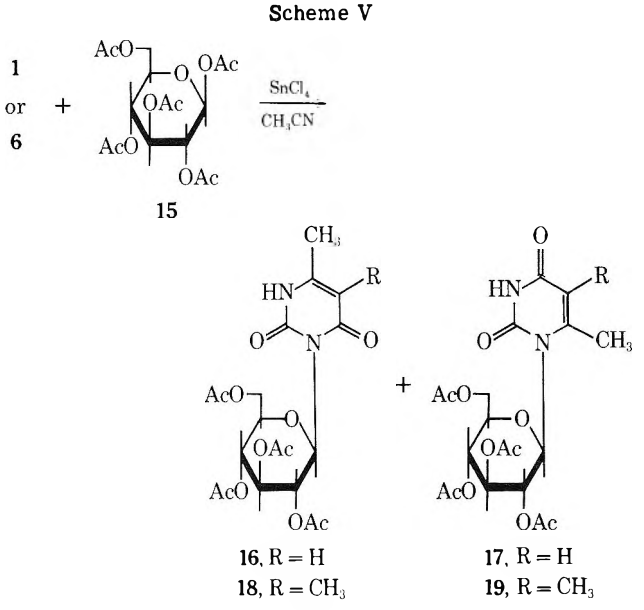
The reaction of silylated 2-thio-5,6-dimethyluracil (**12**) with **2** (Scheme IV) gave analogously only the benzoylated S-nucleoside **13** as well as some N_3-nucleoside **14**.

S-Alkylation of silylated 2-thiouracils has been observed before[10] and might be especially favored here because of the steric hindrance of the N_1 position by the 6-methyl group. Thus steric hindrance not only blocks the rearrangement of the S-nucleoside to the N_1-nucleoside, but even the rearrangement to the sterically favored N_3-nucleoside seems to be impeded and dependent on the catalyst–solvent complex.

The structures of **10** as well as **13** were proved by cleavage with H_2S–pyridine[10,11] to 6-methyl-2-thiouracil as well as 5,6-dimethyl-2-thiouracil. The benzoylated S-riboside **10** rearranged furthermore on treatment with $HgBr_2$[12] in boiling toluene in moderate yield to the protected N_3-riboside **11**.

Since steric factors seem to determine the formation of either N_1- or N_3-nucleosides in the case of a 6-methyl substituent, we studied the reactions of the silylated uracils **1** and **6** with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**15**)[13] which was expected to give a more bulky cation than **2** (Scheme V).

Scheme V



On reaction of **1** with **15** and $SnCl_4$ in acetonitrile we isolated in 42.3% yield the crystalline N_3-glucoside[6,14] **16** but no N_1-glucoside **17** could be detected. However, **6** gave with **15** in acetonitrile besides 1.2% N_3-glucoside **18** a 22.4% yield of the crystalline N_1-glucoside **19**.

Bärwolf, Kowollik, and Langen[15] discovered recently that silylated 6-fluorothymine reacted with acetobromoglucose in the presence of $SnCl_4$ to afford the N_1-nucleosides in excellent yields. Thus the size of the 6 substituent is critical since Pichat and Chatelain[16] found that silylated 6-chlorouracil gave with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride on heating to 190° only the 6-chloro N_3-riboside in low yield. Analogously Winkley and Robins[17] allowed silylated 6-methylmercaptouracil and 1-bromo-2,3,5-tri-*O*-benzoyl-D-ribofuranose to react in acetonitrile and obtained only the corresponding 6-methylmercapto N_3-riboside in 75% yield, which could be desulfurized to 3-β-D-ribofuranosyluracil after saponification.

It can therefore be anticipated that silylated orotic acid or orotic esters will yield probably only the N_3-nucleosides thus limiting the chemical synthesis of orotidine at present to the efficient Ueda method[18] starting from 2′,3′-*O*-isopropylidene-5-bromouridine.

Experimental Section

For instruments and the purification of solvents as well as the work-up of the reaction mixtures compare part I.[1]

Column chromatography was performed on neutral alumina Woelm and silica gel Merck (Darmstadt). Tlc system: A [ethyl acetate–hexane (2:1)].

6-Methyl- and 5,6-dimethyluracil were purchased from EGA-Chemie KG, Steinheim a. Albuch. 2-Thio-6-methyl- and 5,6-dimethyluracil were prepared according to Draminski and Fiszer.[19]

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-6-methyl-1,2,-3,4-tetrahydropyrimidine-2,4-dione (4) and 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (3). To **1** (12 mmol) and **2** (5.04 g, 10 mmol) in CH_3CN (150 ml), $SnCl_4$ (1.5 ml, 12.9 mmol) in CH_3CN (100 ml) was added under stirring at 14° and stirred 4 hr at 22°. After work-up,[1] chromatography on neutral alumina (300 g, activity III) gave on elution with *n*-hexane–ethyl acetate (9:1) a mixture of unreacted sugar and N_1,N_3-diriboside **5** (400 mg). **5** was purified by preparative tlc on silica gel using the same solvent system and obtained as a white foam: mp 110–112°; yield 0.170 g (3.4%); nmr ($CDCl_3$) δ 6.64 [d, 1, J = 2 Hz, H-1′ (N_3)], 5.77 [s, 1, H-1′ (N_1)], 5.65 (s, 1, H-5), 2.30 (s, 3, 6-CH_3).

Anal. Calcd for $C_{57}H_{46}N_2O_{16}$ (1015.17): C, 67.44; H, 4.57; N, 2.78. Found: C, 67.54; H, 5.01; N, 2.74.

The less polar N_3-nucleoside was eluted from alumina with ethyl acetate–hexane (2:1) and crystallized from the same solvent giving 2.934 g (51.5%) of **4**, mp 108–109°, $[\alpha]^{20}D$ 31.9° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{31}H_{26}N_2O_9$ (570.53): C, 65.26; H, 4.59; N, 4.91. Found: C, 65.10; H, 4.96; N, 4.92.

The N_1-nucleoside **3** was eluted from alumina with ethyl acetate–methanol (9:1) and crystallized (CH_2Cl_2–pentane) giving 2.316 g (40.6%) of **3**, mp 126–129°, $[\alpha]^{20}D$ −5.0° (*c* 1, $CHCl_3$) (lit.[5] 125–128°).

Anal. Calcd for $C_{31}H_{26}N_2O_9$ (570.53): C, 65.26; H, 4.59; N, 4.91. Found: C, 65.07; H, 4.78; N, 4.88.

The analogous reaction in 1,2-dichloroethane (4 hr at 22°) gave 67% **4** and 13% **3**.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (8) and 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (7). To **2** (7.56 g, 15 mmol) and **6** (18

mmol) in CH_3CN (250 ml), $SnCl_4$ (2.0 ml, 17.1 mmol) in CH_3CN (150 ml) was added under stirring at 0°. After stirring overnight at 22° and work-up,[1] the residue was chromatographed on neutral alumina (350 g, activity II). The less polar nucleoside **8** was eluted with *n*-hexane–ethyl acetate (1:1) and crystallized (ethanol) giving 1.46 g (16.7%) of platelets: mp 200–201°; $[\alpha]^{20}D$ 34.6° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 6.73 (d, 1, $J \approx 1$ Hz, H-1′), 2.17 (s, 3, 6-CH_3), 1.90 (s, 3, 5-CH_3).

Anal. Calcd for $C_{32}H_{28}N_2O_9$ (584.56): C, 65.75; H, 4.83; N, 4.79. Found: C, 65.82; H, 4.87; N, 4.62.

The N_1-nucleoside **7** was eluted with ethyl acetate. Crystallization (CH_2Cl_2–pentane) gave 5.77 g (65.9%) of **7** in needles: mp 176–178°; $[\alpha]^{20}D$ −10.3° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 5.81 (d, 1, $J < 1$ Hz, H-1′), 2.29 (s, 3, 6-CH_3), 1.99 (s, 3, 5-CH_3).

Anal. Calcd for $C_{32}H_{28}N_2O_9$ (584.56): C, 65.75; H, 4.83; N, 4.79. Found: C, 65.50; H, 4.99; N, 4.71.

The analogous reaction in 1,2-dichloroethane (addition of $SnCl_4$ at 0°, then 6 hr at 22°) gave 60.3% **8** and 10.3% **7**.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-6-methyl-2-thio-1,2,3,4-tetrahydropyrimidin-4-one (11) and 2-[(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thio]-6-methyl-3,4-dihydropyrimidin-4-one (10). To **2** (12.6 g, 25 mmol) and 6-methyl-2,4-*S*,*O*-bis(trimethylsilyl)pyrimidine (**9**, 30 mmol) in CH_3CN (300 ml) $SnCl_4$ (10 ml, 85.6 mmol) in CH_3CN (300 ml) was added under stirring at 0°. After 3 hr at 22° and work-up[1] chromatography on neutral alumina (500 g, activity III) gave on elution with ethyl acetate the N_3-nucleoside **11**. The S-riboside **10** was eluted with methanol–H_2O (2:1). **11** crystallized (ethanol) to give 5.75 g (39.3%): mp 192–193°; $[\alpha]^{20}D$ 32.8 (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 7.27 (m, 1, H-1′), 5.75 (s, 1, H-5), 2.11 (s, 3, 6-CH_3).

Anal. Calcd for $C_{31}H_{26}N_2O_8S$ (568.62): C, 63.50; H, 4.47; N, 4.77; S, 5.46. Found: C, 63.15; H, 4.48; N, 4.65; S, 5.68.

10 crystallized (ethanol–ether) to give 2.89 g (19.7%): mp 151–153°; $[\alpha]^{20}D$ −22.8° (*c* 1, $CHCl_3$); uv[20] (CH_3OH) λ_{max} 275 nm (ε 9620), 281 (sh, 8980); nmr ($CDCl_3$) δ 6.45 (d, 1, J = 2.5 Hz, H-1′), 6.04 (s, 1, H-5), 2.21 (s, 3, 6-CH_3).

Anal. Calcd for $C_{31}H_{26}N_2O_8S$ (586.62): C, 63.50; H, 4.47; N, 4.77; S, 5.46. Found: C, 63.23; H, 4.37; N, 4.81; S, 5.67.

The analogous reaction with $SnCl_4$ in 1,2-dichloroethane (4 hr, 22°) gave 26% **11**. In CH_3CN–$AlCl_3$ (addition of 1.5 equiv of $AlCl_3$ at 0°, 5 hr at 22°) 62% **10** and ~5% **11** were obtained.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethyl-2-thio-1,2,3,4-tetrahydropyrimidin-4-one (14) and 2-[(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thio]-5,6-dimethyl-3,4-dihydropyrimidin-4-one (13). To **2** (5.04 g, 10 mmol) and **12** (12.0 mmol) in CH_3CN (200 ml) $SnCl_4$ (3.2 ml, 27.4 mmol) in CH_3CN (80 ml) was added at 14°. After 20 hr at 22° and work-up[1] the residue (5.3 g) was chromatographed on silica gel (260 g). The products were eluted with hexane–ethyl acetate (6:4). The less polar **14** was crystallized (ethanol) giving 1.20 g (20%) of **14**: mp 191–193°; $[\alpha]^{20}D$ −22.7° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 7.50 (d, 1, J = 3 Hz, H-1′), 2.12 (s, 3, 6-CH_3), 1.89 (s, 3, 5-CH_3).

Anal. Calcd for $C_{32}H_{28}N_2O_8S$ (600.56): C, 63.99; H, 4.70; N, 4.66; S, 5.30. Found: C, 63.74; H, 5.10; N, 4.88; S, 5.32.

The more polar **13** crystallized (ethanol–ethyl acetate) giving 2.30 g (38.4%) of **13**: mp 135–137°; $[\alpha]^{20}D$ −20.5° (*c* 1, $CHCl_3$); uv[20] (CH_3OH) λ_{max} 276 nm (10,600), 280 (sh, 10,300); nmr ($CDCl_3$) δ 6.42 (d, 1, J = 2.5 Hz, H-1′), 2.23 (s, 3, 6-CH_3), 1.99 (s, 3, 5-CH_3).

Anal. Calcd for $C_{32}H_{28}N_2O_8S$ (600.56): C, 63.99; H, 4.70; N, 4.66; S, 5.30. Found: C, 64.03; H, 5.21; N, 4.99; S, 5.55.

The analogous reaction with $SnCl_4$ in 1,2-dichloroethane (5 hr at 22°) gave 7.7% **14**, whereas with $AlCl_3$ in CH_3CN (2 hr, 20°) 88% **14** and ~1% **13** were obtained.

Treatment of the S-Ribosides with H_2S–Pyridine. A slow stream of H_2S gas was bubbled through **10** (2.0 g, 3.41 mmol) in dry pyridine (30 ml) and stirred for 2 hr at 22°. After evaporation *in vacuo* the residue was extracted with ethyl acetate and the insoluble material crystallized (ethanol) to give 6-methyl-2-thiouracil (440 mg, 90.8%) with mp 300°, which was identical with an authentic sample.[19]

The analogous treatment of **13** (600 mg, 1 mmol) in dry pyridine (30 ml) with H_2S for 3 hr at 40° gave after evaporation and pouring the ethanolic solution into pentane a precipitate, which afforded after crystallization (ethanol) and sublimation [130° (0.001 mm)] 5,6-dimethyl-2-thiouracil (115 mg, 73.7%), mp 225°, which was identical with an authentic sample.[19]

Rearrangement of 2-[(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thio]-6-methyl-3,4-dihydropyrimidin-4-one (10) with $HgBr_2$. **10** (400 mg, 0.684 mmol) was heated for 2 hr at 100° under argon in benzene–toluene (50 ml, 1:2) with $HgBr_2$ (1.8 g, 4.98 mmol). After filtering and washing with benzene, the filtrate was extracted with KI solution (30%), dried ($MgSO_4$), and evaporated. Tlc (system A) showed that **10** had disappeared and that, beside a sugar derivative, only **11** could be detected in ~10% yield.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (16). To **15** (13.2 g, 33.9 mmol) in CH_3CN (100 ml) and **1** (200 ml, 40 mmol) in CH_3CN, $SnCl_4$ (5.3 ml, 45.3 mmol) in CH_3CN (200 ml) was added. After 3 hr at 22° and work-up[1] the crude nucleoside (8.5 g) was crystallized (ethanol) with charcoal to give 6.54 g (42.3%) of **16**: mp 153–154°; $[\alpha]^{23}D$ −10.1° (*c* 0.595, $CHCl_3$); nmr ($CDCl_3$) δ 6.30 (d, 1, J = 9 Hz, H-1′).

Anal. Calcd for $C_{19}H_{24}N_2O_{11}$ (456.42): C, 49.98; H, 5.30; N, 6.14. Found: C, 49.72; H, 5.44; N, 6.11.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5,6-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (19) and 3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5,6-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (18). To **15** (3.89 g, 10 mmol) and **6** (12 mmol) in dry CH_3CN (120 ml), $SnCl_4$ (2 ml, 17.1 mmol) in CH_3CN (100 ml) was added at 15°. After 15 hr at 22° and work-up[1] the residue (3.84 g) was dissolved in ethyl acetate and poured into *n*-hexane (1.2 l.). The precipitate was collected and the procedure was repeated twice to give 2.83 g of product, which was chromatographed in ethyl acetate on silica gel (150 g). The first eluate fractions afforded **19** which crystallized (ethanol) to give 1.053 g (22.4%): mp 202–204°; $[\alpha]^{23}D$ 20.1 (*c* 1.02, $CHCl_3$); nmr ($CDCl_3$) δ 6.35 (d, 1, J = 9 Hz, H-1′), 2.48 (s, 3, 6-CH_3), 2.06 (s, 3, 5-CH_3).

Anal. Calcd for $C_{20}H_{26}N_2O_{11}$ (470.60): C, 51.05; H, 5.57; N, 5.99. Found: C, 51.06; H, 5.57; N, 6.17.

Following **19** impure **18** (56.4 mg, 1.2%) was eluted: uv (CH_3OH + H_2O) λ_{max} (pH 1) 270 nm, λ_{min} (pH 1) 242 nm, λ_{max} (pH 13) 299 nm, λ_{min} (pH 13) 253 nm; nmr ($CDCl_3$) δ 6.18 (d, 1, J = 7 Hz, H-1′).

Acknowledgment. We are indebted to Dr. G.-A. Hoyer and Dr. D. Rosenberg for the nmr spectra and Diplom-Ing. G. Huber for the analyses.

Registry No.—**1**, 31111-31-6; **2**, 6974-32-9; **3**, 23316-76-9; **4**, 24744-17-0; **5**, 25691-87-6; **6**, 31111-32-7; **7**, 25691-82-1; **8**, 52523-05-4; **9**, 32865-97-7; **10**, 52523-06-5; **11**, 29881-44-5; **12**, 52523-07-6; **13**, 52523-08-7; **14**, 52523-09-8; **15**, 604-69-3; **16**, 52554-31-1; **18**, 52523-10-1; **19**, 52523-11-2.

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A General Synthesis of N-Glycosides. III.[1,2] A Simple Synthesis of Pyrimidine Disaccharide Nucleosides

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Received March 29, 1974

Silylated uracils as well as 6-azauracils react smoothly with peracetylated reducing disaccharides in the presence of $SnCl_4$ to give the corresponding disaccharide nucleosides. Preliminary experiments show that tri- and tetrasaccharides react analogously.

Wolfrom and coworkers[3] have described the synthesis of acetylated purine disaccharide nucleosides *via* the chloromercuric salts, which gave the pure crystalline 9β-disaccharide purine nucleosides in ~10–30% overall yields. More recently Rao and Lerner[4] prepared analogously 1β-cellobiosyl- and 1β-lactosylbenzimidazole, but, to our knowledge, no disaccharide pyrimidine nucleosides have as yet been prepared starting from disaccharides prior to our own work.

Thus we wondered whether the readily available peracetylated oligosaccharides with a reducing end group, especially acetylated disaccharides like octaacetylcellobiose, -lactose, and -maltose, would not react with silylated pyrimidines and $SnCl_4$ to give the corresponding pyrimidine disaccharide nucleosides. We expected a smooth reaction since it is well known[5] that Friedel–Crafts catalysts like $SnCl_4$ or $TiCl_4$ cleave the 1-O-acetyl bond in these acetylated oligosaccharides in preference to the glycosidic linkage between the sugar residues to give a C-1 cation.

However, in our initial reactions of crystalline disaccharide octaacetates with silylated pyrimidines and $SnCl_4$ the yields of acetylated pyrimidine disaccharide nucleosides varied widely and several other products were formed.

A detailed investigation of the reaction of octaacetylcellobiose (1) with silylated 6-azauracil (2) revealed that commercial as well as our own samples of 1 always contained up to 0.5% ethanol or other alcohols from recrystallization. Since alcohols and acetic acid react with $SnCl_4$ or $TiCl_4$ to give HCl,[2] the disaccharide bond in 1 or in the already formed disaccharide nucleoside 3 was cleaved. Thus not only 3 but also the 6-azauracil *N*-glucosides 4 and 5 were formed by the reaction of 2 with the cations obtained by the indicated types of glycosidic bond cleavage of 1 and 3 (Scheme I).

The nucleoside 4 was identified by tlc comparison with an authentic sample. Furthermore both acetylated nucleosides 4 and 5 gave on saponification the known free 2-(β-D-glucopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (8),[1] thus making the structure of 5 highly probable.

To avoid formation of HCl the acetylated cellobiose was therefore pulverized and dried at elevated temperature in high vacuum or by azeotropic distillation. Repetition of the reaction of dried 1 with 2 and $SnCl_4$ in boiling 1,2-dichloroethane now gave the crystalline acetylated disaccharide nucleoside 3 in 80% yield as the only product.

Reaction of 2 with hepta-*O*-acetylcellobiosyl chloride[5] in the presence of $SnCl_4$ in 1,2-dichloroethane gave beside 3 the N_3- as well as the N_1,N_3-bis(disaccharide) nucleoside.[6]

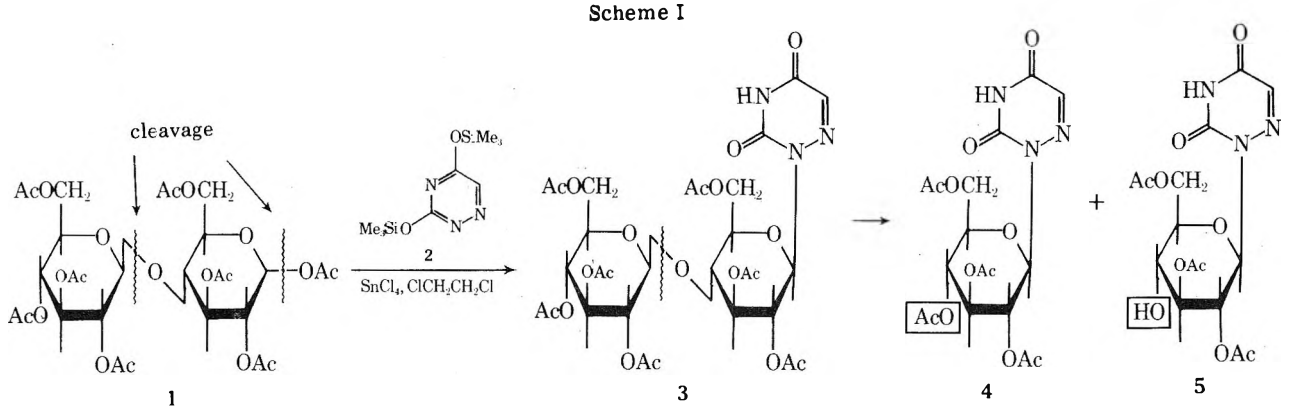
In most subsequent experiments the carefully dried peracetylated disaccharides were treated with silylated pyrimidines and $SnCl_4$ in boiling 1,2-dichloroethane yielding 60–80% of the corresponding peracetylated disaccharide nucleosides, which often either crystallized spontaneously or after purification over a column of alumina. Methanolysis with sodium methylate in methanol gave in high yields the free disaccharide nucleosides.

The structures of the acetylated disaccharide nucleosides are supported by their mass spectra as exemplified by the fragmentation of the maltose nucleoside 6 (Scheme II). Further obvious fragments observed were *m/e* 744 (M − H), 685 (M − CH_3COOH), 684 (744 − CH_3COOH), 625 (M − 2 CH_3COOH), 624 (744 − 2CH_3COOH).

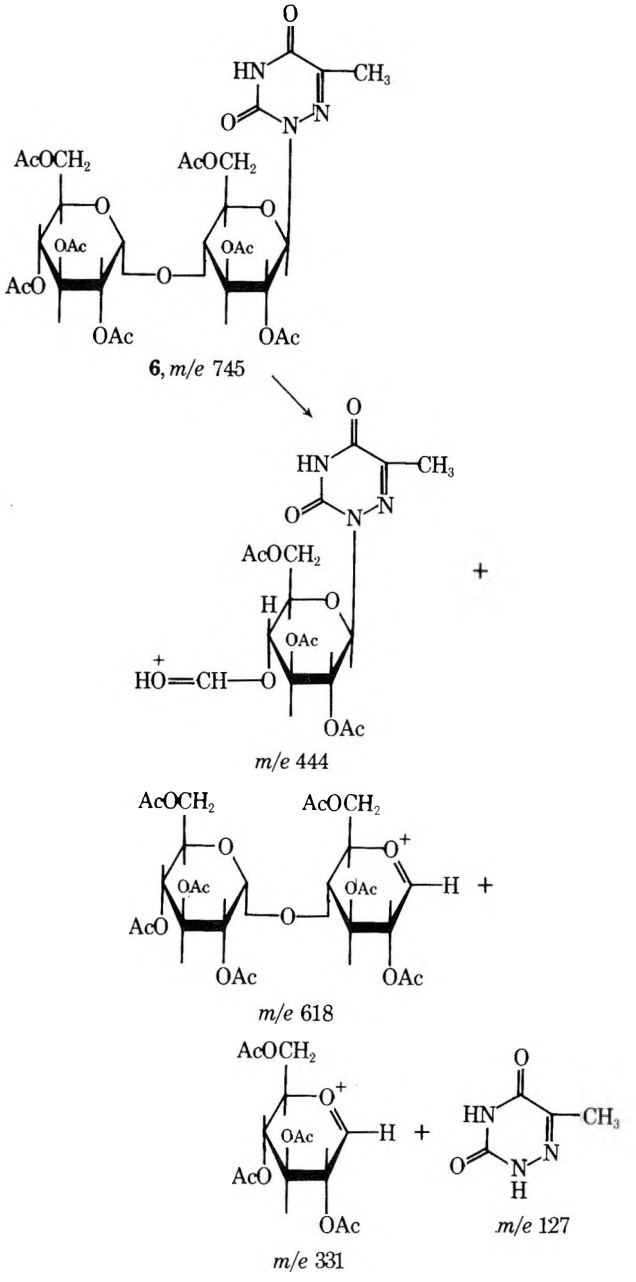
An additional proof for the structure of the free disaccharide nucleosides was provided when the free disaccharide nucleoside 7a with an α-glucosidic bond was incubated with maltase (α-glucosidase) in aqueous buffer solution to give the glucoside 8 in practically quantitative yield, which was identical with an authentic sample (Scheme III).

Since peracetylated tri- and tetrasaccharides are not commercially available we prepared and reacted a mixture of peracetylated cellotriose (9) and cellotetraose (10) with silylated 6-azauracil (2) and obtained a mixture of the acetylated oligosaccharide nucleosides 11 and 12 in ~70% yield, which were separated by preparative tlc, and the

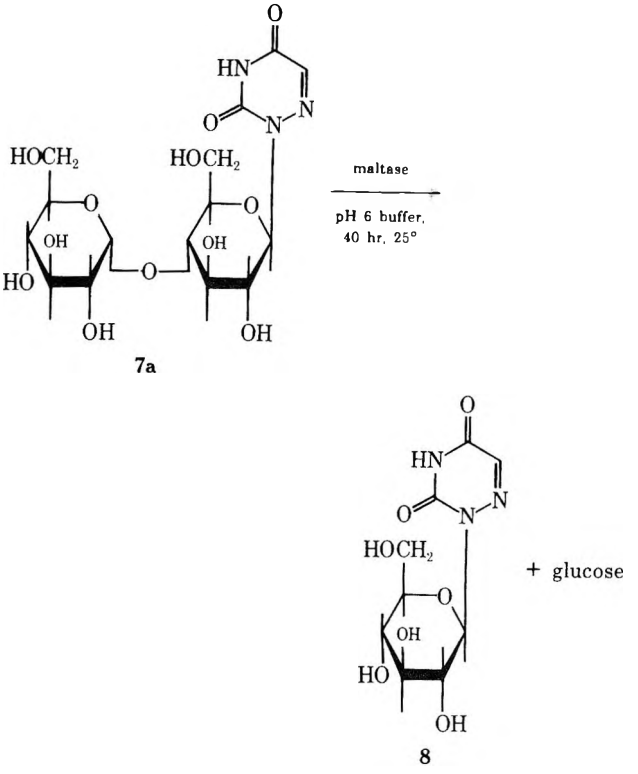
Scheme I



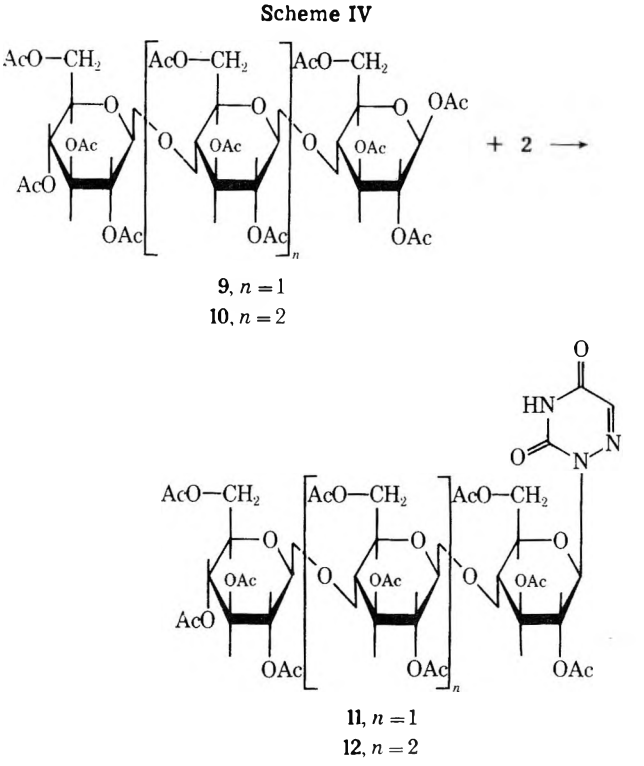
Scheme II



Scheme III



Scheme IV



structures were assigned by nmr ratio of H-5 and H-1′ to acetyl CH_3 (Scheme IV).

In Tables I and II the formation of acetylated and free disaccharide nucleosides is summarized. Besides the already mentioned octaacetylcellobiose (**1**), octaacetylmaltose (**13**) and octaacetyllactose (**14**) were treated with 3,5-bis(trimethylsilyloxy)-1,2,4-triazine (**2**), 6-methyl-3,5-*S,O*-bis(trimethylsilyl)-1,2,4-triazine (**15**), 6-methyl-3,5-bis(trimethylsilyloxy)-1,2,4-triazine (**16**), 5-ethyl-2,4-bis-(trimethylsilyloxy)pyrimidine (**17**), 2,4-bis(trimethylsilyloxy)pyrimidine (**18**), and 2,4-*O,N*-bis(trimethylsilyl)-2-hydroxy-4-aminopyrimidine (**28**).

Experimental Section

For instruments and the purification of solvents compare part I of this series.[2]

Tlc systems follow: system A [toluene–acetic acid–H_2O (5:5:1)];[7] system B (ethyl acetate); system C [ethyl acetate–hexane (2:1)]; system D [*n*-butyl acetate–methyl glycol–H_2O (4:1:2)]; and system E [1-propanol–aqueous NH_3 (7:3)]. For the column chromatography neutral alumina (Woelm) and standard silica gel Merck (Darmstadt) were used.

Preparation of the Acetylated Disaccharides. The acetylated disaccharides were prepared according to standard methods and dried either by heating 1–2 hr to 80–100° (10^{-3} mm) or by azeotropic distillation with 1,2-ethylene chloride: Octaacetyl-α-cellobiose,[8] octaacetyl-β-maltose,[9] octaacetyl-β-lactose[10] were obtained.

Preparation of Acetylated Oligosaccharides. The acetolysis of cellulose was performed according to Hess and Dziengel.[11] The crude product was dried *in vacuo* at 50° for 2 days and extracted with hot methanol several times. The methanolic solution was concentrated *in vacuo*. On stirring over night crystals of octaacetyl-α-cellobiose (**1**, mp 222–223°) had formed, which were filtered.

Table I

Silylated pyrimidine	Peracetyled disaccharide	Protected nucleoside Yield, %[a]	Mp,[b] °C	$[\alpha]^{20}D$[c]	H-1',[d]	Formula (mol wt)	Analysis, % calcd (found) C	H	N	S
2	1	3 80	241–242	−59.0	5.88	$C_{29}H_{37}N_3O_{19}$ (731.64)	47.61 (47.50)	5.10 (5.31)	5.74 (6.03)	
2	13	7 72	130–132	−31.5	5.88	$C_{29}H_{37}N_3O_{19}$ (731.64)	47.61 (47.40)	5.10 (5.48)	5.74 (5.93)	
15	1	19 95		−17.1	6.61	$C_{30}H_{39}N_3O_{18}S$ (761.73)	47.31 (47.02)	5.16 (5.46)	5.51 (5.56)	4.21 (4.20)
16	1	20 63	150–153	−48.0	5.73	$C_{30}H_{39}N_3O_{19}$ (745.66)	48.32 (48.02)	5.27 (5.40)	5.64 (5.63)	
15	13	21 70	181–182	−68.9	6.60	$C_{30}H_{39}N_3O_{18}S$ (761.73)	47.31 (47.02)	5.16 (5.50)	5.51 (5.61)	4.21 (4.11)
16	13	22 63	125–126	−35.7	5.86	$C_{30}H_{39}N_3O_{19}$ (745.66)	48.32 (47.97)	5.27 (5.49)	5.64 (5.51)	
2	14	23 80		−29.6	5.91	$C_{29}H_{37}N_3O_{19}$ (731.64)	47.61 (47.67)	5.10 (5.38)	5.74 (5.56)	
15	14	24 66		−3.1	6.61	$C_{30}H_{39}N_3O_{18}S$ (761.73)	47.31 (47.34)	5.16 (5.39)	5.51 (5.72)	4.21 (4.17)
16	14	25 69		−31.5	5.75	$C_{30}H_{39}N_3O_{19}$ (745.66)	48.32 (48.07)	5.27 (5.33)	5.64 (5.65)	
17	1	26 78			5.80	$C_{32}H_{42}N_2O_{19}$ (758.71)	50.66 (50.39)	5.58 (5.76)	3.69 (3.61)	
18	13	27 71			5.85	$C_{30}H_{38}N_2O_{19}$ (730.81)	49.31 (49.06)	5.34 (5.39)	3.86 (3.75)	
28	14	29 81		9.1	6.15	$C_{30}H_{39}N_3O_{18}$ (729.67)	49.38 (49.19	5.39 (5.55)	5.76 (5.61)	

[a] According to standard procedure. [b] From ethanol. [c] *c* 1, $CHCl_3$. [d] $CDCl_3$, parts per million (d, J = 9 Hz).

Table II

Protected nucleoside	Free nucleoside Yield, %[a]	Mp,[b] °C	$[\alpha]^{20}D$,[c]	H-1',[d]	Formula (mol wt)	Analysis, % calcd (found) C	H	N	S
3	3a 95	202–205	−39.0	5.63	$C_{15}H_{23}N_3O_{12}\cdot H_2O$ (455.50)	39.55 (39.74)	5.53 (5.84)	9.22 (8.96)	
7	7a 75	188–190	−47.3	5.66	$C_{15}H_{23}N_3O_{12}\cdot H_2O$ (455.50)	39.55 (39.84)	5.53 (5.76)	9.22 (8.97)	
19	19a 74	274–275[e]	−18.8	6.65	$C_{16}H_{25}N_3O_{11}S$ (467.47)	41.11 (41.02)	5.39 (5.48)	8.99 (8.81)	6.86 (6.68)
20	20a 82	260[e]	−33.3[f]	5.65	$C_{16}H_{25}N_3O_{12}$ (451.40)	42.57 (42.83)	5.59 (5.82)	9.31 (9.07)	
21	21a 65	207–209	−60.8	6.63	$C_{16}H_{25}N_3O_{11}S\cdot CH_3OH$ (499.62)	40.87 (40.60)	5.88 (5.93)	8.45 (8.35)	6.59 (6.49
22	22a 79	174–175	−55.7[f]	5.65	$C_{16}H_{25}N_3O_{12}$ (451.40)	42.57 (42.43)	5.59 (5.71)	9.31 (9.19)	
23	23a 72	292–294	−24.3	5.68	$C_{15}H_{23}N_3O_{12}$ (437.38)	41.19 (41.17)	5.30 (5.44)	9.61 (9.47)	
24	24a 83	218–221	−10.0	7.30[g]	$C_{16}H_{25}N_3O_{11}S$ (467.47)	41.11 (40.84)	5.39 (5.56)	8.99 (8.84)	6.86 (6.72)
25	25a 78	256–258[e]	−20.8[f]	5.65	$C_{16}H_{25}N_3O_{12}$ (451.40)	42.57 (42.84)	5.59 (5.84)	9.31 (9.18)	
26	26a				$C_{18}H_{28}N_2O_{12}$ (464.42)	46.55	6.08	6.03	
27	27a				$C_{16}H_{24}N_2O_{12}$ (436.37)	44.03	5.54	6.42	
29	29a 90		11.0[f]	5.70	$C_{16}H_{25}N_3O_{11}$ (435.40)	44.14 (43.86)	5.79 (5.93)	9.65 (9.49)	

[a] According to standard procedure. [b] From ethanol-H_2O. [c] *c*, 0.4 (ethanol-H_2O, 3:1). [d] D_2O, parts per million (d, J = 9 Hz). [e] Decomposition. [f] *c*, 0.4 (ethanol-H_2O, 3:2). [g] In pyridine-d_5.

The residual oil gave on methanolysis[12] the free oligosaccharides. The methanolic solution was neutralized with H_2SO_4 and evaporated *in vacuo* to dryness. The aqueous extract[13] was reacetylated according to Hess and Dziengel[11] with acetic anhydride–pyridine to give the acetates, which were separated by column chrmatography on silica gel eluting with mixtures of ether–acetone.

The purity of the oligosaccharide fractions was checked by tlc (system A). The spots were detected by spraying with H_2SO_4 and heating to 110° for 5 min. For the silyl Hilbert–Johnson reaction a chromatography fraction was used, which according to tlc (system A) consisted of ~60% hendecaacetylcellotriose (**9**), tetradecaacetylcellotetraose (**10**), and some octaacetylcellobiose (**1**).

Preparation of the Heterocycles. The 1,2,4-triazine derivatives were prepared according to Gut[14] and silylated according to standard methods.[2]

A. General Procedure for the Preparation of Disaccharide Nucleosides. To a solution of peracetylated disaccharide (15 mmol) and of the persilylated pyrimidine (16.5 mmol) in 1,2-dichloroethane (150 ml) $SnCl_4$ (1.26 ml, 10.8 mmol) in 1,2-dichloroethane (20 ml) was added. The reaction mixture was either refluxed for 2 hr under exclusion of moisture (preparation of **3, 7, 14–20, 29**) or kept for 4 hr at 60° (preparation of **21, 22**). The cooled solution was diluted with methylene chloride (200 ml) and poured into ice–saturated $NaHCO_3$ solution (200 ml). The organic layer was separated and the aqueous solution was washed with methylene chloride (100 ml). The combined organic solution was filtered through sand–Celite, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on neutral alumina (activity III) and eluted with ethyl acetate–methanol.

B. General Procedure for the Methanolysis of Acetylated Disaccharide Nucleosides. Acetylated disaccharide nucleoside (4.4 mmol) was suspended in dry methanol (20 ml) and 1 *N* $NaOCH_3$ solution (8.8 mmol) was added whereupon the substance dissolved and after 30–40 min a white precipitate was formed.

After stirring the reaction solution overnight at room temperature the alkaline solution was neutralized by addition of wet Dowex 50 H^+, whereupon the precipitate dissolved. The resin was filtered and washed with methanol and water. After evaporation of the combined filtrates the residue was crystallized from ethanol or a mixture of ethanol–water.

2-(Hepta-*O*-acetyl-β-D-cellobiosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (3). On reaction of impure **1** (containing alcohol) the crude reaction mixture showed on tlc evaluation (system B) besides **3** a number of less polar products, one of which was identical with an authentic sample of **4**. A mixture of **4** and the slightly slower moving **5** was isolated by preparative tlc (system B) and saponified with methanolic ammonia to give a product which gave only a single spot on tlc (system E) identical with an authentic sample of **8**.

Reaction of Hepta-*O*-acetylcellobiosyl Chloride with 2. To a chilled solution of hepta-*O*-acetylcellobiosyl chloride (2.5 g, 3.8 mmol) and **2** (4.5 mmol) in dry 1,2-dichloroethane (30 ml), $SnCl_4$ (0.1 ml, 0.86 mmol) in 1,2-dichloroethane (5 ml) was added. After 4 days at 22° and work-up the crude product contained according to tlc examination (silica gel, system C) at least two products. The nucleosides were separated by fractional precipitation from ethanol. On dissolving the crude reaction product in a small volume of hot ethanol a precipitate of pure **3** was obtained. Further fractional precipitation gave the N_4- as well as the N_2,N_4-bisglycoside.

Yield of **3**: 1.68 g (60.5%); λ_{max} (CH_3OH) 263 nm, λ_{max} (CH_3OH + NaOH) (0.1 *N*) 262 nm.

4-(Hepta-*O*-acetyl-β-D-cellobiosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione: yield, 0.25 g (8.9%); λ_{max} (CH_3OH) 259 nm, λ_{max} (CH_3OH + NaOH) (0.1*N*) 305 nm.

2,4-Bis(hepta-*O*-acetyl-β-D-cellobiosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione: yield, 0.148 g (5.3%); λ_{max} (CH_3OH) 263 nm, λ_{max} (CH_3OH + NaOH) (0.1 *N*) 262 nm; nmr ($CDCl_3$) δ 7.35 (s, 1, H-5), 5.83 (m, 2, H-1′N_4, H-1′ N_2), 2.2–1.8 (m, 42, OAc).

Enzymatic Cleavage. 2-(β-D-Maltosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (**7a**, 60 mg, 0.37 mmol) was dissolved in acetate buffer, pH 6 (10 ml, 0.1 *N*). After addition of α-glucosidase (2 mg, Boehringer-Mannheim, suspension in 3.2 *m* ammonium sulfate solution, pH ~6, 1 ml) the reaction was incubated at 25° and the enzymatic cleavage was followed by tlc. After 40 hr all starting material had disappeared and a new product had formed, which was identical in polarity with 2-(β-D-glucopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (**8**). The solution was filtered over a column of Dowex 50 H^+ and the column was washed with methanol–H_2O. Filtrate and washings were combined and evaporated *in vacuo* to dryness. Preparative tlc on silica gel (system E) gave a fluorescent band which was eluted with methanol–H_2O and crystallized from ethanol to give 35.9 mg (95.1%) of **8** as white needles, mp 211–212° (lit.[2] 210–212°).

Reaction of a Mixture of Hendecaacetylcellotriose (9) and Tetradecaacetylcellotetraose (10) with 2. To a mixture of **9, 10,** and some **1** (2.0 g) and **2** (8 mmol) in 1,2-dichloroethane (100 ml), $SnCl_4$ (0.8 ml, 6.8 mmol) was added. After 2 hr of reflux and work-up (2.1 g colorless foam) an aliquot of the mixture of **11** and **12** (1.6 g) was subjected to preparative tlc (silica gel, system D) to give the nucleosides **11** and **12**.

2-(Deca-*O*-acetyl-β-D-cellotriosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (**11**): nmr ($CDCl_3$) δ 7.39 (s, 1, H-5), 5.84 (d, 1, *J* = 9 Hz, H-1′), 2.2–1.9 (m, 30, OAc).

2-(Trideca-*O*-acetyl-β-D-cellotetraosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (**12**): nmr ($CDCl_3$) δ 7.39 (s, 1, H-5), 5.83 (d, 1, *J* = 9 Hz, H-1′), 2.2–1.8 (m, 39, OAc).

Acknowledgment. We are indebted to Dr. G.-A. Hoyer and Dr. D. Rosenberg for the nmr and mass spectra and Diplom-Ing. G. Huber for the analyses.

Registry No.—**1**, 5346-90-7; **2**, 17331-61-2; **3**, 38909-08-9; **3a**, 38909-17-0; **7**, 38909-10-3; **7a**, 38909-16-9; **9**, 31873-41-3; **10**, 52523-12-3; **11**, 39020-67-2; **12**, 52523-13-4; **13**, 20880-60-8; **14**, 52554-32-2; **15**, 52571-10-5; **16**, 17331-64-5; **17**, 31167-05-2; **18**, 10457-14-4; **19**, 52523-14-5; **19a**, 52523-15-6; **20**, 38909-07-8; **20a**, 38909-15-8; **21**, 38909-09-0; **21a**, 38909-18-1; **22**, 38909-06-7; **22a**, 38909-14-7; **23**, 38909-11-4; **23a**, 38909-19-2; **24**, 38909-12-5; **24a**, 38909-20-5; **25**, 52523-16-7; **25a**, 52523-17-8; **26**, 38909-23-8; **26a**, 38909-24-9; **27**, 52523-18-9; **27a**, 52523-19-0; **28**, 18037-10-0; **29**, 52523-20-3; **29a**, 52523-21-4.

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A General Synthesis of N-Glycosides. IV.[1] Synthesis of Nucleosides of Hydroxy and Mercapto N-Heterocycles

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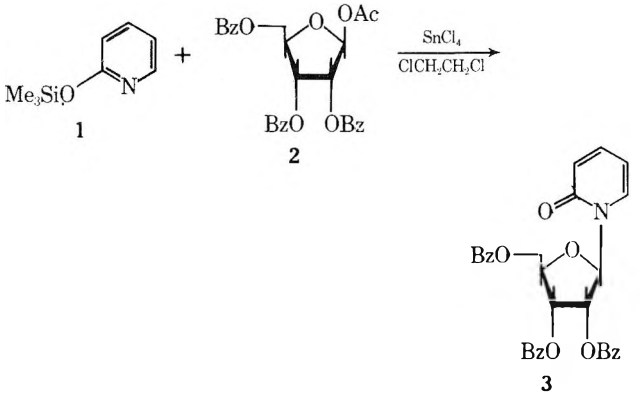
Received March 29, 1974

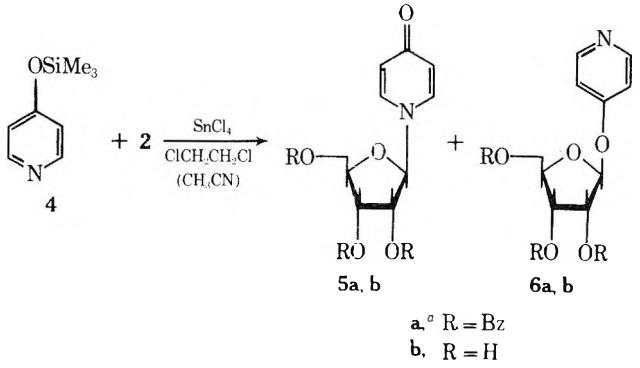
A variety of silylated hydroxy and mercapto N-heterocycles react with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of Friedel–Crafts catalysts to give N-ribosylated heterocycles in generally good yields. In the case of silylated pyrimidin-4-one both possible N-ribosides are obtained.

The smooth reaction of silylated uracils with 1-O-acylated mono-[2] and oligosaccharides[1] in the presence of $SnCl_4$ to give the corresponding nucleosides in good to excellent yields induced us to investigate analogous reactions of silylated hydroxy and mercapto N-heterocycles.

On reaction of silylated pyridin-2-one (**1**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) in the presence of $SnCl_4$ we obtained the crystalline benzoylated nucleoside **3** in 85% yield, which had been prepared previously by Pischel and Wagner[3] *via* the O-glycoside followed by



O,N rearrangement. Even in the presence of a large excess of $SnCl_4$ and longer reaction times at room temperature silylated pyridin-4-one (**4**) gave with **2** in either 1,2-dichloroethane or acetonitrile the expected benzoylated nucleoside **5a** and the crystalline O-glycoside **6a** (both products in ~10% yield). On refluxing the reaction mixture for 1 hr in 1,2-dichloroethane, only 2% O-ribcside **6a** was still present and 63% nucleoside **5a** was obtained, which gave on methanolysis the crystalline free nucleoside **5b**. **5a** had been pre-

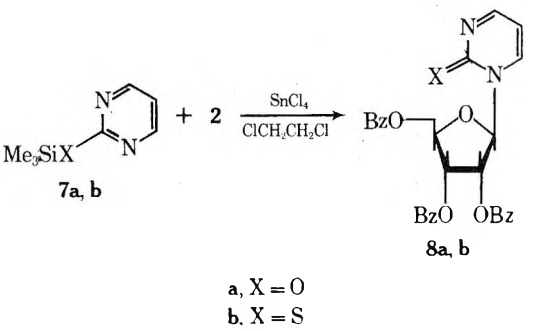


[a] After methanolysis.

pared earlier by Pischel and Wagner[3] by a Hilbert–Johnson reaction of 4-ethoxypyridine as well as by rearrangement of **6a** with $HgBr_2$ in boiling toluene. Our experiments to rearrange **6a** with $SnCl_4$ in boiling 1,2-dichloroethane as well as acetonitrile gave mostly decomposition products and only low yields of **5a**.

These results support the hypothesis that the N-glycosides are usually obtained directly *via* the N-quaternary salt from the silylated heterocycle and the sugar component in the presence of $SnCl_4$ and that a side reaction leads to the formation of O- or S-glycosides, which are then partially rearranged to the N-glycosides or decomposed by the catalyst.

Silylated pyrimidin-2-one (**7a**) afforded **8a** in 73% yield, which had been prepared earlier by the mercuric salt[4,5] method.



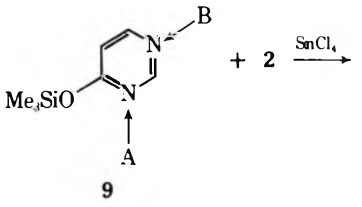
a, X = O
b, X = S

The silylated 2-mercaptopyrimidine (**7b**) gave analogously the 2-thio nucleoside **8b** in 97% yield, which was readily identified by the typical downfield shift of the H-1′ proton ($\delta_{H\text{-}1'}$ 7.02) compared to **8a** (6.35) of 1 ppm.[6] **8b** was recently prepared by Wightman and Holý[7] *via* the S-riboside and subsequent rearrangement with $SnCl_4$ in acetonitrile.

To gain further insight into the mode of electrophilic attack of sugar cations on silylated hydroxy N-heterocycles we treated silylated pyrimidin-4-one (**9**) with **2** in the presence of $SnCl_4$ and obtained beside the expected crystalline ortho quinoid nucleoside **10a** (attack A) also the crystalline para quinoid product **11a** (attack B). Depending on the polarity of the solvent[8] we isolated 26% **10a** and 60% **11a** in 1,2-dichloroethane and 27% **10a** and 38% **11a** in acetonitrile.

The formation of **11a** was surprising since methylation of 4-hydroxypyrimidine had yielded >50% 1,6-dihydro-1-methylpyrimidin-6-one (corresponding to **10**) and ~20% 4-methoxypyrimidine but apparently no 1,4-dihydro-1-methylpyrimidin-4-one.[9] Furthermore, the mercuric salt[5,10] as well as the fusion method[11] had apparently afforded only the ortho quinoid nucleoside **10a**.

The structures of **11a** as well as **11b**, which had been prepared previously by Raney nickel desulfurization of 2-thiouridine,[12] can be deduced from their typical uv **11b** [(CH_3OH), λ_{max} 243 nm (ε 15,290)]; 1,4-dihydro-1-methylpyrimidin-4-one (H_2O), λ_{max} 240 nm (ε 14,640)[9]] as well as nmr data.[13]



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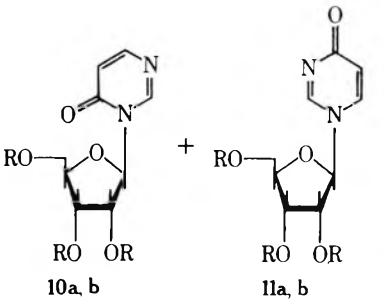


10a, b 11a, b

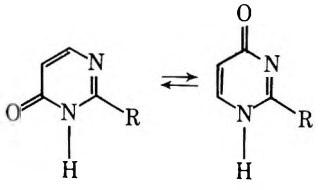
a, R = Bz

b,[a] R = H

[a] After methanolysis.

The preferential formation of **11a** in the silyl Hilbert–Johnson reaction in 1,2-dichloroethane might be due to the steric hindrance of the N-3 nitrogen by the bulky trimethylsilyloxy group, favoring attack B on **9.**

Thus the preponderance of the ortho quinoid **12a** over the para quinoid form **13a** as proved by uv, ir,[14] as well as nmr evidence[13] does not necessarily have a bearing on the reactions of the silylated form **9.** Furthermore, Pitha[15] demonstrated by uv measurements, in the case of 2-ethoxypyrimidin-4-one (**13b**), that the ortho quinoid form **12b** predominates over **13b** only in chloroform, while in water both the ortho quinoid **12b** and the para quinoid form **13b** are present in about equal amount. Thus the energy difference between the forms **12** and **13** is probably very low.

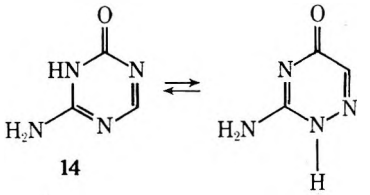


12a, b 13a, b

a, R = H

b, R = OEt

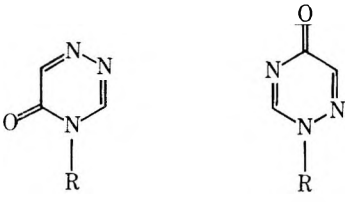
Since 6-azaisocytosine occurs mainly in the para quinoid form **15** and not in the ortho quinoid form **14**,[16] we wondered how *as*-triazin-5-one (5-hydroxy-*as*-triazine) would behave in the silyl Hilbert–Johnson reaction.



14 15

Uv data as well as alkylation studies had established for *as*-triazin-5-one (5-hydroxy-*as*-triazine)[17] that both possible tautomers, **16a** and **17a,** are present. On methylation with diazomethane in methanol as well as with methyl iodide and sodium methoxide the corresponding *N*-methyl derivatives **16b** and **17b** were obtained in roughly equal yields.[17]

In contrast to the methylation studies, silylated *as*-triazin-5-one (**18**) afforded on reaction with **2** and $SnCl_4$ in

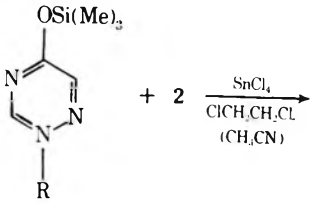


16a, b 17a, b

a, R = H

b, R = CH_3

1,2-dichloroethane as well as acetonitrile almost exclusively the crystalline para quinoid nucleoside **19a** in 67% yield and apparently only traces of the expected ortho quinoid **20a,** which was not isolated.



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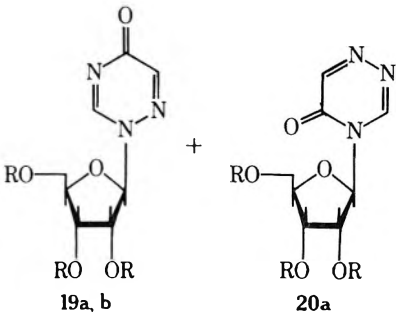


19a, b 20a

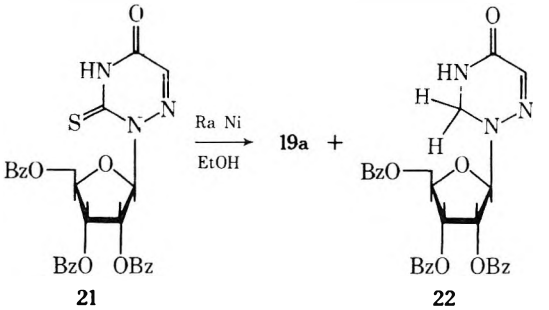
a, R = Bz

b,[a] R = H

[a] After methanolysis.

The structure of **19a** and the free nucleoside **19b** is supported by nmr data [**19a** (H-1′), δ 5.96; **19b** (H-1′), δ 5.79] and especially by the uv spectrum of **19b** in methanol [λ_{max} 242 nm (ϵ 13,600), 269 (sh, 5240)], which agrees closely with the uv spectrum of the methyl derivative **17b** (EtOH) [λ_{max} 242 nm (ϵ 11,400), 260 (sh, 4670)[17]].

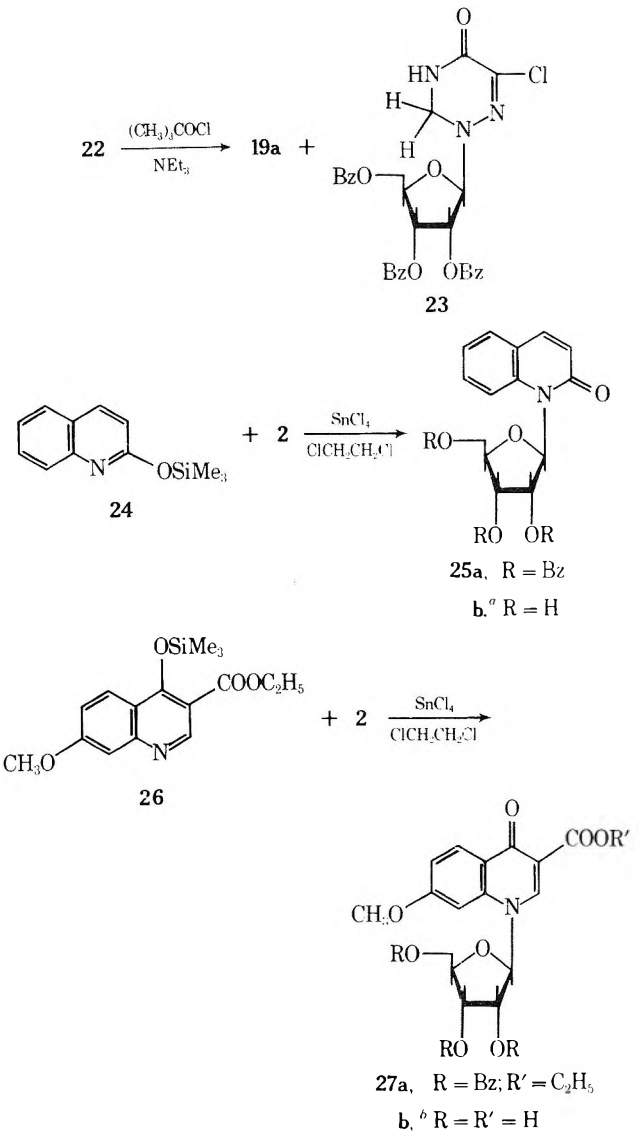
The para quinoid nucleoside **19a** was also prepared by Raney nickel desulfurization of 2′,3′,5′-tri-*O*-benzoyl-β-D-2-thio-6-azauridine (**21**), which gave, besides **19a,** the corresponding crystalline 1,2-dihydro nucleoside **22** in about equal yield. Oxidation of **22** with *tert*-butyl hypochlorite–



21 22

triethylamine[18] gave 60% **19a** as well as 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-chloro-2,3,4,5-tetrahydro-1,2,4-triazin-5-one (**23**).

Analogously, the silylated quinolin-2-one (**24**) was converted into the nucleoside **25a** in 79% yield. Silylated 7-methoxyquinolin-4-one-3-carboxylic acid ethyl ester (**26**) afforded the nucleoside **27a** in about 82% yield.



[a] After methanolysis. [b] After saponification.

These results demonstrate that a wide variety of silylated ortho or para quinoid hydroxy or mercapto N-heterocycles react with **2** and in all probability with other suitable sugar derivatives[2] in the presence of $SnCl_4$ to give the corresponding N-glycosides in good to excellent yields.

Following our preliminary publication,[2] a number of different groups have successfully used our procedure for the synthesis of nucleosides of hydroxy N-heterocycles.[19-25]

Experimental Section

For instruments, adsorbents, and the purification of solvents compare part I.[2] Tlc systems: system A [ethyl acetate–methanol (9:1)]; system B (ethyl acetate); and system C [*n*-butyl acetate–methyl glycol–H_2O (4:1:2)].[26]

The heterocyclic bases were purchased from Fluka AG. The *as*-triazin-5-one was prepared according to Lee and Paudler.[17a] The 3-carbethoxy-7-methoxy-1,4-dihydroquinolin-4-one was a gift from Dr. Albrecht, Schering A. G. The heterocyclic bases were silylated in high yields according to standard methods.[2]

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2-dihydropyridin-2-one (3). To **2** (9.1 g, 18 mmol) and 2-trimethylsilyloxypyridine (**1**, 22.6 mmol) in 1,2-dichloroethane (200 ml) $SnCl_4$ (2.9 ml, 24.8 mmol) in 1,2-dichloroethane (50 ml) was added. After stirring overnight and usual work-up[2] crystallization (CCl_4) gave **3** in long needles; yield, 8.3 g (85.2%); mp 139–140° (lit.[3] 139–142°); $[\alpha]^{20}D$ 61° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 6.59 (d, 1, *J* = 4 Hz, H-1′)

Anal. Calcd for $C_{31}H_{25}NO_8$ (539.55): C, 69.01; H, 4.67; N, 2.60. Found: C, 68.99; H, 4.84; N, 2.73.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,4-dihydropyridin-4-one (5a), 4-[(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-oxy]pyridine (6a). To **2** (4.5 g, 8.9 mmol) and **4** (1.7 g, 10 mmol) in 1,2-dichloroethane (150 ml) $SnCl_4$ (1.2 ml, 10.25 mmol) in 1,2-dichloroethane (50 ml) was added and the mixture was refluxed for 1 hr. After work-up, the residue was chromatographed on silica gel (250 g). Elution with ethyl acetate gave the crystalline O-riboside **6a** (ethanol) (tlc, system A): yield, 165 mg (2.3%); mp 139–140° (lit.[3] 139–142°); nmr ($CDCl_3$) δ 6.1–5.9 (m, 3, H-1′, H-2′, H-3′).

Anal. Calcd for $C_{31}H_{25}NO_8$ (539.55): C, 69.01; H, 4.67; N, 2.60. Found: C, 68.75; H, 4.78; N, 2.54.

Ethyl acetate–methanol (9:1) eluted the N-riboside **5a**: yield; 3.227 g (63%); amorphous; nmr ($CDCl_3$) δ 5.9–5.6 (m, 3, H-1′, H-2′, H-3′); $[\alpha]^{23}D$ −150.5° (*c* 1, $CHCl_3$)

Anal. Calcd for $C_{31}H_{25}NO_8$ (539.55): C, 69.01; H, 4.67; N, 2.60. Found: C, 68.83; H, 4.79; N, 2.52.

1-(β-D-Ribofuranosyl)-1,4-dihydropyridin-4-one (5b). **5a** (1.5 g, 2.8 mmol) was kept in dry methanolic ammonia (60 ml) overnight. After evaporation *in vacuo* and partition between water and ether, the aqueous layer was concentrated *in vacuo* to a viscous oil, which crystallized (ethanol) in colorless prisms: yield of **5b**, 514 mg (81.3%); mp 128–130°; $[\alpha]^{23}D$ −89.6° (*c* 1, ethanol + H_2O = 2:1); nmr (D_2O) δ 5.57 (d, 1, *J* = 3.5 Hz, H-1′); uv (CH_3OH) λ_{max} 266 nm (18,420).

Anal. Calcd for $C_{10}H_{13}NO_5$ (227.22): C, 52.86; H, 5.77; N, 6.17. Found: C, 52.81; H, 5.89; N, 6.08.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2-dihydropyrimidin-2-one (8a). To **2** (5.045 g, 10 mmol) and **7a** (13.4 mmol) in CH_3CN (100 ml) $SnCl_4$ (1.73 g, 14.1 mmol) in CH_3CN (50 ml) was added. After 22° and work-up the residue (5.5 g) was chromatographed on silica gel (250 g) using ethyl acetate–methanol (9:1) as eluent to give **8a** as a white amorphous powder after precipitation from *n*-hexane: mp 139–142° [after precipitation from ethanol, mp 155–158° (lit.[6] mp 154–158°)]: yield; 3.89 g (72.9%); nmr ($CDCl_3$) δ 6.35 (d, 1, *J* = 3.5 Hz, H-1′).

Anal. Calcd for $C_{30}H_{24}N_2O_8$ (540.54): C, 66.66; H, 4.48; N, 5.18. Found; C, 66.59; H, 4.52; N, 5.19.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2-dihydropyrimidine-2-thione (8b). To **2** (5.045 g, 10 mmol) and **7b** in CH_3CN (100 ml) $SnCl_4$ (1.73 ml, 14.1 mmol) in CH_3CN (100 ml) was added. According to tlc (system B) the reaction was complete after 5 min at 22° and was worked up after an additional 5 min. The residue was dissolved in ethyl acetate (50 ml) and added slowly to *n*-hexane (2 l.). The precipitate, a yellow powder (5.23 g), was homogenous according to tlc (system B). The hexane solution was evaporated to dryness and the residue (0.49 g) was dissolved in ethyl acetate and again precipitated by *n*-hexane to give a second crop (0.18 g): total yield of **8b**, 5.41g (96.7%); amorphous; $[\alpha]^{23}D$ 189.7° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 7.02 (d, 1, *J* = 2 Hz, H-1′).

Anal. Calcd for $C_{30}H_{24}N_2O_7S$ (559.63): C, 64.39; H, 4.86; N, 5.01; S, 5.73. Found: C, 64.31; H, 4.97; N, 5.03; S, 5.66.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,6-dihydropyrimidin-6-one (10a) and 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,4-dihydropyrimidin-4-one (11a). A. Reaction in 1,2-Dichloroethane. To **2** (4.14 g, 8.20 mmol) and **9** (10 mmol) in 1,2-dichloroethane (100 ml) $SnCl_4$ (1.60 ml, 13.67 mmol) in 1,2-dichloroethane (50 ml) was added. After 0.5 hr at 15°, 3.5 hr at 22°, and work-up, tlc (system A) showed the formation of two products. The residue was dissolved in hot ethyl acetate (~150 ml) from which **11a** crystallized in long needles: yield, 2.66 g (60%); mp 224–226°; $[\alpha]^{23}D$ −138.9° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 5.9–5.6 (m, 3, H-1′, H-2′, H-3′).

Anal. Calcd for $C_{30}H_{24}N_2O_8$ (540.39): C, 66.66; H, 4.48; N, 5.18. Found: C, 66.61; H, 4.59; N, 5.28.

11a (1.4 g, 2.6 mmol) gave with methanolic ammonia (16 hr at 22°) **11b** (521 mg, 87.8%): mp 122–124° (ethanol–H_2O); $[\alpha]^{23}D$ −75.8° [*c* 1, ethanol–H_2O (2:1)]; nmr (D_2O) δ 5.67 (d, 1, *J* = 5 Hz, H-1′).

Anal. Calcd for $C_9H_{12}N_2O_5$ (228.21): C, 47.37; H, 5.30; N, 12.28. Found: C, 47.45; H, 5.67; N, 12.15.

The mother liquor of **11a** was concentrated *in vacuo* and poured into *n*-hexane to remove sugar derivatives. The precipitate crystallized (ethyl acetate–*n*-hexane) to give **10a** in needles: yield, 1.16 g (26.4%); mp (128–132°, changing point) 157–158° (lit.[5] 157–157.5°); nmr ($CDCl_3$) δ 6.24 (d, 1, *J* = 3 Hz, H-1′).

B. Reaction in CH_3CN. To **2** (5.045 g, 10 mmol) and **9** (10 mmol) in CH_3CN (100 ml) $SnCl_4$ (2.0 ml, 17.1 mmol) in CH_3CN (100 ml) was added. After 0.5 hr at 15° and 3.5 hr at 22° work-up gave 27% **10a** and 38% **11a**.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2,5-dihydro-1,2,4-triazin-5-one (19a). To a solution of **2** and **18** (12 mmol) in

CH_3CN (60 ml) $SnCl_4$ (1 ml, 8.16 mmol) in CH_3CN (40 ml) was added. After 24 hr at 22° and work-up the crude product (5.3 g) was chromatographed on silica gel (250 g) using *n*-hexane–ethyl acetate (1:9) as eluent. The crude nucleoside was dissolved in ethyl acetate and poured into pentane. The precipitate crystallized (ethanol) to give **19a** as needles (3.61 g, 66.6%): mp 117–119°; $[\alpha]^{23}D$ −94° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 8.53 (d, 1, J = 1.5 Hz, H-3), 5.96 (d, 1, J = 3.5 Hz, H-1′).

Anal. Calcd for $C_{29}H_{23}N_3O_8$ (541.53): C, 64.32); H, 4.28; N, 7.76. Found: C, 64.25; H, 4.41; N, 7.68.

2-(β-D-Ribofuranosyl)-2,5-dihydro-1,2,4-triazin-5-one (19b). **19a** (2.5 g, 4.62 mmol) in dry methanolic ammonia (60 ml) was stored overnight to give **19b** in needles (2-propanol–H_2O): yield, 876 mg (83.5%); mp 116–119°; $[\alpha]^{23}D$ −74.2° [c 1, ethanol–H_2O) (2:1)] nmr (D_2O) δ 8.93 (d, 1, $J \approx 1$ Hz, H-3), 8.01 (d, 1, $J \approx 1$ Hz, H-6), 5.79 (d, 1, J = 3.5 Hz, H-1′.

Anal. Calcd for $C_8H_{11}N_3O_5$ (229.20): C, 41.92; H, 4.84; N, 18.34. Found: C, 41.95; H, 5.12; N, 18.19.

Desulfurization of 2-Thio-6-azauridine 2′,3′,5′-Tri-*O*-benzoate (21) to 19a and 2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2,3,4,5-tetrahydro-1,2,4-triazin-5-one (22). **21** (2.869 g, 5 mmol) and benzoic acid (0.61 g, 5 mmol) were suspended, stirred in abs ethanol (150 ml), and cooled to 0°, and freshly prepared W-2 Raney nickel[27] (12 g) was added, which had been washed with ethanol. After 4, 8, and 12 hr further portions of Raney nickel (10 g each) were added at 0° until the starting material had nearly disappeared according to tlc (system C). Thiourea (2 g) was added and stirring was continued for 1 hr at 0°. After filtering the excess Raney nickel, washing with cold ethanol (500 ml), and extracting the reagent with boiling ethanol (1 l.) the filtrates were evaporated and the residue was taken up in chloroform (200 ml). The chloroform solution was extracted with saturated $NaHCO_3$ solution (150 ml), dried ($MgSO_4$), and evaporated to give a crude product (1.828 g), which consisted according to tlc (system C) of an ~ 1:1 mixture of **19a** and the slightly slower moving **22.** On standing in ethanol (30 ml) **22** crystallized: yield, 0.82 g (30%); mp 193–197°; $[\alpha]^{23}D$ 4.4° (c 1, $CHCl_3$); nmr ($CDCl_3$ + D_2O) δ 6.75 (s, 1, H-6), 5.34 (d, 1, J = 3.5 Hz, H-1′); uv (CH_3OH) λ_{max} (pH 7) 281 nm (ϵ 5340), λ_{max} (pH 13) 301 (3490), λ_{max} (pH 1) 281 (5350).

Anal. Calcd for $C_{29}H_{25}N_3O_8$ (543.51): C, 64.08; H, 4.64; N, 7.73. Found: C, 63.65; H, 4.74; N, 8.13. An aliquot (0.2 g) of the evaporated mother liquor (0.98 g) was separated by preparative tlc on silica gel (system C) to give pure **19a** (83 mg, 16%), which was identified by tlc and by comparison of melting point and ir spectrum with authentic **19a.**

Conversion of 22 to 19a and 2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-6-chloro-2,3,4,5-tetrahydro-1,2,4-triazin-5-one (23). A solution of **22** (543 mg, 1 mmol) in chloroform (20 ml) and triethylamine (0.14 ml, 1 mmol) was stirred at −10° and *tert*-butyl hypochlorite was added with vigorous stirring until **22** had disappeared according to tlc (system C). The yellow solution was washed with sodium thiosulfate solution, dried (Na_2SO_4), and evaporated to a light brown oil, which was chromatographed on silica gel (50 g). Elution with hexane–ethyl acetate (1:1) gave first **23** (112 mg, 19.3%) followed by **19a** (316 mg, 58.4%), which was identified by tlc and ir comparison with an authentic sample of **19a.**

23 was recrystallized (2-propanol): mp 173–175°; $[\alpha]^{23}D$ −18.8° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 5.30 (d, 1, J = 3.5 Hz, H-1′).

Anal. Calcd for $C_{29}H_{24}N_3O_8Cl$ (577.99): C, 60.26; H, 4.19; N, 7.27; Cl, 6.13. Found: C, 60.64; H, 4.08; N, 7.66; Cl, 6.18.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2-dihydroquinolin-2-one (25a). To **2** (5.045 g, 10 mmol) and **24** (12 mmol) in CH_3CN (100 ml) $SnCl_4$ (1.5 ml, 12.2 mmol) in CH_3CN (670 ml) was added. After 42 hr at 22° and work-up, the residue was treated with charcoal and chromatographed on silica gel (250 g) using *n*-hexane–ethyl acetate (2:1) as eluent. **25a** was obtained as a white foam: yield; 4.65 g (78.9%); amorphous; $[\alpha]^{23}D$ 4.7° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 6.77 (d, 1, J = 3 Hz, H-1′), 6.61 (d, 1, J = 9 Hz, H-3).

Anal. Calcd for $C_{35}H_{27}NO_8$ (589.61): C, 71.30; H, 4.62; N, 2.38. Found: C, 71.19; H, 4.90; N, 2.45.

25a (2.9 g, 4.92 mmol) gave with methanolic ammonia crystalline (ethanol) **25b** (1.20 g, 87.9%): mp 142–143°: $[\alpha]^{23}D$ −9.6° [c 1, ethanol–H_2O (2:1)]; nmr (pyridine-d_5) δ 8.09 (d, 1, J = 9 Hz, H-4), 7.12 (d, 1, J = 5 Hz, H-1′), 6.57 (d, 1, J = 9 Hz, H-3).

Anal. Calcd for $C_{14}H_{15}NO_5$ (277.28): C, 60.64; H, 5.45; N. 5.05. Found: C, 60.57; H, 5.73; N, 4.99.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3-carbethoxy-7-methoxy-1,4-dihydroquinolin-4-one (27a). To **2** (1.73 g, 3.43 mmol) and **26**)1.2 g, 3.76 mmol) in 1,2-dichloroethane (60 ml) $SnCl_4$ (0.5 ml, 4.27 mmol) in 1,2-dichloroethane (10 ml) was added. After 2 hr at 22° and work-up the residue was crystallized (ethanol) to give **27a** as needles (1.93 g, 81.5%): mp 133–136°: $[\alpha]^{20}D$ −80.4° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 8.94 (s, 1, H-2), 6.45 (d, 1, J = 4.5 Hz, H-1′), 3.75 (s, 3, Ar OCH_3).

Anal. Calcd for $C_{39}H_{33}NO_{11}$ (691.70): C, 67.72; H, 4.81; N, 2.03. Found: C, 67.58; H, 4.97; N, 2.11.

27a (0.448 g, 0.695 mmol) in 0.5 *N* methanolic sodium hydroxide (30 ml) was stirred for 2 hr at 22° and passed through a column of Dowex 50 H^+ (20 ml), which was washed with methanol–H_2O (3:1). The filtrate was evaporated and the residue was partitioned between water and ether. The aqueous solution was evaporated *in vacuo* and the residue crystallized (ethanol–H_2O) to give **27b:** yield, 199 mg (81.6%); mp 213°.

Anal. Calcd for $C_{16}H_{17}NO_8$ (351.32): C, 54.70; H, 4.88; N, 3.99. Found: C, 54.82; H, 4.97; N, 3.86.

Acknowledgment. We are indebted to Dr. G.-A. Hoyer and Dr. D. Rosenberg for the nmr and mass spectra and Diplom-Ing. G. Huber for the analyses.

Registry No. 1, 18292-04-1; **2,** 6974-32-9; **3,** 5116-31-4; **4,** 27248-04-0; **5a,** 18342-24-0; **5b,** 52554-33-3; **6a,** 18342-23-9; **7a,** 52523-22-5; **7b,** 52523-23-6; **8a,** 52523-24-7; **8b,** 49625-10-7; **9,** 52523-25-8; **10a,** 5116-20-1; **11a,** 52523-26-9; **11b,** 21052-20-0; **18,** 52523-27-0; **19a,** 52523-28-1; **19b,** 52554-34-4; **21,** 27089-55-0; **22,** 52523-29-2; **23,** 52523-30-5; **24,** 52523-31-6; **25a,** 52523-32-7; **25b,** 52523-33-8; **26,** 52523-34-9; **27a,** 35068-46-3; **27b,** 35068-65-6.

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A General Synthesis of N-Glycosides. V.[1,2] Synthesis of 5-Azacytidines

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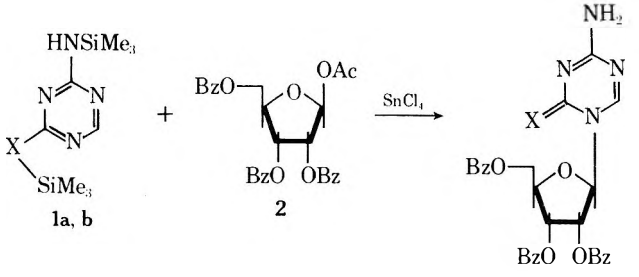
Received March 29, 1974

Reaction of silylated 5-azacytosines as well as their silylated 2-thio analogs with protected 1-*O*-acyl sugars in the presence of $SnCl_4$ gave the corresponding 5-azacytidines in good yields.

The cancerostatic 5-azacytidine, which is highly active against leukemia,[3] and certain analogs were first prepared *via* a multistep synthesis starting from peracetylated 1-glycosyl isocyanates by Píškala and Šorm.[4] Subsequently, 5-azacytidine was isolated as a new antibiotic by Hanka, *et al.*,[5] from *Streptoverticillium ladakanus*. More recently Winkley and Robins[6] treated silylated 5-azacytosines with acylated 1-halo sugars but obtained only fair yields of 5-azacytidine and its 2′-deoxy and other analogs.

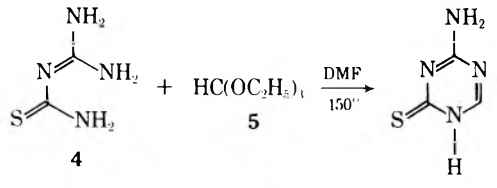
The biological importance of 5-azacytidine[3] induced us to apply our new Friedel–Crafts catalyzed silyl Hilbert–Johnson procedure[7] to the synthesis of 5-azacytidines. Reaction of silylated 5-azacytosine (**1a**) and 2-thio-5-azacytosine (**1b**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) in 1,2-dichloroethane or acetonitrile in the presence of $SnCl_4$ gave the corresponding O-benzoylated 5-azacytidines **3a** and **3b** in yields of up to 80%, thus making these interesting compounds readily available.[8]



a, X = O
b, X = S

The preparation of the base 5-azacytosine[9] was simplified by direct synthesis from *N*-cyanoguanidine and formic acid–acetic anhydride in 35% yield.

The new 2-thio-5-azacytosine (**6**) was obtained by condensation of thiocarbamoylguanidine (**4**) with ethyl orthoformate (**5**) in dimethylformamide at 150° in analogy to Píškala[9] to give **6** in 72% yield, which could be readily silylated to the crystalline *S,N*-bissilyl compound **1b**.

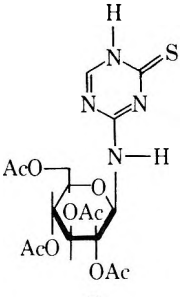


During the reaction of **1b** with pentaacetyl-β-D-glucopyranose (**10**) the N^4-(glucosyl)-2-thio-5-azacytosine (**7**) was isolated as a side product and characterized by uv and nmr spectra. The anomeric H-1′ proton [δ 5.73 (dd, $J = J' \approx 9$ Hz)] is split by the NH group, which disappears on exchange with D_2O to give a doublet [δ 5.72 (d, $J = 9$ Hz)].

Table I
Preparation of Acylated 5-Azacytidine and Analogs

Silylated s-triazine	Acylated sugar	Acylated nucleoside	Yield, %
2,4-*O*,*N*-Bis(trimethylsilyl)-4-amino-1,3,5-triazine (**1a**)	1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**)	**3a**	81
	1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose (**8**)	**9a**	50
	1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (**10**)	**11a**	78
	1,2,3,4-Tetra-*O*-acetyl-β-D-ribopyranose (**12**)	**13a**	52
	2-Deoxy-3,5-di-*O*-*p*-toluoyl-α-D-ribofuranosyl chloride, (**14**)	**15a**	42[a]
2,4-*S*,*N*-Bis (trimethylsilyl)-4-amino-2-mercapto-1,3,5-triazine (**1b**)	1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**)	**3b**	82
	1,2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranose (**10**)	**11b**	59
	1,2,3,4-Tetra-*O*-acetyl-β-D-ribopyranose (**12**)	**13b**	56

[a] Yield of β anomer, total yield 77%.



7

The saponification of the O-benzoylated 5-azacytidine (**3a**) to free 5-azacytidine is difficult and best results are obtained following closely the procedure of Píškala and Šorm.[4] However, all attempts to saponify or transesterify the O-benzoylated 2-thio-5-azacytidine (**3b**) and its analogs failed. Apparently the heterocyclic ring in **3b** opens readily under basic conditions. The cleavage is accompanied by a

shift in the uv maxima from 283 to 277 nm and by disappearance of the H-6 proton at δ 8.2 in the nmr spectrum.

In Table I the preparation of acylated analogs of **3** is summarized.

Experimental Section

For instruments and the purification of solvents compare part I[7] of this series.

A. 4-Amino-1,2-dihydro-1,3,5-triazine-2-one. A mixture of 98–100% formic acid (80 ml, 2.12 mol), acetic anhydride (80 ml, 0.816 mol), and *N*-cyanoguanidine (dicyandiamide, Merck, Darmstadt) (84.08 g, 1 mol) was heated to 100°, whereupon the reaction started to boil vigorously. The solid dissolved and after a short time a colorless precipitate separated. The reaction was completed by heating to 140° for 2 hr. After cooling to 22° the solid was filtered and the crude material extracted three times with boiling ethanol to give after drying *in vacuo* a white powder (38.8 g, 34.6%) with mp 350°, which could be readily silylated in high yields according to standard procedures to give **1a**.[9]

Anal. Calcd for $C_3H_4N_4O$ (112.10): C, 32.15; H, 3.60; N, 49.99. Found: C, 31.87; H, 3.69; N, 50.13.

B. 4-Amino-1,2-dihydro-1,3,5-triazine-2-thione (6). A suspension of freshly prepared **4**[10] (118.2 g, 1 mol) and **5** (148.2 g, 1.8 mol) in dry dimethylformamide (500 ml) was refluxed (oil bath, 160°) for 2 hr with exclusion of moisture, whereupon the solid dissolved and after a few minutes a crystalline product separated. After cooling to 22° the crystalline material was filtered, washed with ethanol, and dried *in vacuo* at 50° to give 92.5 g (72%): mp >330°; nmr (NaOD) δ 8.00 (s, 1, H-6); uv (CH_3OH) λ_{max} 210 nm (ϵ 10,900), 270 (16,900).

Anal. Calcd for $C_3H_4N_4S$ (128.16): C, 28.12; H, 3.15; N, 43.72; S, 25.02. Found: C, 27.84; H, 3.31; N, 43.69; S, 24.84.

C. 2,4-*S,N*-Bis(trimethylsilyl)-4-amino-2-mercapto-1,2,5-triazine (1b). **6** (38.45 g, 300 ml) was suspended in a mixture of HMDS (400 ml), pyridine (1.2 l.), and trimethylchlorosilane (1 ml). The mixture was refluxed, whereupon the solid dissolved almost completely. The solution was filtered from the solid under nitrogen and concentrated *in vacuo* to 400 ml. **1b** crystallized from the hot solution and was filtered in an atmosphere of nitrogen and washed with a small amount of absolute benzene. The product was dried *in vacuo* at 50°: yield, 68.2 g (83.7%).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-amino-1,2-dihydro-1,3,5-triazin-2-one (3a). To **2** (5.0 g, 9.91 mmol) and **1a** (12.5 mmol) in 1,2-dichloroethane (150 ml) $SnCl_4$ (1.68 ml, 14.16 mmol) in 1,2-dichloroethane (20 ml) was added at 10°. After stirring at 10° for 2 hr the solution was diluted with CH_2Cl_2 and washed with ice-cold saturated $NaHCO_3$ solution. The organic phase was filtered through a layer of Celite, which was washed with a small amount of CH_2Cl_2. After drying (Na_2SO_4) and evaporation, the residue was dissolved in toluene and filtered through Celite to remove unreacted 5-azacytosine. After evaporation *in vacuo* the residue (5.2 g) was dissolved in ethanol and filtered again through Celite. **3a** crystallized from the filtrate as needles: yield, 4.45 g (80.7%); mp 186–187°; $[\alpha]^{20}D$ −33.1° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 8.21 (s, 1, H-6), 6.1–5.9 (m, 3, H-1′, H-2′, H-3′).

Anal. Calcd for $C_{29}H_{24}N_4O_8$ (556.54): C, 62.59; H, 4.35; N, 10.07. Found: C, 62.43; H, 4.41; N, 10.21.

3a gave on methanolysis[4] 5-azacytidine, mp 232–233° (EtOH) (lit.[4] 230–231° dec).

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4-amino-1,2-dihydro-1,3,5-triazin-2-one (9a). To **8** (6.36 g, 20 mmol) and **1a** (25 mmol) in CH_3CN (200 ml) $SnCl_4$ (4 ml, 34.2 mmol) in CH_3CN (100 ml) was added at 22°. After 30 min at 22° and work-up[11] crystallization (ethyl acetate) gave 3.68 g (49.7%) of **9a**: mp 160–161°; $[\alpha]^{23}D$ 3.41° (c 1.04, $CHCl_3$); nmr ($CDCl_3$) δ 5.82 (d, 1, J = 3.5 Hz, H-1′).

Anal. Calcd for $C_{14}H_{18}N_4O_8$ (270.33): C, 45.41; H, 4.90; N, 15.13. Found: C, 45.55; H, 5.05; N, 15.33.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-amino-1,-2-dihydro-1,3,5-triazin-2-one (11a). To **10** (15.56 g, 40 mmol) and **1a** (50 mmol) in CH_3CN (300 ml) $SnCl_4$ (8.5 ml, 72.65 mmol) in CH_3CN (150 ml) was added. After 5.5 hr at 22° and work-up[11] recrystallization (ethyl acetate–pentane) gave 13.32 g (77.6%) of **11a**: mp 213–214°; $[\alpha]^{20}D$ 10.6° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 8.21 (s, 1, H-6), 5.98 (d, 1, J = 9 Hz, H-1′).

Anal. Calcd for $C_{17}H_{22}N_4O_{10}$ (442.40): C, 46.15; H, 5.01; N, 12.67, Found: C, 46.31; H, 5.19; N, 12.59.

1-(2,3,4-Tri-*O*-acetyl-β-D-ribopyranosyl)-4-amino-1,2-dihydro-1,3,5-triazin-2-one (13a). To **12** (3.18 g, 10 mmol) and **1a** (12.5 mmol) in 1,2-dichloroethane (150 ml) $SnCl_4$ (1.68 ml, 14.36 mmol) in 1,2-dichloroethane (20 ml) was added. After 2 hr at 22° and work-up[11] the residue (3.14 g) was chromatographed in ethyl acetate on silica gel (200 g). **13a** crystallized from ethanol: yield, 1.92 g (51.9%); mp 128–136° (solvated); $[\alpha]^{20}D$ 30.6° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 6.11 (d, 1, J = 10 Hz, H-1′).

Anal. Calcd for $C_{14}H_{18}N_4O_8$ (370.33): C, 45.41; H, 4.90; N, 15.13. Found: C, 45.26; H, 5.03; N, 15.02 [after drying for 2 hr at 50° (10^{-3} mm)].

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-ribofuranosyl)-4-amino-1,2-dihydro-1,3,5-triazin-2-one (15a). To **14** (3.89 g, 10 mmol) and **1a** (12.5 mmol) in 1,2-dichloroethane (150 ml) $SnCl_4$ (0.84 ml, 7.18 mmol) in 1,2-dichloroethane (20 ml) was added. After 2 hr at 22° and work-up[11] crystallization (toluene) afforded a mixture of the anomeric nucleosides (3.55 g, 76.6%) from which **15a** was obtained by fractional crystallization (ethyl acetate): yield, 1.93 g (41.6%); mp 196°; $[\alpha]^{20}D$ 23.7° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 8.37 (s, 1, H-6), 6.27 (dd, 1, J = 8 + 6 Hz, H-1′).

Anal. Calcd for $C_{24}H_{24}N_4O_6$ (464.49): C, 62.06; H, 5.21; N, 12.06. Found: C, 62.35; H, 5.38; N, 12.08.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-amino-1,2-dihydro-1,3,5-triazine-2-thione (3b). To a suspension of **1b** (1.64 g, 6 mmol) in CH_3CN (50 ml) $SnCl_4$ (1.6 ml, 13.7 mmol) in CH_3CN (50 ml) was added. After addition of **2** (2.522 g, 5 mmol) and 30 min at 22°, work-up[11] gave crude **3b** (2.86 g), which crystallized as needles (ethyl acetate): yield, 2.34 g (81.7%); mp 201–203°; $[\alpha]^{20}D$ −24.2° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 8.52 (s, 1, H-6), 7.15 (d, 1, J = 3 Hz, H-1′).

Anal. Calcd for $C_{29}H_{24}N_4O_7S$ (572.61): C, 60.83; H, 4.23; N, 9.79; S, 5.60. Found: C, 60.75; H, 4.34; N, 9.87; S, 5.49.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-amino-1,-2-dihydro-1,3,5-triazine-2-thione (11b). To a suspension of **1b** (3.26 g, 11.9 mmol) in CH_3CN (150 ml) $SnCl_4$ (3.2 ml, 27.4 mmol) in CH_3CN (70 ml) was added (**1b** dissolved), followed by **10** (3.89 g, 10 mmol). After 30 min at 22° and work-up[11] **11b** crystallized (ethanol) as colorless needles: yield, 2.72 g (59.4%); mp 246–247°; $[\alpha]^{20}D$ 20.8° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 8.37 (s, 1, H-6), 7.10 (d, 1, J = 9 Hz, H-1′).

Anal. Calcd for $C_{17}H_{22}N_4O_9S$ (458.46): C, 44.54; H, 4.84; N, 12.22; S, 6.99. Found: C, 44.37; H, 4.99; N, 12.30; S, 6.88.

Reaction in 1,2-dichloroethane gave 38% **11b**. From the mother liquor the N_4-glucoside **7** was isolated by preparative tlc (silica gel, ethyl acetate): yield, 213 mg (3%); amorphous; $[\alpha]^{23}D$ 7.1° (*c* 0.48, ethyl acetate); nmr ($CDCl_3$) δ 8.45 (s, 1, H-6), 5.73 (dd, 1, $J = J'$ = 9 Hz, H-1′).

Anal. Calcd for $C_{17}H_{22}N_4O_9S$ (458.46): C, 44.54; H, 4.84; N, 12.22; S, 6.99. Found: C, 44.38; H, 4.96; N, 12.16; S, 7.11.

1-(2,3,4-Tri-*O*-acetyl-β-D-ribopyranosyl)-4-amino-1,2-dihydro-1,3,5-triazine-2-thione (13b). To **1b** (3.26 g, 11.9 mmol) in CH_3CN (100 ml) $SnCl_4$ (3.2 ml, 27.4 mmol) in CH_3CN (70 ml) was added (**1b** dissolved), followed by **12** (3.18 g, 10 mmol). After 1 hr at 22° and work-up[11] **13b** crystallized (ethanol) as needles: yield, 2.08 g (56.2%); mp 237–239°; $[\alpha]^{20}D$ 72.0° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 8.23 (s, 1, H-6), 7.23 (d, 1, J = 9 Hz, H-1′).

Anal. Calcd for $C_{14}H_{18}N_4O_7S$ (386.40): C, 43.52; H, 4.70; N, 14.50; S, 8.30. Found: C, 43.41; H, 4.78; N, 14.56; S, 8.26.

Acknowledgment. We are indebted to Dr. G.-A. Hoyer and Dr. D. Rosenberg for the nmr spectra and Diplom-Ing. G. Huber for the analyses.

Registry No.—**1a**, 52523-35-0; **1b**, 35782-62-8; **2**, 6974-32-9; **3a**, 28998-36-9; **3b**, 29845-69-0; **4**, 2114-02-5; **5**, 122-51-0; **6**, 36469-86-0; **7**, 52523-36-1; **8**, 13035-61-5; **9a**, 10302-78-0; **10**, 604-69-3; **11a**, 29845-67-8; **11b**, 30009-99-5; **12**, 4049-34-7; **13a**, 30370-22-0; **13b**, 30370-25-3; **14**, 4330-21-6; **15a**, 10302-79-1; 4-amino-1,2-dihydro-1,3,5-triazin-2-one, 931-86-2.

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Mixed Alkylation (Methylation and Ethylation) of Adenosine by Diazoethane in Aqueous 1,2-Dimethoxyethane[1]

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Received August 13, 1974

Synthesis of 2′-*O*-ethyladenosine by treatment of adenosine with diazoethane in aqueous 1,2-dimethoxyethane produced several unexpected alkylation products. Characterization of the products by several methods, including mass spectrometry of their trimethylsilyl ethers, indicated that methylation was occurring to approximately the same extent as ethylation. Analysis of the reaction conditions employing palmitic acid as an alkyl acceptor implicated the solvent (1,2-dimethoxyethane) as a potential source of the extraneous methyl groups since only ethylation was observed when diethyl ether was employed as an alternate solvent.

The reaction of adenosine and diazomethane in aqueous 1,2-dimethoxyethane has been used extensively to prepare 2′-Am[2] since the 2′-hydroxyl group is preferentially methylated under these conditions.[3-5] When adenosine was treated with diazoethane under similar reaction conditions, several unexpected products were observed. In this paper these products are identified and found to indicate the occurrence of mixed alkylation. Evidence is presented which is consistent with involvement of the solvent (1,2-dimethoxyethane) in the alkylation reaction under these conditions.

Adenosine and diazoethane were combined in a solvent of aqueous 1,2-dimethoxyethane, the reaction was permitted to reach completion, and the products were resolved by ion exchange chromatography.[6] Six prominent uv-absorbing fractions were observed as shown in Table I, whereas only four fractions were observed following alkylation of adenosine with diazomethane.[5]

Some preliminary conclusions concerning the nature of the six fractions may be reached from their relative yields and column retentions. By analogy to the reaction of adenosine and diazomethane, one of the major products would be 2′-Ae while lesser amounts of the 3′-ethyl ether and dialkylated products would be obtained.[3] Furthermore, the degree of retention of nucleosides on the ion-exchange column may be correlated with increasing ionization potential of available ribose hydroxyl groups.[7] Therefore, the expected order of elution is: dialkylation products, 2′-*O*-alkylation products, and finally 3′-*O*-alkylation products. Compounds with both 2′- and 3′-hydroxyl groups available are not eluted under these conditions. On the basis of yield and elution pattern, fractions 3 and 4 may contain 2′-alkyl ethers, one of which should be 2′-Ae, while fractions 5 and 6 may contain 3′-alkyl ethers.

Components of all six fractions were characterized by descending paper chromatography in the four solvent systems described in Table II. Fractions 3, 4, 5, and 6 each gave a single uv-absorbing spot in all four solvent systems and were estimated to be greater than 97% pure. Although the reaction of diazoethane with adenosine was expected to yield only ethylated products, surprisingly, the compound in fraction 4 migrated with 2′-Am in all four systems and the compound in fraction 6 migrated with 3′-Am in all four systems (Table II). The compounds in fractions 3 and 5 migrated faster than 2′-Am or 3′-Am, respectively, and were well resolved from each other by solvent D. These results were consistent with the tentative identification of fraction 3 as 2′-Ae and fraction 4 as 3′-Ae since the 3′-ethyl ether should have been retained longer than the 2′-ethyl ether on the ion exchange column as discussed above.

Both fractions 1 and 2 were resolved into several components by paper chromatography with the four solvents. Analytical studies on the first two column fractions in the comparable methylated adenosine series indicated they

Table I
Fractionation of Alkylated Nucleosides on Bio-Rad AG 1 Column[a]

Fraction no.	Identity	Registry no.	Tubes pooled in each fraction	Recovery, % of adenosine applied
1			12–24	3.8
2			38–44	1.7
3	2′-*O*-Ethyladenosine	52842-98-5	45–58	11.9
4	2′-*O*-Methyladenosine	2140-79-6	68–81	9.8
5	3′-*O*-Ethyladenosine	52928-62-8	105–120	3.8
6	3′-*O*-Methyladenosine	10300-22-8	179–210	2.8

[a] The column consisted of Bio-Rad AG 1-X2 (OH^-), 200–400 mesh, 4 × 40 cm, equilibrated with 40% ethanol prior to use. The crude reaction mixture (95,100 A_{260} units) was applied in 40% ethanol and eluted with 40% ethanol at a flow rate of 2 ml/min; the tube volume was 20 ml.

Table II
Paper Chromatography of Alkylated Adenosine Derivatives[a]

Compound	R_f Solvent A	Solvent B	Solvent C	Solvent D
Adenosine	0.37	0.19	0.23	0.63
Fraction 3	0.70	0.53	0.57	0.82
Fraction 4	0.61	0.38	0.47	0.76
2′-*O*-Methyladenosine	0.63	0.37	0.47	0.77
Fraction 5	0.73	0.51	0.55	0.68
Fraction 6	0.60	0.35	0.40	0.64
3′-*O*-Methyladenosine	0.59	0.37	0.40	0.64

[a] Solvents were: (A) 2-propanol–NH_4OH–0.1 *M* boric acid (7:1:2); (B) ethyl acetate–1-propanol–H_2O (4:1:2, upper phase); (C) 1-butanol–NH_4OH–H_2O (86:5:14); and (D) ethanol–1 *M* ammonium acetate (pH 7.5) (7:3); all solvent proportions by volume.

were 2′,3′-di-*O*-methyladenosine and 2′-*O*,N^6-dimethyladenosine, respectively.[5] Mixed alkylation occurring within a single molecule when adenosine was treated with diazoethane in aqueous 1,2-dimethoxyethane would account for the mixture of components noted above for fractions 1 and 2.

Based on the above chromatographic characterizations, fractions 4 and 6 were expected to contain a methyl ether on the ribose moiety while fractions 3 and 5 were expected to contain an ethyl ether on the ribose moiety. Nucleoside alkyl ethers treated with perchloric acid release the alkyl group as free alcohol,[8] which can be identified by gc of the hydrolysate.[9] Alkyl groups occurring on the base do not interfere with the analysis since the hydrolysis specifically released ether groups from the ribose moiety.[9] As expected, fractions 4 and 6 released methanol when characterized in this manner, while fractions 3 and 5 released ethanol. These results confirm the presence of ribose methyl ethers in fractions 4 and 6 and ribose ethyl ethers in fractions 3 and 5.

With these preliminary characterizations in mind, a mass spectral analysis of the nucleosides as their trimethylsilyl derivatives was performed to confirm structures. Fractions 4 and 6 were shown to be 2′-Am and 3′-Am, respectively, by comparison with authentic samples. Fractions 3 and 5 were identified as 2′-Ae and 3′-Ae, respectively, by comparison of the mass spectra of their trimethylsilyl derivatives with those of their 2′- and 3′-*O*-methyl isomers. (See paragraph at the end of paper regarding supplementary material.)

The occurrence of extensive methylation during the reaction of adenosine and diazoethane raised the question as to the origin of the methyl groups. One possibility was the presence of a potential methyl donor in the alkylating reagent, *e.g.*, the inadvertant generation of diazomethane during the preparation of diazoethane. An alternate possibility was the spontaneous formation of a methyl donor under the reaction conditions. These possibilities could be distinguished by employing diethyl ether as an alternate solvent in a diazoethane reaction. Palmitic acid was chosen as an appropriate acceptor molecule since it is soluble in both diethyl ether and 1,2-dimethoxyethane. Palmitate esters were formed under the two reaction conditions described in Table III. The products were dissolved in hexane and characterized by their gc retention times relative to standards and by combined gas chromatography–mass spectrometry.

Significant levels of methyl palmitate were produced during the reaction in the presence of aqueous 1,2-dimethoxyethane, although ethyl palmitate was the major product (Table III). However, only ethyl palmitate was formed when the reaction occurred in diethyl ether. The presence of as little as 0.01% of methyl ester relative to ethyl ester could have been detected under the conditions employed. The results indicate that the diazoethane preparation was not contaminated with a potential methyl donor such as diazomethane, but suggest the spontaneous formation of a methyl donor in the presence of aqueous 1,2-dimethoxyethane.

Table III
Gas Chromatography of the Alkyl Esters of Palmitic Acid

	% of total ester product	Rel retention[a]
Ester standards		
Methyl palmitate		0.78
Ethyl palmitate		1.00
Diazoethane in aqueous 1,2-dimethoxyethane[b]		
Methyl palmitate	6.8	0.78
Ethyl palmitate	93.2	1.00
Diazoethane in diethyl ether[c]		
Methyl palmitate	<0.01	
Ethyl palmitate	100.0	1.00

[a] Gc conditions: Hewlett-Packard F&M 402; column of U-shaped glass tubing (6 ft × ⅛ in. i.d.) packed with 3% SE-30 on silanized Supelcoport (100–200 mesh); N_2 carrier gas at 50 ml/min; oven temperature, 155° [b] Palmitic acid (23 mg) was placed in 1 ml of water and heated to 80°, and 2 ml of 1,2-dimethoxyethane containing diazoethane at 18° was added. The reaction proceeded for 1 hr at room temperature. The aqueous phase was extracted two times with 4 ml of ether, the ether layers were combined and washed with 4 ml of water, and the ether phase was evaporated in a stream of N_2. [c] Palmitic acid (23 mg) was dissolved in 1 ml of diethyl ether and 2 ml of ethereal diazoethane was added at room temperature. The reaction proceeded for 1 hr, at which time the sample was evaporated under a stream of N_2.

The source of the methyl groups occurring in the products of these alkylation reactions has not been characterized, but a potential source is the methyl ether groups of the solvent, 1,2-dimethoxyethane. The exchange of the ethyl donor with these methyl groups could involve formation of a trialkyloxonium ion intermediate. Both triethyloxonium ion[10] and trimethyloxonium ion[11] have been prepared as their fluoroborate salts. This postulated intermediate could then dissociate to form a methyl donor or serve as a direct alkylating agent.

A clear precedent for solvent participation in diazoalkylation reactions is not known, but it is interesting to note that methyl ether formation of glucopyranosyl derivatives with diazomethane was catalyzed by the presence of methanol.[12] In addition, Williams and Sweeley[13] have observed that the use of methanol as a component of the solvent in esterification of *p*-hydroxybenzoic acid by diazomethane resulted in complete formation of the *O*-methyl ether in addition to the ester; in the absence of methanol, only about 1–5% of the *O*-methyl ether was formed.

Acknowledgments. We are indebted to Dr. C. C. Sweeley for use of the mass spectral facility, to Dr. M. Bieber, Dr. R. Hammond, and Dr. R. Laine for helpful discussions in interpretation of mass spectra, and to J. Harten for running the mass spectra. We wish to thank Dr. W. H. Reusch and Dr. J. C. Speck for critically reading the manuscript prior to publication.

Registry No.—Adenosine, 58-61-7; diazoethane, 1117-96-0; 1,2-dimethoxyethane, 110-71-4.

Supplementary Material Available. The mass spectral characterization of column fractions 3–6 and authentic 2′-Am and 3′-Am as their trimethylsilyl derivatives will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3674.

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(2) The abbreviations used in this paper are as follows: gc, gas chromatography; 2′-Am, 2′-*O*-methyladenosine; 3′-Am, 3′-*O*-methyladenosine; 2′-Ae, 2′-*O*-ethyladenosine; 3′-Ae, 3′-*O*-ethyladenosine.
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Kinetics of the Formation of *N*-Arylsydnones from *N*-Nitroso-*N*-Arylglycines

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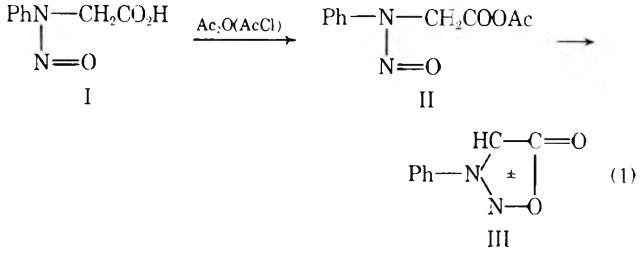
Received May 28, 1974

The formation of *N*-arylsydnones by the reaction of *N*-nitroso-*N*-arylglycines with acid anhydrides (mainly dichloroacetic anhydride) has been kinetically studied by means of uv spectrophotometry of the produced sydnones in dioxane or other solvents. The rate is expressed as $v = k_2[R^1C_6H_4N(NO)CHR^2COOH][(RCO)_2O]$, and virtually no effect was observed on addition of RCO_2H or pyridine. An electron-withdrawing group on *N*-phenyl (R^1) retards the reaction, while the same group on the α carbon (R^2) accelerates it. An electron-withdrawing group on acid anhydride accelerates the reaction in general. These findings suggest a mechanism involving rate-determining cyclization of the hydrogen-bonded acid anhydride of the substrate by a nucleophilic attack of the nitroso oxygen on the carbonyl carbon.

Since the discovery of sydnone,[1] which was prepared by the condensation of *N*-nitroso-*N*-phenylglycine with acetic anhydride, some analogous mesoionic compounds have been prepared, but no kinetic study on the formation has appeared.[2,3]

A mechanism involving acetyl glycinoyl anhydride (II) (eq 1) has been postulated on the basis of the formation of II by the reaction of I with acetyl chloride, the formation of sydnone (III) from II on heating, and some other facts.[3b]



However, since no kinetic study was done, the mechanism is still obscure. That is, is the main path truly that *via* anhydride II? Which step is rate determining? Does an attack of nitroso oxygen on carbonyl carbon or an attack of carbonyl oxygen on nitroso nitrogen occur? To clarify these uncertainties, we carried out kinetic studies of the reaction by means of uv spectrophotometry of the product with some *N*-nitroso-*N*-arylglycines and with some substituted acetic anhydrides. The following is a summary of our results which suggest a probable and more accurate mechanism for the reaction.

Table I
Second-Order Rate Constant for the Reaction of *N*-Nitroso-*N*-phenylglycine with Dichloroacetic Anhydride in Dioxane at 23°

Initial concn (10^{-4} *M*)		
Substrate	Acid anhydride	k_2, M^{-1} sec^{-1}
2.74	6.00	9.5
2.74	9.01	11.5
2.74	12.01	8.6
2.74	30.03	11.7
3.28	6.00	9.4
3.83	6.00	11.7
4.38	6.00	10.1
4.93	6.00	11.6
5.47	6.00	10.0

Results

Kinetics. The rates of the reactions of all the glycines and acid anhydrides studied can be expressed as $v = k[ArN(NO)CH_2CO_2H][(RCO)_2O]$. A typical kinetic run for the reaction of *N*-nitroso-*N*-phenylglycine with dichloroacetic anhydride in dioxane is shown in Table I, where the second-order rate constants hold a satisfactory constancy. No reaction occurs with *N*-nitrosophenylglycine ester in the presence of dichloroacetic anhydride, in agreement with the observation in acetic anhydride by Baker, *et al.*[3b]

Effect of Acid and Base. The reaction gives rise to acetic acid, but, as shown in Table II, virtually no effect of ace-

Table II
Effect of Acid and Base on the Second-Order Rate Constant k_2 for the *N*-Nitroso-*N*-phenylglycine with Acid Anhydride in Dioxane at 50°

[PhN(NO)-CH_2CO_2H], *M*	[$(RCO)_2O$], *M*	[Acid], *M*	[Base], *M*	k_2, M^{-1} sec^{-1}
0.952	Ac_2O (10.58)			1.47×10^{-5}
0.824	Ac_2O (9.86)	AcOH (1.19)		1.67×10^{-5}
1.87	Ac_2O (10.28)			1.71×10^{-5}
Av				1.62×10^{-5}
5.46×10^{-3}	$(ClCH_2CO)_2O$ (6.01×10^{-2})			2.59×10^{-2}
5.46×10^{-3}	$(ClCH_2CO_2)O$ (6.00×10^{-2})		Pyridine (6.18×10^{-2})	2.71×10^{-2}

Table III
Effect of Structure of Acid Anhydride on the Second-Order Rate Constant for the Reaction of *N*-Nitroso-*N*-phenylglycine with Acid Anhydride

Acid anhydride	Registry no.	pK_a of parent acid at 25°	Solvent	Temp, °C	k_2, M^{-1} sec^{-1}
Ac_2O	108-24-7	4.76	Dioxane	50	~0
			Ac_2O	50	1.62×10^{-5}
$(ClCH_2CO)_2O$	541-88-8	2.86	Dioxane	50	2.65×10^{-2}
$(Cl_2CHCO)_2O$	4124-30-5	1.29	Dioxane	23	10.3
$(Cl_3CCO)_2O$	4124-31-6	0.63	Dioxane	23	3.26×10^{-2}
			Dioxane	40	0.205
$(F_3CCO)_2O$	407-25-0	0.23	Dioxane	23	

Table IV
Second-Order Rate Constants for the Reactions of *N*-Nitroso-*N*-arylglycines with Dichloroacetic Anhydride in Dioxane at 23°

Substituent in Ph	Initial concn, *M*: Substrate	Initial concn, *M*: Acid anhydride	k_2 (av),[b] M^{-1} sec^{-1}
p-CH_3O	3.41–6.02	6.03–12.05	24.0 ± 1.0
p-CH_3	6.03	6.00–18.01	18.7 ± 0.9
H[a]			10.3 ± 0.3
p-Cl	4.00–6.00	6.01–18.07	5.21 ± 0.37
m-Cl	4.01–6.02	6.02–18.07	3.32 ± 0.22

[a] See Table I. [b] ± denotes standard deviation of several runs.

tic acid was observed on the rate even in the presence of added acetic acid. Also there is no effect of added base, pyridine, on the rate, although the addition of pyridine raises the yield by 10–20%.

Effect of Substituent in Anhydride. The introduction of halogen into acetic anhydride exerts such a remarkable acceleration influence on the reaction that the reaction temperature must be lowered as shown in Table III. The table shows apparently that an increase of acidity of the parent acid results in the acceleration of the reaction, except for trichloroacetic anhydride for which the formed trichloroacetic acid should decompose the produced sydnone rapidly. Trifluoroacetic anhydride was easily vaporized (bp 39°) and induced the decomposition of sydnone; hence the rate measurement with this anhydride was inaccurate.

Effect of Substituent in Phenylnitrosoglycine. The rate data for some ring-substituted *N*-nitroso-*N*-phenylglycines with dichloroacetic anhydride at 23° are compiled in Table IV. The data fit Hammett's equation (Figure 1) giving a ρ value of −1.34 (r = 0.994) with σ.

Table V
Second-Order Rate Constants for the Reaction of α-Substituted *N*-Nitroso-*N*-phenylglycine with Dichloroacetic Anhydride in Dioxane at 23°

α substituent	Initial concn, *M*: Substrate	Initial concn, *M*: Acid anhydride	k_2 (av),[b] M^{-1} sec^{-1}
CH_3	2.00–6.01	5.97–17.92	8.62 ± 0.46
C_6H_5	1.00–2.00	2.01–6.02	16.3 ± 0.3
p-ClC_6H_4	1.02	1.00–3.99	59.6 ± 9.8
H[a]			10.3 ± 0.3

[a] See Table I. [b] ± denotes standard deviation of several runs.

Table VI
Effect of Solvent on the Second-Order Rate Constants for the Reaction of *N*-Nitroso-*N*-phenylglycine with Dichloroacetic Anhydride

Solvent	Temp, °C	k_2, M^{-1} sec^{-1}	ϵ[a]	E_T[b]
Dioxane	23	10.3	2.21 (25°)	36.0
Acetonitrile	23	3.18	37.5 (20°)	46.0
Acetone	24	0.338	20.7 (25°)	42.2
Chloroform	24	0.0255	4.81 (20°)	39.1
Tetrahydrofuran	23	0.00305	7.58 (25°)	37.4
Acetic anhydride	22	0	20.7 (19°)	

[a] Dielectric constant: J. A. Riddick and W. B. Bunger, "Techniques of Chemistry," Vol. II, 3rd ed, Wiley-Interscience, New York, N. Y., 1970. [b] Transition energy estimated from the absorption of a reference compound: K. Dimroth, C. Reichardt, T. Siepmann, and F. Bohlmann, *Justus Liebigs Ann. Chem.*, **661**, 1 (1963); **669**, 95 (1963).

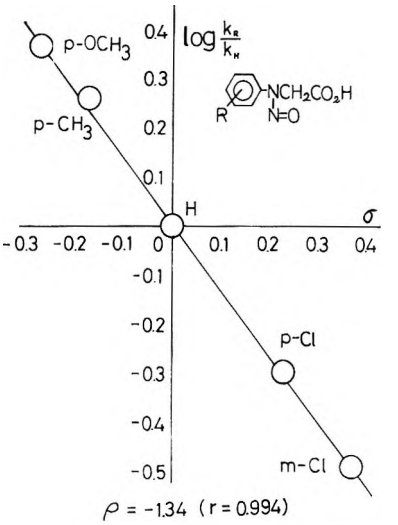


Figure 1. Hammett plots for the reaction of *N*-nitroso-*N*-arylglycines with dichloroacetic anhydride in dioxane at 23°.

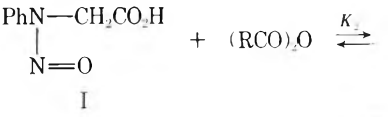
Table V shows the effect of the α substituent in the glycine under the same conditions as above, in which it is apparent that an electron-withdrawing α substituent increases the rate.

Solvent Effect. The effect of solvent on the rate of reaction of *N*-nitroso-*N*-phenylglycine with dichloroacetic anhydride at 22–24° is listed in Table VI, which indicates that dioxane is the most suitable solvent among them for the reaction.

Discussion

Our observed results are summarized as follows. (i) The rate is $v = k[\text{substrate}][(RCO)_2O]$. (ii) Ethyl *N*-nitroso-*N*-phenylglycinate which does not react with acid anhydride cannot give sydnone. (iii) Added acetic acid or pyridine only slightly influences the rate. (iv) The reaction with dichloroacetic anhydride is very slow in an excess amount of acetic anhydride. (v) Electron-withdrawing groups in acetic anhydride accelerate the reaction except for Cl_3 or F_3 groups. (vi) An electron-withdrawing group in the *N*-phenyl group of the substrate retards the reaction ($\rho = -1.34$), while an electron-withdrawing group in α carbon accelerates the reaction.

These observations suggest a mechanism which involves a rate-determining attack of nitroso oxygen on the carbonyl carbon (activated by hydrogen-bonded acetic acid) of mixed anhydride (IV), giving a cyclized product which rapidly eliminates acetic acid and proton to form sydnone.



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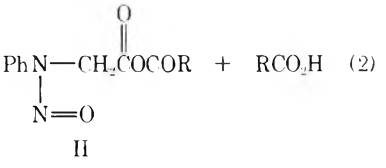
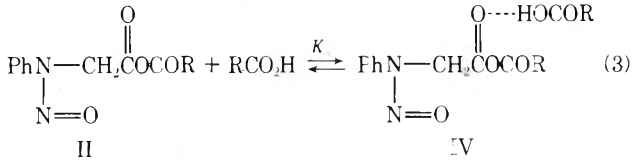
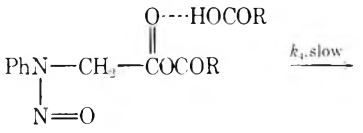
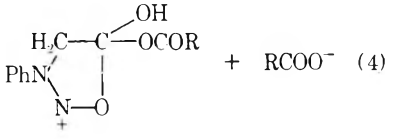


II (2)



II IV (3)





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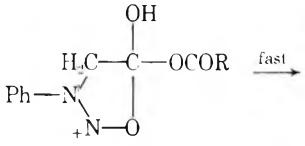
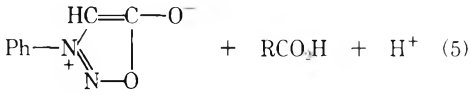


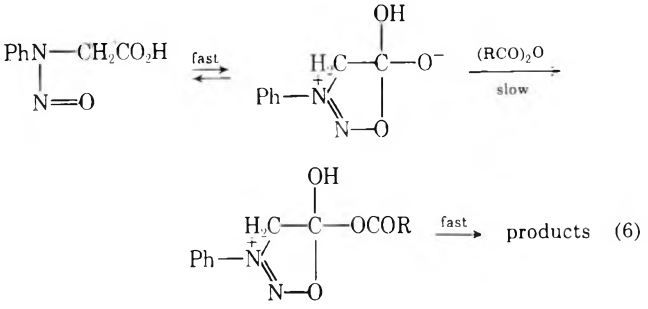


III (5)

This mechanism, with the rate-determining step of eq 4, leads to the following rate equation, which is unaffected by added acetic acid or pyridine: $v = K_2K_3k_4[I][(RCO)_2O]$. If unassociated anhydride $PhN(NO)CH_2COOCOR$ (II) were cyclized, the rate law would be $v = K_2K_3k_4[I][(RCO)_2O]/[RCO_2H]$, which disagrees with our observation.

Very strong acid can accelerate the decomposition of sydnone and hence lowers the apparent rate constant, while pyridine suppresses the decomposition of product and increases the yield. The retardation of reaction with dichloroacetic anhydride in excess acetic anhydride is ascribed to the very low equilibrium concentration of $PhN(NO)CH_2COOCOCHCl_2$ because of the shift of equilibrium to $PhN(NO)CH_2COOCOCH_3$ which is much more slowly cyclized than the former.

Another mechanism, shown in eq 6, is consistent with kinetics and the other observations (i–iii, v, and vi), but this is inconsistent with observation iv, since the rate with dichloroacetic anhydride according to eq 6 should be higher or comparable in acetic anhydride compared with that in dioxane. Also, the isolation of acid anhydride intermediate



(6)

II by Baker, *et al.*,[3b] and the lower electrophilicity of COOH than that of COOCOR disfavor the mechanism of eq 6.

A mechanism involving an irreversible slow attack of the glycine on the anhydride (eq 2 in the forward direction only) fits the rate law, but it is inadequate in view of (i) the observation that an electron-withdrawing α substituent in nitrosophenylglycine increases the rate and (ii) the isolation of mixed anhydride II in the other case.[3b]

The observed *ca.* 10^3-fold faster rate for dichloroacetic anhydride than that for acetic anhydride seems to be too large, since Cl atoms are three atoms away and the inductive effect decreases *ca.* $(2.8)^3$-fold. However, this observation is conceivable because (i) dichloroacetic acid has an acidity constant 3.5 pK units (8×10^3-fold) higher than acetic acid, although the chloro substituent of $CHCl_2CO_2H$ is two atoms away from the oxygen atom, and (ii) $k_{obsd} = K_2K_3k_4$, and all the constants would increase by introduction of the Cl atom; that is, the effect is triplicated in k_{obsd}.

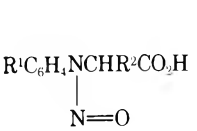
Substituent Effect. As stated above, electron-withdrawing groups in acetic anhydride accelerate the cyclization because they increase the electrophilicity of carbonyl carbon of the substrate. On the contrary, an electron-withdrawing group in the phenyl ring retards the reaction, since it lowers the nucleophilicity of nitroso oxygen which attacks the carbonyl carbon, although the group can more weakly raise the electrophilicity of carbonyl carbon. Reasonable trends were observed with substituents on α carbon, *i.e.*, an electron-withdrawing group on α carbon accelerates the cyclization because of an increase of electrophilicity of the carbonyl carbon. It is of interest to note that the steric hindrance effect is rather small in view of the comparison of α-CH_3 and α-C_6H_5.

The failure of reaction with ethyl *N*-nitroso-*N*-phenylglycinate supports the above mechanism, since the more electron-attracting acyl group in anhydride II is favorable for a nucleophilic attack of NO compared with the ethoxy group in ester.

An alternative mechanism involving a rate-determining nucleophilic attack of COO^- on N of N=O is inconsistent with these substituent effects, *i.e.*, the reverse polar effect would be observed in this mechanism.

Solvent Effect. Table VI shows that the dielectric constants of solvent are related little to the rate constant, while the E_T value, which is a measure of solvent polarity,[7] parallels fairly well with rate except for dioxane having a large k value. This is convincing, since the rate-determining step is the separation of opposite charges. The abnor-

Table VII
Ultraviolet Absorption Peaks and Extinctions of *N*-Nitroso-*N*-arylglycines and Sydnones[a] and Melting Points of Sydnones



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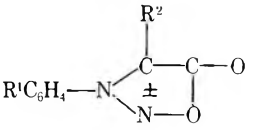
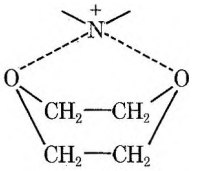


III

Substituent		I			III				
R^1	R^2	λ_{max}, nm	Registry no.	ϵ_{max}	λ_{max}, nm	Registry no.	ϵ_{max}	Mp, °C	Lit. mp, °C
H	H	270	6415-68-5	5520[b]	310	120-06-9	4,490[b]	138.0	137[5]
p-CH_3O	H	284	52827-01-7	7580	323[c]	3815-80-3	5,050	123.5	126 dec[3c]
					279		8,600		
p-CH_3	H	276	52827-02-8	6560	320	3483-19-0	5,070	145.5	145[3a]
p-Cl	H	276	13728-11-5	7720	322	829-31-2	3,770	112	113[3a]
m-Cl	H	273	52827-03-9	6530	323	52827-07-3	3,770	141	145.5
H	CH_3	266	52827-04-0	5800	315	3483-16-7	5,050	99	99[1]
H	C_6H_5	257	52827-05-1	4950	340	3815-83-6	9,640	189	185[3a]
H	*p*-ClC_6H_4	256	52827-06-2	5510	343	52827-08-4	12,120	129.5	129 dec[3b]

[a] In dioxane. [b] In methanol. [c] Shoulder.

mal acceleration in dioxane may be ascribed to its ability for the facile solvation of cation in the form of VI as reported in some other cases.[4]



VI

Experimental Section

Materials. *N*-Arylglycines were prepared by the reaction of the corresponding anilines with chloroacetic acid or its ester in ethanol.[3a] The obtained *N*-arylglycines were nitrosated[5] with aqueous HNO_2 at 0°, giving *N*-nitroso-*N*-arylglycines. Identification of obtained *N*-arylglycines and *N*-nitroso-*N*-arylglycines was done by their ir and nmr spectra and also by the comparison of melting points with those of literature. The substituents and melting points of obtained *N*-nitroso-*N*-arylglycines were: none, 105–105.3° (lit.[5] mp 103–104°); *p*-OMe, 114–115° dec (lit.[3c] 121° dec); *p*-Me, 107–109° dec; *p*-Cl, 119–119.5° dec (lit.[3a] mp 114°); *m*-Cl, 109–111° dec (lit.[6] mp 106.5–107.5°).

α-Substituted *N*-nitroso-*N*-phenylglycines were similarly prepared by the nitrosation of the corresponding substituted phenylglycines.[3b] The α substituents, melting points of *N*-phenylglycine, and melting points of *N*-nitroso-*N*-phenylglycine were: CH_3, 167°, 88.6–89.0° (lit.[1] mp 80–81°); Ph, 183.7° (lit.[3a] mp 185°), 98–99°; *p*-ClC_6H_4, 185–186° (lit.[3b] mp 178°), 83.5–84.5°.

Acetic anhydride was purified by distillation over P_2O_5, bp 137° (lit.[7] 139°). Other carboxylic anhydrides were prepared by refluxing the corresponding carboxylic acid with P_2O_5 for *ca.* 10 hr[8] by checking the absence of carboxylic acid by ir spectra. Their boiling points were: $(ClCH_2CO)_2O$, 203–215°; $(Cl_2CHCO)_2O$, 120–122° (29–30 mm); $(Cl_3CO)_2O$ 114–116° (23 mm); $(CF_3CO)_2O$, 41.6°. Their identification was done by ir spectra.

Authentic samples of sydnones were prepared by refluxing the corresponding *N*-nitroso-*N*-arylglycine with acetic anhydride.[5] Their melting points and uv absorptions together with the uv absorption of parent nitrosoarylglycines are listed in Table VII.

Kinetics. For the substrates of the slower reaction, which was completed within 1 hr, the kinetic experiments were conducted in a flask dipped in an ordinary thermostat. Aliquots (1–0.5 ml) were pipetted out from the reaction solution at appropriate time intervals, diluted with methanol to 6×10^{-4} *M* sydnone to measure its concentration by means of uv spectrophotometry at a wavelength of 340 nm.

For the rapid reactions, dilute solutions (each 5 ml) of nitrosoarylglycine and acid anhydride were mixed and transferred immediately to a thermostated photocell. The rate was directly measured similarly by uv spectrophotometry (340 nm or otherwise 343 nm for phenyl-*N*-nitroso-α-chlorophenylglycine alone). Second-order rate constants were calculated from the slopes of plots of log $(b - x)/(a - x)]$ *vs.* time, where a and b $(a \neq b)$ denote the initial concentrations of nitrosoglycines and acid anhydrides, respectively, and x is the concentration of formed sydnones. With a large excess of acid anhydride, pseudo-first-order rate constants can be calculated from plots of logarithmic extinction *vs.* time. It should be noted that the humidity of the air, especially over 60%, tends to decompose the used acid anhydride and lowers the reproducibility of data.

References and Notes

(1) J. C. Earl and A. W. Mackney, *J. Chem. Soc.*, 899 (1935).
(2) For a review of the preparation of mesoionic compounds see: (a) W. Baker and W. D. Ollis, *Quart. Rev., Chem. Soc.*, **11**, 15 (1957); (b) M. Ohta and H. Kato, "Nonbenzenoid Aromatics," J. P. Snyder, Ed., Vol. 1, Academic Press, New York, N. Y., 1969, Chapter 4.
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(8) R. F. Clark and J. H. Simons, *J. Amer. Chem. Soc.*, **75**, 6305 (1953).

Kinetics of the Oxidation of Benzhydrols to Benzophenones by Iodine in Alkaline Methanol

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Received June 3, 1974

Oxidation of benzhydrols by iodine in alkaline methanol to give benzophenones has been kinetically studied. The rate is expressed as: $v = k_3[\mathrm{ArAr'CHOH}][\mathrm{I_2}]_a^2$, if $[\mathrm{I_2}]_a < [\mathrm{MeONa}]_a$, and $v = k_3[\mathrm{ArAr'CHOH}][\mathrm{MeONa}]_a^2$, if $[\mathrm{I_2}]_a > [\mathrm{MeONa}]_a$, where $[\ ]_a$ denotes the concentration of added reagents. The effect of ring substituent on the rate gives a good correlation with σ^+ but not with σ, affording a ρ^+ value of -0.677 ($r = 0.987$). The results are discussed in terms of a mechanism involving a rate-determining removal of hydride ion from the α carbon of hypoiodous benzhydroxy ester by methyl hypoiodite.

There have been a number of works on the oxidation of alcohols with halogen to carbonyl compounds.[1-4] As to the mechanism, previous workers seem to have concentrated on the following: (i) structural speculation on the transition state; (ii) the confirmation of attacking agents and the relative reactivities of various halogen-containing species.

Deno and Potter[1] suggested the similarity between the mechanism for the oxidation of alcohols with halogen and that with chromic acid involving an ester intermediate. The mechanism involving an ester-like intermediate was preferred because of the following reasons: (i) alkyl hypohalite decomposes to aldehyde or ketone and hydrogen halide;[2a] (ii) the pH–rate profile exhibits a bell-shaped curve;[1b] (iii) stereoselectivities are similar to those of the chromic acid oxidation.[3]

In contrast, Kaplan's mechanism, generally accepted for the oxidation of alcohols by bromine in acidic aqueous solutions, involves an oxidative transfer of a hydride ion (but not a proton) from α carbon.[4] Kaplan ruled out a mechanism involving alkyl hypohalites as intermediates,[4a,b] and Perlmutter suggested that molecular halogen but not hypohalous acid is an effective oxidizing agent in these reactions.[4c,d] Most other workers support the mechanism involving an attack of "molecular halogen" on α hydrogen followed by "hydride removal."[4]

However, all these previous experiments were conducted

Table I
Pseudo-First-Order Rate Constants for the Oxidation of Benzhydrols by Iodine in Alkaline Methanol at 25°

Substrate	$[\mathrm{MeONa}]_a$, M	$[\mathrm{I_2}]_a$, M	$10^4 k_{obsd}$, sec^{-1}	Substrate	$[\mathrm{MeONa}]_a$, M	$[\mathrm{I_2}]_a$, M	$10^4 k_{obsd}$, sec^{-1}
$(C_6H_5)_2CHOH$	0.073	0.0909	0.217		0.145	0.227	8.73
	0.146	0.0909	0.457		0.200	0.227	15.9
	0.292	0.0909	0.680		0.267	0.227	20.9
	0.438	0.0909	0.655		0.0667	0.125	1.34
	0.0364	0.136	0.202		0.133	0.125	3.10
	0.0723	0.136	0.345		0.200	0.125	7.42
	0.109	0.136	0.783		0.267	0.125	6.08
	0.146	0.136	1.83		0.333	0.125	7.60
	0.214	0.136	1.77		0.0667	0.125	1.02[a]
	0.292	0.136	1.69		0.133	0.125	2.25[a]
	0.0182	0.182	0.232		0.200	0.125	3.25[a]
	0.0723	0.182	0.362		0.267	0.125	4.33[a]
	0.123	0.182	1.64		0.333	0.125	6.78[a]
	0.182	0.182	2.80		0.727	0.125	7.32[a]
	0.364	0.182	2.76				
	0.573	0.182	2.42	$(p\text{-}CH_3OC_6H_4)(p'\text{-}$ $CH_3C_6H_4)CHOH$	0.200	0.025	0.385
	0.073	0.227	0.292		0.200	0.040	1.75
	0.109	0.227	0.732		0.200	0.050	1.76
	0.182	0.227	2.51		0.200	0.065	3.55
	0.291	0.227	3.54		0.200	0.075	3.94
	0.437	0.227	3.54		0.200	0.090	5.81
	0.728	0.227	3.37		0.200	0.150	16.4
					0.050	0.188	1.72
$(p\text{-}CH_3OC_6H_4)(C_6H_5)$- CHOH	0.727	0.0455	0.996		0.075	0.188	3.83
	0.727	0.0909	3.83		0.100	0.188	7.23
	0.727	0.136	7.3		0.150	0.188	15.1
	0.727	0.182	14.0		0.250	0.188	24.2
	0.727	0.227	20.3		0.350	0.188	25.4
	0.0364	0.227	0.632		0.400	0.188	23.6
	0.0723	0.227	1.93		0.600	0.188	23.6
	0.109	0.227	4.47				

[a] Sodium iodide ($[\mathrm{NaI}]_a = 0.048\ M$) was added.

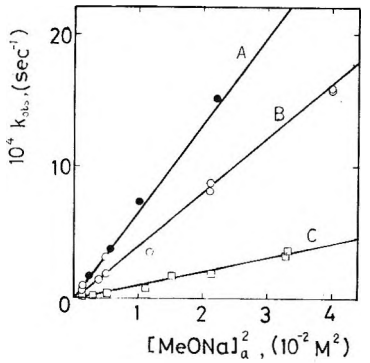


Figure 1. The plot of k_{obsd} *vs.* $[MeONa]_a^2$ for the oxidation of (A) *p*-methoxy-*p'*-methylbenzhydrol, (B) *p*-methoxybenzhydrol, and (C) benzhydrol by iodine in alkaline methanol ($[I_2]_a > [MeONa]_a$) at 25°, where [ ]$_a$ denotes the concentration of added reagent. The lines in this figure correspond to those in Figure 2.

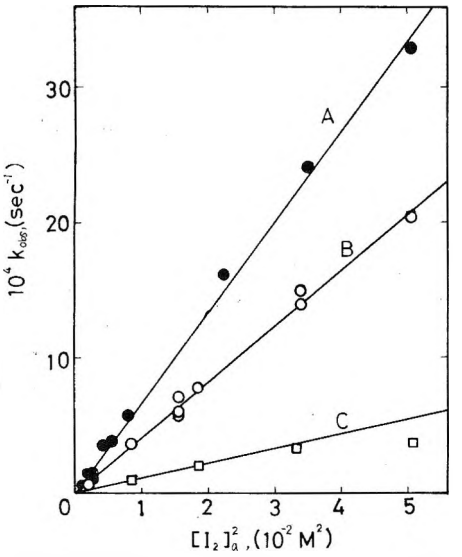


Figure 2. The plot of k_{obsd} *vs.* $[I_2]_a^2$ for the oxidation of (A) *p*-methoxy-*p'*-methylbenzhydrol, (B) *p*-methoxybenzhydrol, and (C) benzhydrol by iodine in alkaline methanol ($[I_2]_a < [MeONa]_a$) at 25°, where [ ]$_a$ denotes the concentration of added reagent.

in acidic solutions. In basic aqueous solutions, halogen is mostly converted to inert hypohalite anion (OX^-),[5] so that the reaction is suppressed and kinetics are complicated. Hence, it is not certain whether the oxidation mechanism in acidic solutions involving the hydride removal can be applied also to that in basic solutions.

This paper reports a study on the kinetics of the oxidation of one kind of alcohol, benzhydrols, by iodine in basic conditions by following the rate by means of glc analysis of the remaining benzhydrol.

Results

Rate. The rates of the reaction of benzhydrols with a mixture of iodine and sodium methoxide in dry methanol at 25° were measured by following the decrease of benzhydrols by means of glc. Rates of iodine (45.5–227 × 10^{-3} *M*) and sodium methoxide (36.4–727 × 10^{-3} *M*) far exceed benzhydrol (4–10 × 10^{-3} *M*) so that the pseudo-first-order kinetics applied; appropriate plots were linear up to 60–80% conversion. Therefore, the decreasing amount of iodine caused by the oxidation of solvent methanol has little effect on the kinetics under these conditions.

$$v = k_{obsd}[ArAr'CHOH] \quad (1)$$

The kinetic data are listed in Table I. Figure 1 shows the plot of k_{obsd} *vs.* the square of the concentration of added sodium methoxide ($[MeONa]_a^2$) for the reaction of some benzhydrols, where a subscript a indicates the concentration of added reagent. The rate is proportional to $[MeONa]_a^2$ and independent of the amount of added iodine ($[I_2]_a$), when $[MeONa]_a$ is smaller than $[I_2]_a$.

$$v = k_3[ArAr'CHOH][MeONa]_a^2 \quad (2)$$

However, when $[MeONa]_a$ is larger than $[I_2]_a$, the rate is independent of $[MeONa]_a$ (Table I). Figure 2 shows the plot of the observed rate constant against $[I_2]_a^2$, where $[I_2]_a$ is smaller than $[MeONa]_a$. The rate is proportional to $[I_2]_a^2$, and the observed slope agrees with that in the plot of Figure 1.

$$v = k_3[ArAr'CHOH][I_2]_a^2 \quad (3)$$

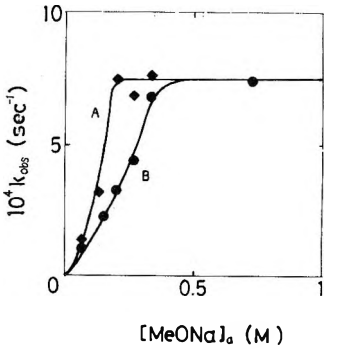


Figure 3. Plot of k_{obsd} *vs.* $[MeONa]_a$ for the oxidation of *p*-methoxybenzhydrol by iodine ($[I_2]_a$ = 0.125 *M*) in alkaline methanol at 25°: (A) $[NaI]_a$ = 0 *M*; (B) $[NaI]_a$ = 0.048 *M*.

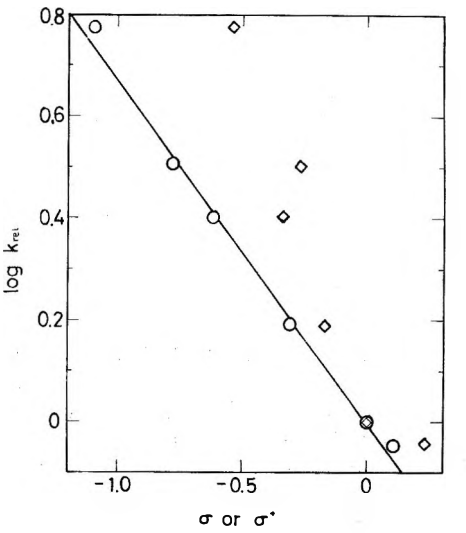


Figure 4. Hammett plot for the oxidation of benzhydrols by iodine in alkaline methanol at 25°: (○) σ^+; (◇) σ.

Figure 3 shows the effect of added iodide ion ($[NaI]_a$ = 0.048 *M*) on the rate of oxidation of *p*-methoxybenzhydrol by iodine ($[I_2]_a$ = 0.134 *M*) in methanol. The rate is suppressed by iodide ion in solutions of lower basicity but is independent of iodide ion in a solution of higher basicity.

Substituent Effect. Some ring-substituted benzhydrols were oxidized with iodine in the presence of sodium methoxide in dry methanol at 25°. The rate constant k_3 was calculated by means of eq 2 and 3, and then the relative rate, k_3(substituted)/k_3(unsubstituted), was evaluated. The relative rates are listed in Table II and plotted against Hammett's σ and Okamoto-Brown's σ^+ in Figure 4. The relative rate (k_{rel}) is correlated with σ^+ rather than σ, giving a ρ^+ value of −0.677 (r = 0.987).

Table II
Substituent Effect on the Relative Rate for the Reaction of Benzhydrols with Iodine in Alkaline Methanol at 25°

Substituent	Registry no.	k_{rel}
p-MeO, *p'*-Me	838-22-2	6.01
p-MeO	720-44-5	3.70
p,*p'*-Me_2	885-77-8	3.57
p-Me	1517-63-1	1.54
Unsubstituted	91-01-0	1
p-Cl	119-56-2	0.902

Table III
Effect[a] of Temperature on the Rate of the Reaction of *p*-Methoxybenzhydrol with Iodine in Alkaline Methanol

Temp, °C	10^2k_3, M^{-2} sec^{-1}
50.0	18.7
40.0	10.2
30.0	7.21
25.0	4.12
10.0	1.85
0.0	0.614
−14.0	0.241

[a] $\Delta H^* = 11.7$ kcal/mol, $\Delta S^* = -27.8$ eu.

Effect of Temperature. *p*-Methoxybenzhydrol is an appropriate substrate, since it is oxidized at a suitable rate. The rate of the oxidation of *p*-methoxybenzhydrol by iodine was measured in dry methanol at various temperatures. The data are listed in Table III, which gives the enthalpy and entropy of activation as 12.3 kcal/mol and −27.8 eu, respectively.

Discussion

Bell-shaped pH–rate profiles were reported in the oxidation reaction of 2-propanol[1b] and α-hydroxy acids[5a,6] with aqueous bromine. Deno[1b] and Barker[6] interpreted these phenomena by assuming hypobromous acid (HOBr) to be an effective oxidizing agent, *i.e.*, the rate increases with increasing hypobromous acid concentration at lower pH values and decreases with increasing conversion of hypobromous acid to inert hypobromite ion (OBr^-) at higher pH values.

However, under our conditions with alkaline methanol as solvent, hypoiodite ion (OI^-) cannot be formed, but iodine is converted to methyl hypoiodite (MeOI).[7]

$$I_2 + MeO^- \overset{K_4}{\rightleftharpoons} MeOI + I^- \quad (4)$$

$$K_4 = \frac{[MeOI][I^-]}{[I_2][MeO^-]} \quad (5)$$

Assuming that the equilibrium constant K_4 for eq 4 in methanol is similar to that in an aqueous solution, which has a value of 30–200 at 25°,[8] the concentration of methyl hypoiodite ([MeOI]) is nearly equal to the amount of added sodium methoxide ($[MeONa]_a$) in a solution of lower basicity ($[MeONa]_a < [I_2]_a$), while [MeOI] is equal to added iodine ($[I_2]_a$) in a solution of higher basicity ($[MeONa]_a > [I_2]_a$).[9]

According to Deno's mechanism,[1b] which involves the intermediary formation of hypohalite ester (2) followed by the elimination of hydrogen halide, the rate would be proportional to the concentration of methyl hypoiodite, but this was not observed.

The rate law observed by us suggests two mechanisms.

Scheme I

$$\underset{1}{ArAr'CHOH} + MeOI \overset{K_6}{\underset{fast}{\rightleftharpoons}} \underset{2}{ArAr'CHOI} + MeOH \quad (6)$$

$$\underset{2}{ArAr'CHOI} + MeOI \xrightarrow[slow]{k_7} \underset{3}{ArAr'C{=}O} + MeOI + HI \quad (7)$$

One is shown in Scheme I, which involves an attack of methyl hypoiodite on hypoiodite ester of substrate (2) formed by a mobile equilibrium of benzhydrol (1) with methyl hypoiodite. In Scheme I, with rate-determining step 7, the rate should be expressed as

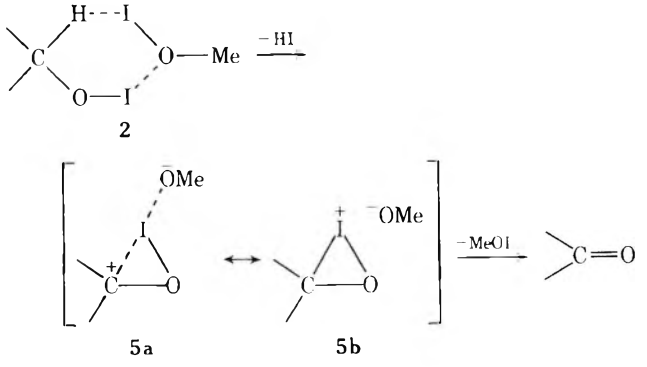
$$v = k_7K_8[1][MeOI]^2 \quad (8)$$

Since [MeOI] is nearly equal to $[MeONa]_a$ at $[MeONa]_a < [I_2]_a$ and is nearly equal to $[I_2]_a$ at $[MeONa]_a > [I_2]_a$,[9] eq 8 leads to eq 2 and 3.

An alternative mechanism is that of Perlmutter-Hayman[4d] (see Scheme IIIA), which involves an attack of molecular iodine on α hydrogen of alkoxide anion ($ArAr'CHO^-$, 4) formed by a mobile equilibrium of 1 with methoxide ion. The observed rate law is consistent with this mechanism, *i.e.*, this mechanism leads to the rate expression $v = k[1][MeO^-][I_2] = kK_4[1][MeOI][I^-]$, which is equal to eq 8, since $[I^-]$ is equal to [MeOI] in the absence of added iodide ion.[9] However, Figure 3 shows that added iodide ion suppresses the reaction. This can be explained by Scheme I but not by Perlmutter-Hayman's mechanism; that is, the concentration of methyl hypoiodite should be decreased by adding iodide ion (eq 5) so that the rate should be decreased. However, $[MeO^-]$ and $[I_2]$ are increased by addition of iodide ion. Hence, Scheme I is more favorable than Perlmutter-Hayman's mechanism.

Furthermore, the observed substituent effects support Scheme I. The relative rates are correlated with Okamoto-Brown's[10] σ^+ but not Hammett's σ, giving a ρ^+ value of −0.677; this fact indicates that the rate-determining step is an electrophilic attack on the α carbon of substrate or the elimination of hydride ion from α carbon and that the transition state should have a carbonium ion property.[10] The α-hydride abstraction of 2 may be accelerated by the anchimeric assistance[11] or bridging[12] by an iodine atom (Scheme II). Transition state 5 should be stabilized by an

Scheme II



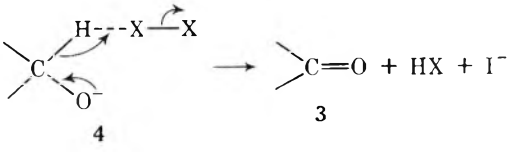
iodine atom of hypoiodite 2 by neighboring group participation.[12,13]

However, if anion 4 were attacked by molecular halogen, the transition state would not be carbonium ion like, and then the substituent effect would be correlated with σ but

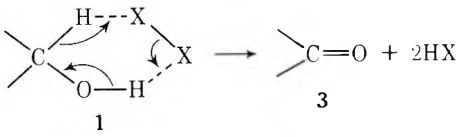
not with σ^+,[10] since the negative charge should shift to carbon simultaneously with hydride elimination (Scheme IIIA). The ρ value of −2.29 with σ (but not σ^+) has been reported for the oxidation of benzyl alcohol with bromine in aqueous acetic acid,[3h] where the mechanism involves a rate-determining removal of hydride ion from α carbon with a synchronous removal of hydroxylic proton (Scheme IIIB). Perlmutter's mechanism[4d] is based on the correlation between pK of substrate and the pH at which k_{obsd} starts increasing.[1b,4c,d] But this correlation is also explicable by our mechanism (Scheme I), *i.e.*, pK_6 should be proportional to the pK of the substrate.

Scheme III

A. Reaction of Substrate Anion (RO^-) with Molecular Halogen (X_2) (Perlmutter-Hayman's Mechanism)[4d]

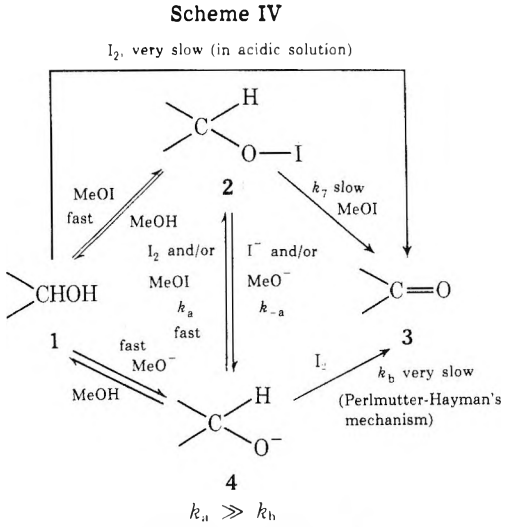


B. Reaction of Substrate (ROH) with Molecular Halogen (X_2) in Acidic Solutions[4a,f-h]



Hence Scheme I is preferable to Perlmutter-Hayman's mechanism. Benzhydroxide ion 4 should be attacked by molecular iodine and/or methyl hypoiodite on an oxygen atom rather than on an α-hydrogen atom to give hypoiodite ester **2**, *i.e.*, $k_a \gg k_b$ (Scheme IV), since the equilibria in Scheme IV are very fast.[8a] The concentration of 2 should be much higher than that of 4 at lower basicity in analogy with the case of methanol (eq 4 and 5), and the concentration of iodine [I_2] is much lower than methyl hypoiodite [MeOI] at higher basicity, so that the oxidation of 4 by molecular iodine may be much slower than that of 2 by methyl hypoiodite.

Scheme IV



$k_a \gg k_b$

$k_7[\mathbf{2}][\text{MeOI}] \gg k_b[\mathbf{4}][I_2]$

The values of ΔH^* (12.3 kcal/mol) and ΔS^* (−27.8 eu) also support our mechanism, *i.e.*, the values of ΔH^* and ΔS^* were reported to be 13.9 kcal/mol and −25.2 eu, respectively, for the Br_2 oxidation of benzyl alcohol,[4h] where a rupture of a C-H bond occurs.

Experimental Section

Materials. Unsubstituted benzhydrol is of guaranteed grade and used without further purification. *p*-Methoxy-*p'*-methyl- and *p,p'*-dimethylbenzhydrols were prepared by treatment of corresponding benzophenone with a mixture of zinc powder and sodium hydroxide in aqueous ethanol.[14] *p*-Chloro-, *p*-methyl-, and *p*-methoxybenzhydrols were prepared from the corresponding benzaldehyde by the reaction with phenylmagnesium bromide in dry ether. Prepared benzhydrols were recrystallized from *n*-hexane. The substituent of benzhydrol, melting point, and glc retention time were as follows: unsubstituted, mp 67.0–67.3° (lit.[14] 68°), 11.4 min; *p*-Cl, mp 63.0–63.2°, 17.9 min; *p*-Me, mp 53.0–54.0°, 12.4 min; *p*-MeO, mp 66.9–67.2°, 21.9 min; *p,p'*-Me_2 mp 54.5–55.2°, 19.3 min; *p*-MeO-*p'*-Me, mp 64.0–64.2°, 23.6 min. A Hitachi K-53 gas chromatograph with a flame ionization detector was used with a column packed with DEGS (13%) on Chromosorb W at temperatures increasing by 10°/min from 140 to 225° with N_2 as a carrier gas at a flow rate of 45 ml/min.

Kinetics. The reaction of benzhydrols with a mixture of iodine and sodium methoxide is irreversible. The rate of the reaction of benzhydrols (4–10 × 10^{-3} M) in methanol with an excess of iodine (45.5–227 × 10^{-3} M) and sodium methoxide (0.0364–0.727 M) was measured by means of glc analysis of the remaining benzhydrols. The rate could not be measured by following the iodine or hypoiodite concentration because they were unstable, changing their concentration by spontaneous decomposition or by their reaction with methanol solvent, although this change may be small. The concentration of iodine in a mixture of 0.5 M I_2 and 0.5 M MeONa in methanol decreased *ca.* 5% after 15 min, which is the longest time for kinetic runs.

A typical kinetic procedure was as follows. A mixture of appropriate amounts of methanolic sodium methoxide and benzhydrol was thermostated. The reaction was started by addition of a methanolic solution of iodine. At appropriate time intervals, aliquots were taken out and extracted with ether. The ether extract was washed with aqueous $Na_2S_2O_3$ to eliminate iodine and hypoiodite, and concentrated by evaporation of the solvent, the content of benzhydrol being measured by glc with a column packed with DEGS (13%) as stated above.

The plot of log ([ArAr'CHOH]/[ArAr'CHOH]$_0$) against time gives a straight line up to 60–80% conversion, where subscript 0 denotes initial concentration. The relative rates for all benzhydrols were calculated from k_3 values which are slopes of the lines in Figures 1 and 2.

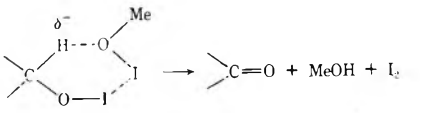
Registry No.—Iodine, 7553-56-2.

References and Notes

(1) (a) N. C. Deno and N. H. Potter, *J. Amer. Chem. Soc.*, **89**, 3550 (1967); (b) N. C. Deno and N. H. Potter, *ibid.*, **89**, 3555 (1967).
(2) (a) F. D. Chattaway and O. G. Backberg, *J. Chem. Soc.*, **123**, 3000 (1923); (b) F. D. Chattaway and O. G. Backberg, *ibid.*, **125**, 1097 (1924).
(3) R. Filler, *Chem. Rev.*, **63**, 21 (1963).
(4) (a) L. Kaplan, *J. Amer. Chem. Soc.*, **76**, 4645 (1954); (b) L. Kaplan, *ibid.*, **80**, 2639 (1958); (c) B. Perlmutter-Hayman and Y. Weissmann, *ibid.*, **84**, 2323 (1962); (d) B. Perlmutter-Hayman and Y. Weissmann, *ibid.*, **91**, 668 (1969); (e) C. G. Swain, R. A. Wiles, and R. F. W. Bader, *ibid.*, **83**, 1945 (1961); (f) I. R. L. Barker, W. G. Overend, and C. W. Rees, *J. Chem. Soc.*, 3263 (1964); (g) I. R. L. Barker and R. H. Dahm, *J. Chem. Soc. B*, 650 (1970); (h) P. Aukett and I. R. L. Barker, *J. Chem. Soc., Perkin Trans. 2*, 568 (1972); (i) J. G. Mason and L. G. Baird, *J. Amer. Chem. Soc.*, **94**, 6116 (1972); (j) R. M. Bater and J. S. Littler, *J. Chem. Soc. B*, 205 (1967).
(5) (a) J. M. Pink and R. Stewart, *Can. J. Chem.*, **49**, 649 (1971); (b) J. M. Pink and R. Stewart, *ibid.*, **49**, 654 (1971).
(6) P. Aukett and I. R. L. Barker, *J. Chem. Soc., Perkin Trans. 2*, 965 (1973).
(7) There may be other equilibria such as (a) $I_2 + I^- \rightleftarrows I_3^-$ (K_a), and (b) $I_2 \rightleftarrows I^- + I^+$ (K_b). However, the concentrations of reagents ([I_2] and [MeOI]) were calculated by neglecting these equilibria because of the following reasons: (i) their equilibrium constants are very small (K_a = 1.4 × 10^{-3} and K_b = 1.9 × 10^{-5} at 25° in aqueous solution); (ii) I_3^- is inert for the oxidation of alcohol.[1,4]
(8) (a) A. Skrabal, *Monatsh.*, **32**, 169 (1911); *Chem. Abstr.*, **5**, 2591 (1911); (b) Y. Chia, *U. S. Atomic Energy Comm.*, **UCRL-8311**, 87 (1958); *Chem. Abstr.*, **53**, 2914 (1958); (c) C. H. Li, *J. Amer. Chem. Soc.*, **64**, 1147 (1942).
(9) Equation 4 can be written in the form: $[\text{MeOI}]^2 - (1/K_4)[\text{MeOI}][I^-] - ([I_2]_a + [\text{MeONa}]_a)[\text{MeOI}] + [I_2]_a[\text{MeONa}]_a = 0$. Since $[I^-]$ is equal to [MeOI] when sodium iodide is not added, $(1 - 1/K_4)[\text{MeOI}]^2 - ([I_2]_a +$

$[MeONa]_a)[MeOI] + [I_2]_a[MeONa]_a = 0$. Since K_4 is considerably larger than unity, [MeOI] is equal to $[MeONa]_a$ (if $[MeONa]_a < [I_2]_a$) or $[I_2]_a$ (if $[MeONa]_a > [I_2]_a$).

(10) (a) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *J. Amer. Chem. Soc.*, **79**, 1897 (1957); (b) Y. Okamoto and H. C. Brown, *ibid.*, **79**, 1903 (1957); (c) *ibid.*, **79**, 1909 (1957).
(11) (a) P. S. Fredricks and J. M. Tedder, *J. Chem. Soc.*, 3520 (1961); (b) *ibid.*, 144 (1960).
(12) (a) D. S. Ashton, J. M. Tedder, M. D. Walker, and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1346 (1973); (b) W. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1973).
(13) The reviewer suggested an alternative scheme in which hydride is abstracted by an oxygen atom of methyl hypoiodite.



However, since the electrophilicity of oxygen of methyl hypoiodite should be less than that of iodine, this scheme is less probable.

(14) (a) S. R. Hooley and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1053 (1973); (b) P. M. Henrichs and P. E. Peterson, *J. Amer. Chem. Soc.*, **95**, 7449 (1973).
(15) F. Y. Wiselogle and Sonneborn, III, "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1944, p 90.

Solvents of Low Nucleophilicity. XV. Effects of Substituents at C-17 upon the Rates of Solvolysis of 3-Tosyloxy Steroids[1]

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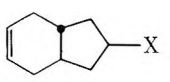
Received July 26, 1974

Rates of solvolysis of 3α- and 3β-tosyloxy androstanes having substituents at C-17 were determined in the solvents acetic acid, formic acid, and trifluoroacetic acid. Electronegative substituents at C-17 cause decreased solvolysis rates by factors up to sixfold. Simple electrostatic calculations show that dipole–dipole interactions are almost certainly too small and dipole–charge interactions are probably too small to account for the effects. Partial removal or delocalization of both negative poles of the dipoles *via* hydrogen bonding interactions with solvent, especially in trifluoroacetic acid, can account for the results. A larger effective dielectric constant for the interactions involving negative charges may be a contributing factor.

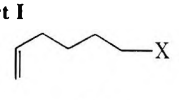
It has been generally believed that in unhindered saturated systems the effect exerted by electronegative substituents upon rates and equilibria[2] is small for substituents separated from a reaction center by several carbon atoms. However, it is now known that remote substituents may exert substantial effects particularly in various carbonium ion reactions. Typical values of k_H/k_X, the ratios of rate constants for reactions of compounds bearing the substituents H and X, respectively, are shown in Chart I for addition of trifluoroacetic acid to comparable bicyclic and acyclic alkenes.[3] The similar magnitude of effects in additions to alkenes and in tosylate solvolyses is illustrated by the data given in Chart II.[4] Based on these comparisons and on the data given in Chart III for the reaction of a 10-substituted 1-undecene, substituent effects exerted across the entire steroid polycyclic skeleton would be expected to be observable in the solvolysis of steroidal tosylates of general formula **6** (Chart III). In the present paper we report the observation of substituent effects in the acetolysis, formolysis, and trifluoroacetolysis of the steroidal tosylates, **6**. The known geometry of the steroid skeleton allows us to draw important conclusions regarding the origin and solvent dependence of the substituent effects.

Chart I



1

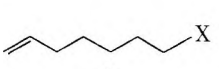
X = CN; $k_H/k_X = 152$



2

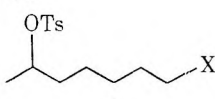
X = CN; $k_H/k_X = 61.8$

Chart II



3

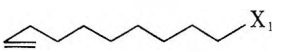
X = Cl; $k_H/k_X = 5.00$



4

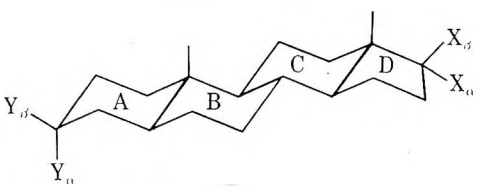
X = Cl; $k_H/k_X = 3.88$

Chart III



5

X = CN, $k_H/k_X = 2.10$



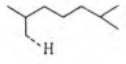
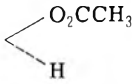
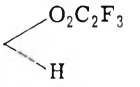
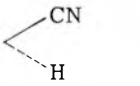
6

Y_β = OTs Y_α = H or

Y_β = H Y_α = OTs

Description and Results. The steroidal tosylates **6**, whose structures are indicated in Table I were synthesized. Rates of solvolysis were determined, and the results are given as k_H/k_X values in Table I. Values of k_X may be calculated from data in the footnotes of Table I. The key to the preparation of the 17-cyanohydrins proved to be prior introduction of the tosylate group, followed by the reaction of the 17-ketone group with liquid hydrogen cyanide for a prolonged time. Several C-17 steroid cyanohydrins which are analogous in structure to ours are reported to be mixtures, with one isomer predominating to the extent of 85–90%.[5] In a 1946 paper,[5c] the predominant isomer was said to be the β-hydroxy compound (formerly called α). Rereading the earlier papers did not lead us to the source of this assignment, although there is a hint[5c] that optical rotations may have been used as indicators of stereochemistry. Nevertheless, subsequent workers in the steroid field have accepted the β-hydroxy configuration of the predominant isomer. This isomer, somewhat surprisingly, is said[5c] to undergo acylation (possibly because the hydroxyl is pseudoequatorial) considerably more rapidly than the α-hydroxy

Table I
Values of k_H/k_X for Steroidal Tosylate Solvolyses

Registry no.	17-Substituent	k_H/k_X Trifluoroacetic acid[a]	Formic acid[b]	Acetic acid[c]
	3α Series			
52522-73-3	H_2	1[d]	1[e]	1[f]
10429-00-2	=O	4.66	2.68	1.44
52522-74-4 52555-20-1	 (OH (mixed isomers?), CN)	4.68	2.10	
52522-75-5	 (O_2CCF_3, CN)	6.07	3.25	
	3β Series			
1254-34-8	H_2	1[g]		1[h]
3381-52-0		1.13, 1.23[i]		1.04
52522-76-6	 (O_2CCH_3, H)	2.55		
52522-77-7	 ($O_2C_2F_3$, H)	2.62, 2.39[i]		
52522-78-8	 (CN, H)	3.33		
10429-07-9	=O	3.55		1.31
52522-79-9 52522-80-2	 (OH (mixed isomers?), CN)	4.72		
52522-81-3	 (O_2CCF_3, CN)	6.02		

[a] For solvolysis at 25.0° of solutions 0.05 *M* in tosylate and 0.125 *M* in sodium trifluoroacetate. [b] For solvolysis at 25.0° of solutions 0.05 *M* in tosylate. [c] For solvolysis at 70.0° of solutions 0.1 *M* in tosylate and 0.11 *M* in sodium acetate. [d] 10^5k = 352 sec^{-1}. [e] 10^5k = 26.8 sec^{-1}. [f] 10^5k = 16.0 sec^{-1}. [g] 10^5k = 16.6 sec^{-1}. [h] 10^5k = 262 sec^{-1}. [i] Duplicate values are given to indicate the precision obtained.

isomer, with precipitation of β-acylated product. These observations suggest that the crystalline cyanohydrin trifluoroacetates which we prepared are the β-trifluoroacetoxy compounds. In the study reported here, the cyanohydrins and their trifluoroacetates were included only as convenient illustrations of the maximum substituent effect which can be obtained by placing electronegative groups at C-17 and at a comparable position in an acyclic system. Inclusion of results for these compounds, even in the case of the presumed epimeric mixtures of cyanohydrins, tends to confirm the consistent picture of substituent and solvent effects which we found, but our discussion of geometrically defined substituents will be based on those compounds where the geometry is unambiguous.

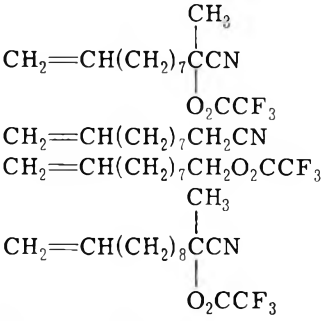
In our preparation of 3α-tosyloxy-17β-trifluoroacetate the 3α-tosyloxy group was introduced prior to sodium borohydride reduction of the 17-ketone function, to give the 17β-alcohol which, upon trifluoroacetylation, yielded the 17β-trifluoroacetate. Here the β configuration seems assured from the many analogous cases of α attack upon C-17 carbonyl groups reported in the steroid literature.[6a] The same comment applies to the 17β-cyano compound which we obtained by catalytic hydrogenation of the α,β-unsaturated nitrile.[6b] In contrast with the cases mentioned above, several of our preparations (*cf.* Experimental Section) utilized the more obvious route involving introduction of the sensitive tosylate group in the last reaction step.

Table II
Products from Trifluoroacetolysis of 3α- and 3β-Tosyloxy-5α-androstane

Isomer	Olefin, %	Alcohols, rel % 3α	3β
3α-Tosyloxy	90.8[a]	79[d]	21[d]
	89.5[a]		
3β-Tosyloxy	61.5[a]	54[c]	46[c]
	56.1[b]	55[d]	45[d]

[a] From hydrogen uptake. [b] From column chromatography on alumina. [c] Quantitative tlc. [d] Quantitative ir.

Table III
Relative Rate of Addition of Trifluoracetic Acid to Alkenes, 60.0°

Compounds	k_H/k_X
	3.22[a]
CH_2=CH$(CH_2)_7CH_2CN$	2.10[b]
CH_2=CH$(CH_2)_7CH_2O_2CCF_3$	1.79[b]
	2.14[c]

[a] Calculated by dividing log k_H/k_X for 2-cyano-2-trifluoroacetoxy-11-dodecene by the attenuation factor 0.65 to get the estimated value of log k_H/k_X for the undecene derivative. [b] From ref 3. [c] Measured in this study.

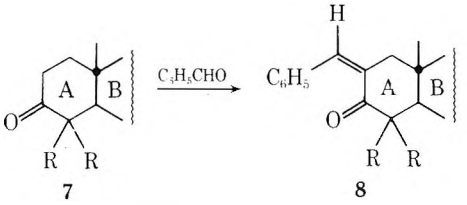
The products of trifluoroacetolysis of 3α- and 3β-tosyloxyandrostane were studied by a combination of techniques with the results given in Table II.

Finally, the cyanohydrin trifluoroacetate of 11-dodecen-2-one was prepared,[7] and the rate of addition of trifluoroacetic acid to the double bond was measured in order to assess the inductive effect of the cyanohydrin trifluoroacetate substituent. The result is given in Table III, along with previously determined data for comparison. In Table III, we also give the estimated k_H/k_X value for the addition of trifluoroacetic acid to the cyanohydrin trifluoroacetate of 11-undecen-2-one, whose substituent is at the correct distance for comparison with our steroids (*cf.* formula 5).

Discussion

Absence of Conformational Transmission. Inspection of Table I reveals that substituents at the C-17 position lead to rate depressions for solvolysis at C-3 by factors up to sixfold (for the cyanohydrin trifluoroacetate substituent). All rates are qualitatively in accord with the operation of inductive substituent effects (polar effects; *cf.* footnote 2) of the approximate magnitude anticipated from the comparison made in the introduction. However, we must also consider the possible role of another type of substituent effect, Barton's well-publicized "conformational trans-

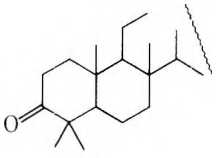
mission" effect.[8] This effect was discovered in the base-catalyzed condensation of benzaldehyde with triterpenoid and steroidal ketones which reacted according to eq 1.[8] Struc-



7 8 (1)

tural modifications, including introduction of double bonds in ring B or substituents at C-11, led to rate variations, typically by factors of less than five. The authors state that "the differences in rate from the standard probably arise, in main part, from conformational distortion produced by unsaturated substituents (and to a small extent by saturated ones)." We imagine that this distortion is transmitted through the saturated molecules by a slight flexing of valency angles and alteration of atomic coordinates.[8] It was concluded from the study of triterpenoids that in the absence of some disturbing unsaturation, the partial system **9**, (Chart IV) has an essentially constant reaction rate.

Chart IV



9

It may be seen from inspection of the C-17 substituents of our own study (*cf.* Table I) that they are "saturated" at the bond attaching them to the ring (except for the ketone) and that they, furthermore, fall outside the "active region" (formula **9**), suggesting that "conformation transmission" is not an important source of our substituent effects. This tentative conclusion is strengthened by the absence of an appreciable effect (k_H/k_X = 1.1–1.2) of the C_8H_{17} side chain at C-17 in the 3β-tosylate trifluoroacetolysis. The alkyl substituent should be larger than the trifluoroacetoxy substituent (for which k_H/k_X = 2.4–2.6) and should presumably give a larger "conformational substituent effect," quite in contrast with our observations.

Recently a study of the quantitation of long-range effects in steroids by molecular orbital calculations appeared.[9] Although the authors concluded that two types of conformational transmission were the source of long-range effects, we believe their molecular orbital model, involving interaction of CH_3F (taken as a model electronegative substituent) with an ethylene molecule, does not adequately represent effects in reactions having ionic (charged) transition states (the usual case). Accordingly, the conclusion[9] that electrostatic effects are negligible is inapplicable to a cited paper[10] and to our study.

Evidence for Inductive Effects. Inductive effects (that is, polar effects which may be field effects[2]) of substituents at C-3 and at C-17 upon rates of addition of bromine to Δ-5,6-steroids have been reported.[11] The inductive origin of the effects was inferred from the parallelism which was observed upon substitution at the two sites.[11] Similarly, an electrostatic origin of effect of C-17 substituents upon the relative rates of α and β epoxidation of Δ-4,5-3-keto steroids has been postulated.[12] The unavailability of one of the epimers in the case of the parent compound (having hydrogens at C-17) hinders the interpretation of the results, as does the observation of some further oxidation of the epoxides to acidic products under the reaction conditions. In other published work rate variations by factors of 1.2 or less were observed when the effect of substituents at C-17 upon the rate of substitution activated vinyl chloride by methoxide at C-4 was investigated.[13] Rate effects of four- to sevenfold upon reactivity at C-6 attended the introduction of electronegative substituents at C-3 in the acetolysis of 6α-tosyloxy-3α- and -3β-chloro-5α-cholestane.[14] The 1.8-fold slower rate for the 3β compound at 75° was ascribed to the smaller attractive interaction between the cationic reaction center and the negative end of the C-3 dipole in this isomer. Repulsive interactions dominated more strongly in this circumstance. Finally, yield increases in acetylation of 3-substituted 12α-hydroxy-5β-cholanates have been observed when the 3-substituent is electronegative.[15]

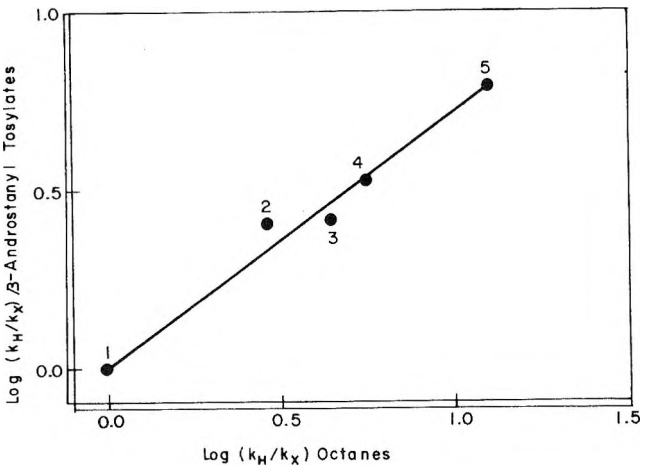


Figure 1. Plot of substituent effects in C-17 substituted steroidal tosylate trifluoroacetolyses *vs.* substituent effects in the addition of trifluoroacetic acid to ω-substituted 1-octenes. Substituents: 1, H; 2, $OCOCH_3$; 3, $OCOCF_3$; 4, CN; 5, CN and $OCOCF_3$. For substituent 5 the octene value was estimated using an attentuation factor (*cf.* Table III).

In Figure 1 is shown a plot of log k_H/k_X for the rates of trifluoroacetolysis of our 3α-steroid tosylates *vs.* log k_H/k_X for the addition of trifluoroacetic acid to ω-substituted 1-octenes. The alkene data are chosen as a source of substituent effects instead of the standard σ_I or σ^* values of the Hammett–Taft equation, log $k_X/k_H = \rho\sigma_I$, because trifluoroacetic acid is known to increase the σ_I value of oxygen- and nitrogen-containing substituents by hydrogen bonding to the substituents.[16] The approximate linear free energy relationship of Figure 1 provides solid support for an inductive origin of our substituent effects, although the range of substituents is more limited than would be desirable. The absence of an effect of the alkyl side chain ($\sigma_I \simeq 0$) is again particularly impressive.

In previously studied aliphatic tosylate solvolyses,[4] successively decreasing ρ_I values (−5.36, −4.49, and −2.71, respectively, based on 4-chloro-2-butyl tosylate solvolysis) were obtained as the solvent was varied in the order trifluoroacetic acid, formic acid, acetic acid. The similarity of these effects to those observed in the present study (Table I) provides a second line of evidence for an inductive origin of our steroid substituent effects.

A possible source of effects of remote substituents is substituent influence upon micelle formation, which has not been ruled out as the source of an unusual effect of the C-17 C_8H_{17} side chain upon C-3 ketone homologation.[17] A substituent effect upon the formation of aggregates, including dimers, arising from the previously understimated[18] attractive forces in σ-bonded systems, is also a conceivable factor in our studies as are effects (*e.g.*, conformational

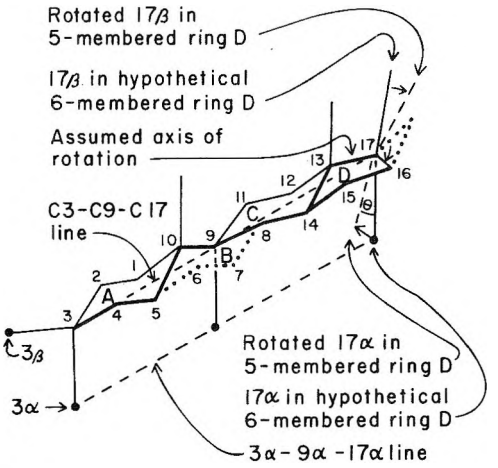


Figure 2. Illustration of geometric relationships which characterize C3–C17 interactions.

changes or modification of dielectric properties) arising from clustering of solvent molecules around the substituent. However, none of these factors presently appears to offer the demonstrated predictive capacity of the hypothesized inductive (polar) origin of our substituent effects.

Calculation of Maximum Expected Electrostatic Interactions. Considerable success has been attained in the estimation of the magnitude of substituent effects by calculation of the electrostatic interaction of charged and dipolar substituents with the reaction site.[19] Stock and coworkers have provided new evidence for the nature of electrostatic effects in the form of reversed substituent effects,[19b,c] in addition to supplying recent examples of calculations involving the Westheimer–Kirkwood cavity model.

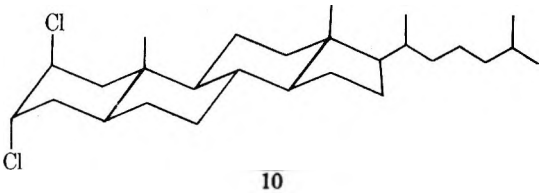
In our study, it was of particular interest to see if the effects of truly remote substituents, reported in the present study, are of the general magnitude expected of electrostatic interactions. Accordingly, we calculated the effect of an array of electronic charges located at C-3 (positive), at the 3α or 3β position (negative), at C-17 (positive), and at the 17α or 17β position (negative) (*cf.* Figure 2). Only the four r_i values (distances) between the substituent and the reaction site are counted in eq 2, which gives the desired electrostatic energy. In eq 2, the r values are in ångstroms, q is

$$E = \sum_i qq'/r_i D_E = \sum_i (3.32 \times 10^5)(qq'/r_i D_E) \quad (2)$$

in units of electronic charge, D_E is the effective dielectric constant, taken to be 2 in order to obtain a maximum interaction, and E is in calories per mole.[20] The results of our calculations for steroids of hypothesized geometry to be mentioned, along with results for steroids **10**, **11**, and **12** (Chart V) whose coordinates were available from X-ray crystal structures,[21] are given in Table IV. The use of charges at the atomic coordinates to represent dipoles finds precedent in recent work of Golden and Stock,[19b] and Dewar, Golden, and Harris.[22]

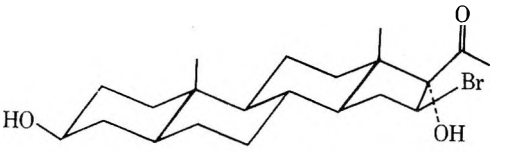
For the calculations reported in Table IV (except those based on X-ray data), the C-3–O-3 bond and C-17–X bonds were assumed to be 1.54 Å in length except as noted later for C=O and C—C≡N substituents. In Figure 2, the geometry associated with the five-membered ring D which we used is compared with that of a hypothetical homosteroid (dotted lines) in which ring D is a chair cyclohexane unit. The 17α bond is rotated by the angle θ, compared to the bond in the homosteroids, and 17β is similarly rotated. (We assumed a rotation of 30° about the 17–13 bond, based on inspection of Dreiding models.) When a C-17 ketone substituent was present, it was assumed to be half-way between C-17 α and β substituents. That is, the assumed oxygen-17-13-12 dihedral angle was +30°. In this instance the assumed C-17–O bond distance was 1.23 Å and the C-13 to C-17 bond distance was 1.516. Not surprisingly, the calculated (Table IV) ketone dipole interaction with an axial C-3 substituent, 79 cal/mol, lies between the values 453 and −178 for α and β C-17 dipoles. For 17α-CN and 17β-CN substituents the C-17–C and C≡N bond lengths were taken to be 1.46 and 1.16 Å, respectively.

Chart V



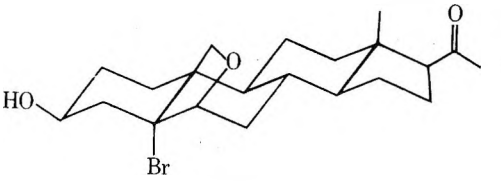
10

2β,3α-Dichloro-5α-cholestane



11

16β-Bromopregnane-17α,3β-diol-20-one



12

5α-Bromo-6,19-oxidopregnan-3β-ol-20-one

Included in Table IV are energies for various combinations of interaction in which the substituent or reaction site is considered to be positively charged, instead of dipolar. Those dipoles having both ends at similar distances from the charge give relatively small interactions, which may be negative (attractive) as illustrated for α-C≡N with the charge considered to be on carbon. The larger charge–dipole interactions are approximately 2 kcal/mol, whereas the calculated charge–charge interaction is 19 kcal/mol.

The negative values for some of the calculated interactions (Table IV) appear at first to be surprising. However, careful examination shows that these values arise from geometries in which the dipoles have an attractive orientation, the negative end of one being near the positive end of the other. Although the calculations are suggestive of opportunities for the observation of reversed substituent effects, which have been found in a dihydroanthracene system,[19b] we shall see that our experimental results suggest that dipole–dipole interactions are an unrealistic model for interactions in solvolysis transition states.

Comparison of Calculated and Measured Substituent Effects. In Table V selected observed substituent effects from Table I are tabulated in units of kcal/mol in $\Delta\Delta G^*$. For comparison, calculated values from Table IV are listed, scaled to represent the actual substituents C–O and C≡N by multiplying values from Table IV by 0.049 and 0.074, respectively. These scale factors represent the fractions of an electronic charge, which, when separated by the C–O and C≡N bond distances, d, reproduce the dipole moments of these groups.[23]

Table IV
Energies of Interaction (Calories per Mole), C-3 to C-17, for Model Steroid (Selected Actual Steroid Values in Parentheses)

Type of C-3 group	Interaction type	17α-C^+X^-	17α-$C^+=O^-$	17β-C^+X^-	17α-C^+N^-	17β-C^+N^-
3α, axial	3-Dipole, 17-dipole	453	79	−178 (−223[a])	314	−56
3β, equatorial	3-Dipole, 17-dipole,	28 (−19[b])	240	507 (676)[b] (570)[c]	138	344
3 positively charged	3-Charge, 17-dipole	390	964	1837	626	1363
3α, axial	3-Dipole, 17- or 20-charged	256[d]			−197[e]	434[f]
3β, equatorial	3-Dipole, 17- or 20-charged	2525[d]			2499[e]	2020[f]
3,positively charged	3-Charge, 17-charge	19,067				

[a] Value for the steroid **10** (Chart V). [b] Value for **11** (Chart V). [c] Value for **12** (Chart V). [d] For C-17 positively charged. [e] For 17α-$C^+=$ (17α-$C^+=N^-$ with negative charge absent. The positive carbon is numbered C-20.). [f] For 17β-$C^+=$17β-C^+X^-.

Table V
Comparison of Selected Observed Substituent Effects and Calculated Maximum Effects

C-3 orientation	C-17 substituent	2.303RT log k_H/k_X, kcal/mol	Energy,[a] dipole-dipole	Energy,[a] C-3 charged	Energy,[a] C-17 charged
α, OTs	O_2CCF_3 CN	1.0			
α, OTs	=O	0.58	0.039	0.472	0.125
β, TsO	=O	0.65	0.117	0.472	1.240
β, TsO	β, CN	0.71	0.255	1.006	1.495
β, TsO	β, O_2CCF_3	0.55			
β, TsO	O_2CCF_3 CN	1.06			

[a] kcal/mol.

The data of Table V allow us to state what is possibly the most important result of our study. The observed interactions for the keto steroids are several times larger than the calculated maximum dipole–dipole interactions, and the interaction in the cyano steroid is also significantly larger. These results support the intuitive feeling that substituent effects are larger than expected for solvolyses in trifluoroacetic acid, and, by inspection of Table I, for solvolyses in formic acid. Below we discuss two types of charge delocalization which may lend to large observed interactions.

We first consider the possible effect of delocalization of positive charges by polarization of adjacent carbon atoms, or, particularly for carbonium ions, by a perhaps equivalent partial filling of the vacant orbital by overlap with adjacent C–H or C–C bonds (hyperconjugative delocalization). The effect of such positive charge delocalization is given in Table VI for various "charge ratios," which we define by giving an example. The charge ratio is said to be 0.2 if the ratio of the charge on each carbon atom adjacent to the cationic center to that on the center itself is 0.2, the total charge being one unit. Charges farther than three atoms distant were ignored (assumed to be zero). In the calculations the substituent positive charge was also considered to be delocalized to the same extent as the carbonium ion charge, and all interactions between the substituent and the reaction site were summed. It may be seen in Table VI that substantial increases in dipole–dipole energy are produced by moderate amounts of delocalization. The possible importance of this effect in causing the slow fall-off of the inductive effect with distance for cationic reactions in trifluoroacetic acid has been pointed out.[4] This type of delocalization somewhat resembles the so-called classical or through-bond inductive effect. However, the latter, by tradition, has no geometric dependence and, accordingly, differs from our postulated delocalized charge effect. Extraordinarily, no physical model (in terms of charge distribution) for the through-bond inductive effect has ever been proposed, and it seems somewhat surprising that so much time has been spent disproving the importance of a concept which has no theoretical underpinning.

Table VI
Comparison of C-3–C-17 Electrostatic Interactions for Delocalized *vs.* Localized Positive Charges

Charge ratio	Ratio of energy: delocalized/localized Dipole-dipole	Charge-dipole	Charge-charge
0.0	1	1	1
0.1	1.28	1.10	1.02
0.2	2.01	1.35	1.09
0.3	3.26	2.01	1.19

Although a dominant role for internal charge delocalization previously seemed possible, we note (*cf.* Table VI) that the calculated interaction of such charges for a molecule of known geometry falls short of that found for "charge ratios" up to 0.3. The value of 0.3 is larger than the expected one, based on molecular orbital calculations in the propyl cation which shows a Mulliken population of the empty orbital of only 0.198 for the 2-butyl cation.[24]

Accordingly, in order to explain our results, we turn to what might be termed "negative charge delocalization," namely, delocalization of the negative ends of the dipoles into the solvent. Hydrogen bonding of solvent to the negative atom, or in the extreme, protonation, presumably may partially or completely cancel the negative charge. Indeed, Dewar and Grisdale have implicitly assumed such an effect in their earlier F–M treatment of substituent effects,[25] but have reduced the cancellation due to solvation from 100 to 10% in their more recent correlation.[21] There is no indication that 10% was shown to give optimum results, however.

The results of dropping the tosylate negative charge only, or both negative charges, are shown in Table IV

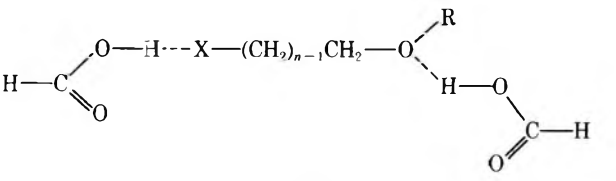
(charge–dipole and charge–charge energies, respectively). [The effect of also considering partial positive charge delocalization for charge–dipole interactions is given (Table VI) for comparison with the dipole–dipole case.] Replacing the C-3 dipole by a positive charge is seen (Table V) to achieve good, presumably fortuitous, agreement beteen calculated and observed values. Placing the charge at C-17 is somewhat less satisfactory in that the calculated difference in interactions of 3α and 3β dipoles is not found experimentally. Actually, there is strong evidence that trifluoroacetic acid does hydrogen bond strongly to oxygen- and nitrogen-containing substituent groups, causing their substituent effects to be enhanced with respect to those of halogen substituents. Accordingly, the observed substituent effects probably reflect substantial negative charge dispersal for both dipoles.[26] The calculated effects in such instances could be substantially larger than the charge–dipole interactions shown in Table V, although not as large as the charge–charge interaction of 19 kcal/mol (Table IV). Substantially increased magnitudes of values calculated according to the assumptions used are presumably necessary for any realistic reconciliation of observed and calculated data, since the effective dielectric constant will presumably[27] be larger than the assumed value, 2, and since the change in charge on C-3 and on the attached tosylate oxygen upon going from reactant to transition state will certainly be less than the assumed one electronic charge unit.

A priori, a *large* effective dielectric constant might have been found in our formolyses. According to the Westheimer–Kirkwood model, the effective dielectric constant for long, thin ellipsoids having interacting charges at the foci (or, alternatively, for molecules having the interacting charges near the surface)[28] approaches that of the solvent. The dielectric constants of acetic, formic, and trifluoroacetic acid are 8.42, 57.9, and 6.15, respectively.[29] Consulting Table I we note that there is no indication that the large dipole moment of formic acid has an appreciable effect on the results. The results suggest that experimentally accessible rigid molecules exhibit little solvent influence upon the Kirkwood–Westheimer effective dielectric constant in solvolysis transition states.

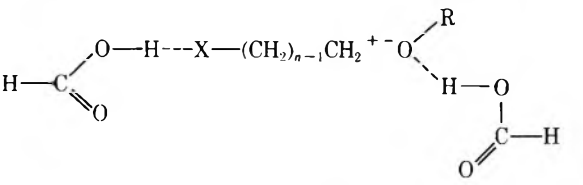
The apparently similar results for formic and trifluoroacetic acid also suggest that the large magnitudes of substituent effects are not primarily a result of the negative ends of the dipoles sensing a higher effective dielectric constant. Golden and Stock[18b] have considered the possibility that such an effect is important in other systems, as have Henbest and Jackson.[12] The small substituent effects observed for reactions in acetic acid (Table I) parallel the results observed for aliphatic systems[4] and may be connected with the occurrence of SN2- or E2-like transition states in this solvent.[30] One additional observation in regard to the influence of solvent is that extremely high ratios (approximately 17) of k for solvolysis of corresponding axial and equatorial tosylates in trifluoroacetic acid are noted (*cf.* values, Table I, footnotes). In the present paper, we refrain from examination of the possible nature of the solvolysis transition states in the light of the axial–equatorial effects, in order to focus on the nature of the substituent effects which we observed.

It seems appropriate here to mention the possible implications of our results for future studies. Our tentative hypothesis that solvation of the negative ends of the dipoles through hydrogen bonding drastically modifies substituent–reaction site interactions in solvolyses in formic and trifluoroacetic acid suggests that attempts to match experiment results with Kirkwood–Westheimer type calculations would suffer from the apparent lack of an *a priori* basis for choosing the type of interactions (charge–dipole, etc.) to be fitted to the model. On the other hand, it would appear promising to apply molecular orbital calculations in which hydrogen bonding solvation is included at the substituent and reaction site, one molecule per site, as illustrated in the example of Chart VI.

Chart VI



reactant



transition state

Ab initio molecular orbital calculations for fluorine substituent effects in carbonium ions in the gas phase showed an attenuation of interactions with distance between the substituent and the reaction site by ~2/3 per CH_2 group[24] similar to the values reported for carbonium ion reactions in trifluoroacetic acid. It is interesting that the calculated interactions were of the charge–dipole type, again suggesting that for the reactions in solution the negative end of the tosylate dipole in the transition state may be partially lost by hydrogen bonding solvation. It is to be noted that the molecular orbital calculations are subject to the same ambiguity mentioned for Kirkwood–Westheimer calculations. That is, one might have presumed that calculations which include a negative counterion weakly bonded to the cationic center would be the appropriate ones for comparison with solvolytic data, and such may prove to be the case for solvolyses in solvents more weakly solvating than formic acid. The alternatives are to determine experimentally which theoretical model matches the data, or, as mentioned above, to include a solvent molecule at the reaction site and make the calculations themselves the basis for deciding whether the solvent hydrogen bond has a major role in determining the substituent effect.

Conclusion. Although it might seem that substituent effects have been explored to the point of exhaustion, our work suggests that an area of study involving strongly solvated substituents exists which has not been extensively explored. Our demonstration and others cited that the remoteness of substituents separated from reaction sites by the entire steroid skeleton does not preclude study of their effects considerably expands the possibilities for additional work.

Experimental Section

General Information. Starting materials (Sigma Chemical Co.) and previously reported compounds showed the melting point reported in the literature. Analyses were performed by Scandanavian Microanalytical Laboratories. The nmr spectra were taken on a Varian A-60 spectrometer.

3α- and 3β-Tosyloxy-5α-androstan-17-one. The reported tosylates[31] were prepared from androsterone and epiandrosterone, respectively.

3α-Tosyloxy-17β-hydroxy-17α-cyano-5α-androstane. 3α-Tosyloxy-5α-androstan-17-one (3.11 g, 7 mmol) was dissolved in

20 ml of tetrahydrofuran and cooled to 5°. To this solution 15 ml of liquid hydrocyanic acid (prepared by a previously described method)[32] and a drop of saturated solution of sodium cyanide were added. After stirring for 45 min at 5°, the mixture was allowed to warm to room temperature and was stirred for an additional 1 hr. It was then neutralized with a few drops of cold 25% aqueous sulfuric acid solution. A semisolid organic material was precipitated on addition of 10 ml of water. The mixture was extracted with ether. The ether solution was washed with water, dried, and concentrated in rotary evaporator. Attempted crystallization from different solvents gave amorphous yellow powder, mp 132–134°, presumed to be too unstable for analysis; yield 2.30 g (70%). The stereochemical assignment and the possibility of the presence of some of the C-17 epimer have been discussed (*cf.* ref 5). The nmr spectrum and the ready conversion into a pure trifluoroacetate provide evidence for the predominance of one C-17 epimer

The infrared spectrum showed -OH and -CN absorptions at 3400 and 2232 cm^{-1}, respectively. The nmr spectrum showed angular methyl peaks at δ 0.77 and 0.85, singlet for -OH at δ 3.68, and a broad peak of 3β-hydrogen, centered at δ 4.82.

3β-Tosyloxy-17β-hydroxy-17α-cyano-5α-androstane. The compound, possibly containing some C-17 epimer, was prepared from 3β-tosyloxy-5α-androstan-17-one in a manner similar to that described for the 3α epimer, mp 136–142°.

3α-Tosyloxy-17β-trifluoroacetoxy-17α-cyano-5α-androstane. For preparation of the compound whose assignment of stereochemistry at C-17 has been mentioned in the Discussion, a solution of 3α-tosyloxy-17β-hydroxy-17α-cyano-5α-androstane (0.950 g, 2 mmol) in 10 ml of anhydrous ether was cooled to 0° with ice. To this solution 1.0 g (10 mmol) of trifluoroacetic anhydride was added. After 12 hr, white crystals of trifluoroacetate had deposited on the side of the flask. These crystals were collected by suction filtration, washed with a mixture of ether–pentane (1:1) and dried under high vacuum. The mother liquor yielded a second crop. Recrystallization from ether–pentane gave 1.05 g (91%) of trifluoroacetate, mp 104–105°. The infrared spectrum showed a strong carbonyl absorption at 1788 cm^{-1}.

Anal. Calcd for $C_{29}H_{36}F_3NO_5S$; C, 61.36; H, 6.32. Found: C, 61,24; H, 6.33.

3β-Tosyloxy-17β-trifluoroacetoxy-17α-cyano-5α-androstane. The compound presumed to have the designated configuration at C-17 (*cf.* Discussion), mp 111–113°, was prepared from 3β-tosyloxy-17β-hydroxy-17α-cyano-5α-androstane in a manner similar to that described for the 3α epimer.

Anal. Calcd for $C_{29}H_{36}F_3NO_5S$: C, 61.36; H, 6.32. Found: C, 61.41; H, 6.27.

3α-Tosyloxy-5α-androstane. 3α-Hydroxy-5α-androstane was prepared from the C-17 ketone by following the procedure described by Huang-Minlon[33] to give the known 3α-hydroxy-5α-androstane,[34] 4.2 g (95%). The tosylate was prepared, white crystals from ethanol, mp 98–99°, 3.9 g (91%). The nmr spectrum showed angular methyl peaks at δ 0.75 and 0.83, and 3β-hydrogen at δ 4.6–4.8.

3β-Tosyloxy-5α-androstane. The reported[35] compound was prepared from the alcohol in 94% yield.

Dihydrocholestryl Tosylate. This tosylate[36] was prepared from dihydrocholesterol in 92% yield

3β-Acetoxy-17β-cyano-5α-androstane. 3β-Acetoxy-Δ^{16}-17-cyano-5α-androstane[37] (2 g, 6 mmol) was reduced over palladium catalyst (10% on charcoal, 100 mg) in acetic acid (25 ml) at atmospheric pressure. After the reduction was complete, the solution was poured into 200 ml of water. The precipitates were collected by filtration and washed with water. After crystallization from ethanol it had mp 129–134°.

Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.73; H, 9.73.

3β-Hydroxy-17β-cyano-5α-androstane. The 3β-acetate was hydrolyzed with 2 *N* sodium hydroxide solution in ethanol. The crude alcohol had mp 142–151°.

3β-Tosyloxy-17β-cyano-5α-androstane. The tosylate was prepared in 95% yield; mp 132–134°.

Anal. Calcd for $C_{27}H_{37}NO_3S$: C, 71.17; H, 8.18. Found: C, 70.98; H, 8.26.

3β-Tosyloxy-17β-trifluoroacetoxy-5α-androstane. 3β-Tosyloxy-5α-androstan-17-one was reduced with sodium borohydride in ethanol at 5° by a conventional method. The resulting alcohol obtained had mp 93–94° after crystallization from ether. The infrared spectrum showed hydroxyl absorption at 3400 cm^{-1}.

Anal. Calcd for $C_{26}H_{38}O_4S$: C, 69.92; H, 8.58. Found: C, 69.89; H, 8.64.

The above alcohol was trifluoroacetylated with trifluoroacetic anhydride in ether. The trifluoroacetate obtained had mp 142–144°, after one crystallization from ether–pentane mixture. The infrared spectrum showed a strong carbonyl absorption at 1755 cm^{-1}.

Anal. Calcd for $C_{28}H_{37}O_5SF_3$: C, 61.98; H, 6.87. Found: C, 61.95; H, 6.76.

10-Undecylenealdehyde. This aldehyde was prepared by passing 10-undecylenyl alcohol (30 g) through a hot column packed with a copper catalyst. A slow stream of dry nitrogen was passed through the column during this operation. The copper catalyst was obtained from cupric oxide wire which was reduced in a slow current (three to four bubbles per second) of hydrogen and nitrogen mixture (1:10) at a temperature of 280 to 300°. Reduction required 4 hr under these conditions. During the preparation of the aldehyde the dropping time was adjusted so that the column temperature was maintained at 325°. The product obtained was a mixture of the alcohol and the aldehyde. Fractional distillation of this mixture afforded 10-undecylenealdehyde (14 g, 43%), bp 67–68° (0.6 mm).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.39; H, 11.89.

11-Dodecen-2-ol. Methylmagnesium iodide was prepared from magnesium turnings (2.5 g, 0.105 g-atom) and methyl iodide (15.23 g, 0.105 mol) in anhydrous ether (50 ml) under nitrogen atmosphere. 10-Undecylenealdehyde (16.8 g, 0.1 mol) in anhydrous ether (100 ml) was added slowly over a period of 30 min, and the mixture was stirred for 2 hr at room temperature. It was then cooled in an ice bath to 0°, 3 *N* hydrochloric acid (50 ml) was added cautiously, and the mixture was stirred until all the precipitate dissolved.

The layers were separated, and the organic layer was washed with dilute sodium carbonate solution and water. After drying, the solvent was removed by distillation and the product was distilled under reduced pressure to give 11-dodecen-2-ol (XIX), bp 92–94° (0.4 mm); yield 14.6 g (79%).

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.28; H, 13.03.

11-Cyano-11-trifluoroacetoxy-1-dodecene. This cyanohydrin was prepared in 85% yield from 4.55 g (25 mmol) of 11-dodecen-2-one, 4.9 g (0.1 mol) of sodium cyanide in 120 ml of aqueous ethanol (5:1), and 3 ml of sulfuric acid (0.11 mol) in 10 ml of water. Trifluoroacetylation gave the product, bp 92–95° (0.3 mm). The infrared spectrum showed the expected peaks at 1800 (carbonyl) and 910 and 990 cm^{-1} (terminal double bond). The nmr spectrum showed the presence of a CH_3 group, δ 1.89 (3 H), and terminal vinyl group, δ 4.85–6.05 (3 H).

Anal. Calcd for $C_{15}H_{22}NO_2F_3$: C, 59.00; H, 7.26. Found: C, 60.17; H, 7.56.

The cause for the high carbon analysis is unknown.

Rates. Rates of acetolysis and trifluoroacetolysis were followed as described previously.[4] For compounds, which were soluble enough for preparing 0.05 *M* solutions in formic acid, the rates were determined by ultraviolet spectroscopic analysis of quenched solutions, as previously described[4] for trifluoroacetolysis. However, the solubilities of 3α- and 3β-tosyloxy-5α-androstanes were too low for the quenching method. A modified procedure was used for these toluenesulfonates. 3α-Tosyloxy-5α-androstane (28 mg) was placed in 40 ml of formic acid and stirred for 3 min. The turbid solution was filtered quickly through a sintered glass funnel, and the clear solution obtained was placed in 25.0° bath. The whole operation took 8 min. The solution was withdrawn in intervals and pipetted into ultraviolet cells. Spectra were recorded on a Bausch and Lomb Spectronic 505 spectrometer using formic acid as the reference. The time was noted when the maximum at 272 mμ appeared on the chart. The total time taken after the withdrawal of the solution to the appearance of the maximum at 272 mμ was never more than 90 sec. The maximum at 272 mμ was used in measuring rates, as reported[4] for trifluoroacetolysis.

Trifluoroacetolysis of 3β-Tosyloxy-5α-androstane. A solution of 1.2356 g of 3β-tosyloxy-5α-androstane in 75 ml of trifluoroacetic acid, 0.1271 *M* in sodium trifluoroacetate, was kept at 25° for 8.5 hr (7 half-lives) under hydrogenation conditions using 25 mg of 10% palladium on charcoal (presaturated with hydrogen) as catalyst. The volume of the hydrogen uptake under the experimental condition (temp 25.0°, pressure 758 mm) was 41.10 ml corresponding to 61.5% elimination.[38] The solution was filtered through a sintered glass funnel and was diluted with 1 l. of water. The product was extracted six times with 100-ml portions of ether. The ether extract was washed with a saturated solution of sodium car-

bonate and water and was dried over anhydrous magnesium sulfate. Ether was removed by distillation and the residue obtained was chromatographed over 45 g of neutral alumina (Woelm activity I).

Successive elution with the indicated solvents gave the fractions: (1) 200 ml of pentane, 419 mg of liquid hydrocarbon, corresponding to 56.1% elimination; (2) 150 ml of ether–benzene (1:1), 292 mg of the solid alcohol,[38] mp 101–108°, from hydrolysis of the trifluoroacetates on the column. The alcohol yield corresponds to 36.9% substitution. A 1:1 mixture of authentic 3α- and 3β-hydroxy-5α-androstane had mp 104–112°. The total recovery of alcohols and alkane product (possibly partly rearranged) was 93%. Thin layer chromatography of the alcohol fraction on silica gel gave two spots with R_f values 0.473 and 0.327 in benzene, corresponding to the authentic 3α- and 3β-hydroxy-5α-androstane, respectively.

Quantitative Tlc. The plates were prepared by spreading a slurry of 40 g of silica gel GF_{254} (E. Merck) in 80 ml of distilled water on 20 × 20 cm glass plates. The plates were coated to a thickness of 0.25 mm and allowed to dry at room temperature for about 1 hr. They were then placed in an oven at 150° for 20 min and stored in a desiccator until they were used for separation of compounds.

Acknowledgment. We are indebted to D. Warren Vidrine for providing most of the calculated values of Table IV and for the comparison of these results for unit electronic charges at the atomic coordinates with those applicable to actual dipoles. Support of this work by the National Science Foundation (Grant GP 30683 and earlier grants) is gratefully acknowledged.

Registry No.—3β-Acetoxy-17β-cyano-5α-androstane, 52522-82-4; 3β-acetoxy-Δ^{16}-17-cyano-5α-androstane, 52522-83-5; 3β-hydroxy-17β-cyano-5α-androstane, 52522-84-6; 3β-tosyloxy-17β-hydroxy-5α-androstane, 32625-08-4; 10-undecylenealdehyde, 112-45-8; 10-undecylenyl alcohol, 112-43-6; 11-dodecen-2-ol, 21951-49-5; 11-cyano-11-trifluoroacetoxy-1-dodecene, 52555-19-8.

References and Notes

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Aromatic Substitution. XXVII.[1] Kinetics of Nucleophilic Substitution of Some Fluoropyridines and -picolines with Methoxide, Thiomethoxide, and Thiophenoxide Ions

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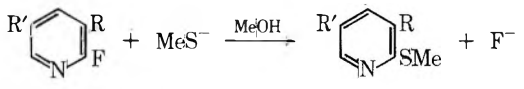
Received June 10, 1974

The rates and activation parameters were determined for the reactions of KSMe and KOMe in methanol with 2-fluoro-, 2-fluoro-3-methyl-, and 2-fluoro-5-methylpyridine, and of KOMe, KOPh, and KSPh with 2-fluoropyridine in hexamethylphosphoramide. The F/Br mobility ratios for 2-halogenopyridines with MeO^-, MeS^-, and PhS^- in methanol were compared with those in HMPA and the results are discussed.

Quantitative studies[2,3] on the reactivity of thiomethoxide ion with halogenonitrobenzenes in methanol revealed a high value of the ratio F/I, similar to that observed for nucleophiles of low polarizability such as methoxide. With the iodo derivatives an increase in the free energy was associated with low $\Delta S^\dagger$ values which were regarded as steric in origin, reflecting interaction between the bulky leaving group and the sulfur nucleophile.

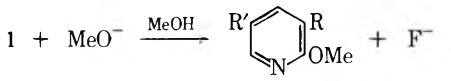
In order to determine if the halogen mobility in the pyridine series would reflect such a heavy (sulfur) nucleophile effect, the kinetics of the reaction of 2-fluoropyridines (1) with thiomethoxide ion in methanol to give 2 were studied;



1 2

the kinetic data for the reactions with 2-bromopyridines were reported earlier.[1] The rate data and Arrhenius parameters are summarized in Table I. An examination of the specific rate constants shows that the order of reactivities was 2-fluoro > 2-fluoro-3-methyl- > 2-fluoro-5-methylpyridine and follows the order of energies of activation. The lesser deactivation of the ortho than of the para position by a 3-methyl group parallels that reported earlier for the 2-bromopyridines with MeS^- [4] and MeO^- [4] in methanol. Unlike the 2-bromopyridines with PhS^- in methanol,[5] an *o*-methyl group does not activate the 2 position in 2-fluoropyridine toward attack by MeS^- in methanol.

In order to compare the F/Br ratios obtained with MeS^- in methanol with those for MeO^-, it was necessary to study the kinetics of the reaction of fluoropyridines with MeO^- in methanol. The reaction of 2-fluoropyridine with MeO^- was reported earlier.[4] The rate data and activation parameters are summarized in Table II. The order of reactivities was again the same as that reported earlier[4] for the bromo-



3

pyridines with methoxide ion, *i.e.*, 2-F > 2-F-3-Me > 2-F-5-Me-pyridine, and was dependent upon E_{act}.

For the reaction of CH_3O^- with halogenopyridine derivatives in methanol the typical[2,6-9] leaving group pattern [F > Br (Table III)] was observed. This pattern is a result of the electronegativity (α) effect, which lowers E_{act} by *ca.* 3 kcal/mol for the reactions of the fluoro- (Table II) compared with the bromopyridines.[4]

With thiomethoxide in methanol the F/Br ratio (Table III), although slightly greater than unity, cannot be attributed to a lower E_{act} for the fluoro isomer; in fact, the E_{act} is consistently larger (1–2 kcal/mol) for the fluoro (Table I) than for the bromo derivatives.[4] The E_{act} value is probably best looked upon as being normal for the fluoro compounds while the lower values for the bromo analogs are most likely a result of attractive dispersion forces between the polarizable nucleophile and the leaving group.[10] Although this reduction in E_{act} for the bromo compounds is not large enough to counterbalance the heavy (sulfur) nucleophile steric interaction between entering and leaving groups, and thus not large enough to reverse the observed mobility pattern (F > Br), the F/Br mobility ratio is reduced substantially compared with that observed with MeO^-.

On going from 2-bromo- to 2-fluoropyridine the polarizability of the leaving group is reduced.[11] This permits a more useful comparison of the *o*-Me:*p*-Me rate ratios for MeO^- and MeS^- with the fluoro- than with the bromopyridine derivatives. An examination of these rate ratios, given in Table IV, suggests once again[1] that more than just ion–dipole attractive interactions between the 3-methyl group and MeS^- are involved. If only ion–dipole effects were im-

Table I
Kinetic Data and Activation Parameters for the Reaction of 2-Fluoropyridines with Potassium Thiomethoxide in Methanol

	Pyridine		
	2-Fluoro	2-Fluoro-3-methyl	2-Fluoro-5-methyl
$10^4 k_2$, M^{-1} sec^{-1} (temp, °C)	3.07(90), 7.11(100), 17.3(108), 28.9(115), 42.6(120)	0.985(90.3), 2.61(100.2), 6.34(110), 9.85(114.9), 16.5(120)	0.373(100.4), 0.973(110), 2.35(120), 6.32(130)
$10^4 k_2$, M^{-1} sec^{-1} (at 110°)	19.1	6.34	0.97
E_{act}, kcal/mol[a]	25.3	26.6	28.3
$\Delta S^\dagger$, eu	−7.4	−6.1	−5.3
$\Delta F^\dagger$, kcal/mol (at 100°)	27.3	28.1	29.6

[a] Experimental errors are ±0.2 kcal in E_a and ±0.4 eu in $\Delta S^\dagger$.

Table II
Kinetic Data and Activation Parameters for the Reaction of 2-Fluoropyridines with Potassium Methoxide in Methanol

	Pyridine		
	2-Fluoro[b]	2-Fluoro-3-methyl	2-Fluoro-5-methyl
10^4k_2, M^{-1} sec^{-1} (temp, °C)[a]	11.8(100), 33.5(113.0), 72.0(123.2), 135(131.2)	3.32(100), 8.09(110.2), 11.8(115), 18.6(120), 33.7(128)	2.69(100), 4.01(105), 9.34(115), 14.1(120), 25.7(128)
10^4k_2, M^{-1} sec^{-1} (at 110°)[a]	26.9	7.85	6.08
E_{act},[c] kcal/mol	23.3	24.7	25.3
$\Delta S\dagger$, eu	−11.9	−10.8	−9.5
$\Delta F\dagger$, kcal/mol (at 110°)	27.0	27.9	28.1

[a] [MeO^-] = [fluoropyridine] = 0.0959 N = 0.00480 mol of reactants. [b] Taken from ref 4. [c] Experimental errors are ±0.2 kcal in E_{act} and ±0.4 eu in $\Delta S\dagger$.

Table III
Halogen Mobility and Nucleophilic Rate Ratios in Reactions of Potassium Methoxide and Potassium Thiomethoxide with Halogenopyridine Derivatives in Methanol at 110°

Substituent	F/Br mobility ratio: MeO^-	F/Br mobility ratio: MeS^-	Rate ratios MeS^-/MeO^-
2-F			0.71
	28.5	4.3	
2-Br			4.7
2-F-3-Me			0.81
	32.8	1.43	
2-Br-3-Me			11.2
2-F-5-Me			0.16
	39.4	1.40	
2-Br-5-Me			4.5

portant one might have expected methoxide ion to yield a higher *o*-Me:*p*-Me ratio than would the larger thiomethoxide ion. The results summarized in Table IV show that, not only is the ortho:para ratio in fluoride ion displacement by methoxide (1.3) lower than that for thiomethoxide (6.5), but also that the latter ratio is larger than the ratio (3.9) observed when bromide ion is displaced by thiomethoxide.[1] Since London interactions between methoxide and an *o*-methyl group are small,[11] the $k_{o\text{-Me}}/k_{p\text{-Me}}$ ratio being greater than unity with both bromo and fluoro compounds must represent contributions from an ion–dipole[12,13] attractive interaction. With thiomethoxide, however, London dispersion forces between the nucleophile and the ortho substituent become more important and larger $k_{o\text{-Me}}/k_{p\text{-Me}}$ rate ratios result.

Di Nunno and Todesco[14] have suggested that the reactivity of a nucleophile represents both the aptitude to bind a positive group as well as polarizability effects.[15] On comparing CH_3O^- with CH_3S^- (Tables I and III) we see that for 2-fluoropyridine, where polarizability effects are minimal, CH_3O^- is a better nucleophile since it reacts with 2-fluoropyridine faster than does thiomethoxide (k_{MeS^-}/k_{MeO^-} = 0.71), *i.e.*, nucleophilicity follows the order of relative carbon basicities. This basicity difference is manifested in the E_a term which is *ca.* 2 kcal/mol lower for the reaction of CH_3O^- than for the reactions of CH_3S^- with the 2-fluoropyridine derivatives.

In the case of the 2-bromopyridine derivatives, where polarizability factors should be more important, the relative carbon nucleophilicities of CH_3O^- and CH_3S^- ions are in the reverse order of their basicities, *i.e.*, $k_{MeS^-} > k_{MeO^-}$. This reactivity order reflects significant involvement of polarizability between attacking and departing groups, which contributes to the lowering of E_a for CH_3S^- by *ca.* 3 kcal/mol. These results are consistent with those reported by Di Nunno and Todesco[14] who found that the rate ratio k_Z/k_N (where k_Z is the rate constant for a polarizable nucleophile and k_N for a nonpolarizable one) varied linearly with the polarizability of the leaving group. For example, the relative nucleophilic abilities of PhS^- and CH_3O^- are in the reverse order of their basicities, *i.e.*, $k_{PhS^-} > k_{MeO^-}$, for the reactions with 2-halo-6-nitrobenzothiazoles, 2,4-dinitrohalobenzenes, and *p*-halogenonitrobenzenes.[14] On the other hand, with 2-fluorobenzothiazole,[14] 2-chloroquinoline,[16] and 2-bromopyridine[4,5] the rate ratio $k_{PhS^-}/k_{MeO^-} < 1$. In the case of 2-bromopyridine, polarizability attractive interactions between PhS^- and the bromine substituent are probably operative,[14] but these alone are not of sufficient magnitude to overcome the greater basicity of MeO^- (or MeS^-) and any steric repulsion in the transition state involving the bulky sulfur nucleophile (PhS^- is less basic than MeS^- due to delocalization of the negative charge in PhS^-).

Table IV
Rate Ratios for Reactions of 2-Fluoro-3- or 2-Fluoro-5-methylpyridine with Potassium Thiomethoxide and Potassium Methoxide in Methanol at 110°

R	$k_{o\text{-R}}/k_{p\text{-R}}$	$(k_{MeS^-}/k_{MeO^-})_R/(k_{MeS^-}/k_{MeO^-})_H$	$(k_{MeS^-}/k_{MeO^-})_{o\text{-R}}/(k_{MeS^-}/k_{MeO^-})_{p\text{-R}}$
CH_3	6.5 (MeS^-) 1.3 (MeO^-)	1.14 (*o*-Me), 0.226 (*p*-Me)	5.05

Our attention was directed next to the reactions of 2-fluoropyridine in hexamethylphosphoramide (HMPA) with MeO^-, MeS^-, and PhS^-. The rate constants and activation parameters are summarized in Table V. In order to facilitate the comparison of solvent effect upon halogen mobility, kinetic data for the reactions of these same nucleophiles in methanol with 2-fluoro- and 2-bromopyridine[1,4,5] are also included in Table V.

In both HMPA and methanol the order of reactivity with 2-fluoropyridine, $MeO^- > MeS^- > PhS^-$, followed the order of the proton basicity of the nucleophiles; with 2-bromopyridine where entering–leaving group polarizability factors are more important, the order of reactivity was $MeS^- > MeO^- > PhS^-$. It appears that the activating entering–leaving group interaction between thiophenoxide and bromine is not large enough (perhaps due to unfavorable steric effects[3]) to overcome the lower nucleophilicity of PhS^- compared with both MeO^- and MeS^-.

A comparison of F/Br mobility ratios in methanol and HMPA is given in Table VI. Except for thiomethoxide in HMPA, the nucleophiles in both HMPA and methanol reacted faster on going from 2-bromo- to 2-fluoropyridine, *i.e.*, $k_F/k_{Br} > 1$, which rate increase was dependent upon E_a [$E_{a(2\text{-F})} < E_{a(2\text{-Br})}$].

In the halogenonitrobenzene series a correlation of halide mobility or magnitude of F/I ratio with which of the two transition states is rate determining is often difficult.

Table V
Rate Constants and Activation Parameters for the Reaction of 2-Fluoropyridine with MeO^-, MeS^-, PhS^- Ions in HMPA. Comparison with 2-Bromopyridine[a] and with Kinetics in Methanol

Nucleophile	Solvent	10^3k_2, M^{-1} sec^{-1} (°C)	10^4k_2 at 110°	E_{act},[b] kcal/mol	$\Delta S^\dagger$, eu	$\Delta F^\dagger$ (100°)
CH_3O^-	HMPA	23.8 (40.4) 5.5 (24) 1.42 (10)	33100 [3390][a]	16.3 [14.8][a]	−15.8 [−24.0][a]	21.6
	MeOH[c]		27.0 [0.94]	23.3 [26.8]	−11.8 [−9.2]	
CH_3S^-	HMPA	0.65 (24) 1.85 (40) 4.14 (54)	692 [17400]	12.0 [13.6]	−34.6 [−24.1]	24 36
	MeOH		19.1 [4.4]	25.3 [24.3]	−7.4 [−12.9]	
PhS^-	HMPA	1.98 (70) 4.17 (80) 18.7 (100.2)	490 [202]	19.0 [19.2]	−17.9 [−18.5]	24.9
	MeOH		0.34 [0.214][d]	−[25.6][d]	−[15.6][d]	

[a] Values in brackets are the corresponding values for 2-bromopyridine.[1] [b] Experimental errors are ±0.4 kcal in E_{act} and ±0.8 eu in $\Delta S^\dagger$. [c] Reference 4. [d] Reference 1, footnote 16, and ref 5.

Table VI
Comparison of Halogen Mobility in Reactions of 2-Halogenopyridines with MeO^-, MeS^-, and PhS^- in Methanol and in HMPA at 110°

Solvent	F/Br mobility ratio		
	CH_3O^-	CH_3S^-	PhS^-
MeOH	28.5[a]	4.3	1.6
HMPA	9.8	0.039	2.4

[a] See ref 4.

For example, the F/I ratio is <1 for the less reactive nucleophiles SCN^-,[17,18] $PhNHCH_3$,[19] and I^-,[20] while the formation of the second transition state is rate limiting with the fluoro derivatives; however, with the more reactive thiomethoxide ion[2,9] the F/I ratio is 3.7×10^3 compared with a value of 2.3 for thiophenoxide.[3] Calculations of the transition state energies for reactions of both PhS^- and MeS^- with fluoronitrobenzenes showed the second transition state to be rate limiting.[3,21] Miller[21] pointed out that for anionic nucleophiles in which the nucleophilic atom is in the first horizontal row of the Periodic Table, the characteristic mobility pattern is F ≫ Cl > Br > I. With heavy nucleophiles (those whose nucleophilic atom is in the second or lower horizontal row of the Periodic Table) the mobility of fluorine relative to the other halogens is typically reversed due to the second transition state formation being rate limiting. Whereas thiocyanate ion behaves as a nucleophile as do heavy halide ions in relation to the halogen mobility order, the more typical second row reagent, thiomethoxide ion, appears to be borderline with respect to its influence on the mobility order of displace groups; PhS^- ion behaves much more typically as a heavy nucleophile.[21]

The borderline behavior of MeS^- with respect to its influence on halogen mobility is displayed in its reactions with fluoro- and bromopyridines (Table VI). Whereas the F/Br ratio is >1 in methanol for the reaction of 2-halogenopyridine with MeS^-, it is reduced by a factor of approximately 10^3 in HMPA (from 4.3 to 0.039). In the 2-halogenonitropyridine series, as with the halogenonitrobenzene series, we do not observe a direct correlation of the magnitude of F/Br ratio with which transition state is rate determining. The second transition state is probably rate limiting for the reactions of MeS^- and PhS^- with 2-fluoropyridine[21] and yet the F/Br ratio is <1 for MeS^- in HMPA and >1 for MeS^- in MeOH and for PhS^- in both MeOH and HMPA. With 2-fluoropyridine in HMPA we observed a substantial difference in the E_a values for the two sulfur nucleophiles, $\Delta E_{(PhS^- - MeS^-)} = 7$ kcal/mol. A low F/Br ratio (0.039) as is observed for MeS^- in HMPA, in which $E_{a(2\text{-F})} < E_{a(2\text{-Br})}$, but $\Delta\Delta S^\dagger$ (= $\Delta S^\dagger_{2\text{-Br}} - \Delta S^\dagger_{2\text{-F}}$) = 10.5 eu, is not without precedent in the literature. Hammond and Parks[19] found that in the reaction of $PhNHCH_3$ with 1-halogeno-2,4-dinitrobenzenes in $PhNO_2$, the F/Br ratio of 0.0205 reflected the lower $\Delta S^\dagger$ for the fluoro compound ($\Delta\Delta S^\dagger$ = 12 eu), although E_a for the fluoro compound (10 kcal/mol) was lower than that for the bromo analog (11 kcal/mol).

Ho, Miller, and Wong[3] ascribed the high MeS^-/MeO^- rate ratios in protic solvents to solvation factors; for example, in reactions with halogenonitrobenzenes the higher reactivity of thiomethoxide over methoxide ion was attributed to the lower heat of solvation of the former more than compensating for unfavorable differences in strengths of the bonds formed and of electron affinities. On this basis, a reversal or leveling out of this order in nonprotic solvents (such as HMPA) where both nucleophiles are poorly solvated was predicted.[3] The solvent clearly plays a key role in these reactions, since with thiomethoxide ion in methanol, the expected (on the basis of a heavy nucleophile effect) order, $\Delta S^\dagger_{2\text{-Br}} < \Delta S^\dagger_{2\text{-F}}$ is observed. This appears to rule out ground-state solvation of MeS^- as the determining factor since this is the same in the reaction with both 2-fluoro- and 2-bromopyridine. If ground-state solvation of the two pyridines had been the key factor the same pattern would have been observed with both MeO^- and PhS^-. Any secondary steric effects between the entering heavy nucleophile and leaving group would have led to $\Delta S^\dagger$ being lower for reaction with 2-bromo- than with 2-fluoropyridine. This leaves solvation of the transition state as a possible explanation of the abnormally low value of $\Delta S^\dagger_{MeS^-(2\text{-F})}$.

On going from methanol to HMPA there is a reduction in the F/Br rate ratio (from 28.5 to 9.8) when methoxide ion is used. This ratio is probably a reflection of the increased reactivity of methoxide in HMPA due to reduced solvation of the small anion, resulting in a reduction of the selectivity of MeO^- for the two halogenopyridines. In the case of MeS^-, the reduction in F/Br mobility ratio (from 4.3 to 0.039) may, in addition, be due to solvation of the 2-F-MeS^- transition state in HMPA, as discussed above. With PhS^- the activation parameters are similar to each other in HMPA for 2-fluoro- and 2-bromopyridine.

The rate of the reaction of MeS^- with 2-bromopyridine[1] increases by a factor of *ca.* 3950 at 110° on going from

Table VII
Comparison of Nucleophilic Rate Ratios in Methanol and in HMPA

Pyridine	MeS^-/MeO^- rate ratios In MeOH	MeS^-/MeO^- rate ratios In HMPA	PhS^-/MeO^- rate ratios In MeOH	PhS^-/MeO^- rate ratios In HMPA
2-F	0.71	0.021	0.013	0.015
2-Br	4.7	5.14	0.23	0.059
2-F-3-CH_3	0.81			
2-Br-3-CH_3	11.2	3.4	1.26	0.13
2-F-5-CH_3	0.16			
2-Br-5-CH_3	4.5	2.9	0.40	0.028

[a] Also reported in Table III.

methanol to HMPA as a result of a reduction in E_a: $\Delta E_{a(MeOH-HMPA)} = 10.7$ kcal/mol, in spite of a smaller $\Delta S^\dagger$ value in HMPA (Table V), $\Delta\Delta S^\dagger_{(MeOH-HMPA)} \simeq 11$ eu. In the reaction of MeS^- with 2-fluoropyridine the rate increases by a factor of 36 at 110° on going from methanol to HMPA; despite a reduction in E_a[$\Delta E_{a(MeOH-HMPA)} \simeq 13$ kcal/mol], the much smaller value of $\Delta S^\dagger$ in HMPA than in methanol results in the smaller rate increase for 2-fluoro- compared with 2-bromopyridine in HMPA. Only one example which might support the prediction[3] that, in those cases in which $k_{MeS^-}/k_{MeO^-} > 1$ in a protic solvent, owing to the greater heat of solvation of the smaller more basic Me^- ion, on going to an aprotic solvent $k_{MeS^-}/k_{MeO^-} < 1$ should be observed was found (Table VII). This is the case in which k_{PhS^-}/k_{MeO^-} for 2-bromo-3-picoline is 1.26 in MeOH and 0.13 in HMPA. This is not valid support, however, for two reasons: (i) it is not really fair to compare PhS^- with MeO^-; it would have been better to compare PhS^- with PhO^-, but this is not possible;[1] (ii) the reason that $k_{PhS^-}/k_{MeO^-} > 1$ in methanol is due to the polarizability attractive interaction between the 3-methyl group in 2-bromo-3-picoline and PhS^- in the transition state, which does not obtain with MeO^-.[1,5] Of more interest is the fact that $k_{MeS^-}/k_{MeO^-} > 1$ in MeOH and, though somewhat reduced in magnitude, this ratio did not become less than unity on going from methanol to HMPA for any of the bromo compounds. The higher reactivity of MeS^- than MeO^- with the bromopyridines in MeOH, therefore, is most likely not just a reflection of the lower heat of solvation of the thiomethoxide ion[3] but probably mirrors the contribution from an attractive interaction between the polarizable entering MeS^- ion and the polarizable leaving bromine atom.

Experimental Section

Materials. HMPA (Dow Chemical Co.) was fractionally distilled, the fraction of bp 65–66° (1 mm) being used. 2-Fluoropyridine was distilled, bp 123–124° (750 mm) [lit.[22] bp 124.8–125.4° (755 mm)].

2-Fluoro-3-methylpyridine. A vigorously stirred solution of 2-amino-3-picoline (40 g) in tetrafluoroboric acid (170 ml) was maintained below 10° while sodium nitrite (25.6 g) was added. After 1 hr at 10°, the solution was heated to 50° to complete decomposition of the tetrafluoroborate salt. The solution was cooled to 5°, neutralized (Na_2CO_3), and steam distilled. The aqueous phase was extracted with ether (4 × 75 ml). The ethereal layer was dried ($MgSO_4$) and concentrated to give a yellow liquid which was distilled to give 2-fluoro-3-methylpyridine as a colorless liquid (16.7 g, 40%), bp 149–151° (755 mm) [lit.[23] bp 150.5–151° (757 mm)]; nmr (CCl_4) δ 8.02 (d, 1, H_6), 7.79 (m, 1, H_4), 7.08 (m, 1, H_5), 2.28 (s, 3, CH_3).

2-Fluoro-5-methylpyridine. This was prepared as described above but starting from 2-amino-5-methylpyridine. The product was a colorless liquid (18.8 g, 45%), bp 154–155° (750 mm) [lit.[23] bp 155–156° (752 mm)]; nmr (CCl_4) δ 7.95 (br s, 1, H_6), 7.50 (m, 1, H_4), 6.73 (m, 1, H_3), and 2.22 (s, 3, CH_3).

Solutions of potassium thiomethoxide and potassium methoxide in methanol and of potassium methoxide, potassium thiomethoxide, and potassium thiophenoxide in HMPA were prepared as previously reported.[1,4]

Reaction Products. These were obtained by a preparative reaction of the appropriate 2-fluoropyridine with potassium thiomethoxide and potassium methoxide in methanol and with potassium methoxide, thiomethoxide, and thiophenoxide in HMPA under the conditions of the kinetic runs. 2-Thiomethoxypyridine had bp 54–55° (3 mm) [lit.[24] bp 197° (760 mm)]. 3-Methyl-2-thiomethoxypyridine had bp 61–62° (2.6 mm) (61%) [lit.[1] bp 61–62° (2.6 mm)]. 5-Methyl-2-thiomethoxypyridine had bp 70–71° (2.6 mm) (53%) [lit.[1] bp 70–71° (2.6 mm)]. 2-Methoxy-3-methylpyridine had bp 157–159° (750 mm) (65%) [lit.[4] bp 38° (6 mm)]. 2-Methoxy-5-methylpyridine had bp 39–40° (2 mm) (73%) [lit.[4] bp 52° (6 mm)]. 2-Methoxypyridine had bp 138–140° (755 mm) [lit.[4] bp 140–142° (740 mm)]. 2-Thiophenoxypyridine had bp 123–124° (1 mm) [lit.[25] bp 160–162° (8 mm)].

Kinetic Procedures. A. Potassium Thiomethoxide and Methoxide in Methanol. The procedure was identical with that reported earlier[1] for the reaction of potassium thiomethoxide with bromopyridines in methanol.

B. Potassium Methoxide, Thiomethoxide, and Thiophenoxide in HMPA. The procedures utilized here were the same as those reported earlier[1] for the 2-bromopyridines in HMPA.

Acknowledgments. We wish to thank the University of Alabama Research Grant Committee for support of this work which was carried out during the tenure (by A.J.N.) of an NDEA fellowship (1968–1970). We also wish to thank Reilly Tar & Chemical Corporation for the gift of some starting pyridines.

Registry No.—2-Fluoropyridine, 372-48-5; 2-bromopyridine, 109-04-6; 2-flucro-3-methylpyridine, 2369-18-8; 2-bromo-3-methylpyridine, 3430-17-9; 2-fluoro-5-methylpyridine, 407-22-7; 2-bromo-5-methy pyridine, 3510-66-5; potassium methoxide, 865-33-8; potassium thiomethoxide, 26385-24-0; 2-amino-3-picoline, 1603-40-3; 2-amino-5-methylpyridine, 1824-81-3.

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The Aromatization of Cyclic Ketones. II. Novel Synthesis of Substituted Dihydroxybenzenes[1]

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Received May 20, 1974

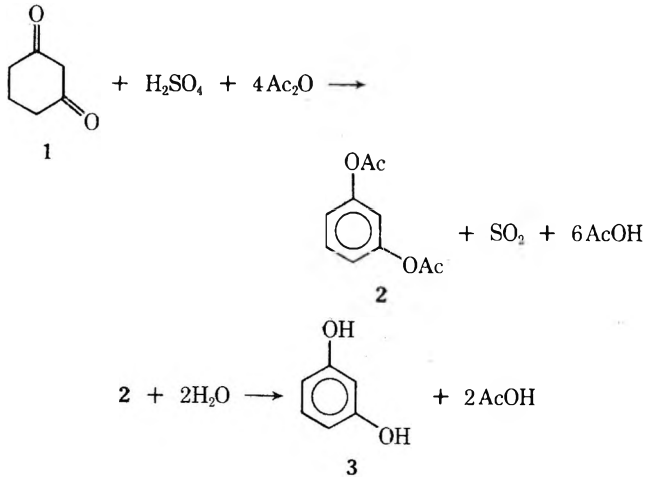
Dihydroxybenzenes are obtained in high yields when the corresponding cyclohexanediones are refluxed with concentrated sulfuric acid in acetic anhydride–acetic acid solvent followed by hydrolysis. 5,5-Dimethyl- and 2-methyl-1,3-cyclohexanediones are aromatized to 4,5-dimethyl- and 2-methyl-1,3-dihydroxybenzenes, respectively. Acetoxycyclohexenonesulfonic acids are believed to be the intermediates in the above aromatization reactions.

To date the syntheses of substituted dihydroxybenzenes from the corresponding cyclohexanediones involve two-step processes. Treatment of 5,5-dimethyl-1,3-cyclohexanedione with 30% oleum gives 5,5-dimethyl-1,3-cyclohexanedione-2-sulfonic acid. Refluxing the sulfonate with acetic anhydride followed by steam distillation gives about 18% yield[2] of 4,5-dimethyl-1,3-dihydroxybenzene. Catalytic dehydrogenation of 5-methyl-1,3-cyclohexanedione is unsuccessful.[3] Bromination of the sodium salts of 4-carboxyethyl-5-alkyl-1,3-cyclohexanediones in 1,2-dimethoxyethane followed by refluxing in DMF gives about a 75% yield of alkyl-1,3-dihydroxybenzenes.[4] Chlorination of 2-alkyl-1,3-cyclohexanediones followed by heating with a 25% solution of dry hydrogen chloride in DMF gives 50–70% yield of the alkyl dihydroxybenzene.[5]

This paper deals with a one-step aromatization of cyclohexanediones to the corresponding diacetoxybenzenes in high yields using acetic anhydride–sulfuric acid reagent.

Results and Discussion

Resorcinol diacetate (1,3-diacetoxybenzene) (**2**) was isolated when 1,3-cyclohexanedione (**1**) was heated in acetic anhydride solvent with concentrated sulfuric acid. Hydrolysis of the diacetate afforded resorcinol (1,3-dihydroxybenzene) (**3**) in 95% yield based on **1**. Sulfur dioxide was isolated as a by-product. The best results were obtained when 1

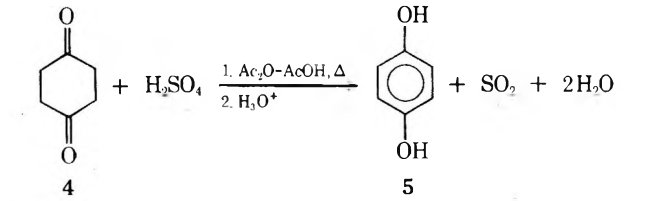


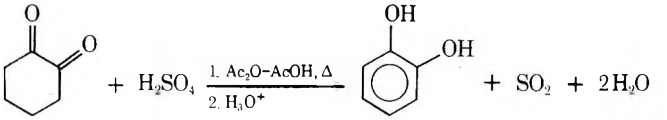
mol of H_2SO_4 was added, preferably at room temperature, to a solution of 1 mol of **1** in Ac_2O–AcOH with at least 4 mol of Ac_2O in a dry nitrogen atmosphere. The yields dropped appreciably (20–30%) when oxygen was bubbled through the reaction mixture during aromatization.

No aromatization occurred when sodium bisulfate, *p*-toluenesulfonic acid, or sulfoacetic acid was substituted for H_2SO_4, or when phthalic or succinic anhyride replaced Ac_2O.

The progress of the reaction was measured by the amount of SO_2 liberated. A quantitative measure of SO_2 gas formed during a typical run showed it to amount to 90% of the theoretical value. At all stages of the reaction, the amount of SO_2 formed corresponded to the amount of dione aromatized.

The aromatization of 1,4- (**4**) and 1,2-cyclohexanediones (**6**) with H_2SO_4 in Ac_2O–AcOH solvent gave after hydrolysis 1,4-dihydroxybenzene (**5**) and 1,2-dihydroxybenzene (**7**), respectively, in over 90% yields. When the aromatization was done in acetic anhydride only, in the absence of acetic acid, **4** gave only **5** while **6** gave **7** in about 60% yield and a minor product (20% yield) identified as a polyhydroxybenzene (more than two hydroxyl groups in the molecule). (Reactions of this type have been observed when α-

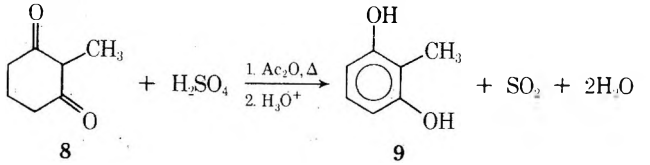


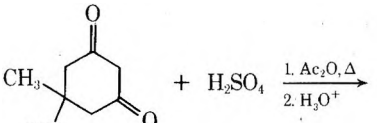


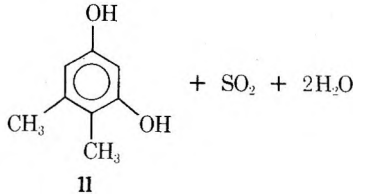
6 + H_2SO_4 $\xrightarrow[2.\ H_3O^+]{1.\ Ac_2O,\ \Delta}$ **7** (60%) + polyhydroxybenzene (20%)

substituted cyclohexanones are aromatized with H_2SO_4–Ac_2O. Such aromatizations will be fully discussed in a separate paper.)

2-Methyl-1,3-cyclohexanedione (**8**) and dimedone (5,5-dimethylcyclohexane-1,3-dione) (**10**) gave 2-methyl-1,3-

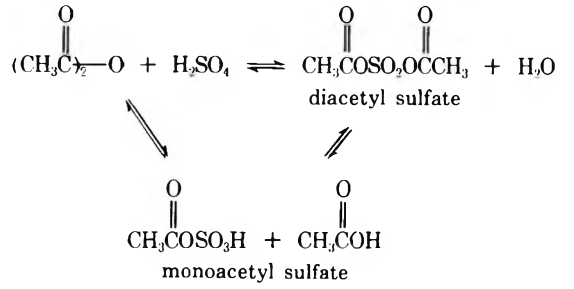




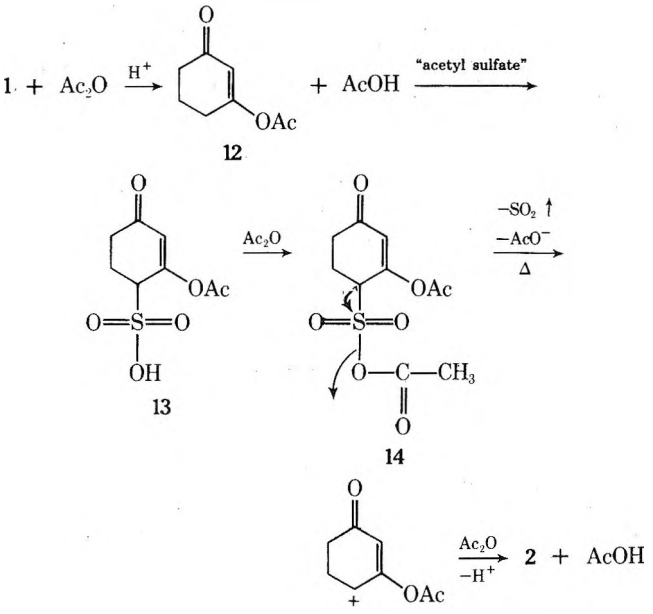


dihydroxybenzene (9) and 4,5-dimethyl-1,3-dihydroxybenzene (11), respectively, when treated with H_2SO_4–Ac_2O. In the latter case, a 1,2-methyl shift occurred during aromatization.

Acetic anhydride and sulfuric acid react at low temperatures to form a sulfonating species believed to be the mono- or the diacetyl sulfate, or both,[6] as shown below. For convenience it will be referred to as "acetyl sulfate." [Prolonged heating of acetyl sulfate affords[7] sulfoacetic acid [HO-$SO_2CH_2C(=O)OH$], which could not be the intermediate since sulfoacetic acid did not aromatize diones.] It is believed that acetyl sulfate is the aromatizing species. This is done by sulfonating the dione or an intermediate which decomposes in the presence of Ac_2O to the aromatized product as shown in Scheme I.

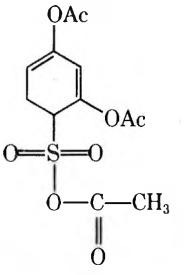


Scheme I



The first step in the aromatization of 1 is the formation of the monoenol acetate **12.** This is based on **12** being the only product isolated when 1 was treated with Ac_2O and catalytic amounts of H_2SO_4. Also **12** was isolated during the aromatization when the reaction mixture was quenched at reflux, prior to the 1-hr heating. Sulfonation of **12** would afford the 4-sulfonic acid **13,** since sulfonation of α,β-unsaturated ketones with acetyl sulfate occurs[8] on a carbon atom separated from the keto group by the vinyl moiety.

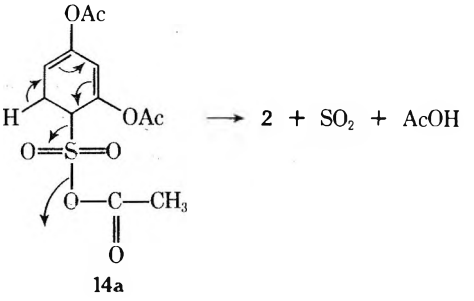
Sulfonates similar to **13** prepared[2] from 3,3,5-trimethylcyclohexenone aromatize to 3,4,5- and 2,3,5-trimethylphenols when refluxed in Ac_2O. Some sulfonates are isolated[9] during the aromatization of 3,3,5-trimethylcyclohexenone with Ac_2O–H_2SO_4, as in the aromatization of **1,** when the reaction mixture is quenched at 100° in anhydrous ethyl ether. The same ratio of 3,4,5- and 2,3,5-trimethylphenols is obtained when the sulfonate intermediates are refluxed in Ac_2O or when 3,3,5-trimethylcyclohexenone is aromatized[9] with Ac_2O–H_2SO_4. Furthermore, 3-phenyl-5,5-dimethylcyclohexenone-4-sulfonic acid, similar to **13,** is aromatized[10] to 3-phenyl-4,5-dimethylphenol when heated in Ac_2O. In all the above cases Ac_2O is essential to the aromatization. The reaction of the sulfonates, such as **13,** with Ac_2O would give the mixed anhydride (14). [Acetylation of the keto group in **13** could occur at this stage to give the intermediate **14a.** Decomposition of **14a,** as in the case of **14,** would give **2.**] The anhydride probably weakens the sulfur–



14a

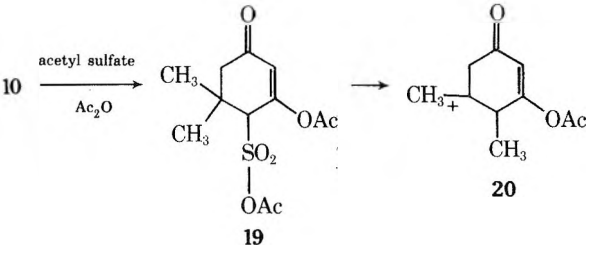
hydroxyl bond of the sulfonic acid thus promoting the decomposition of the anhydride to AcO^-, SO_2, and a carbonium ion. Loss of a proton and subsequent acetylation of the keto group gives **2.** Such decomposition is believed to be initiated by heating.

A concerted one-step mechanism is also postulated. This is shown in the decomposition of the intermediate **14a.**



14a

In the aromatization of **10,** decomposition of the mixed anhydride **19** would be followed by methyl migration to form the tertiary carbonium ion **20.**



Experimental Section

The ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer; the nmr spectra were obtained on a Varian Associates Model V-4311 spectrometer operating at 60 MHz. All glc analyses were run on a SE-30 column programmed from 100 to 250°.

Aromatization of Cyclohexanedione. Into a 300-ml, three-neck flask equipped with a magnetic stirrer, a gas sparger, a condenser, and a thermometer were charged 3.0 g (0.027 mol) of 1,3-cyclohexanedione (1) (crystallized twice before use), 50 ml of Ac_2O, and 50 ml of AcOH. Concentrated sulfuric acid (2.65 g, 0.027 mol) was slowly added at room temperature to the mixture. The reaction mixture was then heated to reflux for 1 hr under nitrogen. The work-up of the reaction mixture was completed by quenching in 150 ml of ice–water and stirring for 30 min to decompose all the Ac_2O, followed by extraction with ether (4 × 50 ml). The combined ether extracts were washed once with 50 ml of saturated $NaHCO_3$ solution and once with 50 ml of saturated NaCl solution, dried, and stripped to give a residue (5.2 g) whose glc analysis indicated

the presence of only one compound. Upon distillation of the residue [105° (25 mm)], 5.0 g (95% yield) of 1,3-diacetoxybenzene (2) was isolated. The product was identified by comparison of its ir and nmr spectra with authentic sample prepared by acetylation of 3 with Ac_2O.

1,4-Cyclohexanedione (5.0 g, 0.045 mol) was aromatized as in the above case with concentrated H_2SO_4 (4.27 g, 0.045 mol) in 50 mol of Ac_2O and 50 ml of AcOH. After work-up and distillation of the residue, 8.1 g (93% yield) of 1,4-diacetyoxybenzene was isolated.

Aromatization of 1,2-cyclohexanedione (5.0 g, 0.045 mol) with 4.27 g (0.045 mol) of H_2SO_4 in Ac_2O–AcOH solvent afforded after distillation 7.8 g (90% yield) of 1,2-diacetoxybenzene.

Isolation of Intermediates in the Aromatization of 1,3-Cyclohexanedione. The aromatization was done as before except that only 0.13 g (1.3 mmol) of concentrated H_2SO_4 were used. After work-up, a glc analysis indicated the presence of only one compound. It was identified as the monoenol acetate of 1,3-cyclohexanedione (12): ir (neat) 5.65 (-OAc), 6.1 (C=C), 5.95 μ (C=O); nmr ($CDCl_3$) δ 5.59 (s, 1 H, >C=CH-), 2.21 [s, 3 H, CH_3-C(=O)O].

When the aromatization was done as in the previous example except that the reaction mixture was quenched at reflux, about 10–15% of 2 was isolated along with 85–90% of 12.

Aromatization of 1,2-Cyclohexanedione in Ac_2O. The aromatization of the title compound was done as before except that 100 ml of Ac_2O was used as solvnet instead of Ac_2O–AcOH. After work-up, a glc analysis indicated the presence of two compounds. The first (70%) was identified as 1,2-dihydroxybenzene diacetate by comparison of its ir and nmr spectra with an authentic sample prepared by acetylation of catechol with Ac_2O. The second compound (25%) is tentatively identified as 1,2,3-trihydroxybenzene triacetate. Further identification of this material and the type of aromatization will be fully discussed in a separate paper.

Aromatization of 5,5-Dimethyl-1,3-cyclohexanedione. The title compound (9.0 g, 0.065 mol) was aromatized with 7.0 g (0.072 mol) of concentrated H_2SO_4 in 100 ml of Ac_2O as in the above example. After work-up and distillation of the residue [115–125° (0.3 mm)], 11.4 g (80% yield) of 4,5-dimethyl-1,3-diacetoxybenzene was isolated. Hydrolysis of the product afforded 11 as identified by ir and nmr and comparison with known material.[2]

Sublimation and recrystallization from benzene gave pure 11, mp 135–135.5° (reported 135.5–136°[2] and 133–134.5°, 134–135°[11]).

Preparation and Aromatization of 2-Methylcyclohexane-1,3-dione. Into a 1-l. flask equipped with a condenser, drying tube, dropping funnel, and thermometer were charged 300 ml of absolute methanol and 21.6 g (0.94 mol) of sodium metal in small pieces, followed by 112.0 g (1.0 mol) of 1. The solution was then cooled to 15°, and 162.0 g (1.14 mol) of methyl iodide in 50 ml of methanol was added slowly through the dropping funnel over a period of 0.5 hr. The solution was then refluxed for 3.5 hr followed by evaporation of the solvent. Water (400 ml) was then added and the residue and solids thus formed were filtered (62.0 g, 50% yield), mp 199–204°. Recrystallization from benzene gave pure 8, mp 205–206° (reported[12] 205–207°).

Aromatization of 8 (3.0 g, 0.024 mol) with 2.34 g (0.024 mol) of concentrated H_2SO_4 in 50 ml of Ac_2O, as in the previous cases, afforded after hydrolysis 2.5 g (85% yield) of 9, mp 97–98°, 106–107.5° when molten compound was seeded with authentic sample (reported[4a] 96–97°, 106–108°, and 106–108°[13]).

Registry No.—1, 504-02-9; 2, 108-58-7; 4, 637-88-7; 6, 765-87-7; 8, 1193-55-1; 10, 126-81-8; 11, 527-55-9; 11 diacetate, 35236-36-3; 12, 50557-37-4.

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Carbon-13 Nuclear Magnetic Resonance Characteristics of 3-Methylcyclohexane-1,2-diols

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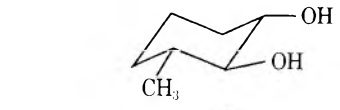
Received April 12, 1974

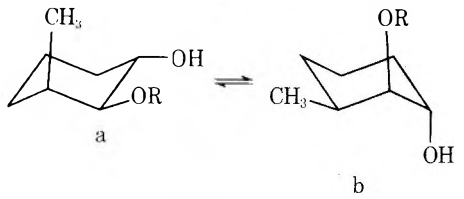
The proton nmr parameters which establish the stereochemistry and conformation of the diols 1–4 are described. The relation between the ^{13}C chemical shifts of the carbon atoms and the stereochemistry of the diols is analyzed with regard to substituent effects and vicinal interactions.

In a recent investigation of the metabolism of toluene[1] we had occasion to prepare a series of 3-methylcyclohexane-1,2-diols to confirm the stereochemistry assigned to a reduction product of the metabolite encountered. We describe here the proton nmr spectra which establish the configuration of these materials, and an investigation of the relation of the ^{13}C chemical shifts of the series to the configurations.

Klein and Dunkelblum[2] have recently described the preparation and characterization of three 3-methylcyclohexane-1,2-diols. The all-trans equatorial configuration 1 was assigned to the diol obtained by the hydroboration of 3-methyl-2-cyclohexenone. The assignment was anticipated from the mode of preparation and supported by the appearance of H-2 as a triplet at 2.80 ppm, J = 9 Hz. The trans,cis diol, configuration 2, was obtained from the reaction of 3-methylcyclohexene with hydrogen peroxide and formic acid. The nmr spectrum defied analysis, but the authors inferred from its complexity that the isomer exists in rapid equilibrium between the conformations 2a and 2b. The cis,trans isomer 4 was obtained from the reaction of 3-methylcyclohexene with either potassium permanganate or

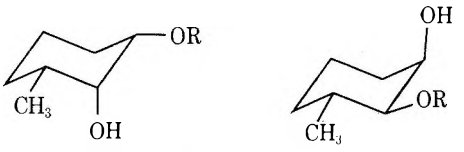


1



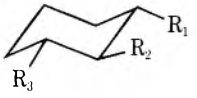
a b

2, R = H
9, R = COPh



3, R = H
10, R = COPh

4, R = H
11, R = COPh



5, R_1 = OH; R_2 = H; R_3 = CH_3
6, R_1 = R_2 = OH; R_3 = H
7, R_1 = OH; R_2 = CH_3; R_3 = H
8, R_1 = OCOPh; R_2 = H; R = CH_3

wet silver acetate and iodine. The assignment was based on the appearance of H-2 as a doublet of doublets, J = 3 and 9 Hz. This isomer possessed an infrared spectrum consonant with an intramolecular hydrogen bond between the *cis*-hydroxyl groups.

Although these authors mention the cis,cis isomer, its mode of preparation was identical with that given for the cis,trans isomer, and no nmr data were reported for the compound. The preparation of an incompletely characterized isomer of the series by hydrogenation of 3-methylcyclohexane-1,2-dione has been described.[3] In our hands hydrogenation of 3-methylcyclohexane-1,2-dione over platinum produced a mixture rich in a new diol. This material was purified *via* its monobenzoate, the proton nmr spectrum of which indicated the cis,cis stereochemistry. Saponification of the monobenzoate provided a pure sample of the parent diol.

It was now possible to examine the proton nmr spectra of the four isomers at 220 MHz, at which higher frequency the chemical shifts and coupling constants of H-1 and H-2 could be clearly distinguished. These appear in Table I. The data on the trans,trans isomer 1 and the cis,trans isomer 4 are in substantial agreement with those reported by the earlier authors.[2] The coupling constants of 4 were confirmed by decoupling experiments. It is clear that the earlier difficulty in the interpretation of the spectrum of the trans,cis isomer 2 resulted from the small difference of the chemical shifts of H-1 and H-2. At higher fields, the coupling constants were readily determined. The data on the new diol 3 fit the anticipated cis,cis stereochemistry.

The data listed in Table I for 1, 3, and 4 correspond well to the generalizations which have been developed for protons on cyclohexane rings in the chair conformation:[4] diaxial couplings are large, *ca.* 9 Hz; axial–equatorial couplings are smaller, approximately 3 Hz. The two equatorial protons (H-2 in 3 and H-1 in 4) occur *ca.* 0.6 ppm at lower field than the axial protons. It is known that the presence of a vicinal equatorial substituent shifts an axial proton further upfield.[5] In the case of H-2 of 1 the presence of two vicinal equatorial substituents results in the remarkable shift of 2.84 ppm. Thus, although it might well be anticipated that the presence of three vicinal substituents might force the system into unusual conformations, the proton data demonstrate that the properties of these three materials can be examined within the framework of normal chair forms, with alternative conformations contributing only a minor proportion of the equilibrium population. However, the diol 2 evidently exists as a mixture of two conformations of similar importance, for observed chemical shifts are intermediate between the typical values for axial and equatorial protons, and the coupling constants observed do not conform to the generalization[6] that the ratio of trans to cis couplings must be greater than 2.0. The earlier speculation on this material must be valid.[7]

Table I
Pmr Parameters

	1	2	3	4
H-1	3.32 ppm	3.64 ppm	3.25 ppm	3.98 ppm
H-2	2.84 ppm	3.45 ppm	3.81 ppm	3.20 ppm
J_{12}	9.6 Hz	8.8 Hz	2.8 Hz	3.0 Hz
J_{23}	9.6 Hz	4.8 Hz	2.8 Hz	9.0 Hz
J_{16}	10.4 Hz	10.0 Hz	4.9 Hz	*a*
	4.6 Hz	4.4 Hz	12.9 Hz	*a*

[a] Coupling constants could not be determined.

Table II
^{13}C Chemical Shifts[a] (in ppm)

	1	2	3	4
C-1	75.1	70.4	73.9	69.8
C-2	81.1	76.9	72.7	77.5
C-3	37.8	33.6	35.6	33.2
C-4	33.6	30.3	28.1	32.7
C-5	23.6	19.3	23.6	19.3
C-6	33.3	32.4	26.7	31.4
CH_3	18.4	12.8	18.1	18.4

[a] Chemical shifts of C-4 and C-6 may be interchanged.

The ^{13}C spectra of these materials were now determined (Table II). The peaks resulting from complete proton decoupling were readily differentiated by off-resonance decoupling, allowing the immediate identification of the methyl carbons as the only quartets, and the 3-carbons as the only doublets at high field. In each spectrum, the triplet at highest field could reasonably be assigned to C-5, as the 3-methyl and 1-hydroxyl groups must shift C-4 and C-6 downfield. Of the remaining two triplets, which did not differ by more than 1.4 ppm, a tentative assignment was made to conform with the expectation that benzoylation would not affect the chemical shift of the carbon atom most distant. When this criterion was not available, the carbon atom at lower field was assigned to C-4, consistent with earlier observations of the effect of substituting methyl or hydroxyl groups.[8]

To aid in the assignment of the ^{13}C chemical shifts the monobenzoates 8, 9, 10, and 11 were prepared from the corresponding diols or alcohol (Table III). Benzoylation shifted the proton resonances sufficiently to allow very ready differentiation of C-1 and C-2 in the diols by single proton decoupling. The chemical shifts of the remaining three carbon atoms in the diols could now be assigned by comparison with the effects produced by the benzoylation of 3-methylcyclohexanol (*cf.* Table IV).

The assignment of the chemical shifts now allowed the examination of the substituent effects in known conforma-

Table III
Chemical Shifts[a] of Benzoates (in ppm)

	8	9	10	11
C-1	73.8	67.3	76.5	67.8
C-2	40.6	77.8	71.7	80.7
C-3	31.6	30.6	35.6	30.9
C-4	34.1	30.0	26.7	32.7
C-5	24.0	19.2	23.5	19.1
C-6	31.3	29.5	24.6	31.3
CH_3	22.3	16.0	18.0	18.1

[a] Chemical shifts of C-4 and C-6 may be interchanged.

Table IV
^{13}C Shifts (in ppm) of Model Compounds[a]

	5	6	7
C-1	70.5	75.7	76.4
C-2	44.6	75.7	40.3
C-3	31.5	33.0	33.8
C-4	35.3	24.5	25.8
C-5	24.3	24.5	25.3
C-6	34.2	33.0	35.6
CH_3	22.4		18.7

[a] Assignments are those of previous workers. The shifts here determined differed only slightly from the previous values.

tions. Previous workers have studied such effects within cyclohexyl systems.[8] It is quite generally observed in the simple systems that carbon atoms bearing axial substituents are more shielded by approximately 6 ppm than those with equatorial substituents, and that such an axial substituent produces a similar upfield shift in atoms in a gauche relation to it. The present study allows the examination of the effect of stereochemical relations upon the chemical shifts of hydroxyl-bearing carbons.

Such comparisons are not readily made for the diol **2**, because it exists as a mixture of similar proportions of the two conformers **2a** and **2b**. However, comparison of the observed chemical shifts with those of the all-equatorial isomer **1** shows the effect of the contribution of forms bearing the axial substituents. Of these, the most obvious effect is upon the methyl group, of which the chemical shift is some 6 ppm to higher field than those of the other isomers. In **2b**, each ring carbon either bears an axial substituent, or exists with an axial substituent three bonds away. In **2a**, this is true of C-1, -3, and -5. As a consequence, the chemical shifts of all of the ring carbons occur to higher field than those of **1**.

In attempts to relate ^{13}C chemical shifts to structure and stereochemistry, Grant, *et al.*,[9] and Roberts, *et al.*,[11] have been concerned with the additivity of substituent effects in substituted cyclohexanes. In the case of alkylcyclohexanols, Roberts, *et al.*, have shown that introduction of an axial methyl or hydroxyl group results in different α, β, and γ shifts than does introduction of an equatorial methyl or hydroxyl group. We were interested in learning if the parameters established for alkylcyclohexanols could be transferred to these diols. In order to establish the effect of introducing an axial or equatorial methyl and/or hydroxyl group we determined the ^{13}C spectra of *cis*-3-methylcyclohexanol (**5**), *trans*-1,2-cyclohexanediol (**6**), and *trans*-2-methylcyclohexanol (**7**) (see Table IV). The effect of adding an equatorial methyl at C-3 can then be determined from a comparison of the spectra of **1** and **6**. A comparison of the spectra of **5** and **7** with **1** yields the parameters associated with introducing an equatorial hydroxyl group. The observed differences are tabulated in Table V and are quite similar to those previously observed,[11] when the addition of the substituent does not involve the formation of an additional gauche interaction with a vicinal substituent. In such cases (*e.g.*, the effect upon C-2 of the addition of the hydroxyl at C-1), the downfield shifts are reduced by approximately 3 ppm. Similarly, comparison of **3** with **5** and **4** with **7** shows the effect of adding the axial hydroxyl group at C-2 and C-1, respectively. Earlier observations of this effect give α, 37.8, β, 5.5 and γ, −7.2 ppm.[10,12] The effects of adding the axial hydroxyl to form **3** and **4** are similar at the γ-carbon atom but are again diminished for α and β in situations in which new gauche interactions with vicinal groups result.

Table V
Substituent Effects

	1–5[a]	1–6[b]	1–7[c]	3–5[d]	4–7[e]
C-1	4.6	−0.6	39.5	3.4	34.2
C-2	36.5	5.4	4.7	28.4	1.1
C-3	6.3	4.8	−2.5	4.1	−7.1
C-4	−1.7	9.3	−0.2	−7.2	−1.1
C-5	−0.7	−0.9	−2.2	−0.7	−6.5
C-6	−0.9	0.3	8.0	−7.5	6.1
CH_3	−4.4		−0.3	−4.3	−0.3

[a] The addition of an equatorial hydroxyl at C-2. [b] The addition of an equatorial methyl at C-3. [c] The addition of an equatorial hydroxyl at C-1. C-1 of **7** is taken to correspond to C-2 of **1**. [d] The addition of an axial hydroxyl at C-2. [e] The addition of an axial hydroxyl at C-1.

Table VI
Effect of Configurational Changes

	3–1[a]	4–1[b]
C-1	−1.2 (β_e)[c]	
C-2		−3.6 (βe)
C-3	−2.2 (β_e)	−4.6 (γe)
C-4	−5.5 (γ(H))	−0.9 (δ(H))
C-5	0.0	−4.3 (γ(H))
C-6	−5.6 (γ(H))	−1.9 (β(H))

[a] Effect of changing C-2 hydroxyl from equatorial to axial. [b] Effect of changing C-1 hydroxyl from equatorial to axial. [c] The values reported earlier, with the signs reversed to correspond to the different reference, are $\beta e = -1.7 \pm 0.3$ and $\gamma_e = -2.8 \pm 0.3$ ppm (13).

In the course of examining the ^{13}C spectra of inositols and sugars Roberts, *et al.*, have developed some parameters to describe the effect on the β and γ carbon atoms of changing the stereochemistry of a hydroxyl group from equatorial to axial.[13,14] "β_e" is the change produced by altering a hydroxyl group from equatorial to axial observed in the chemical shift of a carbon β to the site of the alteration and bearing an equatorial hydroxyl. Values for β_e, γ_e, and δ_e can be obtained from a comparison of **3** with **1** and **4** with **1**. These values are given in Table VI along with Roberts' values. The agreement is poor and suggests that Roberts' parameters apply rather specifically to the sugars.

This study has demonstrated that the chemical shifts of the ring carbons for this series of diols can be correlated with the stereochemistry of the substituents. As the number of substituents on the parent system increases, steric factors, changes in geometry, and vicinal effects partly vitiate the use of parameters previously developed for substituent effects in establishing the stereochemistry of highly substituted systems.

Experimental

The proton nmr spectra were determined on a Varian HR 220-MHz spectrometer in $CDCl_3$ using tetramethylsilane as an internal reference. The chemical shifts are accurate to ±0.02 ppm. The ^{13}C spectra were obtained on a Varian XL-100 spectrometer equipped with a Digilab Fourier transform accessory, using the same solvent and reference. Chemical shifts are accurate to ±0.05 ppm.

Preparation of the Diols. Compound 1 was prepared by hydroboration of 3-methylcyclohexenone as described by Klein and Dunkelblum, mp 39–40° (reported[2] mp 39–40°).

The trans,cis diol **2** was prepared by oxidation of 3-methylcyclohexene with 30% hydrogen peroxide–90% formic acid as described for *trans*-1,2-cyclohexandiol.[17] The crude diol was crystallized from hexane and recrystallized from isooctane, mp 94–95° (reported[2] mp 91–92°). The cis,trans diol **4** was prepared by OsO_4–H_2O_2–*tert*-butyl alcohol oxidation of 3-methylcyclohexene as well as from the solvolysis of the dibromide (prepared by brominating the olefin in carbon tetrachloride at 0°) with silver acetate in acetic acid–water. The diol crystallized from hexane–ethyl acetate, mp 81–82° (reported[15] mp 81–82°).

The monobenzoate **9** and **11** were obtained by reaction of equimolar quantities of **2** or **4** and benzoyl chloride in pyridine. The monobenzoate was purified by chromatography on silica gel, yielding an oil whose proton and ^{13}C nmr spectra were consistent with the structure assigned.

The benzoate **8** was prepared from *cis*-3-methylcyclohexanol as described for **9**: ^1H nmr δ 5.00 (q, J = 3.5, 6.5 Hz), 4.00 (m), 0.98 (J = 7 hz).

The cis,cis isomer **3** was prepared using a procedure similar to that of Garanti and Marchesini[3] in which 3-methylcyclohexane-1,2-dione[16] was hydrogenated in ethanol over PtO_2. Nmr spectra of the crude diol showed it to be a mixture of cis,cis and cis,trans diols. The diol mixture, 3.783 g (2.9 mmol), was treated with benzoyl chloride, 4.51 g (3.2 mmol), in 25 ml of pyridine overnight at room temperature. The reaction mixture was poured into dilute HCl, extracted into ether, washed with aqueous $NaHCO_3$, dried, and concentrated to yield 6.569 g (97%). The monobenzoate **10** was crystallized from methanol–water to yield 4.05 g (62%): mp 82–83°; ^1H nmr δ 4.92 (m, J = 11.4, 4.8, 2.6 Hz), 3.92 (t, J = 2 Hz). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.66; H, 7.61.

The monobenzoate (6.9 g) was hydrolyzed by refluxing in 50 ml of methanol, 2.5 g of KOH, and 10 ml of H_2O followed by extracting into ethyl acetate. The diol was crystallized from hexane–ethyl acetate, mp 64–65°. *Anal.* Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.37; H, 10.91.

Registry No.—**1**, 15806-70-9; **2**, 19700-12-0; **3**, 52730-58-2; **4**, 19700-14-2; **5**, 5454-79-5; **6**, 1460-57-7; **7**, 7443-52-9; **8**, 52699-45-3; **9**, 52748-17-1; **10**, 52759-91-8; **11**, 52759-90-7.

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Proton Magnetic Resonance and Stereochemical Assignments of Polycyclic Ketones and Olefins. Relative Double Bond Shielding Strengths

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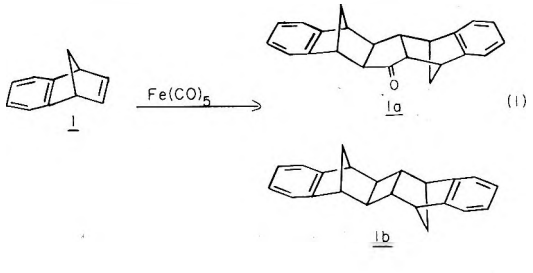
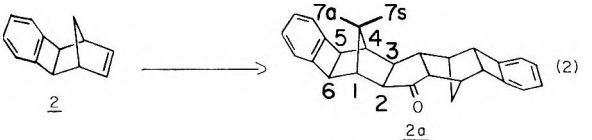
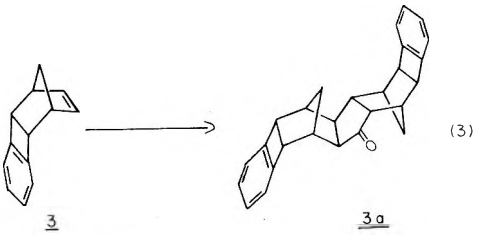
Received April 16, 1974

The proton magnetic resonance assignments of a series of related polycyclic cyclopentanones and their precursor olefins are compared. Stereochemical assignments are based upon observed coupling constants between bridgehead and cyclopentanone protons with iron pentacarbonyl induced coupling leading to exo-trans-exo products. The strengths of the shielding cones of ketonic and olefinic linkages are compared.

Recently, reports[1,2] of iron carbonyl coupling of olefins leading to cyclopentanone derivatives of the type illustrated in reactions 1, 2, and 3 have appeared and the mechanism[3] of this reaction considered. A particularly important aspect of the reaction, both synthetically and as it relates to mechanistic considerations, is product stereochemistry. Olefin reactivity and product stereochemistry are sensitive to the presence of bulky groups[1a] and complexing







groups[2a] at the 7 position of 1 with significant stereochemical changes being observed when 7,7-dimethoxybenzonor-

Table I
Chemical Shift (τ) and Coupling Constant[a] (Hz) Assignments

Proton	Compound 1	2	3
Aromatic	2.92, $J_{1,2}$ = 2.0	2.76, $J_{1,2}$ = 1.7	3.06, $J_{1,2}$ = 1.9
1,4	6.17, $J_{1,7}$ = 1.6	7.22, $J_{1,7a}$ = 2.0	7.05, $J_{1,7}$ = 1.4
2,3	3.25, $J_{2,7a}$ (vs)	3.84, $J_{2,7a}$ (vs)	4.38, $J_{5,7s}$ < 1.0
5,6	$J_{7a,7s}$ = 8.0	6.82, $J_{5,7s}$ (vs)	6.31, $J_{7a,7s}$ = 8.4
7a	7.83	9.12, $J_{7a,7s}$ = 9.0	8.39
7s	7.70	8.71	8.08
	1b	**2a**	**3a**
Aromatic	2.90, $J_{1,7s}$ = 1.5	2.84, $J_{2,3}$ = 7.5	2.87, $J_{2,3}$ = 7.9
1	6.85, $J_{7a,7s}$ = 9.5	7.46, $J_{7a,7s}$ = 11.0	7.40, $J_{1,6} \sim 4.5$
2	8.31	7.87	8.29, $J_{7a,7s}$ = 10.5
3	8.31	8.11	8.85
4	6.85	7.64	7.67
5,6		6.75	6.47
7a	8.42	9.16	8.58
7s	7.98	9.16	8.77

[a] vs = very small but observable.

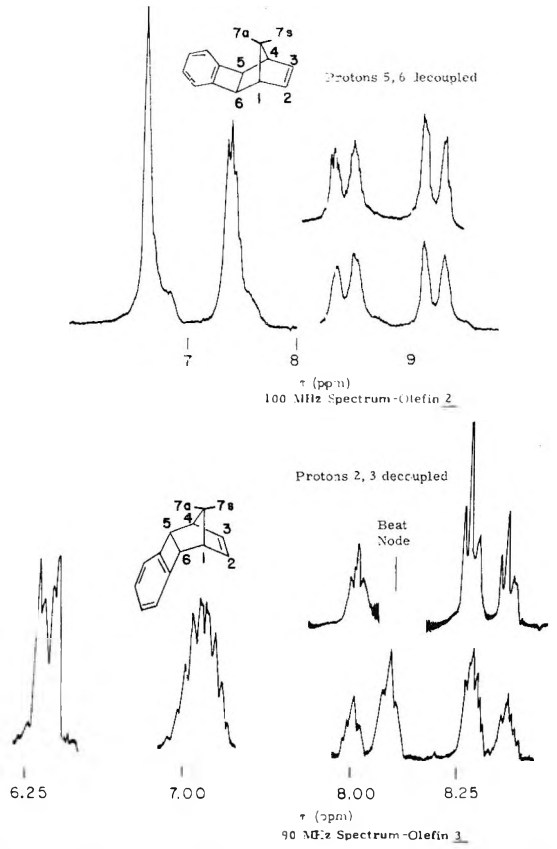


Figure 1. Olefin spectra. Aromatic and olefinic regions not shown.

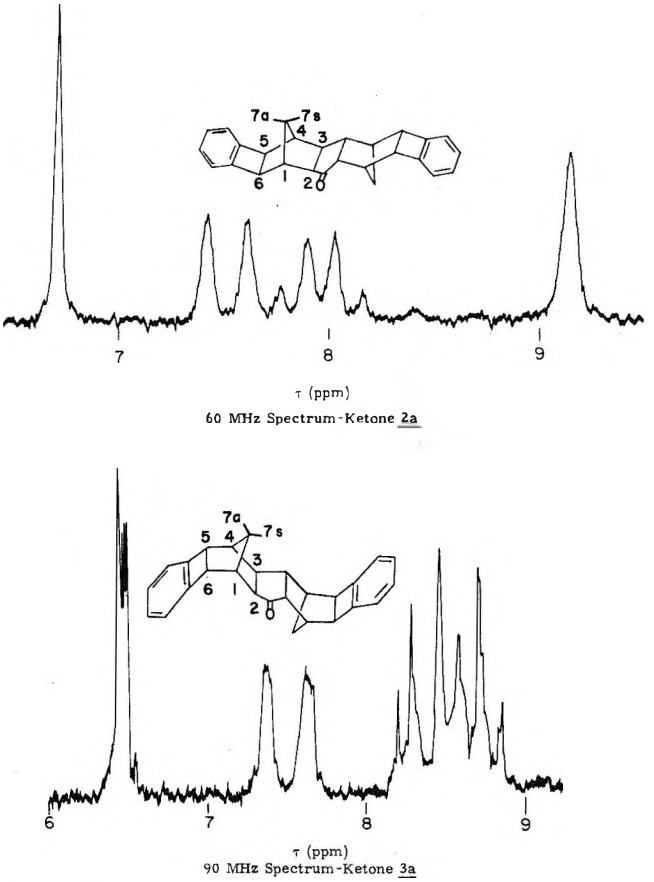


Figure 2. Ketone spectra. Aromatic and olefinic regions not shown.

bornadiene rather than **1** is the reactive olefin. It is remarkable[2b] that norbornen-5-one-2 yields but one isomer.

In the following discussion we present the data and arguments which lead to the conclusion of the stereochemical assignments illustrated in reactions 2 and 3. Proton magnetic resonance assignments appropriate to reactions 2 and 3 are compared to those of reaction 1. The indicated series of seven compounds permits one to draw conclusions regarding the effect of ring strain and relative shielding strengths of olefinic and carbonyl bonds on chemical shifts.

Results and Assignments

Chemical-shift assignments along with available coupling constants are reported in Table I. Partial assignments have been previously reported for olefins[4] **2** and **3** as well as for dimer **1b**;[5] to the extent that interpretations overlap, our conclusions agree with literature assignments. Compound **1a** has been reported.[1,2a] Representative spectra are shown in Figures 1 and 2.

The spectrum of olefin **2** is relatively simple. Protons 5 and 6 appear as a slightly broadened singlet at τ 6.82 only minimally coupled to the 1,4-bridgehead protons as predicted by the Karplus[6] relation for endo protons. When the 5,6 protons are exo to the norbornyl ring as in **3**, they are more strongly coupled to protons 1 and 4 causing the resonance assigned to the 5,6 protons of **3** to be significantly split. In each case, bridgehead protons 1,4 are coupled to bridge protons 7a and 7s with coupling constants of 2 Hz or

less and are further coupled to the olefinic protons. Thus, the multiplet assigned to the 1,4 protons of olefin **3** at τ 7.05 shows additional complexity in comparison to that of olefin **2**. Coupling between protons 1,4 on the one hand and 2,3 on the other is apparent in the triplet character of olefinic resonances.

Assignments of protons 7a and 7s for **2** and **3** result from decoupling studies and from the observation of relative complexity of the 7a,7s AB pattern. Long-range (W rule) coupling between 7a and 2,3 is expected to be sufficient to complicate the resonance of the 7a portion of the AB pattern beyond that which would occur from coupling of the 7a,7s protons to the 1,4 protons alone. Long-range coupling between the 5,6 protons and 7s is to a large extent determined by molecular geometry. Such coupling will not be observable for exo protons, as in **3**, but is expected to be significant when the 5,6 protons are endo as in **2**. The high-field portion of the AB pattern of **3** shows the greater complexity of the two portions and is assigned to the 7a proton. Irradiation of the 2,3 protons (Figure 1, 90 MHz, olefin **3**) removes long-range coupling between protons 2,3 and 7a, degrading the high-field portion to a pattern of triplets arising from coupling between 1,4 and 7. The low-field portion of the AB pattern is thus assigned to the 7s proton. Irradiation of protons 2,3 of compound **2** induces loss of complexity of the high-field portion of the AB pattern while irradiation of the 5,6 protons (Figure 1) reduces the complexity of the low-field portion. Thus, the high-field portion of **2** is assigned to the 7a proton and the low-field portion to the 7s proton.

With the help of decoupling and shift reagent data, pmr resonance assignments observed for ketones **2a** and **3a** are quite straightforward, typical spectra being shown in Figure 2. Once again, when exo, as in **3a**, the 5,6 protons are characterized by a multiplet resulting from strong coupling to the 1,4-bridgehead protons. This is to be contrasted with the endo 5,6 protons of **2a**. As coupling between the 1,4 protons and the 2,3 protons of all three ketones is also unobserved, the 2,3 protons must be endo, as illustrated.

The AB pattern centered at τ 7.99 for ketone **2a** is assigned to the cyclopentanone ring protons, an assignment confirmed by the observation that the lower field portion of this pattern is the most sensitive resonance in the spectrum to the presence of Eu(fod)$_3$. This experiment also confirms the differentiation between protons 2 and 3. While certainly expected, the observed 2,3 coupling constant of 7.5 Hz confirms cis fused rings. Finally, the presence of a C_2 symmetry axis in the molecule, implied by the simplicity of the spectrum, leads to the exo-trans-exo stereochemistry illustrated in reaction 2. The possibility of exo-cis-exo stereochemistry is excluded on the basis of steric hindrance and analogy arguments presented in previous communications.[1]

The accidental magnetic degeneracy of 7a and 7s in **2a** may be lifted by addition of Eu(fod)$_3$, the chemical shift of 7s being more sensitive to shift reagent than that of 7a as a consequence of its greater proximity to the europium coordination site. Upon addition of the shift reagent, the reported 7a,7s coupling constant of 11.0 Hz is observed. Differentiation between resonances resulting from protons 1 and 4 of **2a** also derives from relative motion of chemical shifts of these protons in the presence of the shift reagent although one would certainly anticipate the appearance of 1 at lower field than 4 since it is closer to the electron-withdrawing carbonyl group.

Assignment of resonances to protons 1 and 4 of ketone **3a** is straightforward with the lower field resonance being assigned to proton 1; however, because cyclopentanone ring protons 2,3 and bridge protons 7a,7s resonate in the same region (between τ 7.40 and 8.85), differentiation of these proton resonances required a quantitative shift reagent study. Assignments are based upon relative slopes of the linear chemical-shift change *vs.* added shift reagent plots in combination with decoupling and coupling constant results. Proton chemical-shift sensitivity to shift reagent was observed to be in the order: 2 > 1 > 7s > 3 > 4 > 7a > 5,6. The coupling constant of 4.5 Hz reported for the interaction of protons 1 and 6 (as well as 4 and 5) is estimated from the splitting of the 1 and 4 protons in the presence of large amounts of shift reagent. While probably a good estimate, this value is not to be taken literally due to the fact that protons 5 and 6 are undoubtedly strongly coupled to one another as well as to 4 and 1. Nevertheless, this coupling constant is consistent with the 5,6 protons being exo to the norbornyl ring. Arguments entirely analogous to those described for **2a** lead to the stereochemistry illustrated in reaction 3.

Previously reported[5] pmr assignments of hydrocarbon dimer **1b** did not include differentiation of the 7a and 7s protons. Our assignments, reported in Table I, are similar to literature assignments with the addition of 7a,7s differentiation. While the geometry is correct for long-range coupling between 2,3 and 7a, no such coupling may perturb proton 7s, implying that the 7s resonance should be less complex than that of 7a. Although the low-field side of the high-field portion of the 7a,7s AB pattern is partially buried under the 2,3 resonance at 90 MHz, the high-field side is readily observed. Comparison of this resonance with the corresponding side of the low-field portion of the AB pattern shows it to be somewhat broadened and less well resolved. Thus, the high-field portion is subject to coupling beyond coupling to 1,4 and is assigned to proton 7a. This assignment may be compared to that of ketone **1a**. One would expect the carbonyl group to significantly shield the 7s proton in **1a** with respect to **1b** while not strongly affecting proton 7a; the assignment is at least consistent with this expectation.

Discussion

In general, addition of the rigid, planar[7] five-membered ring to any of the olefins induces diamagnetic shielding, the one exception being the 5,6 protons of **2** → **2a**. The average resonance of these protons is slightly (0.07 ppm) deshielded, a long-range effect presumably resulting from ring conformation modifications. Of significance is the observation that the relative shielding parameters of 7a and 7s are reversed in the ketonic coupling products from the corresponding olefins. A strong contribution to this reversal from the 2′–3′ single bond or from the 2′,3′ protons acting on 7s may be immediately ruled out by observing that, while a similar affect might be expected from these interactions in **1a** and **1b**, the relative shielding of 7a and 7s in **1b** is the same as in **1**. Thus, the shielding cone of the carbonyl group is dominant in establishing 7s at higher field than 7a, as is certainly expected.

One may estimate the effect of the carbonyl group on 7s for each of the three ketones if one assumes that the effect of the carbonyl group on 7a is minimal, that the diamagnetic shift of the 7a protons in progressing from olefins to ketones is a consequence of addition of the strained ring, and that the ring strain effect will be the same on 7a and 7s. The range of values thus calculated is less than 0.2 ppm. While this calculation is approximate at best, it does indicate that the 7s proton is being strongly and similarly shielded by the carbonyl function in each case.

It is interesting to note that the syn methyl group of the isopropyl bridge of β-pinene is shielded with respect to the

same methyl group of α-pinene by 0.13 ppm. This has been interpreted[8] as arising from the fact that the syn methyl group lies closer to the C_2 axis of the double bond for the β isomer than for the α isomer. The external double bond is more effective at shielding the syn methyl group than is the internal double bond.

A related contrast may be drawn between the shielding of 7s by a carbonyl group as in the three ketones under consideration and an olefinic double bond as in the three corresponding olefins. As reversal of relative chemical shifts occurs between these two systems, it appears that the carbonyl shielding cone is far more effective at influencing the 7s proton than is the olefinic double bond. Exact quantitative shifts for the series of compounds in question comparable to that mentioned for the pinene isomers cannot be determined due to the structural insertion of the five-membered ring. Nevertheless, the estimated shifts lie between 0.3 and 0.5 ppm, values well in excess of the symmetry effect observed for the pinenes. Although there is undoubtedly a contribution to this enhanced shielding from the greater proximity of the 7s proton to the double bond C_2 axis in the ketone system than in the olefin system, the change is too great to be explained on this basis alone. Hence we conclude that the carbonyl shielding cone is the stronger of the two.

The shielding effect of the aromatic ring current is observable from the relative chemical shifts of the 2,3 protons for ketones **2a** and **3a**. Disposal of the ring so as to shield these protons induces a diamagnetic shift in proton 2 of 0.42 ppm, a shift not far different from the 0.54-ppm diamagnetic shift observed for the 2,3 protons of the olefins; however, the difference observed is of opposite sign to that expected from the relative geometries of the two compounds. In all likelihood, the small ring shielding of 2 is a consequence of this proton already being strongly affected by the shielding cone of the carbonyl function. The electron density at proton 2 is thus primarily influenced by the ketone and is not subject to substantial further change. The observation of a greater shift (0.74 ppm) for proton 3 is consistent with this presentation.

An inverse but similar effect may be active in bringing about the magnetic equivalency of 7a and 7s in ketone **2a**. Proton 7a is already strongly affected by the aromatic ring in 2 and is not subject to significant shielding upon introduction of the five-membered ketone ring. On the other hand, 7s is much more weakly influenced by aromatic ring current and may be strongly influenced by the carbonyl group thus bringing it into degeneracy with 7a. Consistent with this argument is the observation that both 7a and 7s are shifted to a greater degree between **3** and **3a** than between **2** and **2a**.

Experimental Section

All synthetic procedures have been previously described and the physical properties of the compounds reported. Olefin **1** was prepared according to Wittig and Knauss,[9] olefin **2** according to Simmons,[4] and **3** according to Cava and Mitchell.[10] o-Fluorobromobenzene was purchased from Aldrich Chemical Co. and solvents were distilled prior to use. As implied by previous workers, the preparation of **2** leads to a mixture of products which codistill and which are difficult to separate. We employed liquid chromatography (Waters Associates, Milford, Mass.) to effect purification of **2** using four 2 ft × ⅜ in. lengths of Porasil A and eluting with hexanes (Fisher Scientific, ACS, certified reagent). Six passes for a total of 48 ft of column *via* recycling procedures were necessary to effect base-line separation of the six-component mixture obtained from distillation. After three passes, the first three components were removed so as to prevent remixing. Components 4, 5, and 6 were dominant (differential refractometer) with 4 being the desired olefin. Flow rates of 5 ml/min and initial retention times of slightly in excess of 50 ml were observed. The column dead volume was found to be approximately 48 ml.

Nuclear magnetic resonance spectra were obtained in $CDCl_3$ against an internal TMS standard. Spectra were observed on Varian A60A, Brucker 90-MHz, and Jeol 100-MHz instruments.

Acknowledgment. The author wishes to thank the Research Corporation for financial aid in carrying out this work. Special appreciation to Dr. T. H. Regan of the Eastman Kodak Co., Rochester, N.Y., who obtained the 90-MHz spectra, is gratefully expressed. Appreciation is also expressed to Ms. Ann Jakubowski for obtaining the 100-MHz spectra and to Yale University for the use of their 100-MHz instrument.

Registry No.—**1**, 4453-90-1; **1b**, 10026-43-4; **2**, 27297-14-9; **2a**, 51799-95-2; **3**, 27297-13-8; **3a**, 51830-09-2.

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Observable Magnetic Nonequivalence of Diastereotopic Protons as a Stereochemical Probe

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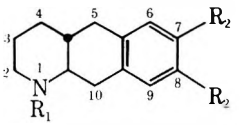
Received June 26, 1974

The *N*-benzyl derivatives of *cis*-decahydroquinoline, *trans*-decahydroquinoline, and *trans*-octahydrobenzo[*g*]quinoline were prepared in order to determine the stereochemistry of the ring juncture. The diasterotopic benzylic protons for the cis stereochemistry appear as an AB quartet in the nmr spectrum with a chemical shift difference of ~24 Hz, while the benzylic protons for the trans stereochemistry appear as an AB quartet with a chemical shift difference of ~60 Hz.

As part of the continuing work[1] in our laboratories on the synthesis of rigid analogs of biologically active phenethylamines, a series of *trans*-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolines (**1**) were prepared. Michne and Albertson[2] have reported on the synthesis of both *cis*- and



1a. $R_1 = H$; $R_2 = H$
b. $R_1 = H$; $R_2 = OCH_3$
c. $R_1 = COPh$; $R_2 = H$
d. $R_1 = COPh$; $R_2 = OCH_3$
e. $R_1 = CH_2Ph$; $R_2 = H$
f. $R_1 = CH_2Ph$; $R_2 = OCH_3$

trans-octahydrobenzo[*g*]quinoline ring systems. Decarboxylation of **2** gave **3** as a mixture of isomers. Conversion of **4** to **5** with 1:5 H_2SO_4:AcOH led to a mixture of approximately 60% *cis*- and 40% *trans*-**5**.[2b] The mixture could be separated by dry column chromatography, and the relative stereochemistry was assigned to each isomer by indirect chemical and spectral evidence.[2a]

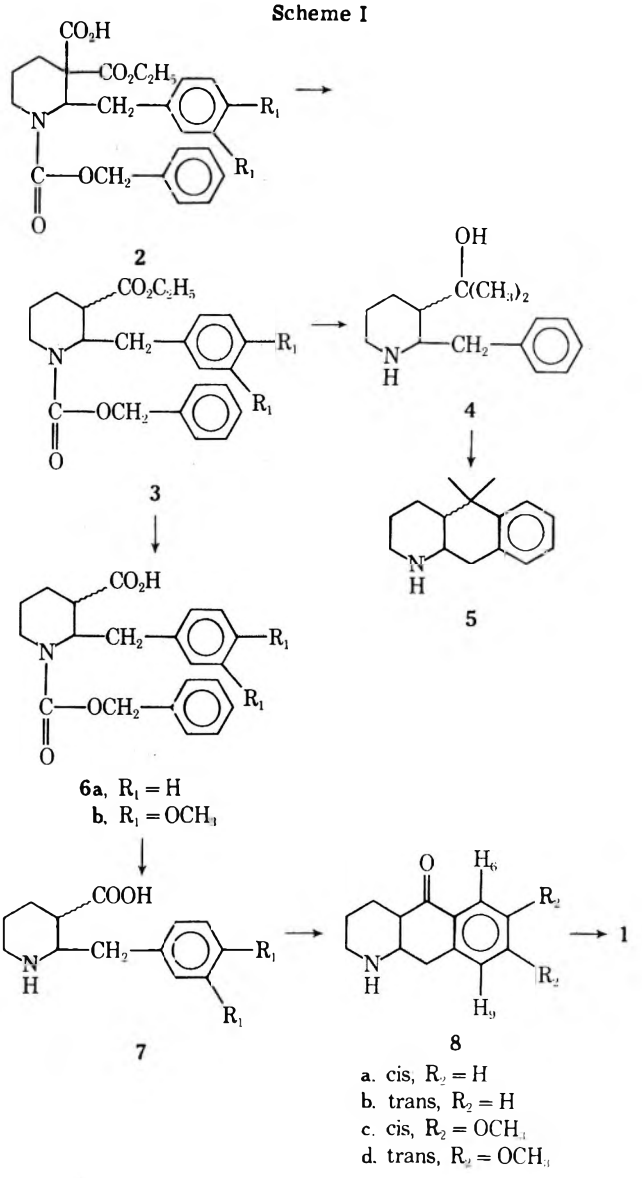
We wished to develop a synthetic procedure which would give only the trans stereochemistry for **1**, and we wanted an unequivocal method for determining this stereochemistry.

Results and Discussion

The synthetic procedure[3] we chose utilizes **3** as starting material and is outlined in Scheme I. Hydrolysis of esters **3a** and **3b** followed by hydrogenation of **6a** and **6b** gave the desired amino acids, **7a** and **7b**, as a mixture of cis and trans isomers. Intramolecular cyclization of **7b** with 95% H_2SO_4 gave a ketone whose nmr spectrum showed three singlets for the aromatic protons in a ratio of 1(δ 7.40):1(δ 7.36):2(δ 6.57). Proton H_6 is in a peri position to the benzylic carbonyl and is deshielded. The nmr resonance for H_6 should lie downfield with relation to that of H_9. The observation that there are two signals of equal intensity lying downfield from the H_9 singlet strongly suggests that sulfuric acid cyclization gives both **8c** and **8d** as products, analogous to the example of Michne and Albertson.[2] However, cyclization of **7b** with polyphosphoric acid (PPA) gave a ketone whose nmr spectrum showed only two singlets for the aromatic protons in a ratio of 1(δ 7.36):1(δ 6.57). Since the PPA cyclization appeared to give only one isomer, the question of the stereochemistry of this product was approached.

Lyle[4] and coworkers have determined the conformational requirements for observable magnetic nonequivalence of benzylic methylene protons in 2- and 3-alkyl-*N*-benzylpiperidines. The diastereotopic benzylic protons appear as an AB quartet in the nmr spectrum if a 2-alkyl substituent is equatorial and appear as a singlet if the 2-alkyl substituent is axial. In the 3-alkyl series, the benzylic protons appear as an AB quartet if the 3-alkyl substituent is either axially oriented or is a branched chain and equatorial. The octahydrobenzo[*g*]quinoline system can be considered as a 2,3-dialkyl-substituted piperidine.

Scheme I



6a, $R_1 = H$
b, $R_1 = OCH_3$

8
a. cis, $R_2 = H$
b. trans, $R_2 = H$
c. cis, $R_2 = OCH_3$
d. trans, $R_2 = OCH_3$

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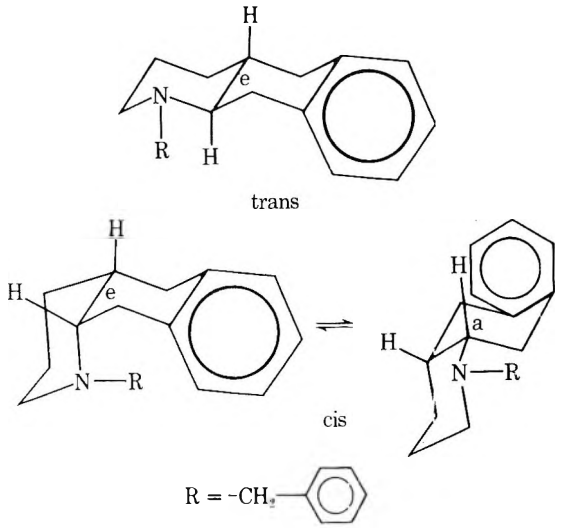
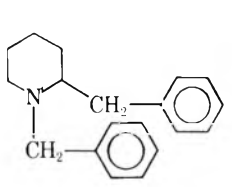
† Deceased, July 14, 1974.



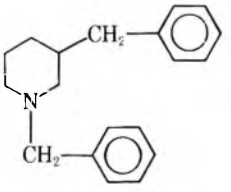
In the rigid trans isomer, the *N*-benzyl group is always adjacent to an equatorial alkyl substituent and the benzylic signal should appear as an AB quartet having a large (~60 Hz) chemical shift difference. The cis series is mobile and can undergo ring flip; thus the *N*-benzyl group is adjacent to a 2-equatorial and 3-axial substituent only part of the time. The benzyl signal would be expected to appear as a singlet or as an AB quartet having a relatively small chemical shift difference. The *N*-benzyl substituent could provide a convenient and absolute probe for determining the configuration of the octahydrobenzo[*g*]quinoline series.

The literature provided ample evidence to encourage our continued study. Compounds **9**, **10**, and **11** can be considered mobile analogs of **1**. Pridgen[5] has determined that the



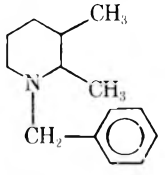
9

J_{AB} = 13.5 Hz
$\Delta\nu$ = 34.9 Hz



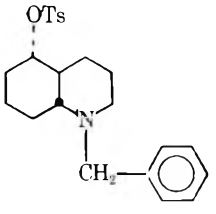
10

J_{AB} = 13.0 Hz
$\Delta\nu$ = 12.9 Hz



11a cis
J_{AB} = 13.8 Hz
$\Delta\nu$ = 7.9 Hz

11b trans
J_{AB} = 13.5 Hz
$\Delta\nu$ = 43.0 Hz

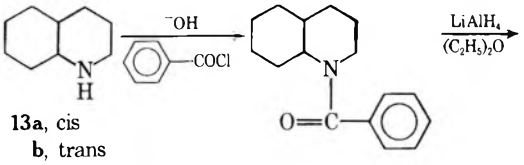


12

AB quartet for the benzylic protons of **11b** has a larger chemical shift difference than that for **11a**. In addition, Johnson, *et al.*,[6] observed that the nmr signal for the benzylic protons of **12** is an AB quartet.

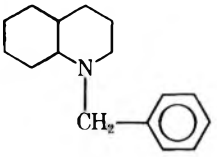
The *N*-benzyl derivatives of *trans*-decahydroquinoline and a mixture of *cis*- and *trans*-decahydroquinoline were prepared.

It has been demonstrated by Johnson[7] and Paulsen[8] that there is a serious steric interaction between an amide group and an adjacent equatorial group in the piperidine ring system. Such steric interactions are sufficient to cause conformational bias, resulting in the preference for axial configuration for the alkyl groups. The rigid *trans*-decahydroquinoline cannot undergo ring flip to alleviate this steric interaction as can the cis isomer. This steric interaction helps explain Johnson's[6] observation that for **16**, the isomer having the cis-ring juncture (**16a**) is the thermodynamically more stable isomer. The *N*-benzyl signal of **15b** appears as an AB quartet with a chemical shift difference of 61.4 Hz. The nmr spectrum of a mixture of **15a** and **15b** showed two AB quartets for the *N*-benzyl signals, one having a chemical shift difference of 23.7 Hz and the other a difference of 60.3 Hz, respectively.

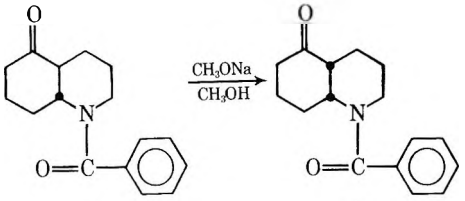


13a, cis
b, trans

14



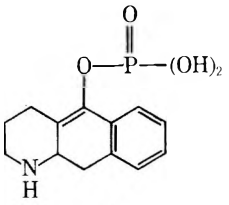
15a, J_{AB} = 13.4 Hz
$\Delta\nu$ = 23.7 Hz
15b, J_{AB} = 13.4 Hz
$\Delta\nu$ = 61.4 Hz



16b **16a**

The ketones **8b** and **8d**, prepared by cyclization with PPA, were subjected to catalytic reduction to give **1a** and **1b**. The benzyl derivatives **1e** and **1f** were then prepared. The benzylic signal appeared as an AB quartet with a chemical shift difference of 59.3 Hz for **1e** and 61.6 Hz for **1f**, substantiating that only the trans isomer was obtained from PPA cyclization.

Cyclization in strong acid results in carbonium ion formation, while cyclization in PPA could result in formation of significant amounts of a phosphate ester intermediate, **17**, which on hydrolysis would lead to the more thermodynamically stable trans product.



17

Experimental Section

Materials and Methods. *trans*-Decahydroquinoline and a mixture of *cis*- and *trans*-decahydroquinoline were purchased from Eastman Chemical Co. The nmr spectra were determined in $CDCl_3$ using a Varian Model T-60 spectrometer, and the chemical shifts are given in δ units measured from TMS as an internal standard. All coupling constants and chemical shift differences are calculated at 100-Hz sweep width. The ir spectra of liquids were recorded as films and of solids as KBr pellets on a Perkin-Elmer Model 727 spectrophotometer. Elemental analyses were determined by James Haug of these Laboratories using a Hewlett-Packard Model 185B C, H, N analyzer. Melting points were taken in open capillaries on a Thomas-Hoover Uni-Melt apparatus and are uncorrected.

***cis*- and *trans*-1-Benzyloxycarbonyl-2-benzyl-3-piperidinecarboxylic Acid (6a).** A solution of 5.3 g (0.014 mol) of a mixture of ethyl *cis*- and *trans*-1-benzyloxycarbonyl-2-benzyl-3-piperi-

dinecarboxylate[2b] and 7.0 g (0.123 mol) of KOH in 150 ml of ethanol was heated at reflux for 3 hr. The solvent was evaporated and the residue was dissolved in 100 ml of water. The aqueous solution was extracted twice with 50 ml of ether, and the aqueous layer was made acidic with concentrated HCl. The white solid which precipitated was collected by filtration, washed with water, and dried to yield 4.9 g (100%) of **6a**. Recrystallization of **6a** from 2-propanol gave a white solid, mp 178–180°: ir 3300–2700 (carboxyl OH), 1710 (carbamate C=O) and 1645 (carboxyl C=O) cm^{-1}; nmr δ 9.57 (s, 1, COOH), 7.15 (s, 10, aromatic).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.36; H, 6.56; N, 3.96. Found: C, 71.51; H, 6.85; N, 4.19.

***cis*- and *trans*-1-Benzyloxycarbonyl-2-(3,4-dimethoxybenzyl)-3-piperidinecarboxylic Acid (6b).** The above procedure with 6.0 g (0.014 mol) of a mixture of ethyl *cis*- and *trans*-1-benzyloxycarbonyl-2-(3,4-dimethoxybenzyl)-3-piperidinecarboxylate[3b] gave 5.6 g (100%) of **6b**, mp 154–156° (*i*-PrOH–H_2O): ir 3400–3000 (carboxyl OH), 1725 (carbamate C=O), and 1665 (carboxyl C=O) cm^{-1}; nmr δ 9.50 (s, 1, COOH), 7.26 (m, 5, aromatic), 6.70 (s, 3, aromatic), 3.81 (s, 3, OCH_3), 3.74 (s, 3, OCH_3).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.38. Found: C, 67.07; H, 6.84; N, 3.32.

***cis*- and *trans*-2-Benzyl-3-piperidinecarboxylic Acid (7a).** A solution of 4.2 g (0.012 mol) of **6a** in 250 ml of CH_3OH was hydrogenated over 1.7 g of 5% Pd/C at 18 psi for 7 hr. The catalyst was removed by filtration, and the filtrate was evaporated to give 2.5 g (96%) of **7a** as a white solid, mp 269–271° dec: ir 1600 (COO^-) cm^{-1}; nmr δ (D_2O) 7.12 (s, 5, aromatic), 3.65–1.32 (m, 10, aliphatic).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.38. Found: C, 71.11; H, 7.98; N, 6.23.

***cis*- and *trans*-2-(3,4-Dimethoxybenzyl)-3-piperidinecarboxylic Acid (7b).** The above procedure with 6.0 g (0.015 mol) of **6b** gave 3.9 g (98%) of **7b** as a white solid, mp 240° dec (CH_3OH–H_2O): ir 1580 (COO^-) cm^{-1}; nmr δ (D_2O) 6.54 (s, 3, aromatic), 3.42 (s, 6, OCH_3), 3.40–1.20 (m, 10, aliphatic).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.57; N, 5.01. Found: C, 64.34; H, 7.48; N, 5.23.

***cis*- and *trans*-7,8-Dimethoxy-5-keto-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (8c and 8d).** A solution of 0.47 g (1.7 mmol) of **7b** and 5 ml of 95% H_2SO_4 was heated on a steam bath for 0.5 hr. The reaction mixture was cooled and diluted with ice, and the solution was made basic with 50% NH_4OH. The base was extracted with ether, and the combined extracts were dried (Na_2SO_4) and evaporated to give 0.15 g (30%) of the base as a clear oil. The hydrochloride, mp 205–208° dec (CH_3OH–Et_2O) was prepared. The nmr spectrum of the base indicated that there was a mixture of **8c** and **8d** present; nmr δ 7.40 (s, 0.5, cis aromatic H_6), 7.37 (s, 0.5, trans aromatic H_6), 6.57 (s, 1, aromatic H_9), 3.83 (s, 6, OCH_3), 3.40–1.00 (m, 10, aliphatic).

***trans*-5-Keto-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride (8b).** The procedure of Smissman, *et al.*,[3a] was modified to produce **8b**. A mixture of 2.2 g (0.01 mol) of **7a** and 35 g of PPA was heated with stirring on a steam bath for 1 hr. The yellow solution was cooled, diluted with 50 ml of ice water, and made basic with 10% NaOH. The basic solution was extracted three times with 75 ml ether, and the combined ether extracts were washed with water, filtered through Na_2SO_4, and treated with gaseous HCl. The resulting solid was collected by filtration, washed with ether, and dried to yield 1.7 g (72%) of **8b** · HCl, mp 206–209° dec (lit.[3a] mp 204–205° dec): ir 1675 (ketone C=O) cm^{-1}; nmr δ 7.85 (m, 1, aromatic H_6), 7.15 (m, 3, aromatic H_7, H_8, H_9), 4.09–1.00 (m, 11, aliphatic).

***trans*-7,8-Dimethoxy-5-keto-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (8d).** The above procedure with 1.4 g (5.0 mmol) of **7b** gave 1.2 g (81%) of **8d** · HCl, mp 210–212° dec (CH_3OH).

Anal. Calcd for $C_{15}H_{20}ClNO_3$: C, 60.50; H, 6.76; N, 4.70. Found: C, 60.24; H, 6.50; N, 4.94.

The base was obtained by partitioning the salt between 10% NaOH and CH_2Cl_2. The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated to give **8d** as white needles, mp 145–146° dec (EtOAc); ir 1670 (ketone C=O) cm^{-1}; nmr δ 7.37 (s, 1, aromatic H_6), 6.57 (s, 1, aromatic H_9), 3.85 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 3.27–1.10 (M, 10, aliphatic).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.32; N, 5.35. Found: C, 69.06; H, 7.47; N, 5.27.

***trans*-1,2,3,4,4a,5,10,10a-Octahydrobenzo[*g*]quinoline (1a).** A solution of 2.1 g (0.009 mol) of **8b** in 200 ml of ethanol and 7 ml of 70% of perchloric acid was hydrogenated over 2.1 g of 10% Pd/C at 60 psi overnight. The catalyst was removed by filtration and the filtrate was concentrated until the perchlorate salt began to precipitate. Water was added and the salt was collected by filtration and recrystallized from 2-propanol to give 1.8 g (75%) of **1a** · $HClO_4$ as a white solid, mp 256–258° dec.

Anal. Calcd for $C_{13}H_{18}ClNO_4$: C, 54.26; H, 6.30; N, 4.87. Found: C, 54.50; H, 6.32; N, 4.58.

The base was obtained by partitioning the perchlorate between 50 ml of CH_2Cl_2 and 25 ml of 10% NaOH. The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated to give **1a** as a clear oil: ir 3300 (N–H) cm^{-1}; nmr δ 7.06 (s, 4, aromatic); 3.56–1.00 (m, 13, aliphatic). The hydrochloride, mp 275–276° dec (ethanol), was prepared from the base in the usual manner.

Anal. Calcd for $C_{13}H_{18}ClN$: C, 69.78; H, 8.11; N, 6.26. Found: C, 70.11; H, 8.29; N, 6.15.

***trans*-7,8-Dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1b).** The above procedure with 1.0 g (3.8 mmol) of **8d** gave 1.0 g (77%) of **1b** · $HClO_4$, mp 279–281° dec. The base was obtained as white plates, mp 105–106° (hexane): nmr δ 6.36 (s, 2, aromatic), 3.69 (s, 6, OCH_3), 3.25–1.00 (m, 13, aliphatic).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.61. Found: C, 73.11; H, 8.11; N, 5.51.

The hydrochloride, mp 235° dec (acetone–ether), was prepared from the base in the usual manner.

Anal. Calcd for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.86; H, 7.94; N, 4.65.

General Procedure for the Preparation of Benzamides. A mixture of 0.020 mol of the secondary amine, 0.022 mol of benzoyl chloride, 50 ml of 5% NaOH, and 25 ml of CH_2Cl_2 was vigorously stirred for 1.5 hr. The layers were separated and the aqueous phase was extracted twice with 15 ml of CH_2Cl_2. The combined CH_2Cl_2 layers were washed once with 25 ml of 5% NaOH, once with 25 ml of H_2O, twice with 25 ml of 1 *N* HCL, and once with 25 ml of H_2O. The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated to give the amide.

***trans*-1-Benzoyldecahydroquinoline (14b).** Using the above procedure, *trans*-decahydroquinoline (Eastman) gave a quantitative yield of **14b**, mp 51–53° (lit.[9] mp 54–55°): ir 1625 (-NHC=O) cm^{-1}; nmr δ 7.23 (s, 5, aromatic), 3.31 (m, 4, aliphatic), 2.20 (m, 12, aliphatic).

***cis*- and *trans*-1-Benzoyldecahydroquinoline (14a and 14b).** Using the above procedure, a mixture of *cis*- and *trans*-decahydroquinoline (Eastman) gave a 98% yield of a mixture of **14a** and **14b** as a brown oil. This mixture was used without further purification, ir 1625 (NHC=O) cm^{-1}.

***trans*-1-Benzoyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1c).** Using the above procedure, **1a** gave an 85% yield of **1c** as white needles, mp 162–163° (*i*-PrOH): ir 1605 (NHC=O) cm^{-1}; nmr δ 7.26 (s, 5, aromatic), 8.95 (s, 4, aromatic), 4.32–1.12 (m, 12, aliphatic).

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.27; N, 4.81. Found: C, 82.44; H, 7.09; N, 4.52.

***trans*-1-Benzoyl-7,8-dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1d).** Using the above procedure, **1b** gave a 71% yield of **1d** as a white solid, mp 165–166° (EtOAc); ir 1610 (NHC=O) cm^{-1}; nmr δ 7.40 (s, 5, aromatic), 6.58 (s, 1, aromatic), 6.55 (s, 1, aromatic), 3.83 (s, 6, OCH_3), 3.62–1.30 (m, 12, aliphatic).

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.17; N, 3.99. Found: C, 75.23; H, 7.23; N, 3.78.

General Procedure for the Reduction of the Benzamides. A mixture of 0.01 mol of the amide, 0.02 mol of $LiAlH_4$, and 25 ml of anhydrous Et_2O was heated at reflux for 5 hr. The excess $LiAlH_4$ was decomposed with 10% NaOH and the ether removed by decantation. The residue was washed thoroughly with ether, and the combined ether layers were evaporated to give the benzylamine.

***trans*-1-Benzyldecahydroquinoline (15b).** Using the above procedure, **14b** gave an 86% yield of **15b** as a yellow oil: nmr δ 7.09 (s, 5, aromatic), 3.50 (AB, J_{AB} = 13.4 Hz, ΔV_{AB} = 61.4 Hz, 2, NCH_2Ph), 2.80–0.80 (m, 16, aliphatic). The hydrochloride, mp 199–201° (*i*-PrOH–Et_2O), was prepared in the usual manner.

Anal. Calcd for $C_{16}H_{24}ClN$: C, 72.29; H, 9.10; N, 5.27. Found: C, 72.05; H, 9.20; N, 5.07.

***cis*- and *trans*-1-Benzyldecahydroquinoline (15a and 15b).** Using the above procedure, a mixture of **14a** and **14b** gave a 65% yield of a yellow oil which was determined by nmr to be a mixture of **15a** and **15b**: nmr δ 7.20 (s, 5, aromatic), 3.53 (AB, J_{AB} = 13.4 Hz, ΔV_{AB} = 60.3 Hz, trans N–CH_2Ph), 3.53 (AB, J_{AB} = 13.4 Hz, ΔV_{AB} = 23.7 Hz, cis N–CH_2Ph), 2.80–0.80 (m, 16, aliphatic).

***trans*-1-Benzyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1e).** Using the above procedure, **1c** gave an 83% yield of **1e** as

a white solid, mp 86–87° (EtOH): nmr δ 7.16 (s, 5, aromatic), 6.93 (s, 4, aromatic), 3.63 (AB, J_{AB} = 13.4 Hz, ΔV_{AE} = 59.3 Hz, 2, N-CH_2Ph), 3.60–0.80 (m, 12, aliphatic).

Anal. Calcd for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.47; H, 8.41; N, 4.83.

***trans*-1-Benzyl-7,8-dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1f).** Using the above procedure, **1d** gave an 87% yield of **1f** as a clear oil: nmr δ 7.20 (s, 5, aromatic), 6.61 (s, 1, aromatic), 6.54 (s, 1, aromatic), 3.89 (s, 6, OCH_3), 3.71 (AB, J_{AB} = 13.4 Hz, ΔV_{AB} = 61.6 Hz, 2, N-CH_2Ph), 3.60–0.80 (m, 12, aliphatic). Conversion of the base to the hydrochloride, mp 159–161° (H_2O), and reconversion of the salt to the base gave an analytically pure sample of **1f**.

Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.63; H, 7.98; N, 4.11.

Acknowledgment. The authors gratefully acknowledge support of this project by the National Institutes of Health Grants NS 90399 and GM 49441.

Registry No.—**1a,** 53011-21-5; **1a** $HClO_4$, 53011-22-6; **1a** HCl, 53011-23-7; **1b,** 53011-24-8; **1b** $HClO_4$, 53011-25-9; **1b** HCl, 53011-26-0; **1c,** 53011-27-1; **1d,** 53011-28-2; **1e,** 53011-29-3; **1f,** 53011-30-6; **1f** HCl, 53011-31-7; *cis*-**3a,** 53011-32-8; *trans*-**3a,** 53060-09-6; *cis*-**3b,** 53011-33-9; *trans*-**3b,** 53011-34-0; *cis*-**6a,** 53011-35-1; *trans*-**6a,** 53011-36-2; *cis*-**6b,** 53011-37-3; *trans*-**6b,** 53011-38-4; *cis*-**7a,** 53011-39-5; *trans*-**7a,** 53011-40-8; *cis*-**7b,** 53011-41-9; *trans*-**7b,** 53011-42-0; **8b,** 53011-43-1; **8b** HCl, 41191-52-0; **8c,** 53011-44-2; **8c** HCl, 53011-45-3; **8d,** 53011-46-4; **8d** HCl, 53011-47-5; **13a,** 10343-99-4; **13b,** 767-92-0; **14a,** 5710-04-3; **14b,** 22218-33-3; **15a,** 53011-48-6; **15b,** 784-85-0; **15b** HCl, 784-85-0; benzoyl chloride, 98-88-4.

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Sodium Borohydride Reduction of Sterically Hindered Pyridinium Salts[1]

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Received July 17, 1974

The sodium borohydride reduction of 1-triphenylmethylpyridinium salts gave a mixture of dihydropyridines, with the 1,2 isomer predominating. Thermal decomposition gave loss of triphenylmethane and the original pyridine, suggesting the use of this derivative for protection of the pyridine ring during hydride reductions. The 2-hydroxyimino-1,1-dimethylethylpyridinium salts gave largely the tetrahydropyridine with sodium borohydride. Thermal or basic decomposition of the product removed the nitrogen substituent to give the 1-unsubstituted-1,2,3,6-tetrahydropyridine. This constitutes the only satisfactory reductive procedure for the synthesis of such compounds.

The mechanism of the reduction of pyridinium ions by sodium borohydride has been well defined, and the effect of substituents on the heterocyclic ring has been explored and can be predicted to some extent.[3] A large nitrogen substituent, because of steric interference to approach of the hydride reagent, causes the reduction to occur to a greater extent at the 4 position and gives the saturated piperidine. A nitrogen substituent with a π bond which can overlap the occupied p orbital of nitrogen stabilizes the intermediate dihydropyridine by decreasing the nucleophilicity of the enamine system.

Synthetic methods were found for preparing two unusual salts of pyridine, the triphenylmethyl- and 2-hydroxyimino-1,1-dimethyl ethyl salts, and examples of these salts were studied with sodium borohydride. The products from these reductions provide interesting applications to organic syntheses.[4]

Pyridine was reported to undergo reaction with triphenylmethylcarbonium ion to form a pyridinium salt with the large triphenylmethyl group on the nitrogen. An improved method of synthesis was used to prepare 1-triphenylmethylpyridinium fluoroborate (**1**) in yields of about 85%. The reduction of 1-triphenylmethylpyridinium fluoroborate (**1**) with sodium borohydride gave a mixture of the 1,4- and 1,2-dihydropyridine (**2** and **3**) which did not undergo further reduction. Addition of water to the solution caused the precipitation of the dihydropyridines which then could be analyzed by the nuclear magnetic resonance spectrum. In this manner a very high yield of crude material was obtained which was shown to be 23% of the 1,4-dihydropyridine (**2**) and 77% of the 1,2-dihydropyridine (**3**). The compounds rapidly underwent decomposition on warming to give pyridine and triphenylmethane. The presence of 1,2-dihydropyridine (**3**) as the predominant product was further demonstrated by the successful Diels–Alder reaction using *N*-phenylmaleimide to give **4**. The stereochemistry and structure of **4** are based on the nmr spectrum. The endo stereochemistry would be expected, and the low-field signal for 2 hydrogens centered at 3.1 ppm suggest that these hydrogens are anti to the double bond.

The attempts to carry out similar reactions with substituted pyridines were less successful. The preparations of 1-triphenylmethyl-3-cyanopyridinium fluoroborate and 1-triphenylmethyl-3-methylpyridinium fluoroborate were accomplished; however, the products could not be obtained in analytical purity. The sodium borohydride reduction reactions on the crude compounds indicated the presence of large amounts of 1,2-dihydropyridine; however, the results were not conclusive.

A second series of pyridinium salts were formed by the reaction of 2-chloro-2-methylpropionaldehyde oxime, formed from isobutylene and nitrosyl chloride, with pyridines. The 1-(2-hydroxyimino-1,1-dimethylethyl)pyridinium chlorides prepared by this method are shown in Table I.

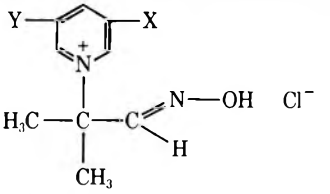
The sodium borohydride reduction of these pyridinium

Table I
1-(2-Hydroxyimino-1,1-dimethylethyl)pyridinium Chlorides

Salt[a] of	Procedure	Yield, %	Mp, °C (dec)	Formula	Anal. Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
Pyridine (5a)	A	95	164–165	$C_9H_{13}ClN_2O$	53.86	6.53	13.96	53.72	6.66	14.07
	B	100	172.5–174							
3-Picoline (5b)	A	98	151–153	$C_{10}H_{15}ClN_2O$	55.94	7.04	13.05	55.88	7.00	12.98
	B	97	153–154.5							
3,5-Lutidine (5c)	A	96	155–156	$C_{11}H_{17}ClN_2O$	57.76	7.44	12.49	57.77	7.69	12.38
	B	84	155–156							
3-Methoxypyridine (5d)	B	98	116–117	$C_{10}H_{15}ClN_2O_2$	52.06	6.55	12.14	48.36	6.87	11.15
3-Methanesulfonyloxypyridine (5e)	B	56	121–121.5	$C_{10}H_{15}ClN_2O_4S$	40.74	5.13	9.50	40.43	4.97	9.26

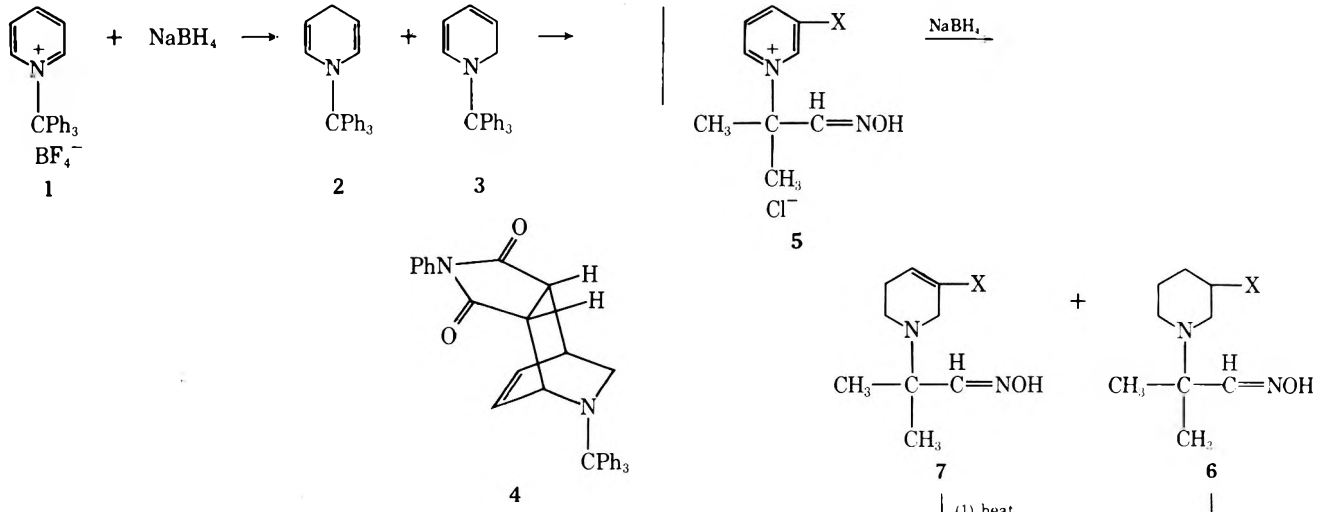
[a] The nmr spectra of these compounds are in complete agreement with the proposed structures.

Table II
Reduction of 1-(2-Hydroxyimino-1,1-dimethylethyl)pyridinium Chloride



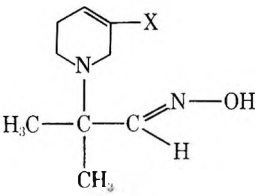
Number	X	Y	In EtOH (%) Yield	Piperidine 6	Tetrahydro 7	In water (%) Yield	Piperidine 6	Tetrahydro 7
5a	H	H	85	1	99	89	15	85
5b	CH_3	H	94	1	98	88	19	74
5c	CH_3	CH_3	83	5	95[a]	88	9	91
5d	CH_3O	H	78	*b*		77	*b*	99
5e	CH_3SO_3	H		*b*		81	*b*	

[a] The product was not purified and characterized except *via* spectral analysis. [b] Some dihydropyridine was present as seen in the nmr.



salts gave tetrahydropyridine and piperidine derivatives which underwent decomposition on heating. The corresponding piperidine (6) or tetrahydropyridine (7) was converted to the *N*-formyl derivative (8 or 9) quantitatively by treating them with methyl formate. The gas–liquid chromatographic analysis of these *N*-formyl derivatives is shown in Table II. The relative yields of the tetrahydropyridine and piperidines seem to be dependent upon the conditions under which the hydrogenations were conducted as

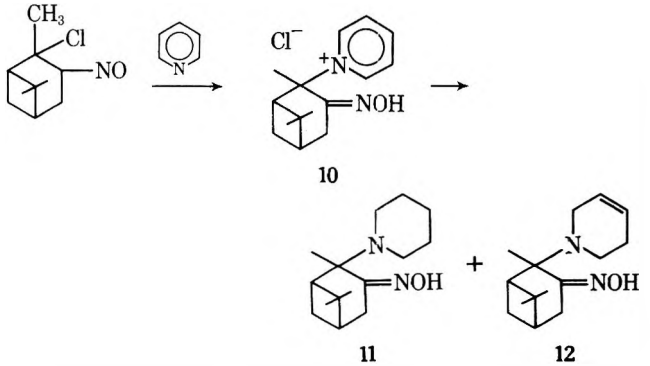
Table III
Properties of Tetrahydropyridines from Table II



Number	X	Mp, °C	Molecular Formula	Anal. Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
7a	H	115–116	$C_9H_{16}N_2O$	63.87	10.12	16.55	64.04	9.88	16.66
7b	CH_3	106–107	$C_{10}H_{18}N_2O$	65.89	9.96	15.37	65.96	10.19	15.56
7d	CH_3O	132–133	$C_{10}H_{18}N_2O_2$	60.58	9.16	14.14	60.71	9.44	14.26
7e	CH_3SO_3	142–143	$C_{10}H_{18}N_2O_4S$	45.78	6.92	10.68	45.93	7.04	10.88

well as upon the structure of the compound (Table III). The use of water or aqueous solutions promoted the formation of piperidines presumably from 1,4-dihydropyridine intermediates. The use of alcoholic solvents, on the other hand, decreased the amount of this product and promoted the formation of only tetrahydropyridines from the 1,2-dihydropyridine. These results suggest that either the nature of the hydride ion causing the reduction or the degree of solvent separation of ion pairs may have very significant bearing on the relative amounts of 1,4- and 1,2-dihydropyridines formed as intermediates.

The related salt (10) of pyridine was prepared from the nitrosyl chloride addition product[5] of α-pinene. The salt (10) was converted to the known piperidine derivative 11[6] by catalytic hydrogenation; however, analysis of the mixture of 11 and the tetrahydropyridine (12) proved to be difficult by nuclear magnetic resonance. The isolated yield of 12 was 65% giving a lower limit for the partial reduction product.



10

11 12

The results of these experiments have synthetic significance in addition to the importance relative to the mode of reaction of borohydride with pyridinium ions. It will be noted that in the case of triphenylmethyl derivatives the reaction stops at the dihydropyridine stage and thermal decomposition of the dihydropyridine returns the compound to its original, aromatic oxidation state. It appears possible that the triphenylmethyl substituent on the pyridine nitrogen could provide a method of protecting this aromatic system during reactions in other parts of the molecule.

The use of the nitrosyl chloride adducts to alkenes to form salts with the pyridine ring provides a method of preparing 1-unsubstituted tetrahydropyridines. It is possible to convert a substituted pyridine to the corresponding 1-(2-hydroxyimino-1,1-dimethylethyl) derivative, which then on reduction with sodium borohydride would give the desired tetrahydropyridine (7). This compound on thermal decomposition or heating with base would produce the 1-unsubstituted tetrahydropyridine. Since reduction of pyridines and acid salts of pyridines to tetrahydropyridines is difficult to achieve, this route provides a convenient method of preparation of such compounds.

Experimental Section

Preparation of 1-Triphenylmethylpyridinium Fluoroborate (1). A solution of 17 g of triphenylmethyl fluoroborate in 200 ml of dry methylene chloride was added to 10 ml of pyridine in 50 ml of dry methylene chloride. The orange color of the triphenylmethylcarbonium ion disappeared immediately, and after a few minutes, solid began to precipitate. The solid was collected to give 17.9 g (85%) of 1-triphenylmethylpyridinium fluoroborate (1), mp 177–186° dec.

Anal. Calcd for $C_{24}H_{20}BF_4N$: C, 70.43; H, 4.92; N, 3.42. Found: C, 70.36; H, 4.83; N, 3.50.

Sodium Borohydride Reduction of 1-Triphenylmethylpyridinium Fluoroborate. To a suspension of 4 g of sodium borohydride in 50 ml of absolute ethanol was added 4 g of 1-triphenylmethylpyridinium fluoroborate (1). The suspension was stirred for 10 min and 100 ml of water was added. The solid which precipitated was removed by filtration and washed with methanol to give 3.05 g (96%) of a mixture of 1-triphenylmethyl-1,4- and 1,2-dihydropyridines. Analysis of the nmr spectrum showed the mixture to be 23% 1,4-dihydro- (2) and 77% 1,2-dihydropyridine (3). Recrystallization of the mixture from ether or methylene chloride–methanol gave an analytical sample of the mixture, mp 80–150°.

Anal. Calcd for $C_{24}H_{21}N$: C, 89.12; H, 6.55; N, 4.33. Found: C, 88.78; H, 6.42; N, 4.20.

A solution of 2.87 g of crude 1-triphenylmethyl-1,2-dihydropyridine (3) in 200 ml of ether was mixed with 2 g of *N*-phenylmaleimide in 25 ml of ether. The solution was concentrated to a total of 150 ml and allowed to stand for 12 hr. The volume was reduced to 30 ml and allowed to stand for 2 days in a refrigerator. The solid which separated was collected and washed with ether to give 1.2 g (27%) of the Diels–Alder adduct (4), mp 203–214°. Recrystallization of the solid from methanol–methylene chloride gave an analytical sample of 4: mp 226–228.5°; nmr δ 7.0–7.7 ppm (m, 20 H, ArH), 5.61 (t, J = 6.5 Hz, 1 H, C=CH), 5.28 (dd, J = 8.0 and 6.5 Hz, 1 H, C=CH), 4.39 (m, 1 H, bridge C—H), 3.72 (dd, J = 8.0 and 4.0 Hz, 1 H, bridge C—*H*), 3.40 (broad d, J = 10 Hz, 1 H, $C(H_{en})H_{ex}$), 3.1 (m, 2 H, -C*H*C*H*-), 2.43 (broad d, J = 10 Hz, 1 H, $C(H_{en})H_{ex}$).

Anal. Calcd for $C_{34}H_{28}N_2O_2$: C, 82.33; H, 5.68; N, 5.64. Found: C, 82.11; H, 5.67; N, 5.57.

3-Hydroxypyridine Methanesulfonate. A solution of 108.5 g of 3-hydroxypyridine hydrobromide and 50 g of sodium hydroxide in 250 ml of water was cooled and treated with 21 g of methanesulfonyl chloride keeping the temperature below 15°. After the addition was complete, stirring was continued for 30 min and the mix-

ture was seeded. The solid which separated was collected by filtration and recrystallized from 750 ml of water with decolorization with charcoal. After seeding, 78.5 g (64%) of 3-hydroxypyridine methanesulfonate, mp 59–60°, was obtained.

Anal. Calcd for $C_6H_7NO_3S$: C, 41.61; H, 4.07; N, 8.09. Found: C, 41.60; H, 3.95; N, 8.02.

1-Nitroso-2-chloro-2-methylpropane. A solution of 76 g of isobutylene in 300 ml of methylene chloride was cooled and 84.0 g of nitrosyl chloride was added at temperatures below 10°. The mixture was cooled in a Dry Ice–acetone bath and the solid which separated was collected and washed with cold ether. The filtrates were concentrated and further solid was collected. The crude solid, 129 g, was dissolved in a minimum of methylene chloride and the solution was filtered and diluted with an equal volume of petroleum ether (bp 30–60°). The product was isolated as a series of crops; first, 77.7 g mp 105–106°, and second, 35.7 g, mp 81–102°.

Preparation of 1-(2-Hydroxyimino-1,1-dimethyl)pyridinium Chloride Derivatives (5). Procedure A. The 1-nitroso-2-chloro-2-methylpropane was mixed with a 6–8-fold excess of pyridine derivative and the temperature maintained near 60° by heating or cooling as necessary. After about 1–1.5 hr the reaction mixture was cooled and the solid which separated was washed with benzene and air dried. The properties for **5** are given in Table I.

Procedure B. A solution of 1-nitroso-2-chloro-2-methylpropane in acetonitrile was cooled and the pyridine was added. The mixture was allowed to stand, and the product was crystallized from solution. The solid was separated by filtration and washed with cold solvent and dried. See Table I for the properties of **5.**

General Method for Reduction of 1-(2-Hydroxyimino-1,1-dimethylethyl)pyridinium Salts (5). A suspension or solution of 0.05 mol of the 1-(2-hydroxyimino-1,1-dimethylethyl)pyridinium salt (**5**) in 150 ml of absolute ethanol was cooled on an ice bath to about 10°. To this suspension was added 3.8 g (0.1 mol) of sodium borohydride in small portions so that the temperature did not rise over 15°. When the addition was complete, the mixture was stirred at room temperature for 30 min, the solution was made acidic with concentrated hydrochloric acid, and any borate salts which separated were removed by filtration. The solution was evaporated under reduced pressure to about 20 ml and the residue was dissolved in 150 ml of water and made basic by the addition of ammonium hydroxide. In most cases, the oil which separated crystallized. If the product did not crystallize, the aqueous mixture was extracted with ether and the ether extracts were dried over magnesium sulfate, filtered, and reduced to dryness.

Crude yields were obtained from these residues. The crude product was sampled by removing 0.5–1 g of material and subjecting this sample to pyrolytic distillation at room temperature.

The distillate was collected in a container partly filled with methyl formate. After several hours standing at room temperature, the excess methyl formate was removed by evaporation on a steam bath. The residue was analyzed by glc on a 1-m column of Carbowax 20M on Chromosorb W. The temperatures ranged from 130° for pyridine to 160° for methoxypyridine. The results are shown in Table II.

Preparation of (*d*)-*N*-(3-Oximino-2-pinanyl)pyridinium Chloride (10). A solution of 20 g (0.16 mol) of *d*-α-pinene in 250 ml of methylene chloride was cooled to about −20° and treated with 10 g of gaseous nitrosyl chloride. The temperature was not allowed to rise over 0°. The reaction mixture was stirred for 15 min at 0° and then for 15 min at −20°. The precipitate which formed was racemic adduct and was removed by filtration, and the filtrate was cooled to −78° on a Dry Ice–acetone bath for 1 hr. The cold blue-green solution was filtered again. The filtrate was treated with 50 ml of pyridine and allowed to warm to room temperature. The methylene chloride was removed under reduced pressure at room temperature. The gummy precipitate which had formed was isolated by filtration and washed thoroughly with pyridine. Washing with pyridine converted the gummy material into a fine crystalline precipitate. The precipitate was dissolved in a minimum amount of water and acetone and the first crop of solid was 3.6 g of largely racemic **10**, mp about 100° dec, $[\alpha]^{22}D$ +61°.

The filtrates were diluted with an equal volume of acetone, and the mixture was cooled to −10°. The crystals were removed by filtration and washed with acetone to give 4.1 g of the dextrorotatory **10**, mp about 100° dec, $[\alpha]^{22}D$ +168°.

Anal. Calcd for $C_{15}H_{21}ClN_2O$: C, 64.16; H, 7.54; N, 9.98. Found: C, 64.14; H, 7.67; N, 10.01.

Catalytic Hydrogenation of *N*-(3-Oximino-2-pinanyl)pyridinium Chloride (10). A solution of 1.4 g of *N*-(3-oximino-2-pinanyl)pyridinium chloride (**10**) in 25 ml of glacial acetic acid was treated with 0.1 g of platinum oxide and hydrogenated for 6 hr under a positive pressure of hydrogen. During the course of the hydrogenation a precipitate appeared. The precipitate and platinum were removed by filtration and the organic precipitate was dissolved in methanol–water. The aqueous methanolic solution was made basic with sodium carbonate and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent gave a crude yield of 1.1 g (91%) of *N*-(3-oximino-2-pinanyl)piperidine (**11**). Recrystallization from ligroin gave pure **11**, mp 119–122° (lit.[6] 118–119°).

Sodium Borohydride of *N*-(3-Oximino-2-pinanyl)pyridinium Chloride (10). A solution of 1.4 g of **10** in 25 ml of methanol cooled in an ice bath was treated with 1.5 g of sodium borohydride in small portions. When the addition was complete, the solution was allowed to warm to room temperature overnight. The inorganic precipitate was removed by filtration and methanol was evaporated under reduced pressure. The residue was taken up in water and extracted with ether. The ether extracts were dried over magnesium sulfate, filtered, and evaporated to dryness. The residue was dissolved in 60–75° ligroin, and the solution was treated with Norite, filtered, and set aside to crystallize. Two crops were obtained which were combined and recrystallized from ligroin to yield 0.8 g (65%) of the tetrahydro derivative (**12**), mp 102–105°.

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.57; H, 10.06; N, 11.35.

Acknowledgment. This research was supported in part by Grants GM-12177 and CA-04143 from the National Institutes of Health.

Registry No.—**1**, 26156-84-3; **2**, 52843-62-6; **3**, 52843-63-7; **4**, 52843-64-8; **5a**, 52843-65-9; **5b**, 52920-66-8; **5c**, 52843-66-0; **5d**, 52920-67-9; **5e**, 52843-67-1; **7a**, 52843-68-2; **7b**, 52843-69-3; **7d**, 52843-70-6; **7e**, 52843-71-7; **10**, 52843-72-8; **11**, 52843-73-9; **12**, 52843-74-0; triphenylmethyl fluoroborate, 341-02-6; pyridine, 110-86-1; sodium borohydride, 16940-66-2; *N*-phenylmaleimide, 941-69-5; 3-methanesulfonyloxypyridine, 52843-75-1; 3-hydroxypyridine HBr, 52843-76-2; methanesulfonyl chloride, 124-63-0; 1-nitroso-2-chloro-2-methylpropane, 44580-06-5; isobutylene, 115-11-7; nitrosyl chloride, 2696-92-6; *d*-α-pinene, 7785-70-8; 3-picoline, 108-99-6; 3,5-lutidine, 591-22-0; 3-methoxypyridine, 7295-76-3.

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(1) This research was presented in part at the 4th Heterocyclic Symposium Brno, Czechoslovakia, Sept 22–24, 1969.
(2) Author to whom correspondence should be addressed.
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(7) Melting points were determined using a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus and were not corrected for thermometer stem exposure. Elemental analyses were determined using an F&M Model 185 C, H, and N analyzer. Infrared spectra were determined using Perkin-Elmer Model 137 or 337 spectrometers with samples prepared as mulls or KBr pellets. The ultraviolet absorption spectra were measured on a Cary 15 spectrometer in the solvent indicated, and the nuclear magnetic resonance spectra were determined using a Varian A-60 spectrometer.

Remarkable Enhancement of Dienophilicity by the Trifluoromethanesulfonyl Group. Phenyl(trifluoromethanesulfonyl)acetylene

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Received July 16, 1974

Phenyl(trifluoromethanesulfonyl)acetylene, prepared from the lithium salt of phenylacetylene and trifluoromethanesulfonic acid anhydride, undergoes exceptionally facile Diels–Alder reactions with tetraphenylcyclopentadienone, 1,3-diphenylisobenzofuran, cyclopentadiene, and 1,3-cyclohexadiene. The rates of these reactions and those of the corresponding reactions with other $C_6H_5C{\equiv}CX$ derivatives were measured and compared. The rate of reaction of phenyl(trifluoromethanesulfonyl)acetylene with cyclopentadiene in ethyl acetate at room temperature was found to be 1.7 times as fast as the rate of reaction of dimethyl acetylenedicarboxylate with this diene. The reasons for the remarkable dienophilicity of phenyl(trifluoromethanesulfonyl)acetylene are discussed.

In the usual Diels–Alder reaction (as opposed to the Diels–Alder reaction with inverse electron demand)[1] electron-withdrawing groups on the dienophile increase the rate of reaction.[1c,2] Thus, Becker and coworkers[3] found that the rate of reaction of methyl esters of substituted phenyl propiolates with tetraphenylcyclopentadienone correlated with Hammett σ constants, and even better with σ^- constants, to give a positive ρ value for the reaction. Dudkowski and Becker reported[4] that increasing the electron-withdrawing power of Y in $C_6H_5C{\equiv}CY$ increased the rate of reaction with tetraphenylcyclopentadienone.

Since the trifluoromethanesulfonyl group is an unusually potent electron-withdrawing group, as evidenced by its extraordinarily large σ constant,[5] dienophiles with such a substituent might undergo especially facile Diels–Alder reactions. This has been found to be the case for phenyl(trifluoromethanesulfonyl)acetylene.[6]

Results

Phenyl(trifluoromethanesulfonyl)acetylene was prepared by treating the lithium salt of phenylacetylene with trifluoromethanesulfonic acid anhydride. The ir, nmr, and mass spectra support this structural assignment. In addition, controlled catalytic hydrogenation of this acetylene produced *cis*-2-phenyl(1-trifluoromethanesulfonyl)ethylene, and reaction of this acetylene with benzenethiol in the presence of sodium thiophenoxide yielded a crystalline monoadduct.

As illustrated in Tables I and II phenyl(trifluoromethanesulfonyl)acetylene reacts faster with tetraphenylcyclopentadienone[7] and 1,3-diphenylisobenzofuran than any other phenylacetylene investigated. Phenyl(trifluoromethanesulfonyl)acetylene reacts 235 and 5.4 times faster than phenylpropioloyl chloride, the next most reactive acetylene studied,[8] with 1,3-diphenylisobenzofuran at 108° and tetraphenylcyclopentadienone at 174°, respectively. Furthermore, phenyl(trifluoromethanesulfonyl)acetylene reacts readily with cyclopentadiene in toluene at 24.0–24.1° with a second-order rate constant of 2.41×10^{-3} l. mol^{-1} sec^{-1}, whereas phenylpropioloyl chloride undergoes no appreciable reaction with cyclopentadiene at room temperature even after 24 hr. Phenyl(trifluoromethanesulfonyl)acetylene reacts 65 times faster than phenylpropioloyl chloride with 1,3-cyclohexadiene at 81.0–81.5° in benzene (the second-order rate constants were 1.68×10^{-3} and 2.58×10^{-5} l. mol^{-1} sec^{-1}, respectively). Surprisingly, phenyl(trifluoromethanesulfonyl)acetylene even reacts faster with cyclopentadiene than does dimethyl acetylenedicarboxylate. In a competition experiment at room temperature phenyl(trifluoromethanesulfonyl)acetylene proved 1.7 times more reactive than dimethyl acetylenedicarboxylate.[9]

Table I
Second-Order Rate Constants for the Reactions[a] of $C_6H_5C{\equiv}CX$ with Tetraphenylcyclopentadienone

Compd	X	$k_2 \times 10^3$, l. mol^{-1} sec^{-1}
1a	SO_2CF_3	38.7
1b	COCl	15.0
1c	CN	11.0
1d	CHO	2.70[b]
1e	CO_2CH_3	1.56[c]
1f	$Si(CH_3)_3$	*d*

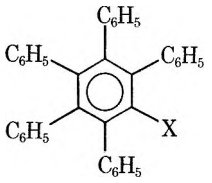
[a] All reactions were run in *p*-cymene as solvent at a temperature of 174.0–174.5° and with an initial concentration of acetylene of 8.10×10^{-2} mol l.$^{-1}$ except for the reaction of **1a** in which the initial concentration of acetylene was 3.85×10^{-2} mol l.$^{-1}$ [b] Dudkowski and Becker report[4] a rate constant of 1.69×10^{-3} l. mol^{-1} sec^{-1} for this reaction. [c] Dudkowski and Becker report[4] a rate constant of 1.27×10^{-3} l. mol^{-1} sec^{-1} for this reaction. [d] There was no appreciable reaction after 48 hr.

Table II
Second-Order Rate Constants for the Reactions[a] of $C_6H_5C{\equiv}CX$ with 1,3-Diphenylisobenzofuran

Compd	X	$k_2 \times 10^3$, l. mol^{-1} sec^{-1}
1a	SO_2CF_3	6.01[b]
		13.6[c]
		27.1[d]
		2940[e]
1b	COCl	12.5
1c	CN	7.04
1d	CHO	1.67
1e	CO_2CH_3	0.690
1f	$Si(CH_3)_3$	*f*

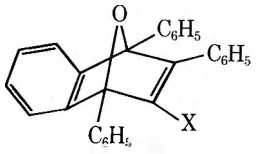
[a] All reactions were run in toluene as solvent at a temperature of 107.5–108.0° except where indicated otherwise. The initial concentration of acetylene was 8.10×10^{-2} mol l.$^{-1}$ for **1a** and **1b** and 2.31×10^{-1} mol l.$^{-1}$ for **1c–f**. [b] Temperature of 23.5°. [c] Temperature of 31.0°. [d] Temperature of 41.0°. [e] Value at 108.0° extrapolated from the data obtained at lower temperatures: E_a = 16.2 kcal mol^{-1} and $A = 4.42 \times 10^9$. [f] There was no appreciable reaction after 48 hr.

Each of the reactions studied kinetically was run on a preparative scale and the product was isolated and characterized. For the reactions with tetraphenylcyclopentadienone, compounds **2a–e** were isolated in good yields. The reactions with 1,3-diphenylisobenzofuran afforded good



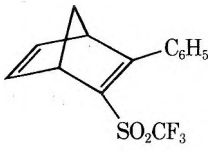
2a, X = SO_2CF_3
b, X = COCl
c, X = CN
d, X = CHO
e, X = CO_2CH_3

yields of adducts **3a–e.** Reaction of phenyl(trifluoromethanesulfonyl)acetylene with cyclopentadiene and 1,3-

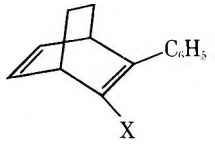


3a, X = SO_2CF_3
b, X = COCl
c, X = CN
d, X = CHO
e, X = CO_2CH_3

cyclohexadiene produced adducts **4** and **5a,** respectively. Phenylpropioloyl chloride and 1,3-cyclohexadiene afforded adduct **5b,** isolated as **5c.**



4



5a, X = SO_2CF_3
b, X = COCl
c, X = CO_2CH_3

Discussion

The remarkable facility with which phenyl(trifluoromethanesulfonyl)acetylene undergoes Diels–Alder reactions is ascribable to the electron-withdrawing electronic effect[10] of the trifluoromethanesulfonyl group. The electronic effect of the sulfonyl group is responsible as well for the enhanced dienophilicity of double bonds appended with chlorosulfonyl[11] or alkyl or aryl sulfonyl groups,[11,12] the marked dienophilicity of aryl sulfonyl cyanides,[13] at least in part for the potent dienophilicity of thiophene 1,1-dioxide,[14] and the high reactivity of chlorosulfonyl isocyanate[15] in cycloaddition reactions. As already pointed out electron-withdrawing groups on the dienophile enhance its dienophilicity. An attractive explanation of this effect is in terms of perturbation molecular orbital theory.[16] The rate of reaction will depend on the magnitude of the energy gap between the highest occupied molecular orbital of the diene and the lowest unoccupied molecular orbital of the dienophile. Thus electron-attracting substituents on the dienophile lower the energy of the lowest unoccupied molecular orbital and, thereby, lessen the energy gap between this orbital and the highest occupied molecular orbital of the diene in the usual Diels–Alder reactions.

Note should be made that the sulfonyl group enhances dienophilicity despite its unfavorable steric and field effects. Nucleophilic substitution at the carbon of α-substituted sulfones is usually extraordinarily difficult[17] (except if the displacement is intramolecular, as in the Ramberg–Bäcklund reaction,[18] or if an exceptionally good leaving group is attached to the α carbon, such as in an α-diazonium ion[19] or α-trifluoromethanesulfonate[20]). This difficulty has been attributed to the steric and field effect of the sulfone group. Nevertheless, in the Diels–Alder reaction these unfavorable effects are overwhelmed by the favorable electronic effect.[21] The reason for this may be that, as suggested by Meyers,[22] the steric effect of the sulfonyl group is small and the field effect of the negatively charged oxygen atoms accounts for the difficulty in effecting nucleophilic displacement at the carbon of α-substituted sulfones. Such a field effect would be expected to strongly disfavor the approach of nucleophiles but the effect on the approach of 1,3-dienes would be relatively modest.

Alternatively, for the Diels–Alder reactions of phenyl(trifluoromethanesulfonyl)acetylene an unsymmetrical transition state[23] could maximize the rate enhancing electronic effect and minimize the steric and field effects of the trifluormethanesulfonyl group. In such a transition state the distance between C-1 of the diene and the carbon bearing the phenyl group in the acetylene would be less than the distance between C-4 of the diene and the carbon bearing the trifluoromethanesulfonyl group. Furthermore, the carbon bearing the trifluoromethanesulfonyl group would have a partial negative charge which the trifluoromethanesulfonyl group could stabilize by inductive and resonance effects.[24] Note, however, that Becker and coworkers[3b,c] proposed that the transition state for the reaction of tetraphenylcyclopentadienone with methyl esters of substituted phenyl propiolates is unsymmetrical but in the opposite sense to that proposed here.

Experimental Section

All reactions were run under anhydrous conditions and under an argon atmosphere Elemental microanalyses were performed by analysts at Spang Microanalytical Laboratory, Ann Arbor, Mich. Molecular weights were determined using a Hewlett-Packard Model 302B vapor pressure osmometer. Infrared spectra were taken on a Perkin-Elmer Model 337 ir spectrophotometer. Proton nmr spectra were recorded using a Varian Model T-60 nmr spectrometer and employing tetramethylsilane as an internal standard. Mass spectra were determined employing a Hitachi Perkin-Elmer Model RMU-6E double focusing mass spectrometer. All melting points are corrected and were determined using a Thomas-Hoover melting point apparatus.

Phenyl(trifluoromethanesulfonyl)acetylene (1a). In a 250-ml three-necked flask, fitted with a pressure-equilibrating addition funnel, a rubber septum, and a gas inlet, were placed *n*-butyllithium (2.74 g, 42.8 mmol) and dry diethyl ether (100 ml). In the addition funnel were placed trifluoromethanesulfonic acid anhydride[25] (12.00 g, 42.8 mmol) and diethyl ether (100 ml). To the solution in the flask, chilled in a Dry Ice–acetone bath, was added freshly distilled phenylacetylene (4.70 ml, 4.36 g, 42.8 mmol) dropwise from a syringe. After stirring for 1 hr at −78°, the solution of anhydride was added dropwise and cautiously over a period of 1 hr to the solution of salt at −78°. The mixture was then stirred 0.5 hr longer at −78°, brought to room temperature, and then stirred for an additional 0.5 hr.

The reaction mixture was extracted successively with several 50-ml portions of water and brine. The combined extracts were washed with ether and the ether layers were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent left a dark oil. Two distillations through a short Vigreux column under reduced pressure (bp 57–62° (0.1 mm)) gave a very lightly colored oil (7.25 g, 72.5%): ir (neat) 2165 (C≡C), 1370 (SO_2), 1195–1230 (CF_3), 1110 (SO_2) cm^{-1}; nmr ($CDCl_3$) δ 7.18–7.72 (m); mass spectrum *m/e* 234 (P), 165 (P − 69), 101 (P − 133).

The product crystallized with difficulty to give a solid of mp 31°. This material darkened on standing at room temperature under nitrogen but could be stored indefinitely when packed in powdered Dry Ice.

Catalytic Hydrogenation of 1a. In a 50-ml three-necked flask were placed glacial acetic acid (10 ml) and 5% palladium-on-charcoal (200 mg). The flask was attached to a catalytic hydrogenator

and the catalyst was saturated with hydrogen. Then **1a** (234 mg, 1.0 mmol) in acetic acid (2 ml) was added by syringe. The system was allowed to take up hydrogen until such uptake ceased. The volume of hydrogen consumed was 37.6 ml (1.68 mmol), corrected to STP.

The catalyst was filtered and the filtrate was taken up in 50 ml of diethyl ether. This solution was extracted successively with several 30-ml portions of saturated aqueous sodium bicarbonate solution, water, and brine. The ether layer was then dried over anhydrous magnesium sulfate. Evaporation of the solvent left a dark oil which was purified by preparative glpc on a 5 ft × 0.25 in. 3% SE-30 on Chromosorb W (80–100 mesh) column: ir (neat) 1370 (SO_2), 1185–1210 (CF_3), 1110 (SO_2), 680 (cis-disubstituted ethylene) cm^{-1}; nmr (CCl_4) δ 7.24–7.78 (m, 6, five aromatic H and one vinyl H), 6.40, 6.20 (d, 1, J = 12 Hz, vinyl H, collapsed to singlet at δ 6.30 when irradiated at δ 7.50); mass spectrum m/e 236 (P), 167 (P − 69), 103 (P − 133).

Anal. Calcd for $C_9H_7F_3O_2S$: C, 45.76; H, 2.97. Found: C, 46.06; H, 2.91.

Addition of Benzenethiol to 1a. In a 25-ml round-bottom flask were placed **1a** (468 mg, 2.0 mmol) and dry tetrahydrofuran (7 ml). The flask was fitted with a pressure-equilibrating addition funnel containing benzenethiol (220 mg, 2.0 mmol), sodium thiophenoxide (10 mg), and tetrahydrofuran (7 ml). The solution of benzenethiol was added dropwise over a period of 0.5 hr to the solution of **1a**.

The solvent was evaporated and diethyl ether (25 ml) was added to the resulting oil. This solution was extracted successively with several 20-ml portions of water and brine. The ether layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was dissolved in benzene (5 ml) and chromatographed on silica gel (35 g). Hexane (100 ml), followed by 2:8 benzene–hexane (300 ml), eluted two bands: one containing benzenethiol and the other phenyl disulfide (both identified by tlc). Additional amounts of 2:8 benzene–hexane eluted the adduct of **1a** with benzenethiol. Evaporation of the solvents followed by two recrystallizations from CCl_4–hexane gave colorless crystals (453 mg, 66%): mp 114–115°; ir (KBr) 1540 (C=C), 1355 (SO_2), 1180–1200 (CF_3), 1105 (SO_2) cm^{-1}; nmr (CCl_4) δ 7.56 (s, 5), 7.40 (s, 5), 5.40 (s, 1); mass spectrum m/e 344 (P), 275 (P − 69), 211 (P − 133), 178 (P − 166), 102 (P − 242).

Anal. Calcd for $C_{15}H_{11}F_3O_2S_2$: C, 52.33; H, 3.20; S, 18.60. Found: C, 52.44; H, 3.18; S, 18.56.

Kinetic Studies. The acetylenes other than **1a** used in the kinetic studies were prepared by known procedures. Phenylpropioloyl chloride was made from phenylpropiolic acid and PCl_5[26] and was converted into both the corresponding amide[27] and methyl ester (bp 55° (0.22 mm)), the latter by addition of 1 equiv each of methanol and triethylamine. Phenylpropiolamide was dehydrated to the corresponding nitrile.[28] Finally, **1f** was prepared from phenylacetylene.[29] Phenylpropiolaldehyde, supplied by Aldrich Chemical Co., was distilled before use.

Tetraphenylcyclopentadienone and 1,3-diphenylisobenzofuran were recrystallized to constant melting point, while cyclopentadiene and 1,3-cyclohexadiene were purified by distillation prior to use.

The solvents (*p*-cymene, toluene, and benzene) were each purified by washing with aqueous potassium permanganate solution, 2 *N* sulfuric acid solution, and water. This was followed by drying over anhydrous magnesium sulfate, heating at reflux over calcium hydride, and then distilling from calcium hydride.

The reagents were dissolved in the appropriate amount of solvent and were placed in a three-necked flask which was fitted with a reflux condenser and a thermometer. Each solution contained an equal concentration of acetylene and diene. The flask was flushed with argon and immediately placed in an insulated bath which had been preheated to a constant temperature. Zero time was taken to be that time at which constant internal temperature was reached.

The reactions were followed by measuring the change in ir absorption in the region 2500 to 2000 cm^{-1} of an accurately diluted (with 100 μl of solvent) measured (30–50 μl) aliquot as a function of time. The size of the aliquot removed depended on the initial concentration of reactant, which varied from 3.35×10^{-2} to 0.231 mol $l.^{-1}$.

The competition between **1a** and dimethyl acetylenedicarboxylate for cyclopentadiene was conducted by placing **1a** (117 mg, 0.5 mmol) and dimethyl acetylenedicarboxylate (71 mg, 0.5 mmol) together with cyclopentadiene (26.4 mg, 0.4 mmol) in ethyl acetate (6.2 ml) in a stoppered 10-ml round-bottom flask under argon. The mixture was stirred for 24 hr at room temperature. The ethyl acetate was evaporated and the residue (224.8 mg) taken up in chloroform (25.0 ml). The ir spectrum of this solution was measured and the concentrations of reactants remaining and products formed were calculated by comparing the absorptions at selected wavelengths with spectra of known concentration for the pure compounds. The wavenumbers chosen were: 2170 cm^{-1} for **1a**, 894 cm^{-1} for dimethyl acetylenedicarboxylate, and 1620 cm^{-1} for dimethyl norborna-2,5-diene-2,3-dicarboxylate. In addition, the amounts of the products formed were determined by isolation. The final amounts of materials were: 0.25 mmol of **1a**, 0.34 mmol of dimethyl acetylenedicarboxylate, 0.24 mmol of **4**, and 0.16 mmol of dimethyl norborna-2,5-diene-2,3-dicarboxylate.

Product Studies. All adducts **2a–5c** were prepared in a similar manner. The diene (3 mmol) and the acetylene (3 mmol) were dissolved in the appropriate solvent (13 ml) and were placed in a round-bottom flask fitted with a reflux condenser. The solvents used were *p*-cymene for **2a–e**, toluene for **3a–e**, and benzene for **4** and **5a,b**. The solution was then placed under an argon atmosphere and heated at reflux for 48 hr with the exception of **4** which was maintained at room temperature for 24 hr and **5b** which was heated at reflux for 100 hr.

After removal of the solvent the crude product was recrystallized to constant melting point. Toluene was used as recrystallization solvent for **2a–e**, and **3a–e**, while petroleum ether was used for **4**. Adducts **5a** and **5c** were purified by chromatography as described below. **5a** was then recrystallized from petroleum ether, while **5c** was distilled.

The adduct from dimethyl acetylenedicarboxylate and cyclopentadiene was prepared according to the literature.[30]

Pentaphenyl Trifluoromethanesulfone (2a): 1.55 g (87.8%); mp 360–362°; ir (KBr) 1360 (SO_2), 1205 (CF_3), 1110 (SO_2) cm^{-1}; nmr ($CDCl_3$) δ 7.08 (s, 10), 6.78 (s, 15); mass spectrum m/e 590 (P), 521 (P − 69), 457 (P − 133).

Anal. Calcd for $C_{37}H_{25}F_3O_2S$: C, 75.26; H, 4.24; S, 5.42. Found: C, 75.39; H, 3.99; S, 5.18.

Pentaphenylbenzoyl Chloride (2b): 1.29 g (83.0%); mp 285–286°; ir (KBr) 1730 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 7.16 (m, 10), 6.82 (m, 15); mass spectrum m/e, no parent at 520, 485 (P − 35), 457 (P − 63). This material was converted to **2e**. The spectra (ir and nmr) of this material are the same as those of authentic **2e**. Furthermore, the mixture melting point with authentic **2e** is undepressed.

Pentaphenylbenzonitrile (2c): 1.21 g (83.5%); mp 280–281° (lit.[31] mp 271–272°).

Pentaphenylbenzaldehyde (2d): 1.30 g (89.4%); mp 253° (lit.[4] mp 265°).

Methyl Pentaphenylbenzoate (2e): 1.37 g (88.6%); mp 344–345° (lit.[4] mp 342°).

Trifluoromethyl (1,2,4-Triphenyl-1,4-epoxynaphthalene)-3-sulfone (3a): 1.39 g (86.2%); mp 192–193°; ir (KBr) 1570 (C=C), 1355 (SO_2), 1185–1200 (CF_3), 1105 (SO_2) cm^{-1}; nmr ($CDCl_3$) δ 7.02–7.80 (m); mass spectrum m/e, no parent at 504, 371 (P − 133).

Anal. Calcd for $C_{29}H_{19}F_3O_3S$: C, 69.05; H, 3.77; S, 6.35; mol wt, 504. Found: C, 69.05; H, 3.91; S, 6.25; mol wt, 510.

1,2,4-Triphenyl-1,4-epoxynaphthalene-3-carboxylic Acid Chloride (3b): 0.97 g (74.5%); mp 177–178° dec; ir (KBr) 1710–1765 broad doublet (C=O), 1570 (C=C) cm^{-1}; nmr (CCl_4) δ 7.02–7.96 (m); mass spectrum m/e, no parent at 434, 399 (P − 35), 371 (P − 63), 270 (P − 164).

Anal. Calcd for $C_{29}H_{19}ClO_2$: C, 80.18; H, 4.38; Cl, 8.07; mol wt, 434. Found: C, 80.10; H, 4.41; Cl, 8.04; mol wt, 431.

1,2,4-Triphenyl-1,4-epoxynaphthalene-3-carbonitrile (3c): 1.02 g (85.5%); mp 189–190° dec; ir (KBr) 2190 (C≡N), 1570 (C=C) cm^{-1}; nmr ($CDCl_3$) δ 7.02–7.84 (m); mass spectrum m/e 397 (P), 319 (P − 78), 270 (P − 127).

Anal. Calcd for $C_{29}H_{19}NO$: C, 87.66; H, 4.79; N, 3.53; mol wt, 397. Found: C, 87.64; H, 4.93; N, 3.29; mol wt, 383.

1,2,4-Triphenyl-1,4-epoxynaphthalene-3-carboxaldehyde (3d): 1.04 g (87.0%); mp 161–162°; ir (KBr) 2810 (C(=O)H), 1655 (C=O), 1570 (C=C) cm^{-1}; nmr ($CDCl_3$) δ 9.70 (s, 1), 7.00–7.98 (m, 19); mass spectrum m/e 400 (P), 372 (P − 28), 270 (P − 130).

Anal. Calcd for $C_{29}H_{20}O_2$: C, 87.00; H, 5.00; mol wt, 400. Found: C, 86.91; H, 5.29; mol wt, 413.

Methyl 1,2,4-Triphenyl-1,4-epoxynaphthalene-3-carboxylate (3e): 1.12 g (86.5%); mp 81–82°; ir (KBr) 1700 (C=O), 1570 (C=C) cm^{-1}; nmr (CCl_4) δ 6.92–7.88 (m, 19), 3.40 (s, 3); mass spectrum m/e, no parent at 430, 399 (P − 31), 371 (P − 59), 270 (P − 160).

Anal. Calcd for $C_{30}H_{22}O_3$: C, 83.72; H, 5.12; mol wt, 430. Found: C, 83.58; H, 5.32; mol wt, 445.

Trifluoromethyl 3-Phenylbicyclo[2.2.1]hepta-2,5-dienyl 2-Sulfone (4): 0.846 g (94.0%); mp 75–76°; ir (KBr) 1590, 1560 (C=C), 1365 (SO_2), 1172–1205 (CF_3), 1110 (SO_2) cm^{-1}; nmr (CCl_4) δ 7.40 (s, 5), 7.00 (m, 2), 3.99, 4.18 (d, 2, J = 11 Hz), 2.10, 2.20, 2.41, 2.56 (m, 2); mass spectrum m/e 300 (P), 231 (P − 69), 167 (P − 133), 66 (P − 234).

Anal. Calcd for $C_{14}H_{11}F_3O_2S$: C, 56.00; H, 3.67; S, 10.67; mol wt, 300. Found: C, 56.02; H, 3.82; S, 10.76; mol wt, 300.

Trifluoromethyl 3-phenylbicyclo[2.2.2]octa-2,5-dienyl 2-sulfone (5a) was eluted with 200 ml 8:2 hexane–benzene from a column of 35 g of silica gel: 0.674 g (71.5%); mp 71–72°; ir (KBr) 1620, 1580 (C=C), 1355 (SO_2), 1175–1200 (CF_3), 1118 (SO_2) cm^{-1}; nmr ($CDCl_3$) δ 7.32 (m, 5), 6.50 (m, 2), 4.00, 4.35 (broad d, 2), 1.65 (m, 4); mass spectrum m/e 314 (P), 286 (P − 28), 260 metastable (corresponds to 314 → 286), 245 (P − 69), 217 (P − 97), 181 (P − 133), 153 (P − 161).

Anal. Calcd for $C_{15}H_{13}F_3O_2S$: C, 57.32; H, 4.14; S, 10.19. Found: C, 57.37; H, 4.16; S, 10.11.

Methyl 3-Phenylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (5c): from 1,3-cyclohexadiene and phenylpropioloyl chloride, followed by methanol and triethylamine; purified by two successive column chromatographs each on 35 g of silica gel. The first involved elution with 200 ml of benzene, while the second involved elution with 500 ml of 1:1 hexane–benzene. The product was the second band eluted in the second chromatography: 0.257 g (35.7%); ir (neat) 1695 (C=O), 1620, 1605 (C=C) cm^{-1}; nmr (CCl_4) δ 7.20 (m, 5), 6.35 (m, 2), 3.90, 4.20 (broad d, 2), 3.55 (s, 3), 1.60 (m, 4); mass spectrum m/e 240 (P), 212 (P − 28), 181 (P − 59), 152 (P − 88).

Acknowledgment. The authors gratefully acknowledge support of this research by the National Science Foundation. D.L.S. expresses his gratitude for the award of an NDEA Title IV Fellowship for September 1973–August 1974. The authors also thank Mr. Edward G. Kabbas for determining the molecular weights reported in this paper.

Registry No.—**1a,** 52843-77-3; 1a monoadduct with benzenethiol, 52855-91-1; **1b,** 7299-58-3; **1c,** 935-02-4; **1d,** 2579-22-8; **1e,** 4891-38-7; **2a,** 52843-78-4; **2b,** 52843-79-5; **2c,** 52843-80-8; **2d,** 52843-81-9; **2e,** 2857-85-4; **3a,** 52843-82-0; **3b,** 52920-69-1; **3c,** 52843-83-1; **3d,** 52843-84-2; **3e,** 52843-85-3; **4,** 52843-86-4; **5a,** 52843-87-5; **5c,** 52843-88-6; tetraphenylcyclopentadienone, 479-33-4; 1,3-diphenylisobenzofuran, 5471-63-6; cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4; trifluoromethanesulfonic acid anhydride, 358-23-6; phenylacetylene, 536-74-3; *cis*-2-phenyl-1-trifluoromethanesulfonylethylene, 52843-89-7; benzenethiol, 108-98-5.

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Cleavage of Sulfur–Sulfur Bonds with Sodium Hydrogen Selenide

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Received September 20, 1974

Sodium hydrogen selenide is shown to be an effective reagent for reduction of alkyl, aryl, aralkyl, and functionally substituted disulfides to thiols under mild conditions in protic solvents. Two-electron transfer from the hydrogen selenide anion, which promotes the cleavage of the S–S bond with concomitant production of elemental selenium, is found to occur only in a narrow pH range. Organic thiosulfates (Bunte salts) also give thiols through the intermediacy of the corresponding disulfide on reaction with sodium hydrogen selenide.

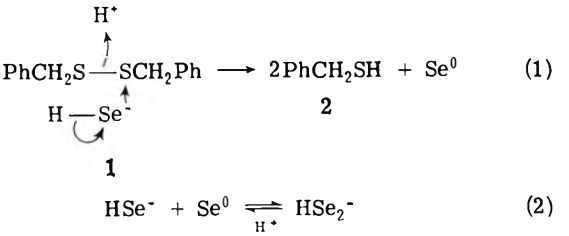
The nucleophilic cleavage of the sulfur–sulfur bond in both organic and inorganic compounds has been of considerable interest for many years and has been the subject of several reviews.[1-5] Studies of the reaction of organic thiosulfates with previously uninvestigated nucleophiles have recently been reported.[6,7] In general, reactions of nucleophiles with organic disulfides result in production of the corresponding thiol and sulfenyl-substituted nucleophile, whereas, in reactions with organic thiosulfates, nucleophiles produce sulfenyl-substituted nucleophile and sulfite ion, which may react further under the reaction conditions.[6,7] Among a myriad of reducing agents other than nucleophiles which have been used to cleave the S–S linkage are lithium aluminum hydride,[8] sodium borohydride,[9] and sodium borohydride–aluminum chloride.[10] We report here a new reagent for the cleavage of sulfur–sulfur bonds, namely, sodium hydrogen selenide. Its reactions with representative organic disulfides and thiosulfates are described.

The study of reactions of the hydrogen selenide anion has been limited, partly because of the inconvenience of standard generation procedures for the anion and partly because of the facility of air oxidation of the anion to elemental selenium, rendering handling of solutions of the material difficult. We present here a study of nucleophilic behavior of this anion, the techniques involved in which are based on the new preparative procedure for sodium hydrogen selenide from elemental selenium and sodium borohydride devised by Klayman and Griffin.[11] This procedure allows the rapid and convenient preparation of aqueous or alcoholic solutions of sodium hydrogen selenide without the necessity of generating dangerously toxic hydrogen selenide gas.

Results and Discussion

Reaction of Sodium Hydrogen Selenide with Organic Disulfides. The reactions of sodium hydrogen selenide with organic disulfides in ethanol solution were studied as follows. After a solution of the reactants had been allowed to stand in an inert atmosphere, dilute hydrochloric acid was added, and elemental red selenium was noted to precipitate immediately from the reaction mixture. Examination of the organic products then allowed assessment of the efficiency of the reaction.

The reactions of dibenzyl disulfide (1), which was chosen as a model compound, with sodium hydrogen selenide, hydrogen selenide, and sodium diselenide are summarized in Table I. Dibenzyl disulfide (1) was shown to undergo reduction to α-toluenethiol (2) by hydrogen selenide anion (expt 1 and 2) A single molar quantity of sodium hydrogen selenide, however, only induced partial reduction of 1 (expt 1), whereas a 50% excess gave total conversion of 1 to 2 (expt 2). The reaction may be viewed as proceeding as illustrated in eq 1, involving a two-electron reduction of the disulfide linkage to produce 2 mol of thiol 2 and 1 g-atom of elemental selenium. The inefficiency of the molar quantity of NaHSe in promoting the reduction may be explained by the forward reaction of eq 2. As elemental selenium is produced as indicated in eq 1, it may interact with unreacted NaHSe to produce a di- or polyselenide anion. That such a process occurs, albeit inefficiently, at the natural pH of sodium hydrogen selenide is indicated by the development of the intense red-brown color (characteristic of polyselenide anions) which is noted shortly after the solutions are mixed. This process would apparently render the sodium hydrogen selenide less active in the reduction process. The selenium thus bound would then be regenerated on acidification (eq 2). Use of excess NaHSe in the reaction gives complete reduction of 1 to 2 and 1 g-atom of elemental selenium, indicating that the competing process may be offset by use of larger quantities of NaHSe. To determine if the diselenide anion was the reducing species in the reaction, sodium diselenide was generated and was combined with 1. As shown in Table I (expt 4 and 5), reduction does indeed take place but incompletely. Apparently the H_2Se produced on disproportionation of the diselenide anion may promote the cleavage, but the competing loss of H_2Se, purged from the solution, reduces its effectiveness as a reducing agent.



(1)

(2)

Hydrogen selenide gas, generated externally and bubbled through a solution of 1, had no reducing effect on 1 at its natural pH (expt 3); however, adjusting the hydrogen ion concentration of the hydrogen selenide saturated solution of 1 to pH 7 with aqueous sodium hydroxide caused precipitation of elemental selenium and complete reduction of 1 to 2. These experiments indicate that the reduction is pH dependent and that the pH range necessary to the reaction may be approached from either the high or low pH side.

The pH dependence of the reduction of the disulfide is not surprising in view of reports of variance of the potential E of thiol–disulfide couples. For example, the potential of the cystine–cyteine couple varies from +0.034 to −0.565 V over a pH range of 0–12 at 25°.[12] Similarly, the oxidation of negative selenium species varies with pH, as the potential for the hydrogen selenide–selenium couple has been calculated to be +0.36 V and that of the selenide (Se^{2-})–selenium couple to be +0.78 V.[13] Comparison of these potential values to those of the system at hand may be only qualita-

Table I
Treatment of Dibenzyl Disulfide (1) with Selenide Reagents

$$C_6H_5CH_2SSCH_2C_6H_5 + HSe^- \xrightarrow{H^+} 2C_6H_5CH_2SH + Se^0$$
1 **2**

Expt no.	Reagent	Moles of reagent/ mol of 1	Yields of organic products, % Absolute	Thiol (2)	Disulfide 1	Gram-atoms[a] of Se[0] obtained after acidification
1	HSe^-	1.00	92	59	41	0.93
2	HSe^-	1.50	99	100	0	1.00
3	H_2Se	5.00	94	0	100	*b*
4	Se_2^{2-}	1.00	94	88	12	2.00
5	Se_2^{2-}	1.50	96	70	30	2.74

[a] Gram-atoms of Se[0] obtained per mole of starting **1**. [b] Not applicable.

Table II
Treatment of Disulfides with Excess Sodium Hydrogen Selenide

$$RSSR + 2HSe^- \xrightarrow{2H^+} 2RSH + Se^0 + H_2Se$$

Expt no.	R	Starting disulfide, mmol	Thiol obtained, mmol	Thiol obtained, %	Se obtained, g-atoms[a]
6	C_6H_5	7.39	14.1	96[b,c]	0.99
7	*tert*-C_4H_9	11.2	0[d]	0	0
8	$HO_2CCH(NH_2)CH_2$	8.32[e]	16.1[f]	97[g]	0.97
9	*n*-$C_{10}H_{21}$	5.65	10.7	95[b,h]	1.00
10	$HN{=}C(NH_2)$ (HCl)	8.97[e]	18.0[i]	101[b]	0.94
11	$H_2NCH_2CH_2$ (HCl)	10.0[e]	19.2[f]	97[g]	0.93

[a] Gram-atom of Se[0] obtained per mole of starting disulfide. [b] Yield determined by isolation of product. [c] Identity and thiol content verified by nmr analysis. [d] No product obtained even on refluxing the reaction mixture for 16 hr or allowing it to stand for 3 months. [e] Reaction conducted in water. [f] Product isolated as HCl salt. [g] Yield determined by titration of an aliquot with 1 *N* I_2 solution. Identity verified by ir and melting point. [h] Thiol content verified by titration with 1 *N* I_2 solution. [i] Thiourea isolated and identified by ir and melting point.

tive, however, since the dissociation constants of the species involved would undoubtedly be different in the alcohol–water solvents used than in the aqueous systems on which the calculations were based. Nevertheless, interpolation of these values reported to the pH corresponding to the one obtained for precipitation of selenium, assuming that values for the cystine–cysteine couple would parallel those for the 1–2 couple, indicates that the oxidation–reduction process would take place. Of major interest and importance, moreover, is the extremely rapid rate observed for the redox process.

The generality of the reduction of disulfides by sodium hydrogen selenide was investigated, and the results are listed in Table II. Essentially quantitative conversion of disulfide to thiol was noted in the following reactions: diphenyl disulfide to benzenethiol (expt 6), cystine to cysteine (expt 8), didecyl disulfide to 1-decanethiol (expt 9), diformamidine disulfide to thiourea (expt 10), and bis(2-aminoethyl) disulfide to 2-mercaptoethylamine (expt 11). The quantities of selenium recovered on acidification corresponded very well to the theoretical values (see Table II). The sterically hindered di-*tert*-butyl disulfide (expt 7) shows negligible reduction to 2-methyl-2-propanethiol under the reaction conditions, even if the pH-adjusted solution of the reactants is heated under reflux for 16 hr or is allowed to stand for 3 months. Such a lack of lability of this compound to reduction is not surprising in view of the arrangement of the atoms of di-*tert*-butyl disulfide in the energetically favored anti conformation of the C–S–S–C bonds. A Fisher–Hirschfelder–Taylor model of the molecule indicates that there exists only a 1.9-Å opening to approach the S–S bond in the most favored conformation which has no eclipsing sulfur–methyl interactions. Even if this eclipsing is permitted, only a 3.0-Å opening exists. Since the hydrogen selenide anion is undoubtedly larger (unprotonated selenide anion has a diameter in crystals of 3.96 Å),[14] the avenue of approach of the anion toward the S–S bond is severely restricted. Other potent reducing agents also have difficulty in cleaving the sulfur–sulfur bond of di-*tert*-butyl disulfide; indeed, even lithium aluminum hydride reduces this disulfide only slowly in boiling tetrahydrofuran.[8]

Thus sodium hydrogen selenide is useful for conversion of aryl, alkyl, aralkyl, and functionally substituted disulfides to the corresponding thiols under mild conditions. This method should find synthetic utility under conditions in which cleavage of S–S bonds, without disturbing other reducible functional groups, is desired. No contamination of the organic products by selenium-containing materials has been encountered with this method. The facile retrieval of the selenium utilized, which may be used to regenerate sodium hydrogen selenide, is an attractive feature of the reaction. Essentially sodium borohydride is the only material consumed, and synthetically the reaction sequence may be viewed as requiring selenium as a catalyst. In contrast, our experience is that sodium borohydride alone, in addition to reducing other functional groups present, requires higher temperatures and longer reaction times to cleave the S–S bond of disulfides than does sodium hydrogen selenide.

Reaction of Sodium Hydrogen Selenide with Organic Thiosulfates (Bunte Salts). The reaction of sodium benzyl thiosulfate (3) with sodium hydrogen selenide was found, after acidification, to give dibenzyl disulfide (1) and α-toluenethiol (2), the relative amounts of which were found to vary according to the sodium hydrogen selenide: Bunte salt ratio (Table III). Trends in Table III deserve comment. First, 0.5–1 mol of sodium hydrogen selenide converts 1 mol of the thiosulfate **3** entirely to disulfide **1** (expt 12 and 13), whereas at least 1.5 mol of the reagent are needed to give disulfide-free thiol **2** (expt 16, 18–20). Sec-

Table III
Treatment of Sodium Benzyl Thiosulfate (3) with Sodium Hydrogen Selenide

$$\underset{\mathbf{3}}{C_6H_5CH_2SSO_3^-} + HSe^- \xrightarrow{H^+} \underset{\mathbf{2}}{C_6H_5CH_2SH} + \underset{\mathbf{1}}{C_6H_5CH_2SSCH_2C_6H_5}$$

Expt no.	Moles of HSe^-/ mol of 3	Yields of organic products, % Absolute	Thiol 2	Disulfide 1	Se obtained, g-atoms[a] Before acidification	After acidification
12	0.50	97	0	100	0.47	0
13	0.55	100	0	100	0.50	0
14	1.00	101	0	100	0.85	0.07
15	1.09	99	8	92	0.91	0.04
16	1.50	98	92	8	0.30	0.98
17	1.50	96	0[b]	100[b]	*c*	*c*
18	1.64	94	100	0	0.16	0.93
19	2.00	91	100	0	0.03	1.50
20	2.19	99	100	0	*d*	*d*

[a] Gram-atoms of selenium obtained per mole of starting Bunte salt. [b] Acid work-up was not employed. At the point at which acid would have been added, the solvent was evaporated, and the organic product was obtained by leaching the residue with ether. [c] Not applicable. [d] Not determined.

ond, the quantity of selenium recovered from the alcohol-insoluble materials collected before acidification represents essentially complete recovery of all selenium used (expt 12–15) in the lower ratios. Finally, the amounts of selenium decrease as the sodium hydrogen selenide:thiosulfate ratio reaches higher values (expt 16, 18, and 19). The trends in product and selenium stoichiometry noted may be explained by eq 3 and 4 in Scheme I.

Scheme I

$$\underset{\mathbf{3}}{PhCH_2SSO_3^-} + HSe^- \longrightarrow \underset{\mathbf{4}}{PhCH_2SSe^-} + HSO_3^- \quad (3)$$

$$PhCH_2S{-}SO_3^- \longrightarrow PhCH_2S^- + SO_3^{2-} \quad (4)$$
$$PhCH_2S{-}Se^- \qquad\quad PhCH_2S{-}Se^0$$
$$\mathbf{1}$$

$$5H^+ + 3HSe^- + SO_3^{2-} \longrightarrow H_2S + 3Se + 3H_2O \quad (5)$$

The initiating reaction in the sequence involves thiophilic attack by hydrogen selenide anion on the sulfenyl sulfur atom of **3**, forming the thioselenol anion **4** and bisulfite ion (eq 3). The intermediate **4** then interacts with unreacted **3**, in a four-centered process analogous to that proposed for the reaction of Bunte salts with hydrodisulfides,[7] to give dibenzyl disulfide, sulfite ion, and elemental selenium (eq 4). An alternative to eq 4, which may not be entirely ruled out, involves the extrusion of elemental selenium from the thioselenol anion **4** to give the anion of **2**. The latter could subsequently attack **3** to give **1** and sulfite ion. The rate of such an extrusion process, however, might be expected to be slower than that observed for the reaction. In our view, this alternate mechanism is less attractive than that shown in eq 4.

In the presence of excess sodium hydrogen selenide, the previously discussed reaction depicted in eq 1 may take place. The disulfide **1** undergoes a two-electron reduction to give 2 mol of α-toluenethiol (**2**) and 1 g-atom of elemental selenium. That the proton participation as shown in eq 1 is necessary to the reduction was demonstrated by performing the reaction without adding acid and isolating only dibenzyl disulfide (**1**) (expt 17).

At higher sodium hydrogen selenide:thiosulfate ratios (*i.e.*, above 0.5:1.0), the stoichiometry of the reaction becomes less clear. At first, larger quantities of elemental selenium are obtained before acidification, indicating that some process other than simple disulfide formation has taken place. Such a process is illustrated in eq 5. Sulfite ion produced as in eq 3 and 4 may oxidize the negative selenium species to elemental selenium while itself being reduced to hydrogen sulfide. The oxidation of hydrogen selenide anion by sulfite accounts for the larger than theoretical quantities of selenium noted on acidification in expt 14 and 15. The production of hydrogen sulfide rather than hydrogen selenide on acidification as shown in eq 5 was verified in one experiment by scrubbing the purge gases through a saturated cadmium(II) chloride trap to produce mustard yellow cadmium(II) sulfide.

As the hydrogen selenide:Bunte salt ratio becomes greater than 1:1, decreasing quantities of selenium are produced before acidification (expt 16, 18, and 19). This observation may be explained if the equilibrium represented in eq 2 comes into play. The hydrogen selenide anion, present in these experiments at higher concentration, reacts with Se^0 and thus causes the elemental selenium produced in eq 4 to dissolve to give a deeply colored solution of red-brown hydrogen diselenide anion. Apparently this process competes with oxidation of hydrogen selenide by sulfite. On acidification, the diselenide species then disproportionates, giving elemental selenium and hydrogen selenide as indicated in eq 2. That the acidic disproportionation occurs as shown was demonstrated by acidifying a solution of sodium diselenide[11] to cause the precipitation of elemental selenium and evolution of hydrogen selenide gas. The elemental selenium collected represented an essentially quantitative yield according to the stoichiometry represented in eq 2.

The pH dependence of the reaction (*vide supra*) was investigated as described below. The reaction of 7.61 mmol of sodium benzyl thiosulfate (**3**) with 11.4 mmol of sodium hydrogen selenide was performed as previously described. The procedure was followed as usual until the acidification stage, and at this point, the reaction mixture was titrated with standard hydrochloric acid. The change in the pH of the solution was monitored, and the results are given in Figure 1. The pH values, taken in a methanol–ethanol–water medium, are reported as apparent pH; however, since the electrode had been soaked in water for several months, the values are probably near the actual ones.[15] An indication of the probable reliability of these values is provided by comparing the initial pH (8.2) of this alcoholic system to that obtained in a purely aqueous solution (pH 8.5).[16]

Adding acid to the initially buffered solution caused elemental selenium to precipitate at the point corresponding to the addition of sufficient acid to protonate the originally present **3**. Because of the complicating influence of sulfite

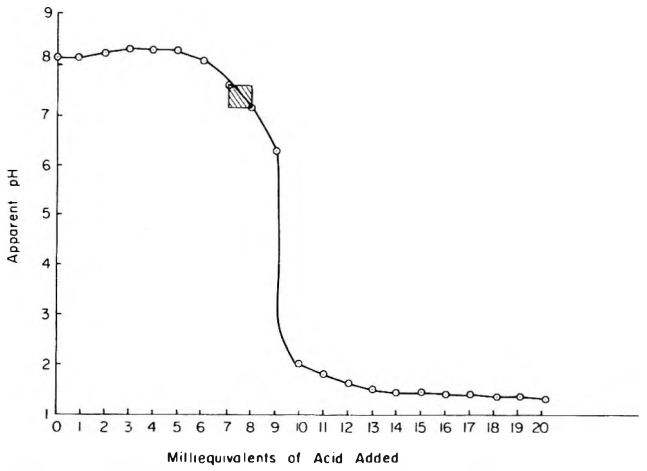


Figure 1. Apparent pH of an alcoholic solution of 7.61 mmol of sodium benzyl thiosulfate (3) treated with 11.4 mmol of solution hydrogen selenide as a function of added acid. (The shaded area indicates the point at which selenium precipitated from the solution.)

ion, the point of precipitation and the quantity of selenium may or may not have significance; however, the important fact to note is the extremely narrow pH range at which the reduction takes place. In contrast, it was noted by us that treatment of **3** with 2 mol of sodium hydrogen *sulfide* produced the disulfide **1** as the sole organic product.

To ascertain the utility of sodium hydrogen selenide in the reduction of Bunte salts to thiols, an investigation was conducted of the reaction of 2-aminoethanethiosulfuric acid (**5**) with the reagent. Attempts to reduce **5** to the corresponding thiol with sodium borohydride have been unsuccessful.[16] Treatment of **5** with sodium hydrogen selenide in aqueous solution, however, gave a quantitative conversion to the thiol product 2-mercaptoethylamine (**6**) (eq

$$\underset{\mathbf{5}}{H_2NCH_2CH_2SSO_3H} + HSe^- \longrightarrow \underset{\mathbf{6}}{H_2NCH_2CH_2SH} + Se + HSO_3^- \quad (6)$$

6). The reduction, in contrast with the case of **3**, required a 4 molar quantity of sodium hydrogen selenide because of the presence of the by-product, inorganic sulfite. The latter, being soluble in the aqueous medium, consumes some of the sodium hydrogen selenide necessary for cleavage of the intermediate disulfide (cystamine) and thus results in high recoveries of selenium. With only 2 mol of sodium hydrogen selenide per mole of thiosulfate, a maximum conversion to thiol of 28% was obtained, indicating that the sulfite oxidation of sodium hydrogen selenide is faster than is the cleavage of the intermediate disulfide by the latter. That the amine groups of **5** were not interfering with the stoichiometry of the reaction was shown by treating 1,6-hexanediamine with 2 mol of sodium hydrogen selenide. No selenium was noted to precipitate on acidification of the reaction mixture.

These experiments demonstrate that sodium hydrogen selenide may be a useful reagent for conversion of Bunte salts to thiols under mild conditions.

Experimental Section

Infrared spectra were taken on a Beckman IR-5 spectrophotometer in KBr pellets, and nmr spectra were taken on a Varian Associates A-60 spectrometer in $CDCl_3$ solution. Chemical shifts are reported as δ (ppm) relative to the internal standard TMS. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Iodometric titrations were carried out using Fisher Scientific 1.0 *N* iodine. The pH measurements were determined with a Beckman Zeromatic meter.

All of the reactions were conducted under an inert atmosphere to prevent air oxidation of the selenide species. The effluent gases from the reactions were scrubbed in two 5% lead(II) acetate traps.

Reactions of Dibenzyl Disulfide (1) with Sodium Hydrogen Selenide. Solutions of sodium hydrogen selenide[11] were generated as follows. To the desired number of gram-atoms of elemental selenium was added a 10 mol % excess of sodium borohydride. Ethanol (100 ml) was added, and the mixture was stirred until homogeneous. To the resulting clear solution was added a solution of 1.00 g (4.06 mmol) of **1** in 100 ml of ethanol. The mixture was stirred for 1 hr, and 15 ml of 1.2 *N* HCl was added. The mixture was stirred and purged for a minimum of 1 hr, and the precipitated selenium was collected, washed with methanol, ethanol, and ether, and dried (*cf.* Table I). The combined filtrate and washings were added to 350 ml of water, and the mixture was extracted with $CHCl_3$, dried ($MgSO_4$), and evaporated to give the organic product(s). In cases in which mixtures of benzyl mercaptan and dibenzyl disulfide were obtained, the relative amounts were determined by nmr utilizing multiple comparative integrations of the SH proton signal at δ 1.57 and the $-CH_2S-$ signals at δ 3.3–3.6. The results of these experiments are summarized in Table I.

Reactions of Dibenzyl Disulfide (1) with Sodium Diselenide. A solution of the desired quantity of sodium diselenide in 150 ml of ethanol was prepared from elemental selenium and sodium borohydride according to the recently described procedure.[11] After the excess H_2Se had been purged from the refluxing solution with argon, the reddish brown solution was cooled to room temperature, and 2.00 g (8.13 mmol) of **1** in 100 ml of degassed ethanol was added. The resulting solution was stirred for 45 min and 50 ml of 1.2 *N* HCl was added. Precipitation of selenium was immediate, and the mixture was stirred and purged with argon for 1 hr. The selenium was collected, and the filtrate was treated as above. The results of these experiments appear in Table I.

Treatment of Dibenzyl Disulfide (1) with Hydrogen Selenide. A. In a three-necked, round-bottomed flask, fitted with a pressure-equalizing dropping funnel, an argon purge tube, and a gas outlet tube, were allowed to interact with stirring 1.58 g (20 mg-atoms) of elemental selenium and 0.83 g (22 mmol) of sodium borohydride in 100 ml of ethanol. The gas outlet tube was directed into an ice bath cooled flask containing 1.00 g (4.06 mmol) of **1** in 100 ml of 10% water in ethanol. To the clear solution resulting from the reaction of selenium and borohydride was added dropwise, over a period of 1 hr, 100 ml of 1 *N* HCl. The H_2Se thus produced was bubbled through the solution of **1**. The H_2Se saturated solution of **1** was stirred and purged with argon for 2 hr, after which the solvent was removed under reduced pressure to give 937 mg (94%) of recovered dibenzyl disulfide, identified by ir and nmr criteria.

B. The above experiment was repeated with 1.0 ml of concentrated HCl added to the ethanolic solution of **1**. No change was noted in the solution when it was saturated with H_2Se. With the electrode of a pH meter inserted, 10% NaOH was added dropwise. As pH 7 was approached, precipitation of selenium, which subsequently redissolved at pH ~8, was noted. Addition of 10% NaOH was continued to pH 9.5, and the solution was allowed to stand for 5 min. To the resulting reddish brown solution was added 1 *N* HCl dropwise. At pH 7 precipitation of selenium was noted. The pH was further lowered to 5, and the precipitated selenium (311 mg, 3.94 mg-atoms, 97%) was collected and treated as above. The filtrate was added to 350 ml of water and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ extract gave 0.994 g (8.02 mmol, 99%) of **2**, pure by nmr criteria.

Reactions of Other Disulfides with 2 Equiv of Sodium Hydrogen Selenide. Aqueous (or ethanolic) solutions containing 2 mol of sodium hydrogen selenide in 100 ml of solvent per mole of starting disulfide were prepared from elemental selenium and sodium borohydride as described above.[11] When the reaction of selenium with sodium borohydride was complete, the disulfide dissolved in 50 ml of argon-purged water (or ethanol) was added to the sodium hydrogen selenide solution with stirring. In all cases, with the exception of that of di-*tert*-butyl disulfide, the solution immediately turned deep red-brown. After the reaction mixture had been stirred for at least 1 hr, a volume of argon-purged ~1.2 *N* HCl sufficient to bring the pH to <2 was added. (*Caution!* Beware of toxic H_2Se evolution during acidification.) The solution was purged with argon for at least 1 hr and the precipitated elemental selenium (*cf.* Table II) was collected. The combined filtrate and washings were treated in one of the following ways. (a) In the cases beginning with diphenyl disulfide, di-*tert*-butyl disulfide, and di-

decyl disulfide (expt 6, 7, and 9, respectively), the filtrate was added to 350 ml of water, and the product (or unreacted starting material) was isolated by extraction with $CHCl_3$. The yields and thiol content of the products were determined as indicated in the summary of these experiments provided by Table II. (b) In the cases of cystine (expt 8) and of cystamine dihydrochloride (expt 11), an aliquot of the filtrate was titrated with 1 N I_2 to determine its thiol content. The remainder of the filtrate was evaporated to give a solid residue which was triturated with ethanol. Filtration and evaporation of the filtrate gave in each case colorless solids which were shown to be cysteine hydrochloride and 2-mercaptoethylamine hydrochloride, respectively, by the methods indicated in Table II. (c) In the case of diformamidine disulfide dihydrochloride (expt 10), the filtrate was evaporated under reduced pressure, and the residue was triturated with ethanol. After filtration, evaporation of the ethanol gave thiourea.

Reactions of Sodium Benzyl Thiosulfate (3) with Sodium Hydrogen Selenide. A. Solutions containing the desired quantities of sodium hydrogen selenide in 100 ml of ethanol were prepared from elemental selenium and sodium borohydride as described above for **1**. When all of the selenium had dissolved, a solution of 1.72 g (7.61 mmol) of **3** in 50 ml of degassed methanol was added with stirring. After the mixture was stirred for at least 1 hr, the precipitated inorganic material was collected, washed with ethanol and ether, and was found to consist of a mixture of sodium sulfite and elemental selenium. The latter was quantitated by washing the precipitate with about 50 ml of water and collecting the residual selenium (*cf.* Table III).

The deep reddish brown filtrate from the above-described procedure was acidified with 15 ml of 1.2 N HCl and the mixture was purged with argon for a minimum of 1 hr. The effluent gases were passed through a 5% lead(II) acetate trap. The precipitated elemental red selenium was collected. The combined filtrate and washings were treated as described above for **1**, and the yields and organic product ratios are given in Table III.

B. With pH Monitoring during Acidification. A solution of 1.72 g (7.61 mmol) of **3** in 50 ml of degassed methanol was added to a solution of sodium hydrogen selenide generated in 100 ml of ethanol from 902 mg (11.4 mg-atoms) of selenium and 976 mg (12.6 mmol) of sodium borohydride. The mixture was stirred for 1 hr, and the precipitated solid (834 mg) was collected and treated as described above to give 168 mg (2.13 mg-atoms) of elemental selenium. To the original filtrate and washings was added 1.00 N standard HCl, and the pH was monitored after the addition of each 1 ml of acid. The change in apparent pH *vs.* addition of acid is plotted in Figure 1. Precipitation of selenium was noted to occur during the addition of the eighth milliequivalent of HCl and between apparent pH 7.6 and 7.2. Selenium (564 mg, 7.14 mg-atoms) was collected after acidification.

Treatment of Sodium Benzyl Thiosulfate (3) with Sodium Hydrogen Sulfide. Into 75 ml of ethanol in which 0.21 g (9 mg-atoms) of sodium metal had been dissolved was bubbled hydrogen sulfide gas until the solution was saturated. The solution was then purged with argon to remove excess H_2S, and 1.01 g (4.47 mmol) of **3** in 50 ml of degassed MeOH was added. The mixture was stirred for 1.5 hr and filtered to give 539 mg (85% based on 1 mol each of sodium sulfite and sodium thiosulfate produced) of colorless solid, identified by ir. To the filtrate was added 15 ml of 1.2 N HCl, and the solution was purged with argon until no further H_2S evolution could be detected. The volume of the solution was reduced to 10 ml, and the residue was extracted with $CHCl_3$. The extracts were dried ($MgSO_4$) and evaporated to give 511 mg (93%) of dibenzyl disulfide with trace polysulfide contaminants, identified by nmr.

Reactions of 2-Aminoethanethiosulfuric Acid (5) with Sodium Hydrogen Selenide. A. In Methanol–Ethanol. To a 100-ml ethanolic solution of sodium hydrogen selenide generated as previously described from 1.42 g (18 mg-atoms) of elemental selenium and 0.748 g (19.8 mmol) of sodium borohydride was added a solution of 1.414 g (9.0 mmol) of 2-aminoethanethiosulfuric acid (**5**) and 0.580 g (10.3 mmol) of potassium hydroxide in 100 ml of MeOH. After the mixture was stirred for 3.25 hr, filtration gave 0.650 g of a colorless solid (a mixture of $KNaSeSO_3$ and $KNaSO_3$, by ir) which gave 61 mg of elemental selenium on acid hydrolysis (indicating 26% $NaKSeSO_3$). To the filtrate was added 25 ml of 1.2 N HCl. The precipitated elemental selenium (1.35 g, 17 mg-atom, 94% recovery) was collected, and the combined filtrate and washings were evaporated to a solid residue which was dried and dissolved in 100 ml of H_2O. Titration of an aliquot with 1.0 N I_2 indicated a maximum of 6% conversion to thiol. Evaporation of the remaining solution and recrystallization of the residue from 2.5 ml of EtOH gave tiny crystals, shown to be cystamine dihydrochloride: mp 213–216° (lit.[17] mp 212–212.5°); ir (KBr) identical with that of authentic material.

B. In Water. Repeating the above experiment in aqueous solution and without the addition of potassium hydroxide gave a 100% recovery of elemental selenium on acidification. From titration of the filtrate with 1.0 N I_2, the amount of conversion to thiol was calculated to be 28%. The effluent gases were scrubbed in a trap containing saturated $CdCl_2$, wherein there formed a precipitate of yellow CdS (CdSe is greenish brown or red), identified by the following experiment. A portion of the Cd salt (~10 mg) was suspended in 0.5 ml of H_2O and concentrated HCl was added dropwise until the mixture became homogeneous. To a few drops of the solution was added 5% H_2O_2; no precipitation of elemental selenium was noted. From the acidic solution could be detected, however, H_2S evolution by moistened $Pb(OAc)_2$ paper. In a control experiment, authentic H_2Se did produce elemental selenium under these conditions.

When the experiment was repeated with 4 equiv of sodium hydrogen selenide/mol of **5**, a 92% recovery of elemental selenium was obtained on acidification. Titration of an aliquot of the filtrate with 1.0 N I_2 indicated a 100% conversion of **5** to the corresponding thiol. Evaporation of the remainder of the filtrate, followed by trituration with ethanol as described for cystamine, gave a crystalline solid which was identified as 2-mercaptoethylamine (**6**) hydrochloride by ir.

Generation and Acidification of Sodium Diselenide. A mixture of 3.00 g (38 mg-atoms) of elemental selenium and 1.00 g (27 mmol) of sodium borohydride was allowed to interact in 100 ml of ethanol under reflux with argon purging to produce sodium diselenide.[11] After reflux for 1 hr, 50 ml of degassed methanol and 30 ml of 1.2 N HCl were added to the cooled solution. The mixture was purged with argon until no further H_2Se evolution could be detected. The precipitated elemental selenium (984 mg, 12.5 mg-atoms) amounted to a 98% yield based on disproportionation.

Treatment of 1,6-Diaminohexane with Sodium Hydrogen Selenide. A solution of 1.00 g (8.61 mmol) of 1,6-diaminohexane in 50 ml of degassed ethanol was added to a solution of sodium hydrogen selenide generated as described above from 2.72 g (34.4 mg-atoms) of elemental selenium and 1.43 g (37.8 mmol) of sodium borohydride in 100 ml of ethanol. Acidification of the solution with 40 ml of 1.2 N HCl gave no precipitation of selenium, but rather copious evolution of hydrogen selenide.

Acknowledgment. The authors are grateful to Dr. T. Scott Griffin for many valuable suggestions and to Mr. Robert L. Runkle for technical assistance.

Registry No.—**1**, 150-60-7; **3**, 6313-36-6; **5**, 2937-53-3; sodium hydrogen selenide, 12195-50-3; sodium diselenide, 39775-40-0; hydrogen selenide, 7783-07-5; di-*tert*-butyl disulfide, 110-06-5; diphenyl disulfide, 882-33-7; didecyl disulfide, 10496-18-1; cystine, 56-89-3; cystamine dihydrochloride, 56-17-7; diformamicine disulfide dihydrochloride, 14807-75-1; 1,6-diaminohexane, 124-09-4.

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Mercury in Organic Chemistry. V.[1] The Direct Esterification of Alkyl Halides

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Received July 1, 1974

The direct esterification of alkyl halides using stoichiometric amounts of sodium, mercury, and silver carboxylates is examined. Treatment of unhindered primary alkyl iodides and bromides, as well as allyl and benzyl chloride, bromide, and iodide, with sodium acetate in HMPA at room temperature provides excellent yields of the corresponding esters. Mercuric acetate in diglyme will react directly only with *tert*-butyl halides, allyl iodide, and benzyl bromide and iodide. However, this reaction is greatly catalyzed by the addition of triacyloxyboranes. Unhindered primary alkyl iodides and *tert*-butyl, allyl, and benzyl chlorides, bromides, and iodides, as well as α-phenethyl chloride, all react to give good to excellent yields of esters. Optically active α-phenethyl chloride gives predominant racemization. These reactions are examined in some detail and appear promising for the direct esterification of hindered highly ionizable alkyl halides such as *tert*-butyl chloride and α-phenethyl chloride. Silver carboxylates show a reactivity pattern similar to that of the mercury salts, but generally give lower yields.

Numerous methods are presently available for achieving the direct esterification of carboxylic acids. Some of these procedures utilize alkyl halides. Seldom, however, have any of these procedures been applied with the synthetic objective of achieving the direct high yield esterification of an alkyl halide. In fact, no systematic survey of this possibility has apparently ever been undertaken. From this viewpoint, therefore, present procedures suffer certain major disadvantages. They often are limited to the esterification of alkyl halides which readily undergo bimolecular nucleophilic substitution reactions, most commonly methyl and ethyl iodide. In a few instances solvolytic conditions have been applied to the esterification of allylic and benzylic halides. No procedures have yet been reported which will effect the direct esterification of tertiary halides in good yield. In most instances a large excess of the halide has been employed and elevated temperatures and/or extended reaction times are required. The presence of bases which might effect elimination or rearrangement in delicate molecules provides an additional complication.

Our earlier work on the direct anti-Markovnikov esterification of alkenes[2] suggested that some of the difficulties encountered with previous procedures might be overcome by the utilization of mercuric carboxylates in the presence of catalytic amounts of triacycloxyboranes. We have examined this possibility and wish now to report a complete study of these reactions, as well as a comparison with the reactions of silver and sodium carboxylates.

Mercury Carboxylates

Introduction. We recently reported a convenient new method for the direct anti-Markovnikov esterification of alkenes using a hydroboration–mercuration–iodination sequence.[2] During the course of that investigation we observed that mercuric acetate readily reacts with primary alkyl iodides in the presence of catalytic amounts of "triacetoxyborane," $B(OAc)_3$, to give excellent yields of the corresponding acetate esters. This discovery initiated a thorough examination of the reaction of mercuric carboxylates with alkyl halides. Particular attention was paid to the effect of various solvents, catalysts, alkyl halides, and mercuric carboxylates on the yield of ester. However, no special effort was made to optimize the yield of ester in any of these reactions. Instead primary emphasis was placed on determining the limitations of these new esterification reactions.

Esterification of *n*-Butyl Iodide. The reaction of *n*-butyl iodide with mercuric acetate has been examined in some detail (Table I) (eq 1). Although no reaction occurs in

$$n\text{-}C_4H_9I + Hg(OAc)_2 \longrightarrow n\text{-}C_4H_9OAc + IHgOAc \quad (1)$$

tetrahydrofuran (THF) at room temperature, the iodide completely disappears upon refluxing 24 hr. However, only a 30% yield of *n*-butyl acetate results. By increasing the polarity of the solvent and hence the solubility of the mercuric acetate, one greatly facilitates the reaction with *n*-butyl iodide (entries 3–9). Thus, utilization of hexamethylphosphoric triamide (HMPA) produces a 96% yield of *n*-butyl acetate in 48 hr at room temperature. However, similar results (99%) can be achieved by the use of sodium acetate, suggesting that the mercury cation plays little role in these reactions.

We have also examined the effect of added mercuric iodide on the reaction of *n*-butyl iodide and mercuric acetate in THF. Mercuric acetate completely dissolves in THF in the presence of mercuric iodide (1:1) probably due to the formation of "iodomercuric acetate," IHgOAc. This reagent, while slightly more reactive than mercuric acetate, is little more effective in the esterification of the halide (9%).

However, the reaction of *n*-butyl iodide and mercuric acetate in THF can be markedly accelerated by the addition of Lewis acid catalysts. Addition of 10% of "triacetoxyborane" (made from "borane" and acetic acid) results in a rapid disappearance of the *n*-butyl iodide and the formation of *n*-butyl acetate in 88% yield. In attempting to utilize both of the acetate groups of mercuric acetate in this reaction, we have examined the use of both "iodomercuric acetate" and mercuric acetate (entries 12 and 13). The reaction of "iodomercuric acetate" is also catalyzed by "triacetoxyborane," but only a 72% yield of ester is obtained, and significant amounts of the alkyl iodide (11%) remain. The use of only half as much mercuric acetate as previously used produces an excellent yield of the ester (83%), but 6% of the iodide remained. Thus, an equimolar ratio of mercuric acetate and alkyl halide appears desirable.

Catalyst Preparation. The remarkable catalytic effects of "triacetoxyborane" in these reactions suggested an examination of alternate routes to this catalyst. Our initial work employed "triacetoxyborane" prepared by the low temperature addition of "borane" to acetic acid (eq 2). It

$$BH_3 + 3HOAc \longrightarrow B(OAc)_3 + 3H_2 \quad (2)$$

was hoped that this reagent might also be generated through an exchange reaction between boron trifluoride and mercuric acetate (eq 3). Addition of boron trifluoride

$$3Hg(OAc)_2 + 2BF_3 \longrightarrow 2B(OAc)_3 + 3HgF_2 \quad (3)$$

to mercuric acetate and *n*-butyl iodide in sufficient

Table I
The Direct Esterification of *n*-Butyl Iodide by Mercuric Acetate

$n\text{-}C_4H_9I \longrightarrow n\text{-}C_4H_9O_2CCH_3$

Entry	Mercuric carboxylate[a]	Catalyst[b]	Solvent[c] (10 ml)	Temp, °C	Reaction time, hr	Ester yield,[d] %	Unreacted alkyl halide,[d] %
1	$Hg(OAc)_2$		THF	25	24	0	100
2				65		30	0
3			DG	25		1	99
4			CH_3OH			5	0
5			DMSO			13	17
6			DMF			25	14
7			Pyridine			38	0
8			HMPA			92	6
9					48	96	1
10	IHgOAc		THF		24	9	66–77
11	$Hg(OAc)_2$	$B(OAc)_3$				88	0
12	IHgOAc					72	11
13	0.5 $Hg(OAc)_2$					83	6
14	$Hg(OAc)_2$	3 $Hg(OAc)_2$–$2BF_3$				34	0
15				−78		26	0
16		3 AgOAc–BF_3		25		18	0
17		$B(OH)_3$–3$(Ac)_2O$				10	60
18		B_2O_3–3$(Ac)_2O$				86	0
19		3 $Hg(OAc)_2$–BH_3				87	0

[a] At 10 mmol unless otherwise indicated. [b] Total boron catalyst was 1 mmol. [c] Abbreviations indicated in the text. [d] Glpc analysis using an internal standard.

amounts to generate 10% of the "triacetoxyborane" catalyst brought about an extremely rapid reaction and complete disappearance of the iodide (entry 14). However, only 34% of the desired ester was obtained. Addition of the iodide to the other reagents (which were stirred 1 hr together prior to addition) gave similar results. Lowering the temperature to −78° only lowered the yield further (26%). It would appear from these results that no exchange between mercuric acetate and boron trifluoride has occurred. Instead, boron trifluoride is functioning as the catalyst in these reactions.

We have also examined the analogous exchange reaction between silver acetate and boron trifluoride (eq 4). Subsequent mercuration provided results similar to those above. Apparently no exchange occurs. Instead a very rapid reaction with *n*-butyl iodide is observed, but only an 18% yield of the ester results. It is apparent that boron trifluoride greatly catalyzes the reaction of alkyl halides with mercury carboxylates, but the yields are substantially lower than those obtained using "triacetoxyborane."

$$3AgOAc + BF_3 \longrightarrow B(OAc)_3 + 3AgF \quad (4)$$

We have attempted the preparation of "triacetoxyborane" through the esterification of boric acid (eq 5) and boric oxide (eq 6).[3] The indicated reagents were stirred together both at room temperature and at reflux in THF for 24 hr. Subsequent esterification of *n*-butyl iodide with mercuric acetate gave 10 and 8% yields from boric acid and 46 and 86% yields from boric oxide, respectively (entries 17 and 18). Thus, the high temperature boric oxide route provides a convenient alternate route to this useful catalyst.

$$B(OH)_3 + 3(Ac)_2O \longrightarrow B(OAc)_3 + 3HOAc \quad (5)$$

$$B_2O_3 + 3(Ac)_2O \longrightarrow 2B(OAc)_3 \quad (6)$$

The rapid reduction of mercuric acetate by "borane" suggested another route to "triacetoxyborane" (eq 7). Indeed, addition of "borane" directly to mercuric acetate at −78° and warming to room temperature generated a catalyst which facilitates the rapid esterification of *n*-butyl io-

$$BH_3 + 3Hg(OAc)_2 \longrightarrow B(OAc)_3 + 1.5H_2 + 1.5Hg_2(OAc)_2 \quad (7)$$

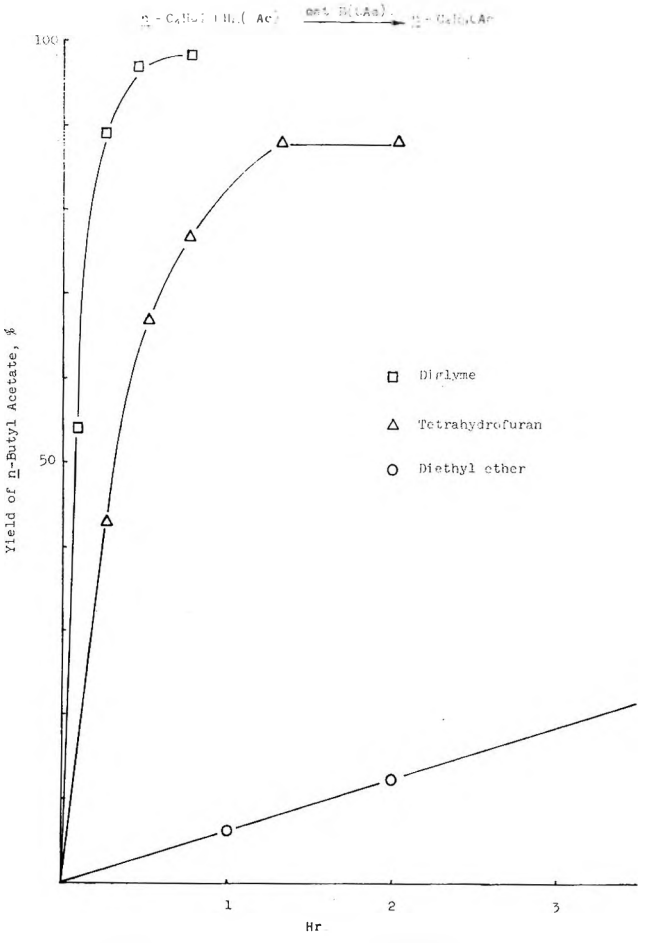


Figure 1. Effect of solvent on rate of esterification.

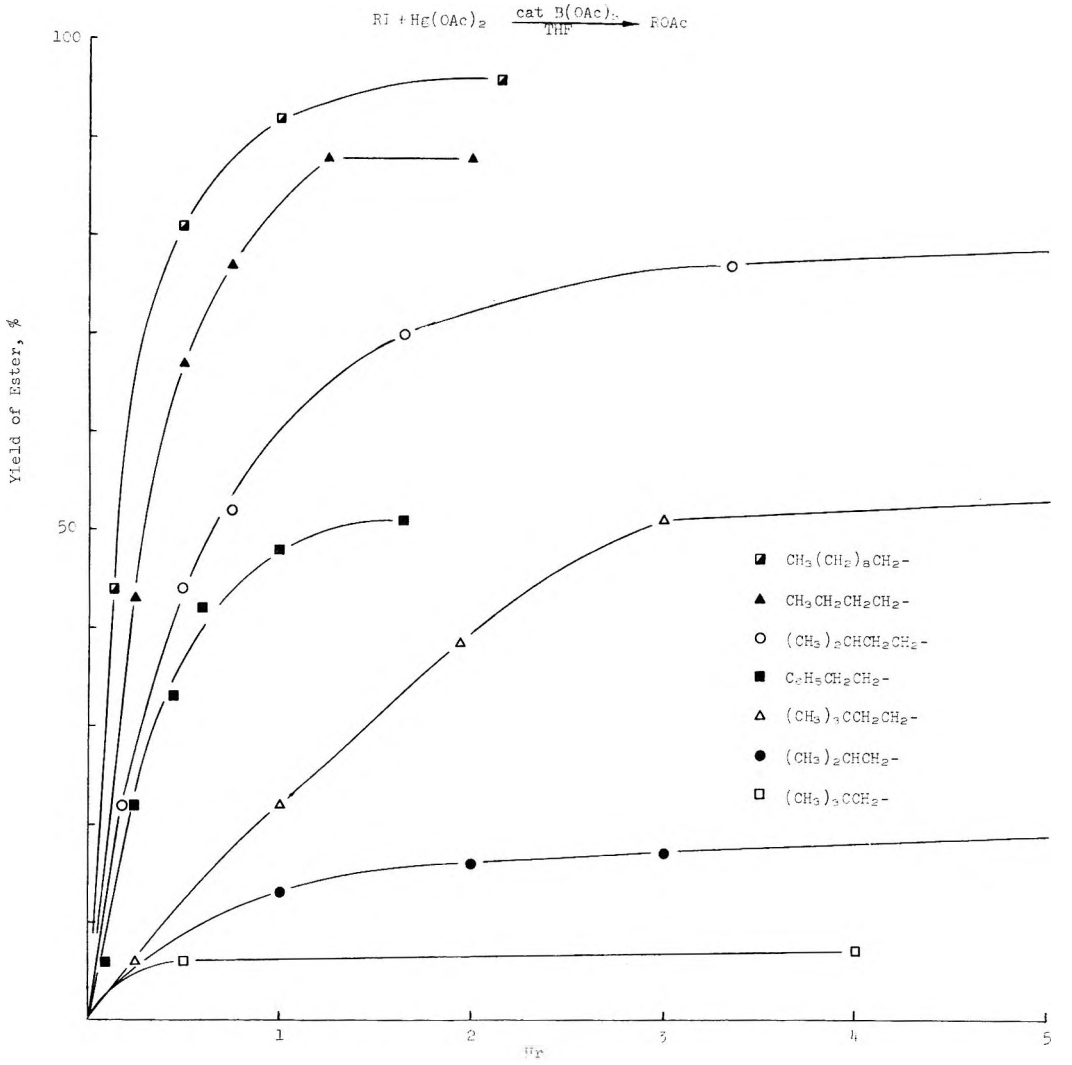
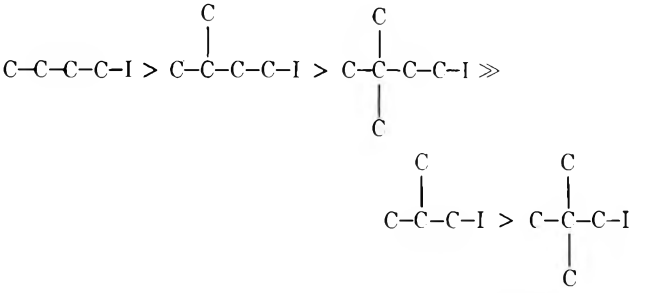


Figure 2. Relative rates of esterification of primary alkyl iodides.

dide by mercuric acetate. After 24 hr at room temperature an 87% yield of the ester was observed. Although perhaps more convenient for some purposes, this procedure produces an insoluble material, presumably mercurous acetate, which makes it impossible to follow the reaction by watching the dissolution of the insoluble mercuric acetate. For this reason the direct reaction of "borane" and the carboxylic acid seemed preferable and was utilized for all subsequent reactions.

Relative Rates. The solvent for these catalytic esterification reactions has a major effect on the rate of the reaction. The reaction of *n*-butyl iodide in diglyme requires only about 0.5 hr to reach completion (99% yield), while THF (88% yield in 75 min) and diethyl ether (99% yield in 120 hr) require considerably longer reaction times (Figure 1). This trend probably results from the decreasing solubility of the mercuric acetate in proceeding from diglyme to THF to diethyl ether. Doubling the concentration of the catalyst from 0.1 to 0.2 *M* further increases the reaction rate (approximately 30 min to reach completion in THF—84% yield).

The effect of the structure of the primary alkyl iodide on the relative rates and yields has been examined in some detail (Figure 2). Increasing the steric hindrance about the methylene iodide portion of the molecule markedly decreases the rate of esterification and results in sharply reduced yields of ester. This is clearly indicated by comparing the following alkyl iodides



The reaction for all practical purposes fails with any kind of substitution on the β-carbon atom.

Yields. The rate of esterification and the yield of ester is significantly increased by the use of diglyme. The yields of a variety of esters have been determined using a standard procedure (10 ml of diglyme, 10 mmol of alkyl iodide, 10 mmol of mercuric carboxylate, and 1.0 mmol of "triacetoxyborane" at room temperature) and are presented in Table II. The reaction generally provides good to excellent yields of esters from unhindered primary alkyl iodides. In attempting to extend the reaction to *n*-butyl bromide and tosylate, no significant amount of *n*-butyl acetate was obtained. However, boron trifluoride catalysis of the *n*-butyl bromide reaction did give a 20% yield of *n*-butyl acetate. This tremendous difference in relative rates has allowed the selective esterification of 1-chloro-3-iodopropane in 95% yield (eq 8).

Table II
The Direct Esterification of Primary Alkyl Halides by Mercuric Carboxylates

$$RX + Hg(O_2CR')_2 \xrightarrow[\text{diglyme}]{B(O_2CR')_3} RO_2CR'$$

Alkyl halide (Registry no.)	Carboxylate[a] (Registry no.)	Yield of ester, %[b]
n-Butyl iodide (542-69-8)	Acetate (1600-27-7)	99
n-Decyl iodide (2050-77-3)		96
Isoamyl iodide (541-28-6)		96
3,3-Dimethyl-1-butyl iodide (15672-88-5)		88
2-Phenylethyl iodide (17376-04-4)		61
Isobutyl iodide (78-83-4)		14
Neopentyl idodide (15501-33-4)		22
1-Chloro-3-iodopropane (6440-76-7)		95
Ethyl iodide (75-03-6)	Butyrate (19348-32-4)	99
n-Butyl iodide	Butyrate	99
n-Butyl iodide	Benzoate (583-15-3)	54[c]
n-Butyl bromide (109-65-9)	Acetate	18[d]

[a] Mercuric carboxylate and triacyloxyborane. [b] Glpc analysis after 24 hr. [c] At 0.5 equiv of tribenzoyloxyborane. [d] Analysis after 190 hr.

$$ICH_2CH_2CH_2Cl \longrightarrow CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_2Cl \quad (8)$$

Other mercuric carboxylates may also be utilized in these esterification reactions. Thus, ethyl iodide produced a 99% yield of ethyl butyrate upon treatment with mercuric butyrate and "tributyloxyborane." The preparation of benzoates, however, proved more difficult. By increasing the amount of "tribenzoyloxyborane" (0.5 equiv) one can obtain a respectable 54% yield of *n*-butyl benzoate from *n*-butyl iodide. The use of mercuric salts of strongly acidic carboxylic acids, such as trifluoroacetic acid, gives sharply reduced yields. Elimination and not substitution appears to predominate. Major limitations to these reactions are evident.

Secondary Alkyl Halides. A brief survey of the esterification of secondary alkyl halides has been undertaken. The reactions of *sec*-butyl and cyclohexyl halides with mercuric acetate in diglyme with and without a catalyst have been examined and are included in Table III.

Of the cyclohexyl halides only the iodide reacts in the absence of a catalyst. However, no ester was observed. Addition of "triacetoxyborane" facilitates reaction, but the yields of ester from both the bromide and iodide were less than 5%. The chloride still failed to react.

The *sec*-butyl halides produced similar results, although the yields were somewhat improved. Thus, only the iodide reacted with mercuric acetate in the absence of a catalyst (32%). The addition of "triacetoxyborane" produced similar results with the iodide (30%) but facilitated conversion of the bromide into sec-butyl acetate (34%). The chloride remained unreactive. Mercuric acetate and boron trifluoride produced only 6% of the ester from *sec*-butyl chloride. The use of THF gave slightly higher yields in most cases.

Although secondary alkyl halides are more reactive than primary halides, the yields are very poor, and direct esterification of secondary alkyl halides by mercury carboxylates does not appear synthetically useful.

Tertiary Alkyl Halides. In view of the results obtained with secondary alkyl halides, it was anticipated that tertiary halides would show high reactivity toward mercuric acetate. However, only trace amounts of the corresponding esters were anticipated. This later pessimism proved unwarranted (Table III). *tert*-Butyl iodide, bromide, and chloride react with mercuric acetate in the absence of a catalyst in diglyme to produce 68, 72, and 54% yields of *tert*-butyl acetate, respectively. THF gives lower yields in all cases. Addition of "triacetoxyborane" catalyst to these reactions fails to improve the yields of ester from the iodide or bromide. However, *tert*-butyl chloride now reacts readily to give a 73% yield.

Table III
The Direct Esterification of Alkyl Halides by Mercuric Acetate

$$RX + Hg(OAc)_2 \xrightarrow[\text{diglyme}]{} ROAc$$

Alkyl halide (Registry no.)	$B(OAc)_3$ catalyst	Yield of alkyl acetate, %
Cyclohexyl chloride (542-18-7)	−	0
chloride	+	0
bromide (108-85-0)	−	0
bromide	+	1
iodide (626-62-0)	−	0
iodide	+	0
sec-Butyl chloride (513-36-0)	−	0
chloride	+	1
bromide (78-77-3)	−	1
bromide	+	34
iodide (513-38-2)	−	32
iodide	+	30
tert-Butyl chloride (507-20-0)	−	54
chloride	+	73
bromide (507-19-7)	−	72
bromide	+	69
iodide (558-17-8)	−	68
iodide	+	54
Allyl chloride (107-05-1)	−	0
chloride	+	59
bromide (106-95-6)	−	5
bromide	+	77
iodide (556-56-9)	−	73
iodide	+	82
Benzyl chloride (100-44-7)	−	1
chloride	+	98
bromide (100-39-0)	−	71
bromide	+	95
iodide (620-05-3)	−	57
iodide	+	70
α-Phenethyl chloride (1459-15-0)	−	78
chloride	+	97

Allylic and Benzylic Halides. It was of obvious interest to see if allylic halides could also be conveniently esterified by mercury carboxylates. Allyl chloride, bromide, and iodide were chosen as representative allylic halides. Only the iodide reacts readily with mercuric acetate in the absence of a catalyst in diglyme (73% allyl acetate). The catalyst promotes rapid reaction of all three halides. Diglyme again results in higher yields than THF. Allyl chloride, bromide, and iodide produced 59, 77, and 82% yields of allyl acetate, respectively.

A similar pattern was observed with the benzyl halides. Both benzyl iodide and bromide react with mercuric acetate in diglyme to give 57 and 71% yields of benzyl acetate, respectively. The chloride fails to react. All three halides (Cl, Br, I) react smoothly with mercuric acetate in diglyme in the presence of "triacetoxyborane" to produce 98, 95, and 56% yields of the ester, respectively. THF again results in lower yields. α-Phenethyl chloride gives a 97% yield of α-phenethyl acetate in diglyme.

Stereochemistry. In order to determine the stereochemical course of these esterification reactions, we have examined the esterification of (+)-(*R*)-α-phenethyl chloride. The chloride was prepared from the corresponding alcohol essentially as described previously.[4] Ten millimoles of 28% optically pure chloride ($[\alpha]_D$ +125.4°)[5] was subjected to our standard catalytic esterification procedure. Glpc purification gave (−)-(*S*)-α-phenethyl acetate ($[\alpha]_D^{21}$ −130.5)[6] of 1.7% optical purity, indicating only very slight inversion of configuration in this reaction. Racemization predominates.

Mechanism. Although a minimum of experimental results are presently at hand, some comment on the mechanism of these esterification reactions seems warranted. The relative reactivities of the alkyl halides exhibit characteristics of both SN1 and SN2 reactions. Thus, the relative rates observed with the primary iodides is indicative of a bimolecular nucleophilic substitution reaction. The increasing reactivity of the halides in the order iodide > bromide > chloride is also consistent with an SN2 reaction. The greater reactivity of the more highly substituted halides (tertiary > secondary > primary) is more in keeping with a unimolecular nucleophilic substitution reaction. Full kinetic details unfortunately are not presently available due to the heterogeneity of these reactions. The nearly complete racemization of α-phenethyl chloride is also consistent with an SN1 type reaction. It is, however, entirely possible that the mechanism of these reactions changes in proceeding from the less reactive primary alkyl halides to the highly reactive allylic and benzylic halides.

It is likely that the major side reaction competing with esterification is elimination to the alkene,[7] although this has not been studied. In general we observe that the boron trifluoride catalyst gives much lower yields than "triacetoxyborane." Similar results are observed in going from mercuric acetate to mercuric trifluoroacetate. The yields of ester also generally decrease in the order chloride > bromide > iodide. Thus, by increasing the electrophilicity of the mercury salt or the leaving ability of the halide, we sharply reduce the yield of ester probably due to ionization followed by elimination.

In this respect it was anticipated that the tertiary halides would undergo complete elimination and the yields of ester would be very low. This has not been observed, however. It seemed plausible that the tertiary esters might be arising instead from an elimination of the hydrogen halide followed by addition of the carboxylic acid as outlined below (eq 9 and 10). In order to test this possibility we have run the esterification of *tert*-butyl chloride in the presence of an excess of styrene as a trap for the *in situ* generated acetic acid. We have also attempted the esterification of α-phenethyl chloride in the presence of an excess of isobutylene. Although the yields of esters were reduced in both cases, none of the ester expected upon addition of acetic acid to the alkene could be observed. This appears to rule out an elimination–addition mechanism and suggests that direct substitution may indeed be occurring in the esterification of even tertiary halides. However, it remains somewhat a puzzle why the yields of tertiary esters should exceed those of the secondary esters which would be expected to undergo substitution more readily.

$$(CH_3)_3CX + Hg(OAc)_2 \longrightarrow (CH_3)_2C{=}CH_2 + XHgOAc + HOAc \quad (9)$$

$$(CH_3)_2C{=}CH_2 + HOAc \longrightarrow (CH_3)_3COAc \quad (10)$$

Table IV
The Direct Esterification of Alkyl Halides by Sodium Carboxylates

$$RX + NaO_2CR' \xrightarrow[HMPA]{} RO_2CR'$$

Alkyl halide (Registry no.)	Sodium carboxylate (Registry no.)	Yield of ester, %[a]
n-Butyl iodide	Acetate (127-09-3)	99
iodide	Benzoate (532-32-1)	96
iodide	Trifluoroacetate (2923-18-4)	70–80
bromide	Acetate	96
chloride (109-69-3)		29
sec-Butyl iodide		38
bromide		19
chloride		0
Cyclohexyl iodide		0
bromide		0
chloride		0
tert-Butyl iodide		0
bromide		0
chloride		0
Allyl iodide		90
bromide		96
chloride		76
Benzyl iodide		62
bromide		92
chloride		93
α-Phenethyl chloride		5

[a] Glpc analysis after 24 hr.

Sodium Carboxylates

Numerous examples of the esterification of alkyl halides by sodium carboxylates have appeared.[8-11] Unfortunately, most of these procedures have had as their major objective the conversion of a particular carboxylic acid into the corresponding methyl or ethyl ester in high yield. Consequently, a large excess of methyl or ethyl iodide has been employed obscuring the scope of these reactions. In those cases where other esters have been prepared, the alkyl halide was again used in large excess. In no case have these reactions been employed to effect high conversions of alkyl halides into esters.

In order to compare and determine the synthetic utility of the mercury esterification reactions, we have had to systematically examine the corresponding reactions with sodium carboxylates (Table IV). *n*-Butyl iodide fails to react

Table V
The Direct Esterification of Alkyl Halides by Silver Carboxylates

$$RX + AgO_2CR' \xrightarrow[THF]{} RO_2CR'$$

Alkyl halide	Silver carboxylate (Registry no.)	Catalyst	Yield of ester, %[a]	Comment
n-Butyl iodide	Acetate (563-63-3)		5	Room temperature
iodide			77	Reaction refluxed
iodide			100	HMPA solvent
iodide		$B(OAc)_3$	77	
iodide		BF_3	12	
iodide	Benzoate (532-31-0)	$B(O_2CC_6H_5)_3$	20	
bromide	Acetate	$B(OAc)_3$	0	No reaction
chloride		$B(OAc)_3$	0	No reaction
Ethyl iodide	Trifluoroacetate (2966-50-9)	$B(O_2CCF_3)_3$	10	
Cyclohexyl iodide			11	
iodide		$B(OAc)_3$	8	
bromide		$B(OAc)_3$	2	
chloride		$B(OAc)_3$	0	No reaction
sec-Butyl iodide			26	
iodide		$B(OAc)_3$	44	
bromide			14	
bromide		$B(OAc)_3$	28	
chloride			0	No reaction
chloride		$B(OAc)_3$	0	No reaction
tert-Butyl iodide			39	
bromide			41	
chloride			47	Reaction refluxed
chloride		$B(OAc)_3$	38	
Allyl iodide			57	
iodide		$B(OAc)_3$	31	
bromide		$B(OAc)_3$	24	
chloride		$B(OAc)_3$	3	
Benzyl iodide			28	
bromide			52	
chloride		$B(OAc)_3$	5	
α-Phenethyl chloride		$B(OAc)_3$	37	

[a] Glpc analysis after 24 hr.

with sodium acetate in THF with or without "triacetoxyborane." If the reaction is carried out in HMPA instead, a 99% yield of *n*-butyl acetate is realized. Sodium benzoate gives a comparable yield (96%). Even sodium trifluoroacetate gives good yields (70–80%), although a considerable amount of the iodide remains even after reaction for a couple of days at room temperature. Doubling the amount of the sodium salt fails to increase the yield. *n*-Butyl bromide (96%) and chloride (29%) also react with sodium acetate in HMPA to give *n*-butyl acetate.

None of the cyclohexyl halides gave any cyclohexyl acetate in 24 hr, and significant amounts of these halides remained unreacted. Under identical conditions, *sec*-butyl chloride failed to react, and the bromide (19%) and iodide (38%) give only poor yields with much of the starting halide still present.

All three *tert*-butyl halides (chloride, bromide, iodide) failed to react completely and gave only traces of *tert*-butyl acetate.

All of the allyl and benzyl halides gave good to excellent yields of allyl and benzyl acetate, respectively: allyl chloride (76%), bromide (96%), iodide (90%), and benzyl chloride (93%), bromide (92%), iodide (62%). However, α-phenethyl chloride gave only 5% of the acetate.

The esterification of alkyl halides with sodium carboxylates works well only in those cases where bimolecular nucleophilic substitution reactions are particularly facile. HMPA is necessary to achieve high yields. In few cases do the actual yields exceed those obtained using the mercury catalyzed reactions. However, these reactions do appear more widely applicable with respect to the types of sodium carboxylates and halides which can be employed.

Silver Carboxylates

Silver acetate has been previously utilized to achieve the direct esterification of alkyl halides.[12–16] Again, however, no systematic survey of the synthetic utility of these reactions has ever appeared. We have briefly examined the generality of these reactions (Table V).

The esterification of primary alkyl halides by silver acetate closely parallels the mercuric acetate reactions. Although *n*-butyl iodide gives only a 5% yield of *n*-butyl acetate after 24 hr at room temperature in THF, a good yield is obtained upon refluxing (77%). Addition of 10% "triacetoxyborane" again greatly facilitates the reaction at room temperature (77%). Boron trifluoride catalysis sharply reduces the yield (12%). The silver benzoate (20%) and trifluoroacetate (10% from ethyl iodide) catalyzed reactions again fail. *n*-Butyl bromide and chloride fail to react.

The secondary alkyl halides again give poor results. Of the cyclohexyl halides only the iodide reacts with silver acetate in the absence of "triacetoxyborane" (11%). Cyclohexyl iodide (8%) and bromide (2%) react in the presence of the catalyst, but the chloride remains unreactive. The *sec*-

butyl halides in THF again give higher yields with (Br, 28%; I, 44%) or without the catalyst (Br, 14%; I, 26%). The chloride fails to react.

tert-Butyl iodide (39%) and bromide (41%) react in minutes with silver acetate in THF. The chloride requires either refluxing (47%) or the addition of "triacetoxyborane" (38%). The yields from mercury carboxylates are higher in almost every case.

Of the allyl halides only the iodide (57%) reacts in the absence of a catalyst. "Triacetoxyborane" in THF again significantly increases the reactivity (I, 31%; Br, 24%; Cl, 3%).

Both benzyl iodide (28%) and bromide (52%) react with silver acetate at room temperature in THF. Although benzyl chloride fails to react, α-phenethyl chloride partially reacts to give a 37% yield of the acetate. Catalysis of the benzyl chloride reaction fails (5%).

Although the silver carboxylates show a pattern very similar to those of the mercuric carboxylates, the yields are lower in practically every case. The greater cost of these salts also makes them of questionable utility for the direct esterification of alkyl halides.

Experimental Section

General Comments. THF, diglyme, and HMPA were distilled from lithium aluminum hydride and stored under nitrogen. All other solvents were used directly as obtained commercially. All alkyl halides used are either commercially available or readily available by standard synthetic procedures. The commercial materials were usually used directly as obtained unless they were obviously quite colored in which case they were distilled before use. The "borane" used was prepared by the procedure of Brown and Sharp.[17] The boron trifluoride, boric acid, and oxide were used directly as obtained commercially, as were the sodium and silver salts. Mercuric acetate (J. T. Baker) was pumped free of acetic acid overnight on a vacuum pump before using. The preparation of the other mercury carboxylates is described elsewhere.[18]

General Esterification Procedures. The following general procedure was employed for most esterification reactions. In a 50-ml round-bottom flask with septum inlet was placed 10 mmol of the metal carboxylate and the flask was flushed with nitrogen. Approximately 1 ml of an appropriate hydrocarbon glpc internal standard was added followed by 10 ml of the appropriate solvent. The reaction mixture was cooled by stirring in an ice bath while the alkyl halide was slowly added. After addition the flask was placed in a room temperature water bath, and microliter samples were taken at the appropriate time and analyzed by glpc. The ester could be isolated by filtering, adding ether, washing with water and aqueous sodium thiosulfate, drying, and distilling.

The triacyloxyborane catalyzed reactions were run essentially as indicated above; however, the catalyst was prepared as indicated below in the appropriate solvent, and the metal salt and alkyl halide were added to the catalyst.

Catalyst Preparation. One millimole of catalyst was used in all catalytic reactions. "Triacetoxyborane" can be prepared by any of the following methods: (1) slow addition of "borane" in THF to acetic acid (3 mmol) in diglyme or THF at −78° and allowing to slowly warm to room temperature, (2) slow addition of "borane" (1 mmol) in THF to mercuric acetate (3 mmol) at −78° and slow warming to room temperature, or (3) addition of acetic anhydride (1.5 mmol) to boric oxide, B_2O_3 (0.5 mmol), and refluxing 24 hr. The various unsuccessful boron trifluoride exchange reactions were also run stoichiometrically so as to generate 1 mmol of the catalyst.

Stereochemistry. (+)-(*R*)-α-Phenethyl alcohol was obtained from Norse Laboratories and used directly. (+)-(*R*)-α-Phenethyl chloride was prepared as follows.[4] To a dry 50-ml round-bottom flask was added 15 ml of freshly distilled thionyl chloride and 15 ml of pentane. To this solution was slowly added 6.1 g (50 mmol) of (+)-(*R*)-α-phenethyl alcohol. A drying tube was placed on the flask and the reaction was allowed to stir overnight. Water (10 ml) was slowly added to the reaction mixture and the reaction mixture was stirred until no more gas evolved. The organic layer was washed with four 10-ml portions of water. The aqueous layers were combined and reextracted with pentane. The combined organic layers were washed with three 10-ml portions of 10% aqueous sodium carbonate solution and dried overnight over anhydrous Na_2SO_4. After filtration, the pentane was removed and the chloride distilled under vacuum: bp 79–80° (16 mm), yield 60%, $[\alpha]D^{25}$ +31.06° (27.7% optical purity).

The esterification was run as follows. To a dry 50-ml round-bottom flask with a septum inlet under nitrogen was added 17.5 ml of dry diglyme and 5.33 mmol of acetic acid. This solution was cooled to −78° and 1.77 mmol of "borane" (0.76 ml of 2.33 *M*) was added. The cooling bath was removed and the mixture was allowed to slowly warm to room temperature. After 3 hr, the mixture was cooled to 0° and 17.7 mmol of mercuric acetate (5.65 g) was added while back-flushing with nitrogen. Then 17.7 mmol of (+)-(*R*)-α-phenethyl chloride (2.49 g) was added by syringe. The reaction mixture was stirred overnight at room temperature. Eighty-five milliliters of ether was added to the reaction mixture and the organic layer was washed with five 25-ml portions of water, and the aqueous portions were reextracted with 35 ml of ether. The combined organic portions were washed with five 35-ml portions of a saturated $Na_2S_2O_3$ solution, and then with two 35-ml portions of a saturated $NaHCO_3$ solution, and finally with five 35-ml portions of water. After having dried over anhydrous Na_2SO_4, the ester solution was filtered, stripped of solvent, and isolated by preparative glpc (160° on a 10% UCON polar column). The (−)-(*S*)-α-phenethyl acetate obtained before and after glpc had essentially the same optical rotation ($[\alpha]D^{25}$ −2.19°) indicating approximately 1.7% optical purity. Predominant racemization with very slight inversion occurs. All readings were taken on an O. C. Rudolph and Sons Inc. Model 63 polarimeter using the sodium D line with benzene as the solvent.

Examination of Possible Elimination–Addition Mechanism. The "triacetoxyborane" catalyzed esterification of *tert*-butyl chloride (10 mmol) was run exactly as indicated above with styrene (20 mmol) added. A 31% yield of *tert*-butyl acetate was observed and no α-phenethyl acetate was evident. In a similar manner α-phenethyl chloride (10 mmol) was esterified in the presence of isobutylene (60 mmol). A 30% yield of α-phenethyl acetate was obtained and no *tert*-butyl acetate was observed.

Acknowledgment. The author gratefully acknowledges the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of this research and the capable assistance of Mr. Gary Molander for determining the stereochemistry of the α-phenethyl chloride reaction.

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Ferric Chloride in Acetic Anhydride. A Mild and Versatile Reagent for the Cleavage of Ethers

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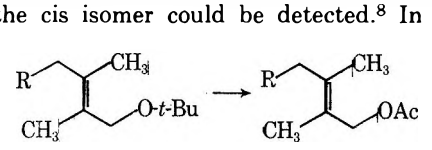
Received September 11, 1974

The reaction of anhydrous ferric chloride in acetic anhydride with a variety of ethers has been examined in order to elucidate the mechanism and scope of this ether-to-acetate transformation. Ethers **1**, **2**, and **8** are transformed to the corresponding acetates **3**, **4**, and **9** without cis–trans olefin isomerization. Cleavage of optically active ethers **5** and **6** affords substantially racemized 2-octyl acetate. *tert*-Butyldimethylsilyl ether **7** is rapidly cleaved with nearly complete retention of configuration. In light of the data presented, a mechanism involving O-acylation followed by SN1 or SN2 attack by acetate is discussed.

In 1914, Knoevenagel observed the formation of ethyl acetate in the reaction of diethyl ether with ferric chloride in acetic anhydride.[1] Since that time, this unusual reagent for the fragmentation of ethers has largely been ignored by the synthetic chemist although other combinations of Lewis acids with carboxylic acid chlorides and anhydrides are known to convert ethers to esters.[2,3] Unfortunately the problem with aliphatic ethers as useful OH protecting groups has always been the dearth of gentle yet effective techniques for releasing the parent alcohol. Recently our own research demanded such a method, consequently we undertook to explore the advantages of ferric chloride–acetic anhydride for this purpose. The current renewed interest in the importance of alcohol protecting groups[4] prompts us to report our remarkable findings with this complex.

We had occasion to prepare the trans-allylic ethers **1** and **2**[5] and hoped to remove the *tert*-butyl protecting group without effecting double bond isomerization. When either **1** or **2** was exposed to a trace of ferric chloride in acetic anhydride as solvent ($FeCl_3$–Ac_2O), these ethers were smoothly converted to the corresponding trans acetates **3** and **4** along with an equivalent amount of *tert*-butyl acetate.[6,7] No trace of the cis isomer could be detected.[8] In contrast,



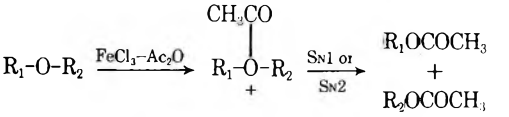
1, R = Cl **3**, R = Cl
2, R = OAc **4**, R = OAc

treatment of the ether **2** with dilute stannic chloride in acetic anhydride at 0° led to significant cis–trans isomerization during formation of diacetate **4**. These and other results are summarized in Table I.

Using this method, simple substances such as di-*n*-butyl or diisopropyl ether were readily transformed into 2 equiv of the corresponding acetate. Exposure of some benzylic ethers to this reagent revealed an interesting phenomenon. Whereas benzyl 2-octyl ether was converted after 17 hr at 80° to equal amounts of benzyl and 2-octyl acetates, benzyl butyl ether afforded by the same procedure butyl acetate but no benzyl acetate. Experiments firmly established that benzyl acetate alone in $FeCl_3$–Ac_2O was rapidly transformed at 80° to a mixture of acetylated products complexed to the Lewis acid and therefore insoluble in hexane. However, when benzyl acetate was exposed to $FeCl_3$–Ac_2O in the presence of an equimolar quantity of either *n*-butyl acetate or 2-octyl acetate, the Friedel–Crafts acetylation was dramatically retarded. Almost all of the benzyl acetate (along with *n*-butyl or 2-octyl acetate) was recovered after 17 hr at 80°. This remarkable effect, although unclear, may be due to selective complexation by the ester carbonyl moiety as a strong Lewis base.

In any event, the preceding experiments clearly distinguish two competing reactions of benzylic ethers in $FeCl_3$–Ac_2O. Evidently benzyl 2-octyl ether was converted to a mixture of acetates faster than it underwent acetylation, but benzyl butyl ether was first acetylated, then cleaved to provide *n*-butyl acetate as the only hexane-soluble product. As expected, diphenyl ether and equilenin were also acetylated but not cleaved at the ether linkage.

The mechanism as well as the stereochemistry of this ether-to-acetate transformation was of interest. When optically active methyl 2-octyl ether (**5**) was heated with $FeCl_3$–Ac_2O, 2-octyl acetate appeared which was largely (96%) racemized and of inverted configuration. However, cleavage of (+)-benzyl *d*-2-octyl ether (**6**) afforded (+)-*d*-2-octyl acetate which had undergone 85% racemization.[9] While cholesteryl methyl ether was smoothly transformed to cholesteryl acetate in high yield, cholestanyl methyl ether (**12**) was converted to a mixture of 3α- and 3β-cholestanyl acetates as well as to Δ^2-cholestene.[3a,10] These data support a dual mechanism involving O-acylation of the ether followed by dissociation of the more stable carbonium ion or by nucleophilic displacement at the oxonium ion by acetate.



The present fragmentation is not limited to classic alkyl ethers alone. Since its inception as an oxygen protecting group,[11] the *tert*-butyldimethylsilyl moiety has been widely employed as an alcohol blocking agent which is easily removed by treatment with tetra-*n*-butylammonium fluoride.[4a] We have observed that these silyl ethers are rapidly cleaved (15 min, 0°) using $FeCl_3$–Ac_2O. For example, (+)-*tert*-butyldimethylsilyl *d*-2-octyl ether (**7**) afforded *d*-2-octyl acetate in 92% yield with 88% retention of configuration. This technique complements the direct deprotection by fluoride and further illustrates the unexplored potential of $FeCl_3$–Ac_2O for selective ether cleavage.

We have also demonstrated the exceptional mildness of this reagent by converting ether **8**[12] into its acetate **9** in quite acceptable yield without olefin isomerization. As is evident from its highly functionalized structure, this sub-

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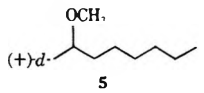
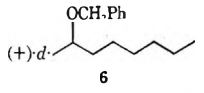
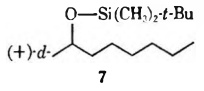
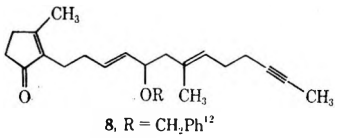
Table I

Ether	Time, hr	Temp, °C	$FeCl_3$, equiv	Product[a] (% yield)[b]
n-Butyl ether (142-96-1)	16	80	0.2	*n*-Butyl acetate (45)
Isopropyl ether (108-20-3)	24	80	0.15	Isopropyl acetate (83)
$PhCH_2O$ *n*-Bu (588-67-0)	17	80	0.32	*n*-Butyl acetate (88)
1	0.25	0	0.1	**3** (83)
2	0.66	38	0.1	**4** (76)
 5	24	80	0.22	2-Octyl acetate (64)
 6	22	80	0.34	Benzyl acetate (45) 2-Octyl acetate (45)
 7	0.25	0	0.15	2-Octyl acetate (92)
 8, R = CH_2Ph[12]	5	50	0.55	**9** (**8**, R = Ac) (44)[c]
3β-Cholesteryl methyl ether (**10**)	1	25	0.16	3β-Cholesteryl acetate (**11**) (87)
3β-Cholestanyl methyl ether (**12**)	17	25	0.15	3β-(Cholestanyl acetate (31) 3α-Cholestanyl acetate (14) Δ^2-Cholestene (10)

[a] These products were identified by their nmr and ir spectra and by comparison with authentic samples. [b] Yields are based on distilled or chromatographed products. [c] This yield has not been maximized.

stance is completely incompatible with the two most common methods for removing benzylic ethers: metal–ammonia reduction or catalytic hydrogenation. Such specificity along with its simplicity and versatility should make the ferric chloride–acetic anhydride reagent a worthwhile alternative to current techniques for dealing with ethers as protecting groups in synthesis.[16]

Experimental Section

Melting points were determined using a Kofler hot-stage microscope. Nmr spectra of deuteriochloroform or deuteriobenzene solutions were recorded on a Varian A-60 or T-60 spectrometer with tetramethylsilane as an internal standard. Ir spectra were determined as neat films or in solution on a Perkin-Elmer 137 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Gas–liquid chromatographic analyses were carried out on a Hewlett-Packard HP-402 or 5750B gas chromatograph using the following columns: (a) 3% XE-60 (6 ft) on 80–100 gas chromatograph Q; (b) 3% SE-30 (5 ft) on Chromosorb W 60–80; (c) 3% OV-17 (6 ft).

Materials. Commercially available di-*n*-butyl and diisopropyl ether (Matheson Coleman and Bell) were distilled from sodium. Benzyl butyl ether (MCB) was washed with $FeSO_4$ and then distilled from sodium. Cholestanyl methyl ether,[13a] cholesteryl methyl ether,[13a] methyl *d*-2-octyl ether,[13] and benzyl *d*-2-octyl ether[14] were prepared as described in the literature. Acetic anhydride (ACS reagent grade, J. T. Baker) was distilled. Anhydrous ferric chloride (MCB) was used directly.

General Procedure for the Cleavage of Simple Dialkyl Ethers. Conversion of Di-*n*-butyl Ether to Butyl Acetate. To a solution of di-*n*-butyl ether (4.64 g, 35.5 mmol) and acetic anhydride (15 ml) in a flask equipped with condenser and drying tube was added anhydrous ferric chloride (1.0 g, 6.2 mmol). A mild exothermic reaction ensued. The dark reaction mixture was heated on a steam bath (internal temperature 80°) for 16 hr, then fractionally distilled to afford *n*-butyl acetate (32 mmol, 46%) along with small amounts of acetic acid and acetic anhydride. These impurities could be removed by washing the distillate with sodium bicarbonate solution.

Cleavage of Benzyl *n*-Butyl Ether. A solution of benzyl *n*-butyl ether (3.0 g, 18.3 mmol) in acetic anhydride (7 ml) was treated with ferric chloride (1 g, 6.2 mmol) and then heated at 80° (steam bath) for 17 hr. After cooling, the dark reaction product was partitioned between hexane and water. Three hexane extracts were combined, filtered, washed twice with water and three times with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. Distillation afforded 1.85 g (88%) of butyl acetate, bp 126–27°, having nmr and ir spectra identical with an authentic sample.

Synthesis of 1-Acetoxy-4-chloro-*trans*-2,3-dimethyl-2-butene (3) from 1. To a solution of **1**[5] (49 mg, 0.26 mmol) in acetic anhydride (2 ml) at 0° under N_2 was added ferric chloride (4 mg, 0.02 mmol). The mixture was stirred 15 min at 0° then worked up by extraction with three portions of hexane. The combined extracts were washed with water and sodium bicarbonate solution, dried ($MgSO_4$), and concentrated. Kugelrohr distillation of the crude product (70°, 100 mm) afforded 39 mg (83%) of **3**: nmr (benzene-d_6) δ 4.44 (s, 2 H), 3.70 (s, 2 H), 2.58–2.68 (broad s, 9 H); ir 5.77 μ; glc (XE-60, 65°) one peak, retention time 8.0 min.

A portion of this material was stirred with 2 equiv of sodium acetate (anhydrous) in hexamethylphosphoric triamide (HMPA) at room temperature for 12 hr. This reaction afforded a sample of diacetate **4** containing only the trans isomer: nmr (benzene-d_6) δ 4.50 (s, 4 H), 1.68 (s, 12 H); (in $CDCl_3$) δ 4.65 (s, 4 H), 2.07 (s, 6 H), 1.80 (s, 6 H), ir (film) 5.78 μ; glc (OV-17, 90°) one peak, retention time 12.2 min. None of the corresponding cis isomer could be detected either by nmr (methylene absorption at δ 4.74) or by glc (OV-17, 90°, retention time 10.8 min).

Synthesis of 4-Acetoxy-*trans*-2,3-dimethyl-2-butenyl *tert*-Butyl Ether (2) from 1. A mixture of **1**[5] (79 mg, 0.4 mmol) and anhydrous sodium acetate (77 mg, 0.94 mmol) in dry HMPA was stirred at room temperature under N^2 for 12 hr. After partitioning between hexane and water, the hexane fraction was dried ($MgSO_4$) and concentrated. The residue was purified by Kugelrohr distillation (70° (100 mm)) to afford 85 mg (95%) of **2** as an oil; nmr ($CDCl_3$) δ 4.62 (s, 2 H), 3.84 (s, 2 H), 2.04 (s, 3 H), 1.80 (s, 6 H), 1.22 (s, 9 H); ir (film) 5.77 μ.

Synthesis of 1,4-Diacetoxy-*trans*-2,3-dimethyl-2-butene (4) from 2. A solution of **2** (45 mg, 0.20 mmol) in acetic anhydride (0.5 ml) was treated with 4 mg (0.02 mmol) of ferric chloride. This mixture was stirred under N_2 at 38° for 35 min. Work-up by hexane extraction as described above afforded an orange oil. Kugelrohr

distillation (80° (100 mm)) yielded 30 mg (76%) of **4** as a colorless oil. Its spectral data were identical with that given above. Again, no cis isomer could be detected by nmr or glc as described above.

Synthesis of Cholesteryl Acetate from Cholesteryl Methyl Ether 10. Cholesteryl methyl ether[3a] (0.253g, 0.63 mmol) was dissolved in 1:1 acetic anhydride–ethyl acetate (4 ml) with gentle warming. After cooling to room temperature, ferric chloride (16 mg, 0.1 mmol) was added and the purple reaction mixture was stirred 1 hr at room temperature, then poured into water and extracted three times with hexane. The combined extracts were washed with water and $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated to a white solid. Column chromatography of this crude product on silica gel eluting with 1:4 ether–hexane afforded 0.217 g (87%) of cholesteryl acetate, mp 109–111° (after one recrystallization from methanol; reported[3a] mp 110–111°), which was identical by ir, nmr, and glc analysis (XE-60, 250°, retention time 5.4 min) with an authentic sample.

Cleavage of Cholestanyl Methyl Ether 12. A solution of **12**[3a] (0.329 g, 0.82 mmol) in ethyl acetate (2 ml) was diluted with acetic anhydride (2 ml). Ferric chloride (20 mg, 0.12 mmol) was added and the reaction mixuture was stirred at room temperature for 17 hr, then worked up by hexane extraction in the usual fashion. Glc analysis of the crude product (XE-60, 250°) indicated three major products. Column chromatography (silica gel, 2:98 ether–hexane) afforded 33 mg (10%) of Δ^2-cholestene. Further elution produced 0.150 g of 32:68 mixture of 3α- and 3β-cholestanyl acetates which represents yields of 14 and 31% for these respective acetates. Their identity was established by glc coinjection with authentic samples (retention times 4.5 and 5.0 min, respectively) as well as by nmr spectroscopy.

Cleavage of Methyl *d*-2-Octyl Ether 5. (+)-Methyl *d*-2-octyl ether (2.0 g, 13.9 mmol, $[\alpha]^{20}D$ +6.90°; prepared[13] using 95% (+)-*d*-2-octanol (Aldrich) $[\alpha]^{20}D$ 9.5°) was dissolved in acetic anhydride (5 ml). Ferric chloride (0.5 g, 3.1 mmol) was added and the reaction mixture was heated (steam bath) at 80° for 24 hr. The usual work-up (hexane extraction; water, $NaHCO_3$ washing) afforded 1.77 g of crude product after solvent removal. Kugelrohr distillation (90–100° (20 mm)) afforded 1.50 g (64%) of 2-octyl acetate identical by ir and nmr with an authentic sample and exhibiting one peak on glc analysis (XE-60, 69°, retention time 2.6 min); $[\alpha]^{20}D$ −0.27° which corresponds to 3.8% inversion of configuration.

The enantiomeric purity of a sample of (+)-*d*-2-octyl acetate (kindly provided by Professor J. P. Collman, Stanford University) was unchanged after heating in $FeCl_3$–Ac_2O for 24 hr at 80°.

Cleavage of Benzyl *d*-2-Octyl Ether 6. Ferric chloride (0.5 g, 3.1 mmol) was added to a solution of **6**[14] (2.0 g, 9.2 mmol, $[\alpha]^{20}D$ +25.57°, 94% enantiomeric purity) in acetic anhydride (5 ml) and the resulting solution was heated at 80° for 22 hr. Work-up by hexane extraction in the usual manner yielded 2.186 g of crude product. Kugelrohr distillation afforded 1.317 g (45%) of a 1:1 mixture of octyl and benzyl acetates by glc analysis (XE-60, 72°, retention times 2.2 and 7.1 min, respectively), having $[\alpha]^{20}D$ +1.01° (c 51, benzyl acetate). This represents 15.2% retention.

Synthesis of *tert*-Butyldimethylsilyl *d*-2-Octyl Ether 7. The procedure of Corey and Venkateswarlu was followed.[1a] A solution of (+)-*d*-2-octanol (3.0 g, 23 mmol, $[\alpha]^{20}D$ 9.25°, 93% optically pure) in dry *N,N*-dimethylformamide (20 ml) was stirred with imidazole (5.42 g, 80 mmol) and *tert*-butyldimethylsilyl chloride (4.5 g, 30 mmol, Willowbrook Labs) under N_2 at room temperature for 15 hr. The reaction mixture was then poured into water and extracted three times with hexane. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Distillation afforded 4.47 g (80%) of **7** as a colorless liquid: bp 117–118° (15 mm); $[\alpha]^{20}D$ 13.56° (93% enantiomeric purity); d^{20} 0.8099; nmr ($CDCl_3$) δ 3.70 (broad t, 1 H, J = 7 Hz), 1.11 (d, 3 H, J = 7 Hz), 0.85 (s, 9 H); ir (film) 3.40, 3.60, 6.80, 6.85, 7.28, 7.38, 7.97, 8.80, 8.91, 9.2–9.5, 9.92, 10.45, 10.62, 11.95, 12.90 μ. *Anal.* Calcd for $C_{14}H_{32}OSi$: C, 68.8; H, 13.1. Found: C, 68.7; H, 13.15.

Cleavage of *tert*-Butyldimethylsilyl *d*-2-Octyl Ether (7). A solution of **7** (0.62 g, 2.5 mmol) in acetic anhydride (1.5 ml) was cooled to 0° under N_2. Ferric chloride (60 mg, 0.37 mmol) was added and 15 min later the reaction mixture was worked up by hexane extraction. Kugelrohr distillation of the crude product afforded 0.85 g (98%) of oil. Glc analysis showed this to be a 1:1 mixture of 2-octyl acetate and *tert*-butyldimethylsilyl acetate. Column chromatography (silica gel, benzene–hexane mixtures) afforded pure 2-octyl acetate (0.40 g, 92%, one peak on glc analysis); $[\alpha]^{20}D$ +5.78° (c 32.6, $CHCl_3$) which corresponds to 88% retention of configuration.

Cleavage of Benzyl Ether (8). Synthesis of 9. Ferric chloride (20 mg, 0.12 mmol) was added to a solution of **8**[12] (75 mg, 0.22 mmol) in acetic anhydride (1.0 ml) and the dark solution was stirred under N_2 at 55° for 5 hr. After cooling and partitioning between hexane and water, the combined organic extracts were washed with $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. Tlc (1:1 ethyl acetate–hexane) and glc (XE-60, 225°) analysis revealed the presence of only one other substance in addition to starting material. Column chromatography (silica gel, 1:3 ethyl acetate–hexane) separated 15 mg of **8** from 24 mg (44%) of the acetate **9**. Its identity with an authentic sample[15] of **9** was confirmed by their superimposable nmr and ir spectra, identical tlc behavior, and glc retention times (XE-60, 225°, 5.2 min): nmr ($CDCl_3$) δ 5.60–5.02 (complex m, 3 H), 2.02 (s, 3 H), 1.70 (broad s, 3 H), 1.61 (broad s, 3 H); ir 3.41, 5.76, 5.89, 6.09, 6.95, 7.22, 7.32, 8.10, 8.50, 9.31, 9.79, 10.41 μ.

Registry No.—**1**, 53060-22-3; **2**, 53060-23-4; **3**, 53060-20-1; **4**, 3780-51-6; **5**, 53142-02-2; **6**, 53060-24-5; **7**, 53060-25-6; **8** (R = CH_2Ph), 53060-26-7; **9**, 53060-21-2; **10**, 1174-92-1; **11**, 604-35-3; **12**, 53109-81-2; $FeCl_3$, 7705-08-0; acetic anhydride, 108-24-7.

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(6) W. Oroshnik and R. A. Mallory, *J. Amer. Chem. Soc.*, **72**, 4603 (1950).
(7) Prolonged reaction of the chloro ether **1** results in eventua displacement of the chloride by acetate.
(8) An authentic mixture of cis and trans **4** may be prepared from *cis,trans*-1,4-dibromo-2,3-dimethyl-2-butene [*cf.* O. J. Sweeting and J. R. Johnson, *J. Amer. Chem. Soc.*, **68**, 1057 (1946)] by reaction with sodium acetate (NaOAc) in hexamethylphosphoric triamide (HMPA). Besides being readily separable using gas–liquid chromatography, nmr spectroscopy in benzene-d_6 (see Experimental Section). The isomeric purity of **3** was determined by conversion to **4** with NaOAc–HMPA and subsequent analysis.
(9) Similar results have been noted in the reaction of *s*-butyl methyl ether with acids such as zinc chloride or stannic chloride: R. L. Burwell, Jr., L. M. Elkin and L. G. Maury, *J. Amer. Chem. Soc.*, **73**, 2428 (1951).
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(12) This compound has been synthesized stereospecifically by W. S. Johnson and S. Escher at Stanford University, and we thank them for a generous sample.
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(16) We wish to thank the Department of Chemistry at Cornell University for generous financial assistance. We also acknowledge support for V.R.S., Jr., by grants (to William S. Johnson) from the National Institutes of Health and the National Science Foundation.

Iodination of Substituted Sodium Phenylpropiolates

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Received July 24, 1974

Rate constants were determined for the iodination by iodine of eleven substituted sodium phenylpropiolates ($XC_6H_4C{\equiv}CCOO^-Na^+$) in water at 30°. Reactions were conducted in the presence of iodide ion (0.1 *M*), and under these conditions the reaction is third order, first order in substrate, free iodine, and iodide ion. Hammett plots using σ or σ^+ are not linear. This is interpreted as indicating that the third-order reaction involves a termolecular transition state in which the extent of bond formation between the electrophilic iodine and the nucleophilic iodide ion and the substrate is not necessarily the same but depends on the nature of the substituent. The major products of the reactions are the substituted *trans*-α,β-diiodocinnamic acids. By-products in some of the reactions are substituted α,β,β-triiodostyrenes. Small amounts of ketonic products (<1%) were detected in all but one of the cases and arise from a small amount of solvent incorporation. Activation parameters were determined for the iodination of five of the sodium phenylpropiolates.

The kinetics of iodination of sodium phenylpropiolate in water is characterized by the three-term equation (eq 1)

$$k_{obsd} = k_t K[I^-]/(K + [I^-]) + k'K/(K + [I^-]) + k''K/[I^-](K + [I^-]) \quad (1)$$

where K is the dissociation constant of the triiodide ion. The experimental rate law is $-d[I_2]_T/dt = k_{obsd}[A][I_2]_T$, in which $[I_2]_T$ represents the total titratable iodine. The three terms have been interpreted to represent respectively an iodide ion catalyzed reaction by free iodine, $k_1[A][I_2][I^-]$, a reaction of free iodine, $k_2[A][I_2]$, and possibly a reaction by the hydrated iodine cation, $k_3[A][H_2OI^+]$, where A is the acetylenic substrate.[2]

The first, termolecular, term presumably involves an electrophilic attack because the anion of the acid reacts slightly faster than the acid itself. However, in the similar iodination of propiolic acid, the corresponding term could not be clearly designated as electrophilic or nucleophilic. It was assumed that in the reaction of propiolic acid, bond making to the nucleophile predominates somewhat over bonding to the electrophile in the rate-controlling step, and *vice versa* for the anion.[3]

In order to gain more insight into the nature of the termolecular term and to see what contributions the electrophile and nucleophile make to the transition state, it seemed of interest to study the effect of substitution on the iodination of substituted sodium phenylpropiolates ($XC_6H_4C{\equiv}CCOO^-Na^+$).

Results

Rates of iodination of 11 substituted sodium phenylpropiolates were determined at 30° in water, and the results are listed in Table I. The rate constants are averages of triplicate runs. The third runs were conducted after suitable time intervals with completely new solutions. The synthesis of the starting acids is described in the Experimental Section.

Effect of Iodide Ions. All reactions were conducted at a 0.1 *M* KI concentration. The contribution of the three terms in eq 1 depends on the iodide ion concentration. At high iodide ion concentration (0.02–0.10 *M*) the first term predominates and contributes over 90% to the total rate. At these concentrations of iodide ion the rate of the reaction is independent of the iodide ion concentrations.[2] Because we were only interested in the third-order term it was necessary first to establish that all the substituted acids follow the same rate law. The iodide ion dependence on the rate was therefore checked for a number of representative acids (Table II). The rate is indeed independent of the iodide ion concentration for these acids at the high iodide ion concentrations mentioned. The small decreases in rate as the iodide ion concentration is reduced from 0.12 *M* to approximately 0.02 *M* are most likely due to an ionic strength effect because the reaction is highly sensitive to variations in the ionic strengths. When reaction is conducted at a constant ionic strength (μ = 2.0 *M*), this effect disappears as shown in Table II for sodium *m*-chlorophenylpropiolate. When the second and third terms in eq 1 begin to gain im-

Table I
Rates of Iodination of Sodium Phenylpropiolates
($[XC_6H_4C{\equiv}CCOONa] \simeq 0.040$ *M*, $[I_2] \simeq 0.02$ *M*, [KI] = 0.100 *M*)

Substituent	Registry no.	$k_{obsd} \times 10^3$, l. (mol sec)$^{-1}$	ΔE_a, kcal/mol	log *A*	$\Delta S^*_{298.2}$, eu
p-OCH_3	53059-90-8	25.6			
p-CH_3	53059-91-9	3.10	15.1	8.35	−22.3
m-CH_3	53059-92-0	1.75			
H	7063-23-2	1.30	15.0	7.93	−24.2
m-OCH_3	53059-93-1	1.15			
p-Cl	2532-21-0	1.11	15.0	7.86	−24.6
p-Br	53059-94-2	0.979			
m-Br	53059-95-3	0.701	15.1	7.73	−25.1
m-Cl	53059-96-4	0.685			
m-NO_2	53059-97-5	0.385			
p-NO_2	53059-98-6	0.310	15.7	7.79	−24.9

Table II
Dependence of the Rate of Iodination on the Iodide Ion Concentration
($[XC_6H_4C{\equiv}CCOONa] \simeq 0.040$ *M*, $[I_2] \simeq 0.005$ *M*)

[KI], *M*	$k_{obsd} \times 10^3$, l. (mol sec)$^{-1}$	[KI], *M*	$k_{obsd} \times 10^3$, l. (mol sec)$^{-1}$
Sodium *p*-methylphenylpropiolate		Sodium *m*-chlorophenylpropiolate	
0.1200	2.82	0.1200	0.678
0.1000	2.79	0.0800	0.652
0.0800	2.78	0.0500	0.629
0.0500	2.81	0.0300	0.612
0.0300	3.04	0.0200	0.626
0.0200	3.50	0.0100	0.660
0.0100	5.12	0.0050[a]	0.606
0.0050[a]	5.59		
Sodium *m*-bromophenylpropiolate		Sodium *m*-chlorophenylpropiolate (μ = 2.00 *M* ($NaClO_4$))	
0.1200	0.695	0.1200	1.17
0.0800	0.677	0.0800	1.17
0.0500	0.661	0.0500	1.20
0.0300	0.654	0.0100	1.39
0.0200	0.653	0.0050[a]	1.22
0.0100	0.700		
0.0050[a]	0.675		

[a] $[I_2] \simeq 0.002$ *M*.

Table III
Product Analysis

Substituent	A,[a] mol %	B,[b] mol %	C,[c] mol %	D,[d] wt %
p-OCH_3	0	0	62	0.67
p-CH_3	0	29	19	
m-CH_3	62	16	9	
H	74		0.5	0
m-OCH_3	65	22	3.3	0.14
p-Cl	109[e]		5.5	
p-Br	104[e]		3.1	0.16
m-Cl	5	99	0	
m-Br	49	24	0	
m-NO_2	30	60	C	
p-NO_2	118[e]		C	0.90

[a] Pure substituted diiodocinnamic acid isolated. [b] Additional substituted diiodocinnamic acid calculated from iodine analysis of residue. See Experimental Section. [c] Substituted triiodostyrene isolated, based on the consumption of 1 mol of iodine per mole of styrene produced. [d] Ketonic material isolated. [e] See Experimental Section.

portance, the rate *increases* with a *decrease* in iodide ion concentration, and this is seen to begin when the iodide ion concentration is lowered to about 0.02 *M*, although the turnover depends somewhat on the substituent. Since all acids tested show the same behavior, it is likely that all substituted acids behave like the unsubstituted one. At the iodide concentration here used it can safely be assumed that the first term in eq 1 greatly predominates, and that this is the reaction in which the substituent effect was studied.

Activation Parameters. These were determined for six of the acids from measurements of the rate constants at six different temperatures over a 25° range. Results are listed in Table I.

Product Isolation. Except a noted below, the major products of the addition reaction were the substituted α,β-diiodocinnamic acids, which by analogy to the unsubstituted acid were considered to be the trans isomers. All showed loss of iodine on melting, characteristic of *trans*- but not of *cis*-1,2-diiodoethylene.[4] The acids were isolated from runs conducted on a large scale, but under conditions of the kinetic runs, and compared through melting points and ir spectra with authentic samples. Only one of the substituted iodinated products had previously been prepared. The others were synthesized as described in the Experimental Section. Because in all runs the concentration of the acetylenic acid was in excess of the iodine, the isolation of the products involved a separation of the two acids, which was difficult in some cases. In the first column in Table III are reported pure isolated acids, while in the second column are additional data obtained from an iodine analysis of the residual acid mixture. These figures are less certain than the former.

The second term in eq 1 is not completely eliminated, and from the reaction corresponding to this term a small amount of products derived from β-keto acids can be anticipated. These are formed by attack of water on a vinyl cationic intermediate followed by ketonization of the enol formed. Some ketonic products were formed from all acids except the unsubstituted acid and were characterized qualitatively by different retention times on tlc plates. In four of the isolation runs the presence of the keto acid was also established quantitatively by extraction with Girard's reagent and subsequent extraction with base (Table III). In the case of the *p*-bromo compound the product was identified more fully as *p*-bromobenzoylacetic acid (as the ethyl ester) by comparison of the nmr spectrum with that of unsubstituted benzoylacetic acid. In the same way, *p*-bromoacetophenone was also detected, which is formed by decarboxylation of the keto acid. Iodine-free material was isolated, since iodide ion, present in the reaction mixture, is known to remove halogen from halo-β-keto acids. It is assumed that all of the ketonic products are derivatives of benzoylacetic acid, because all displayed similar mobilities on tlc plates. The amounts of keto acid formed never exceeded 1% of the total products.

The other by-products are α,β,β-triiodostyrenes ($XC_6H_4CI{=}CI_2$) which were identified by different retention times on tlc and elemental analysis in two cases. The amounts thus formed were small or absent when the substituents are electron withdrawing, but they increased as the substituent releases electrons, until the triiodostyrene became the major product in the case of sodium *p*-methoxyphenylpropiolate.

This was bothersome because in the formation of the styrene additional iodine is used up, and it was necessary to show that the rate constant for iodination of sodium *p*-methoxyphenylpropiolate really represents the rate-determining iodination of the acetylenic acid to the diiodocinnamic acid.

The mechanism of the side reaction which leads to the formation of substituted triiodostyrenes appears to be quite complex. It had been previously shown that α,β-diiodocinnamic acid does *not* react with iodine to form α,β,β-triiodostyrene, and it had therefore been assumed that the styrene was formed from a cationic intermediate as shown.[2]

$$C_6H_5\dot{C}{=}C(I)COO^- \text{ or } C_6H_5C(I^+){=}CCOO^- \longrightarrow C_6H_5C{\equiv}CI + CO_2 \xrightarrow{I_2} C_6H_5CI{=}CI_2$$

Because the third-order reaction does not proceed through a cationic intermediate, and because so much of the styrene was formed in the case of the *p*-methoxy compound, the possibility had to be considered that the sodium *p*-methoxy-α,β-diiodocinnamate first forms and then *does* react with iodine, as shown in eq 2. This proved to be the case. A

$$p\text{-}CH_3OC_6H_4CI{=}CICOO^- + I_2 \longrightarrow p\text{-}CH_3OC_6H_4CI{=}CI_2 + CO_2 + I^- \quad (2)$$

solution of sodium *p*-methoxy-α,β-diiodocinnamate reacts with iodine in the presence of iodide ion to form *p*-methoxytriiodostyrene. Subsequently, the observation was made that sodium *p*-methoxy-α,β-diiodocinnamate even reacts to form the styrene in the *absence* of iodine but in the *presence* of iodide ion, which must therefore furnish the additional iodine.[5] Finally, sodium *p*-methoxy-α,β-diiodocinnamate decarboxylated on standing overnight in water in the absence of iodine or iodide ion, to form what is possibly a mono- or diiodostyrene.[6] There are, therefore, several routes by which the styrene can be formed in this case, which do not necessarily involve the original iodine. The rate of iodination of sodium *p*-methoxyphenylpropiolate is very fast, but the kinetics of the reaction did not behave abnormally. The average extent of reaction in the kinetic runs was 88%, and good second-order rate constants were always obtained. In the isolation runs the reaction was allowed to stand for 2 weeks, and the diiodocinnamic acid formed initially had ample time to react further to form the styrene.

It is therefore assumed that the iodination of *p*-methoxyphenylpropiolate leads in the rate-determining step to the α,β-diiodo acid, which in a series of steps reacts further to form the styrene. This view is strengthened by the observation that, if in the preparative iodination of the methoxy acid at 0 to 5° the product was isolated immediately,

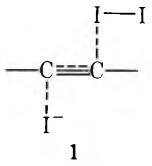
81% of *p*-methoxy-α,β-diiodocinnamic acid is obtained, but if the reaction was carried out at room temperature for 1 day, almost all of the product was the styrene. It is therefore also assumed that the rate constant reported in Table I is the real rate constant for iodination to the diiodo acid, but some doubt about the reliability of this rate constant cannot be erased. This is also true for the *p*-methyl compound, which shows a relatively large amount of styrene formation.

Discussion

The rate constants in Table I indicate that the termolecular term involves essentially an electrophilic attack because the *p*-methoxy compound reacts the fastest and the *p*-nitro acid the slowest. The overall differences in rates are not large, and consequently the activation energies are not very revealing and are all of the same order of magnitude, although the reaction of the *p*-nitro compound has the highest activation energy. The activation entropies have uniformly large negative values as had been observed earlier for the unsubstituted acid.[2] Rate constants and activation parameters for the unsubstituted acid agree well with those previously reported.

Although the general trend of the rate constants is that expected of an electrophilic attack, a Hammett plot of the data against either σ or σ^+ is nonlinear. A break in the straight line, as observed in Figure 1, is often taken as a change in mechanism, but the two straight lines have been drawn rather arbitrarily, and the data can equally well be represented by a smooth least-squares parabola.[1]

The most convincing explanation is similar to one that has been advanced for the bromide ion catalyzed bromination of substituted phenylmethylacetylenes, which behaves very similarly.[7] The third-order terms in iodination,[2,3] in some brominations,[7,8] as well as in hydrochlorination,[9] have generally been considered to involve termolecular reactions of transition states of the type shown in 1 for iodination (Ad_3E). Although the reactions are termolecular, the transition states are assumed to be slightly different for each compound, depending on the substituent. The relative extent of bond formation between the substrate and the electrophilic iodine and the nucleophilic iodide ion has proceeded to a different degree for each of the compounds. When the substituent is strongly electron donating, bonding of the substrate to the electrophile predominates over that to the nucleophile and the transition state will have a considerable amount of carbonium ion character, which is aided by the substituent. When the substituent is electron attracting, the bonding of the nucleophile to the triple bond will have progressed further than bonding to the electrophile, and this is aided by the nitro group. The various transition states will have varying extents of electrophilic and nucleophilic bond formation, although kinetically all are third order.



1

The Hammett plots for the two linear approximations are better when σ^+ rather than σ values are used (Figure 1). The superiority of σ^+ values is understandable if one realizes that only for the most electron-donating substituents are the substituent constants significantly different. It is for compounds with these substituents that a considerable partial positive charge would be generated on the benzylic carbon atom. Because this charge can be effectively delocalized into the ring and the substituent, the correlation of their rates ought to be better with σ^+ constants. A truly synchronous transition state, in which no charge at all is developed, might be expected to be better correlated with σ values.

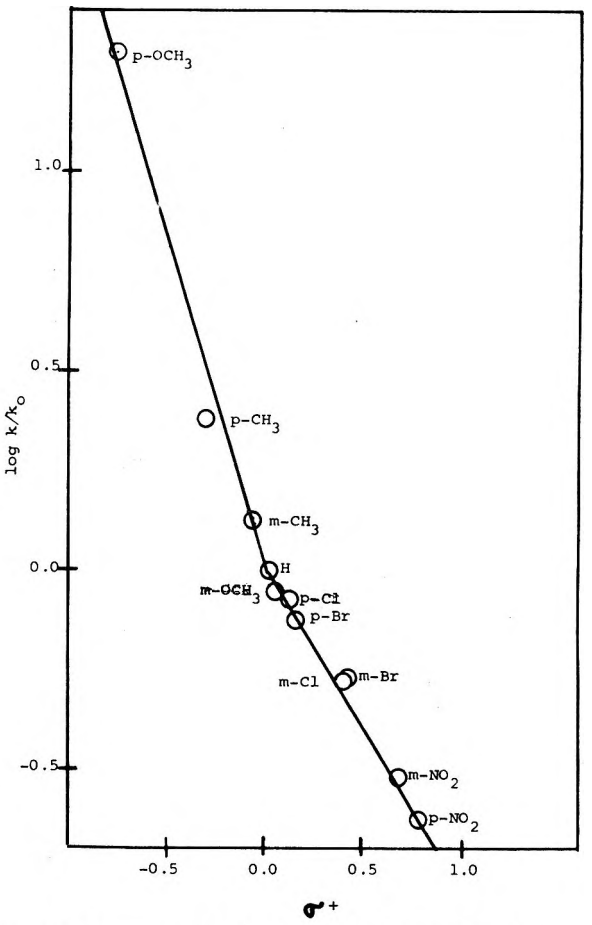


Figure 1. A Hammett plot of rates of iodination against σ^+.

An approximate measure of the degree of electron delocalization and positive charge development can be obtained from the ρ values of the correlations. When plotted against σ^+, ρ is -1.66 ± 0.10 for the three fastest and -0.774 ± 0.01 for the remaining compounds. These are much lower than ρ in those addition reactions to olefins and acetylenes where carbonium ion intermediates are thought to be involved. In those cases ρ is usually around -4.[10] The low ρ values obtained here are, however, in accord with a transition state in which the effects of the electrophile and nucleophile are more nearly balanced. They are compatible with the approximate value of -1.9 reported for the slower compounds in the bromide ion catalyzed bromination of phenylacetylenes.[7]

The behavior of the substituted acids in iodination also strengthens the argument that the third-order term represents, in fact, a termolecular, although not completely synchronous, reaction. The various alternatives that can be considered for this term, such as bimolecular reaction by triiodide ion, or a series of bimolecular reactions, involving iodine and iodide ion and an ionic intermediate, would less well account for the observed behavior, although all are kinetically equivalent.[3] Fast reversible complexing of the acetylene with iodine, followed by attack of iodide ion, would also account for the kinetics and would avoid postulating a termolecular reaction,[11] but it would not be as compatible with the near absence of solvent-incorporated products.

Table IV

Substituent	Registry no.	Mp, deg	Calcd for	Analysis, % Calcd	Found
p-OCH_3	53178-57-7	117.7–118.1 dec	$C_{10}H_8I_2O_3$	C, 27.93 H, 1.88	C, 28.18 H, 1.95
p-CH_3	53059-99-7	158.6–159.4 dec	$C_{10}H_8I_2O_2$	C, 29.01 H, 1.95	C, 28.82 H, 2.04
m-CH_3	53060-00-7	134.1–134.9 dec	$C_{10}H_8I_2O_2$	C, 29.01 H, 1.95	C, 28.83 H, 1.97
p-Cl	53060-01-8	159.0–159.8 dec	$C_9H_5ClI_2O_2$	C, 24.88 H, 1.16	C, 24.76 H, 1.19
m-Cl	53060-02-9	143.1–143.9 dec	$C_9H_5ClI_2O_2$	C, 24.88 H, 1.16	C, 24.67 H, 1.10
p-Br	53060-03-0	158.2–159.0 dec	$C_9H_5BrI_2O_2$	C, 22.57 H, 1.05	C, 22.39 H, 1.08
m-Br	53060-04-1	163.4–164.2 dec	$C_9H_5BrI_2O_2$	C, 22.57 H, 1.05	C, 22.45 H, 1.03
p-NO_2	53060-05-2	174.0–174.8 dec	$C_9H_5I_2NO_4$	C, 24.29 H, 1.13	C, 24.26 H, 1.10
m-NO_2	53060-06-3	148.2–149.0 dec	$C_9H_5I_2NO_4$	C, 24.29 H, 1.13	C, 24.41 H, 1.14

Experimental Section

Melting points were taken with a Hershberg melting point apparatus and are corrected. Infrared spectra were taken on a Perkin-Elmer infracord and nmr spectra on a Varian A-56/60 nmr spectrophotometer in $CDCl_3$ or acetone which contained TMS. All pH measurements were made on a Beckman Model G pH meter. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Materials. Phenylpropiolic acid (Aldrich Chemical Co.) was recrystallized four times from CCl_4 and had a mp of 137.6–138.4° (lit.[12] 136.9–137.5°).

The synthesis of the substituted phenylpropiolic acids started with commerciapavailable substituted benzaldehydes, which were convejzto substituted cinnamic acids by a Doebner reaction. The cinnamic acids were brominated, and the resulting substituted α,β-dibromohydrocinnamic acids were dehydrobrominated with KOH to the substituted phenylpropiolic acids according to individual literature procedures. Yields ranged from 30 (*m*-NO_2) to 75% (*p*-CH_3). The recrystallized acids had the following mp (literature mp in parentheses): *p*-CH_3O 144.8–145.4° (144.0–144.4°);[12] *p*-CH_3 147.0–147.8° (149–150°);[13] *m*-CH_3O 109.5–110.5° (109°);[14] *m*-CH_3 135.6–136.4° (135–136°);[15] *p*-Cl 192.9–194.2° (192–193°);[12] *m*-Cl 146.0–146.8° (144.3–145.1°);[12] *m*-NO_2 144.4–145.1° (143.7–144.4°).[12] Two of the acids were analyzed because their mp differed from literature values. *p*-Bromophenylpropiolic acid, mp 186.7–187.3° (201°).[16] *Anal.* Calcd for $C_9H_5BrO_2$: C, 48.03; H, 2.24. Found: C, 48.19; H, 2.35. *m*-Bromophenylpropiolic acid, mp 163.6–164.4° (135–136°).[17] *Anal.* Calcd for $C_9H_5BrO_2$: C, 48.03; H, 2.24. Found: C, 47.99; H, 2.24. The *p*-nitro compound was prepared by direct nitration of phenylpropiolic acid in 25% yield and had mp 201.3–202.0° dec (204–205° dec).[12] Another 24% consisted of the ortho isomer, mp 158.8–160.8° (160.5–161.0°).[12] Four methyl esters were prepared and had the following mp: *p*-Cl 91.1–92.1° (92–94°);[15] *p*-Br 106.4–107.0° (106°);[16] *p*-NO_2 111.5–113.5° (112–113°);[15] *m*-NO_2 49.5–51.5° (51–52°).[15]

The sodium salts of the acids were prepared in absolute ethanol and ether with sodium ethoxide as previously described.[2]

All of the substituted α,β-diiodocinnamic acids were made by iodination of the corresponding propiolic acid in aqueous solution containing K_2CO_3, I_2, and KI, according to the procedure reported for the synthesis of the *m*-methoxy acid, mp 140.8–141.6° dec (lit. 142°).[14] The main variation was the reaction time which varied from 20 min at 5° for the *p*-methoxy compound to 15 days at room temperature for the *p*-nitro acid. The yields of substituted *trans*-α,β-diiodocinnamic acid ($XC_6H_4CI{=}CICOOH$) averaged 63% after one or two crystallizations from $CHCl_3$–petroleum ether. All decompose at the mp with release of iodine. Mp and analyses appear in Table IV.

Two of the substituted styrenes ($XC_6H_4CI{=}CI_2$) were isolated in sufficient amounts and were analyzed after crystallization from ethanol–water. *p*-Methoxy-α,β,β-triiodostyrene, mp 102.2–102.9° dec. *Anal.* Calcd for $C_9H_7I_3O$: C, 21.12; H, 1.38. Found: C, 21.21; H, 1.38. *p*-Methyl-α,β,β-triiodostyrene, mp 73.5–74.3° dec. *Anal.* Calcd for $C_9H_7I_3$: C, 21.80; H, 1.42. Found: C, 22.02; H, 1.54.

Product Isolation. These were carried out essentially as described before.[2] The isolation runs were 0.04 *M* in substituted sodium phenylpropiolates, 0.025 *M* in I_2, and 0.10 *M* in KI. The volume of solution was 200 or 250 ml. The extent of reaction was determined periodically by titrating 1-ml aliquots and varied from 65 to 100%, with an average of 75%. The solutions were filtered to remove any precipitated triiodostyrene, and the flask was rinsed with chloroform to remove any adhering material. The acidified filtrate afforded the acids. These were filtered and the filtrate was extracted several times with chloroform. The two chloroform extracts were combined.

The acid mixture, which contained starting material and diiodo acid, was crystallized from chloroform–petroleum ether (30–40°) until a diiodo acid of constant mp was obtained. In some cases a second crop of less pure material was also isolated, which may account partly for yields of over 100% reported in Table III. For instance, a 91% yield of pure *p*-bromo-α,β-diiodocinnamic acid was isolated, and subsequently 13% of slightly less pure material was obtained, bringing the total to 104%.

When the acid mixture could not be further separated, it was analyzed for iodine. These figures are only approximate, because the iodine analysis was not completely consistent with a carbon–hydrogen analysis carried out on two of the mixtures. However, though many of the phenylpropiolic and diiodocinnamic acids have similar mp and solubilities, the diiodocinnamic acids all melt with decomposition. The melting point range and extent of decomposition can be used as a rough measure of the iodinated product present. The results in Table III are consistent with these observations. Also, data obtained from iodine analysis constitute usually a minor fraction of the pure isolated product, and only in two cases (*m*-Cl and *m*-NO_2) do they constitute the major part.

All combined residues were further analyzed by tlc. The solvent systems were chloroform saturated with formic acid for acidic substances and 90% petroleum ether (30–40°)–10% ether for nonacidic.[18] R_f values of the acids were compared with those of authentic samples. In addition to the two acids, and, in most cases, the styrene, a fourth substance was found in all but one case, which was more mobile than the two acids in the chloroform–formic acid system. Because it was expected to be ketonic, the residues of four of the isolation runs were treated with Girard's Reagent T, essentially according to the procedure of Fieser.[19] The work-up of this reaction afforded four fractions, an acidic ketonic and nonketonic, and a nonacidic ketonic and nonketonic one. The ketonic acidic product from the reaction of sodium *p*-bromophenylpropiolate was identified by nmr. It had been converted to the ethyl ester during the reaction with Girard's reagent, which contained ethanol and acetic acid. The nmr spectrum of ethyl *p*-bromobenzoylacetate (*p*-$BrC_6H_4COCH_2COOC_2H_5$) showed a three-proton triplet at τ 8.72 and a two-proton quartet at τ 5.83 for the ethyl protons, a two-proton singlet at τ 5.92 for the methylene group, a two-proton multiplet at τ 1.95 for the ortho protons, and a two-proton multiplet at τ 2.48 for the meta protons. The nmr spectrum of unsubstituted ethyl benzoylacetate showed corresponding resonances at τ 8.79, 5.80, 5.87, 1.82, and a three-proton multiplet at τ 2.39 for the remaining aromatic protons. From the ketonic nonacidic fraction, *p*-bromoacetophenone was obtained and similarly identified. The reactions of the *p*-CH_3O, *m*-CH_3O, and *p*-NO_2 compounds did not yield amounts of ketonic material sufficient for further identification but were assumed to have yielded similar products.

Kinetic Determinations. Iodine and all salts were reagent grade chemicals. The salts were dried at 120–140° overnight before use. The temperature of the kinetic runs was 30.00 ± 0.05°, except for those used to determine the activation parameters, which varied from 15.0 to 50.0°. Complete stock solutions were made up at the appropriate temperatures. The procedure for the kinetic runs was that used before.[2] All rate constants were determined by least-squares analysis, and the probable errors in individual rate constants averaged 0.5%. Duplicate runs were carried out for each set of conditions, except for runs used for the Hammett plot, for which triplicate determinations were made. Rate constants of the duplicate or triplicate runs usually agreed within 2%. Additional determinations were made if the error was greater. All reported rate constants are the *observed* rate constants. The true third-order rate constants, k_t (eq 1), can be obtained by dividing the observed rate constants by K (1.55×10^{-3} at 30°).[20] Activation energies had least-squares errors of 0.1–0.2 kcal and activation entropies of 0.1–0.4 eu.

Acknowledgment. This work was supported by National Science Foundation Grant GP-4986, which is gratefully acknowledged. One of us (E.B.) also acknowledges stimulating discussions with Professor P. B. D. de la Mare while at the University of Auckland, New Zealand.

Registry No.—*m*-Bromophenylpropiolic acid, 29835-28-7; *p*-methoxy-α,β,β-triiodostyrene, 53060-07-4; *p*-methyl-α,β,β-triiodostyrene, 53060-08-5; *p*-bromophenylpropiolic acid, 25294-65-9.

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Reactions of Benzaldehyde and Analogs with Ethyl Cyanoacetate in Ethanolic Ammonia[1]

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Received March 1, 1974

Reactions of benzaldehyde and analogs with ethyl cyanoacetate in ethanolic ammonia produce α-cyanohydrocinnamamides, 2,6-dihydroxy-3,5-dicyano-4-phenylpyridines, and dimeric products. Similar reactions in aqueous ammonia or Cope–Knoevenagel condensations also produce some of these products. Those facts suggest that the reaction mechanisms are the same. The report elucidates the structures of dimeric products such as 3,5-dicyano-4,6-diphenyl-5-ethoxycarbonyl-α-piperidones.

LeMoal, *et al.*,[2] and Nagai, *et al.*,[3] have reported the Cope–Knoevenagel condensation of para-substituted benzaldehydes with excess ethyl cyanoacetate to produce ethyl α-cyano-para-substituted cinnamates **1**, but have not yet reported that the reaction products were always accompanied by trace amounts of high melting by-products. In the case of *p*-nitrobenzaldehyde, the above reaction gave a noticeable amount of a dimeric product (**4d**), which was assigned a cyclobutane structure (**6**) by LeMoal, *et al.*[2] From benzaldehyde and ethyl cyanoacetate, a similar dimeric product (**4**) was obtained by Carrick[4] with sodium ethoxide in ethanol or by Issoglio[5] and Guareschi[6] with aqueous ammonia; however, these authors did not elucidate the structure of that product.

Table I shows the results of the reactions of para-substituted benzaldehydes with ethyl cyanoacetate in ethanolic ammonia at 0°. The formula for **3**, the ammonium salt of 2,6-dihydroxy-3,5-dicyano-4-(para-substituted phenyl)pyridines,[5,6] has been assigned on the basis of spectral data.

Table I
Product Yield (mol %) for the Reactions of Para-Substituted Benzaldehydes and Ethyl Cyanoacetate in Saturated-Ethanolic Ammonia at 0°

	Product[a]		
X	2	3[b]	4
H		6.7	38.4
MeO	10.1	9.6[c]	15.5
Cl	23.2	38.7[c]	
NO_2	21.2	34.6[c]	

[a] At the similar reactions in concentrated aqueous ammonia, X = H[6] and X = NO_2,[5] respectively, produced **2**, **3**, and **4**. Ir data of **2a** (Nujol) 3380 and 3195 cm^{-1} (NH_2), 2250 cm^{-1} (CN), 1660 and 1620 cm^{-1} (amide C=O). [b] Yields of **3** of Cope–Knoevenagel condensation: X = H, 0.002%; X = MeO, 0.001%; X = Cl, 0.72%, X = NO_2, 1.18%. These compounds are not dehydrated. [c] Monohydrated.

Table II
Nmr and Uv Spectral Data of 2

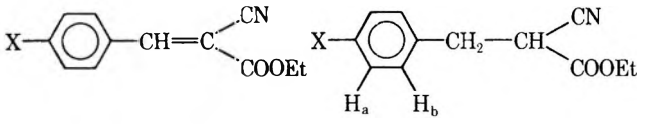
	δ ppm in DMSO-d_6						
	Benzene ring			Side chain			
Compound	H_a (A_2B_2)	H_b (A_2B_2)	OCH_3 (s)	CH_2 (ABX)	CH	NH_2 (s)	λ_{max} (EtOH), mμ (log ε) (in neutral medium)
				$J_{AB} = 13$ Hz, $J_{AX} = 3.5$ Hz, $J_{BX} = 6.5$ Hz			
2a	7.26			3.10	3.96	7.46 7.75	270 (3.89)
2b	6.85	7.18	3.72	3.03	3.88	7.70 7.38	203 (3.94), 227 (4.04), 276 (3.28), 283 (3.19)
2c[a]	7.33			3.11	3.98	7.50 7.97	202 (3.70), 221 (3.93)
2d	8.20	7.60		3.30	4.08	7.83	202 (4.10), 215 s (3.85), 268 (4.01)

[a] *Anal.* data of **2c**, mp 180–181°. Calcd: C, 57.55; H, 4.31; N, 13.43; Cl, 17.02. Found: C, 57.37; H, 4.07; N, 13.22; Cl, 17.06.

Table III
Nmr and Uv Spectral Data of 3

	δ ppm in DMSO-d_6					
	Pyridine ring		Benzene ring			
Compd	OH (s)	NH_4 (s) or (t)	H_a (A_2B_2)	H_b (A_2B_2)	OCH_3 (s)	λ_{max} (EtOH), mμ (log ε) (in neutral medium)
3a	10.85	7.32	7.55			206 (4.30), 259 (4.32), 345 (4.28)
3b	10.55	7.05	7.00	7.33		207 (4.29), 263 (4.37), 287 (3.67), 344 (4.30)
3c[a]	10.70	7.04	7.51	7.46	3.80	206 (4.33), 259 (4.34), 346 (4.24)
3d	10.90	7.23	8.45	7.83		203 (4.40), 266 (4.42), 310 (4.08) 345 (3.97)

[a] *Anal.* (mp 320–325°). Calcd: C, 50.91; H, 3.59; N, 18.27; Cl, 11.58. Found: C, 51.66; H, 3.40; N, 18.05; Cl, 12.05.



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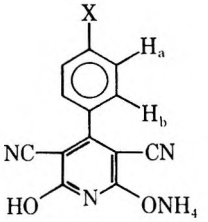
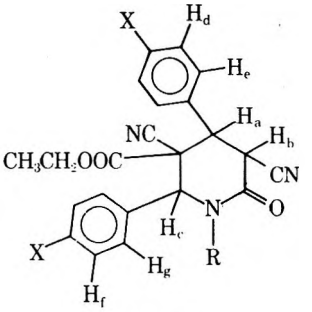
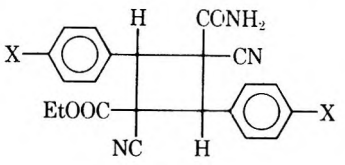


3



4, R = H



6

a. X = H
b. X = MeO
c. X = Cl
d. X = NO_2

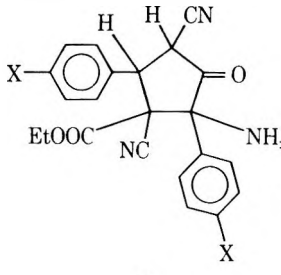
The ir spectra of **3** have absorption bands at about 3200–3400 cm^{-1}, attributable to N–H of the ammonium salts, and a characteristic very strong band at about 2200 cm^{-1} due to C≡N. The nmr spectra of **3** in DMSO-d_6 (Table III) show a triplet signal at 7.50–6.0 ppm, corresponding to ^{14}N–^{1}H (J_{NH}) = 50 Hz) of the ammonium salts; furthermore, they show a signal at 10.65 ppm of the OH or NH group. The base peak $(M - 17)^+$ of the mass spectra of **3**, generally, corresponds to the 2,6-dihydroxy-3,5-dicyano-4-(para-substituted phenyl)pyridines. The second strongest peak is *m/e* $(M - 60)^+$, the fragmentation of $(M - 17)^+$–$(M - 60)^+$ is supported by the following metastable peaks: **3a** m* = 159, **3b** m* = 188, **3c** m* = 192.

The dimeric products (**4**) were assigned their structures on the basis of their similarity in nmr spectra to compound **5** (**4**, N–CH_3 for N–H)[7] as shown in Table IV. We tried several chemical reactions on **4a** to exclude the structures **6** and **7** that were proposed by Böhme.[8] On hydrolysis in concentrated hydrochloric acid–acetic acid, **4a** afforded β-phenylglutaric acid and benzaldehyde, the latter being characterized as a 2,4-dinitrophenylhydrazone. **4a** does not possess a primary amino group as shown in **7** because it could not be acetylated with acetic anhydride. When **4a** was distilled at 160–170° (3 mm) (bath 225–230°), it afforded α-cyanocinnamamide and ethyl α-cyanocinnamate in the ratio of 1:1, and no other substances were found in the distillate. This fact also excludes the cyclopentane formula **7**. Corresponding to this fact, the mass spectra of **4** show the peak which agrees with the molecular weight of α-cyano-para-substituted cinnamamide as the base peak and the peak which agrees with the molecular weight of

ethyl α-cyano-para-substituted cinnamate in appropriate intensity (**4a**, 23%, **4b**, 77%, **4d**, 80%).

The reaction of **4a** with *p*-nitrobenzyl bromide in the presence of sodium carbonate in 95% ethanol produced **8**, as the main product, and **9**. Compound **8**, a mono-para-nitrobenzyl derivative of **4a**, mp 256–267°, was assigned its structure from the nmr spectrum. The spectrum lost the signal of AB type at 4.51 ppm (H_a, d) and 4.75 ppm (H_b, d) of **4a** and showed a new signal at 3.92 ppm and a new signal of AB type at 4.32 ppm (H_h, d) and 3.52 ppm (H_i, d), corresponding to the introduction of the *p*-nitrobenzyl group into H_b of **4a**. The structure of compound **9**, a di-*p*-nitrobenzyl derivative of **4a**, mp 284–285°, was also assigned from its nmr spectrum. The nmr spectrum of **9** is similar to that of **8**, but shows another signal of AB type at a lower magnetic field corresponding to a *N*-*p*-nitrobenzyl substitutent with disappearance of the N–H signal of **8**.

Compound **10**, mp 192–193°, is produced by the hydrolysis of **8** with concentrated hydrochloric acid–acetic acid. The ir spectrum of **10** has the bands 3100–3200 cm^{-1} (NH), and the bands 1725 and 1685 cm^{-1} (C=O); these absorption bands, characteristic of glutarimide, indicate that structure **10** is correct.



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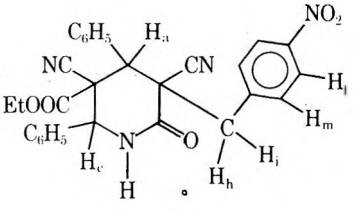

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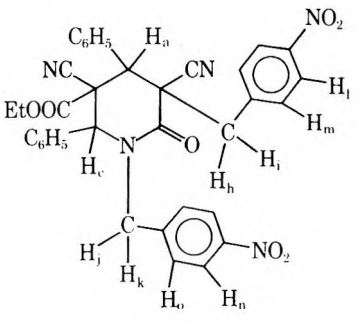

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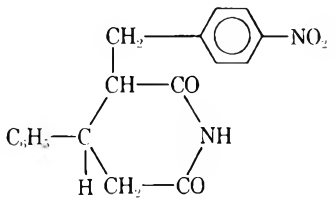


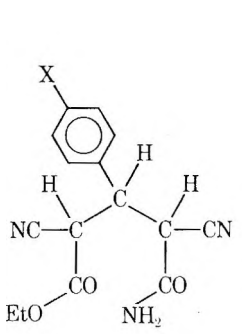
10

The proposed reaction mechanisms for the formation of **2**, **3**, and **4** are considered as follows. First, the para-substituted benzaldehydes react with ethyl cyanoacetate to produce ethyl para-substituted benzylidene cyanoacetate (may be phenyl group *vs.* ester group are trans). For electron attracting substituents (NO_2, Cl), the esters undergo rapid ammonolysis to the amides, which in turn react with excess ethyl cyanoacetate to produce the intermediate **11**. The ring closure of the intermediate **11** affords the 4-(para-substituted phenyl)dihydropyridines, which would give **3** by oxidation–reduction reactions with the para-substituted benzal cyanoacetamides, through the intermediate **12**. The

Table IV
Nmr (δ ppm) and Uv Spectral Data of 4, 5, 8, and 9

Compd	Solvent	Benzene ring						Hetero ring				Benzyl CH_2				Ester		λ max (EtOH), mμ (log ε)	
		H_d (A_2B_2)	H_e (A_2B_2)	H_f (A_2B_2)	H_g (A_2B_2)	H_l (A_2B_2)	H_m (A_2B_2)	H_n (A_2B_2)	H_o (A_2B_2)	OCH_3 (s)	H_a (AB) J_{AB} = 13 Hz	H_b (AB)	H_c (s)	NH (s)	NCH_3 (s)	H_h (AB) J_{AB} = 14 Hz	H_i (AB)	H_j H_k (AB) J_{AB} = 15 Hz	CH_2 (q)	CH_3 (t)	in neutral medium	in basic medium
4a	DMSO-d_6		7.40								4.51	4.73	5.51	7.83					3.86	0.83	215 (4.13), 230 (2.60), 263 (2.70),	218 (4.13), 257 (4.16)
4b[a]	DMSO-d_6	6.96	7.39	6.96	7.42					3.72	4.44	4.84	5.30	8.80					3.83	0.82	205 (3.78), 233 (3.84), 277 (2.80), 281 (2.77)	207 (3.82), 233 (3.99), 253 s (3.78)
4d	DMSO-d_6	8.31	7.65	8.31	7.83						4.90	5.28	5.61	9.20					3.95	0.88	210 (4.35), 265 (4.36)	210 (3.47), 267 (4.49)
5[b]	DMSO-d_6		7.37		7.37						4.53	5.20	5.35		2.67					3.38 (s)		
8[a]	$CDCl_3$		7.80		7.80	8.62	7.88				3.92		5.80	6.39		4.32	3.52		4.04	0.95	212 (4.42), 265 (3.97)	
9[a]	$CDCl_3$		7.25		7.90–7.37	8.09	6.97	8.09	7.47		3.51		4.80			3.95	3.19	5.06 4.31	3.62	0.56	208 (4.19), 270 (3.80)	210 (4.34), 270 (3.82)

[a] *Anal.* data of **4b**, mp 211–214°. Calcd: C, 66.51; H, 5.31; N, 9.69. Found: C, 66.60; H, 5.29; N, 9.63. **8**, mp 265–267°. Calcd: C, 68.50; H, 4.72; N, 11.02. Found: C, 68.26; H, 4.86; N, 10.98. **9**, mp 284–285°. Calcd: C, 67.18; H, 4.51; N, 10.88. Found: C, 67.33; H, 4.65; N, 1084. [b] Lit.[7] shows nmr data of methyl ester of **5**.



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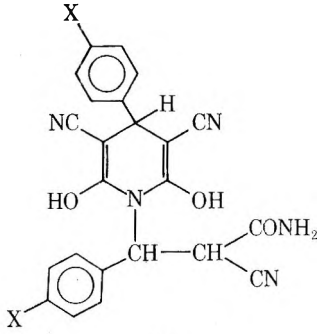

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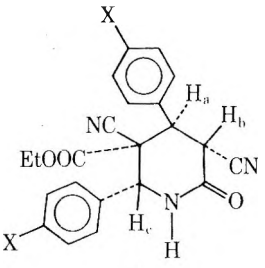

13

para-substituted benzal cyanoacetamides were reduced to **2** at this stage. Compound **3** may be partly formed by the air oxidation of the dihydropyridines. On the other hand, the ethyl α-cyanocinnamates with an electron donating group in the para position, owing to the slow formation of amides, as Dietz suggested,[7] react with the para-substituted benzylidene cyanoacetamides, and then afford ring closing products (**4**). Compound **4** were obtained in a single stereoisomer. The formation of these compounds is apparently thermodynamically controlled; therefore, the conformation is the most stable one in **13**, proposed by the inspection of the Dreiding model.

Experimental Section[9]

The Cope–Knoevenagel Condensation of *p*-Nitrobenzaldehyde with Ethyl Cyanoacetate. In a 200-ml round-bottomed flask with a continuous water separator, a mixture of 25 g (0.17 mol) of *p*-nitrobenzaldehyde, 38 g (0.34 mol) of ethyl cyanoacetate, 13 g (0.17 mol) of ammonium acetate, and 32 g (0.53 mol) of acetic acid in 100 ml of benzene was refluxed in an oil bath at 140–150° for 5 hr, while 5.6 ml of an aqueous layer containing acetic acid and ammonium acetate separated. Yellow crystals separated out in the flask and were collected by vacuum filtration and recrystallized from 1.4 l. of 99% ethanol. The crystals that separated first contained 13.6 g of **1** and were identified by ir analysis. The mother liquor was concentrated to 250 ml, and the crystals that separated out were collected and recrystallized from 300 ml of 99% ethanol. These crystals contained 1.95 g of **1**, and subsequently 0.9 g of **4** was separated and identified by ir analysis. On the other hand, the mother liquor (250 ml) that was concentrated and the crystals which separated already were again concentrated to 100 ml; 0.6 g of **3** was separated out from this solution.

The benzene layer, after it was washed with a saturated sodium carbonate solution and 10% sodium chloride solution, was dried on sodium sulfate, and then concentrated. The residual crystalline substance produced 5.1 g of **1** by recrystallization with 400 ml ethanol.

On the whole, three kinds of the following pure products were obtained in this experiment. **1d,** 20.7 g (yield 49.5%), mp 172–174°, light yellow needles. **3d,** 06. g (yield 1.11%), mp over 300°, yellow needles; ir (KBr) 2840–3540 cm^{-1} (NH_4^+), 2220 cm^{-1} (CN), 1630 cm^{-1} (2,2-dihydroxypyridine), 1525, and 1365 cm^{-1} (NO_2). **4d,** 0.9 g (yield 2.36%), mp 202–204°, white scales or fine white needles; ir (Nujol) 3200 cm^{-1} (NH), 2260 cm^{-1} (CN), 1755 cm^{-1} (ester C=O), 1690 cm^{-1} (amide C=O), 1520, and 1350 cm^{-1} (NO_2).

A similar procedure was used for the condensation of 25 g (0.18 mol) of *p*-chlorobenzaldehyde and 35 g (0.31 mol) of ethyl cyanoacetate. This procedure produced 24.84 g (yield 62.3%) of **1c** (white plates, mp 91–92.5°) and 233 g (yield 0.72%) of **3c** (pale yellow fine needles, mp 320–325°; ir (Nujol) 3440, 3200, and 3070 cm^{-1} (NH_4^+), 2210 cm^{-1} (CN), 1610 cm^{-1} (2,2-dihydroxypyridine), 830 cm^{-1} (para-substituted benzene), 770 cm^{-1} (C–Cl)).

Reaction of Benzaldehyde and Ethyl Cyanoacetate in Ethanolic Ammonia. To a solution of ammonia, 14 g (1.0 mol) in 200 ml of 95% ethanol, 53 g (0.5 mol) of benzaldehyde and 113 g (1.0 mol) of ethyl cyanoacetate were added; the mixture was kept in a refrigerator for 10 days with occasional stirring. Yellow crystals precipitated from the solution and were collected by vacuum filtration, washed twice with 100-ml portions of ethanol, and dried. The crude material, mp over 180°, weighed about 87 g. Further, the filtrate was allowed to stand in the refrigerator, to produce 1.51 g of the crystals (**4a**), mp 207–209°. The crude substance (87 g) having three kinds of CN bands was recrystallized several times from 95% ethanol (1000 ml in total) under continuous monitoring of the infrared spectra, to afford the following three kinds of pure compounds. Cyanoacetamide, 4.3 g, mp 118–121° (lit.[10] 119.5°). **3a,** 8.5 g (yield 6.7%), mp over 300°, white or pale yellow needles; ir (KBr) 3400 cm^{-1} (OH), 3200–2400 cm^{-1} (NH_4^+), 2200 cm^{-1} (CN), 1600 cm^{-1} (2,2-dihydroxypyridine), 1510 and 1470 cm^{-1} (hetero C–N), 1390 cm^{-1} (pyridine ring C–N), 1250 and 1220 cm^{-1} (C–O), 700–680 cm^{-1} (monosubstituted benzene). **4a,** 35.8 g (38.4%), mp 208–210°, white needles; ir (Nujol) 3250 cm^{-1} (NH), 2255 cm^{-1} (CN), 1740 cm^{-1} (ester C=O), 1679 cm^{-1} (amide C=O), 1270, 1250 and 1005 cm^{-1} (ester C–O–C). **2a** was not afforded in any amount.

Similarly, 68 g (0.5 mol) of *p*-methoxybenzaldehyde afforded the following three pure compounds. **2b,** 10.3 g (yield 10.1%), mp 170–171°, white needles; ir (Nujol) 3400, 3320 and 3210 cm^{-1} (NH_2), 2255 cm^{-1} (CN), 1670 and 1620 cm^{-1} (amide C=O), 1245 cm^{-1} (aromatic ether). **3b,** 14.6 g (yield 9.7%), mp 302–305°, colorless fine needles, ir (Nujol) 3400–3200 cm^{-1} (OH and NH_4^+), 2215 cm^{-1} (CN), 1600 cm^{-1} (amide C=O), 1250 cm^{-1} (arom. ether), 840 cm^{-1} (para-substituted benzene), 1180 and 1030 cm^{-1} (C–O–C). **4b,** 16.8 g (yield 15.5%), mp 211–214°, white needles; ir (Nujol) 3300 cm^{-1} (NH), 2255 cm^{-1} (CN), 1735 cm^{-1} (ester C=O), 1690 cm^{-1} (amide C=O), 1610 cm^{-1} (C=C), 1250, 1180, and 1090 cm^{-1} (ester C–O–C), 1020 cm^{-1} (arom. ether), 850 and 830 cm^{-1} (para-substituted benzene).

p-Chlorobenzaldehyde (25 g, 0.18 mol), under a similar procedure, afforded the following two pure compounds. **2c,** 8.2 g (yield 23.2%), mp 180–181°, colorless prisms; ir (Nujol) 3380 and 3180 cm^{-1} (NH_2), 2250 cm^{-1} (CN), 1685 cm^{-1} (amide C=O), 1095 and 1015 cm^{-1} (C–H), 840 cm^{-1} (para-substituted benzene), 790 cm^{-1} (C–Cl). **3c,** 20.2 g (yield 38.7%), mp over 300°, fine long needles.

p-Nitrobenzaldehyde (25 g, 0.17 mol), under a similar procedure, afforded the following two pure compounds. **2d,** 7.7 g (yield 21.2%), mp 169–170°, pale yellow needles; ir (Nujol) 3440 and 3300 cm^{-1} (NH_2), 2240 cm^{-1} (CN), 1670 cm^{-1} (amide C=O), 1610 cm^{-1} (C=C), 1510 and 1340 cm^{-1} (NO_2), 850 cm^{-1} (para-substituted benzene). **3d,** 18.1 g (yield 34.6%), mp over 300°, deep yellow long needles.

Hydrolysis of 4a with Concentrated Hydrochloric Acid and Acetic Acid Solution. A mixture of 19 g (0.051 mol) of **4a,** 200 ml of concentrated hydrochloric acid, and 100 ml of acetic acid was refluxed for 4 hr (bath temperature 130–140°). After cooling, the reaction mixture was diluted with 600 ml of water, then extracted with three 150-ml portions of ether. The ethereal solution was dried and evaporated. The residual oil was allowed to crystallize; the crystals were collected, and dried, weighing 6.83 g. Recrystallization from water gave white crystals, 5.23 g (yield 49.3%), mp 141–142°. From elementary analysis, melting point, and nmr spectra, this substance was found to be β-phenylglutaric acid (lit.[11] mp 142°): nmr (acetone-d_6) δ 10.28 (s, 2, COOH), 7.25 (5, benzene), 3.63 (q, 1, H_C), 2.75 (d, 2, J_{AC} = 6 Hz, H_A), 2.73 (d, 2, J_{BC} = 8 Hz, H_B), J_{AB}, under investigation. *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.40; H, 5.64.

Hydrolysis of 4a with Ethanolic Hydrochloric Acid in Presence of 2,4-Dinitrophenylhydrazine. A mixture of 10.0 g (0.027 mol) of **4a,** 5.5 g (0.028 mol) of 2,4-dinitrophenylhydrazine, 200 ml of concentrated hydrochloric acid, and 200 ml of 95% ethanol was refluxed for 7 hr at a bath temperature of 110–120°. The mixture was filtered while hot, to give orange-red crude crystals, mp 245–246°, which weighed 7.76 g (yield 99%), and recrystallization from 99% ethanol yielded the pure substance, mp 245–246°. *Anal.* Calcd for $C_{13}H_{10}N_4O_4$: C, 54.54; H, 3.52; N, 19.58. Found: C, 54.50; H, 3.68; N, 19.71.

Pyrolysis of 4a. Compound **4a,** 2.0 g (5.3 mmol), was distilled in a Hauben flask at 160–170° (3 mm) (bath temperature, 225–230°). The fore run (783 mg) crystallized upon standing. The nmr spec-

trum showed this fraction to consist of 70.5% of α-cyanocinnamamide and 29.5% of ethyl α-cyanocinnamate. The after run (730 mg) is a pale yellow oil which crystallized gradually too. The nmr spectrum indicated this fraction to be composed of 27.7% of α-cyanocinnamamide and 72.3% of ethyl α-cyanocinnamate. Thus, α-cyanocinnamamide and ethyl α-cyanocinnamate were obtained in 56.7 and 43.3% yield in total.

3,5-Dicyano-5-ethoxycarbonyl-3-*p*-nitrobenzyl-4,6-diphenyl-2-oxopiperidine (8) and 3,5-Dicyano-5-ethoxycarbonyl-1,3-di-*p*-nitrobenzyl-4,6-diphenyl-2-oxopiperidine (9).[12] A mixture of 3.6 g (9.6 mmol) of **4a** and 21 g of anhydrous sodium carbonate in 100 ml of 95% ethanol was refluxed to produce a clear yellow solution. To this solution was added a hot solution of 42 g (20 mmol) of *p*-nitrobenzyl bromide in 100 ml of 95% ethanol. The mixture was refluxed for 3 hr on a steam bath. Pale yellow crystals precipitated out. The organic layer containing the yellow crystals was separated by decantation from the insoluble sodium carbonate while hot. Pale yellow crystals were collected by vacuum filtration from the ethanol solution, washed with a small amount of water, and then dried. The crude white crystals, mp 275–279°, weighed 1.01 g (yield 16.3%); 1.0 g of the crude crystals were recrystallized from 60 ml of acetone to afford 255 mg of a pure substance (**9**), mp 284–285°. The filtrate from the crude crystals stood at room temperature and precipitated white crystals, 1.24 g (yield 25.4%), mp 247–249°. The crude white crystals, 1.2 g, were recrystallized from 200 ml of 99% ethanol to give 930 mg of a pure substance (**8**), mp 265–267°, as white crystals. **9**, ir (Nujol) 2250 cm^{-1} (CN), 1745 cm^{-1} (ester C=O), 1655 cm^{-1} (amide C=O), 1605 cm^{-1} (C=C), 1520 and 1350 cm^{-1} (NO_2), 1260 or 1220 and 1110 cm^{-1} (ester C–O–C), 855 and 840 cm^{-1} (para-substituted benzene), 700 cm^{-1} (monosubstituted benzene). **8**, ir (Nujol) 2250 cm^{-1} (CN), 1733 cm^{-1} (ester C=O), 1695 cm^{-1} (amide C=O), 1520 and 1340 cm^{-1} (NO_2), 1250 and 1110 cm^{-1} (ester C–O–C), 850 cm^{-1} (para-substituted benzene), 700 cm^{-1} (monosubstituted benzene).

3-*p*-Nitrobenzyl-4-phenyl-2,6-dioxopiperidine (10). Compound **8**, 7.10 g (0.014 mol), was refluxed in a mixed solution of 50 ml of concentrated hydrochloric acid and 100 ml of acetic acid for 8 hr, to give a yellow solution which contained a small amount of insoluble substance **9**. After cooling, the insoluble **9** was filtered off, 500 ml of water was added to the filtrate, and the mixture was extracted with three or four portions of 200 ml of ether. The ethereal solution was dried and distilled, to give 4.60 g of the residue. The residue was dissolved into 10 ml of hot 95% ethanol, and stood for several days at room temperature to precipitate considerable amounts of crystals. The crystals were collected, washed with 5 ml of cold ethanol, and then dried. The crude product, mp 155–160°, 1.86 g (yield 41.1%), was recrystallized from acetone to give pure **10**: mp 191–192°; ir (Nujol) 3200 and 3100 cm^{-1} (NH), 1725 and 1685 cm^{-1} (imide C=O), 1959 cm^{-1} (C=C), 1510 and 1350 cm^{-1} (NO_2), 1320 cm^{-1} ($-CH_2-$), 1240 cm^{-1} (C—C–C—C), 1170 cm^{-1} (C—CH_2—C), 860 cm^{-1} (para-substituted benzene); uv max (95% C_2H_5OH), in neutral medium, 206 mμ (log ε 4.51), 275 (4.00); in alkaline medium, 206 mμ (4.67), 235 (4.14), 278 (4.05); in acidic medium, 205 mμ (4.43) and 276 (4.02); nmr (acetone-d_6) δ 9.61 (s, 2, NH), 8.01 and 7.25 (A_2B_2, 4, para-substituted benzene), 7.33 (s, 5, monosubstituted benzene), 3.45–3.73 (m, 6, CH_2—CH=CH—CH_2).

Registry No.—**1c**, 2286-35-3; **1d**, 2286-33-1; **2a**, 6731-58-4; **2b**, 21739-28-6; **2c**, 52906-62-4; **2d**, 52906-63-5; **3a**, 52906-64-6; **3b**, 6327-92-0; **3c**, 52906-65-7; **3d**, 52906-66-8; **4a**, 52906-67-9; **4b**, 52906-68-0; **4d**, 52906-69-1; **8**, 52906-70-4; **9**, 52906-71-5; **10**, 52906-72-6; benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; *p*-chlorobenzaldehyde, 104-88-1; *p*-nitrobenzaldehyde, 555-16-8; ethyl cyanoacetate, 105-56-6; β-phenylglutaric acid, 4165-96-2; benzaldehyde 2,4-DNPH, 1157-84-2.

References and Notes

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(9) Mciroanalyses were performed by the Microanalytical Laboratories of Kyoto University; infrared spectra were determined by means of a Perkin Elmer 180 spectrometer, ultraviolet spectra by means of a Perkin Elmer 202 spectrometer, nmr spectra by means of a Hitachi R-20-B (60 MHz) and a JEOL PS-100 (100 MHz) spectrometer, and mass spectra by means of a Hitachi MU-6 spectrometer.
(10) "The Merck Index of Chemicals and Drugs," Merck, Rahway, N. J., 1952, p 296.
(11) E. H. Rodd, *Chem. Carbon Compounds, B*, **3**, 946 (1956).
(12) In a run using 7.5 g of **4a**, 8.6 g of *p*-nitrobenzyl bromide, and 4.2 g of anhydrous sodium carbonate in 150 ml of 95% ethanol, 9.77 g of product was obtained. Recrystallization from ethanol, under monitoring with ir spectra, afforded **8**, mp 264–265°, 6.514 g (yield 64.1%); and **9**, mp 275–278°, 0.857 g (yield 6.6%).

Studies Directed toward a Mitomycin Synthesis

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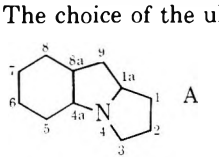
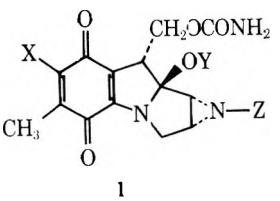
Received July 11, 1974

Alkylations of heterocyclic anion 7 with chloromethyl ethers followed by photooxidation afforded products with the essential framework of the mitomycin antibiotics. A generalized scheme for attaching aziridines to this carbon framework was developed. It involved a photochemical ring contraction of triazolines in the presence of a triplet quencher so as to suppress subsequent photochemistry of the tetracyclic products which may serve as mitomycin models.

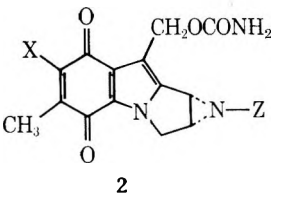
The mitomycins (**1**) are a class of antibiotics of wide-ranging activity. Since their structures were first elucidated in 1962,[1,2] there have been a variety of synthetic approaches to their framework and that of the closely related aziridinomitosenes (**2**). The majority of published routes are concerned with the formation of the tricyclic pyrrolo[1,2-*a*]indole ring system A. The choice of the ultimate bond to be



A



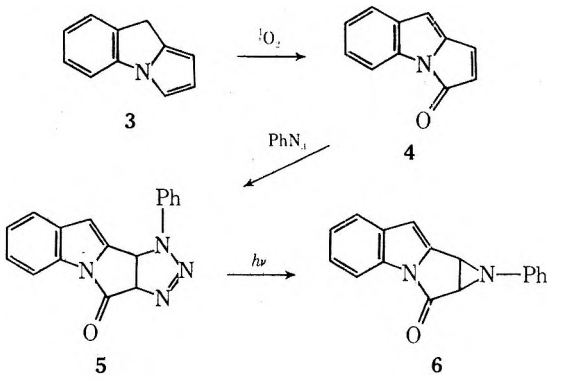
1



2

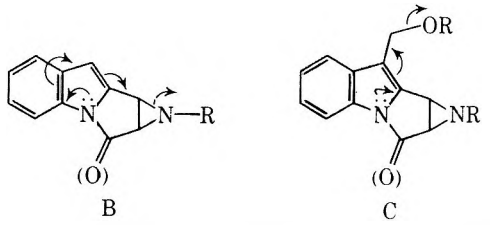
mitomycin A, X = CH_3O; Y = CH_3; Z = H
mitomycin B, X = CH_3O; Y = H; Z = CH_3
mitomycin C, X = NH_2; Y = CH_3; Z = H
porfiromycin, X = NH_2; Y = CH_3; Z = CH_3

Scheme I

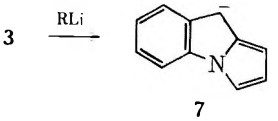


formed includes 8a–9,[3] 1a–9,[4] 4a–4,[5] 8a–9 and 4a–4,[6] 1a–4 and 3–4,[7] 1a–1 and 3–4,[8] 1–2 and 3–4,[4c,9] 4a–5 and 8a–8.[10] There has been a more limited program for introducing the carbamate at C-9[11,9a] and for achieving the correct quinone substitution pattern.[7,9a] There exist only two reports of aziridine introduction into a proper framework,[12] one of which comes from our laboratories and is summarized in Scheme I.[13]

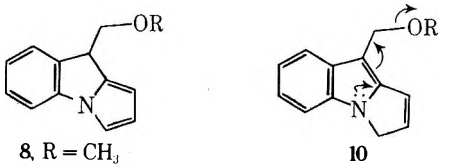
For the most part, these published efforts do not describe reactions that would be compatible with a complete synthesis of a mitomycin. In this paper we wish to describe our approaches to two structural features, solutions which we feel are transferable to a total synthesis. When our compound **6** is compared to a target aziridinomitosene **2**, the functions requiring further elucidation can be readily discerned. First, a one-carbon function, convertible to a carbamate, must be in place at C-9. Second, a substituent other than phenyl on the aziridine nitrogen must be obtained. The third and fourth problems, not dealt with in this article, are the development of a fully functionalized quinone (or potential quinone) that is compatible with the steps to be described in the sequel, and the removal of the carbonyl at C-3 which serves as a shield against internal eliminations initiated by indole nitrogen (B and C). The first problem



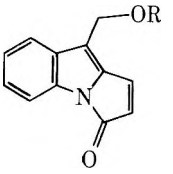
posed seemed capable of solution by using the carbanion **7**, formed upon treatment of heterocycle **3** with strong base.[9c,13,14] Previous work had shown that alkylation with



diethylaminoethyl chloride occurred at C-9 in high yield to afford a stable product. In our current work, alkylations were carried out on the lithium derivative with chloromethyl methyl ether and chloromethyl benzyl ether. In both cases, the presumed initial products **8** and **9** could not be



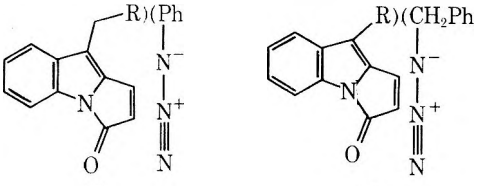
isolated since the crude reaction mixtures decomposed as the solvents were removed. It is difficult to rationalize any inherent instability for structures **8** or **9**. However, if a prototropic shift occurred, **8** and **9** could equilibrate with **10** which would be unstable because the ether would now be indolylic. Such a facile double-bond isomerization between the 3*H*- and 9*H*-pyrrolo[1,2-*a*]indole series has been inferred from work where a regiospecific synthesis of the parent heterocycle related to **10** (the 3H series) resulted in the clean isolation of **3** (the 9H series).[15] Since **8** and **9** could not be isolated, but their existence in dilute solution was presumed, the crude alkylation mixtures were photooxygenated. Work-up of the oxidation medium afforded the heterocycles **11** and **12** along with some **4** (derived from unalkylated **3**). Yields of **11** ranged from 8 to 24% while



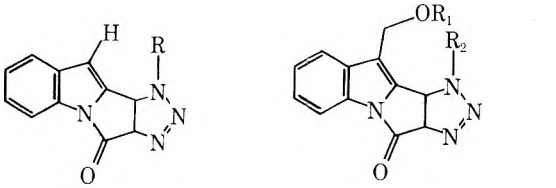
11, R = CH_3
12, R = CH_2Ph

those for **12** were 42–50%. The structural assignments were based on their nmr, ir, and uv spectra which were in good agreement with the data for **4**, save the missing indolic H at C-9 in the nmr, and the slight bathochromic shift in the uv (λ_{max} 360 for **11**, 355 for **4**).

With a direct introduction of the one-carbon function at C-9, the next step, dipolar addition of azides to the C-2,3 double bond, was investigated. In the parent series, phenyl and benzyl azide both added readily to **4**. In the current study, a steric hindrance to dipolar addition to **11** and **12** was observed. That is, phenyl azide was added with difficulty and in low yield whereas benzyl and methoxymethyl azide additions were smooth good yield processes. This can be rationalized as follows. The addition of the azides to the polarized double bond is regiospecific, thus the substituent on the azide and that at C-9 come in close proximity. The bulk of the benzyl group can bend away from the C-9 substituent (as in E) whereas the phenyl cannot (as in F). Of



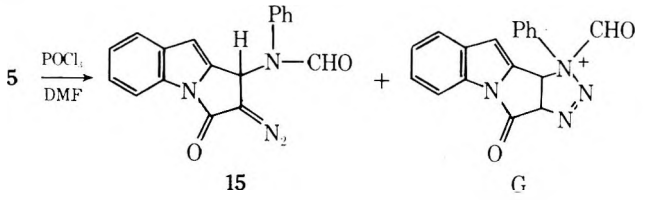
course, in the parent series, the group at C-9 is a proton, which offers no interference to either phenyl or benzyl. This sort of steric effect in dipolar additions does not seem to have been observed previous to this work (although it is not surprising).[16] A variety of triazolines **13** and **14** were



13a, R = CH_2Ph
b, R = CH_3

14a, $R_1 = CH_3$; $R_2 = Ph$
b, $R_1 = CH_3$; $R_2 = CH_2Ph$
c, $R_1 = CH_3$; $R_2 = CH_3$
d, $R_1 = CH_3$; $R_2 = CH_2OCH_2Ph$
e, $R_1 = CH_3$; $R_2 = CH_2OCH_3$
f, $R_1 = CH_2Ph$; $R_2 = CH_2Ph$

prepared using the general procedure of mixing azide and heterocycles **4**, **11**, or **12** in a minimum of solvent and either heating or allowing to stand at room temperature (depending on the thermal sensitivity of the azide). As an alternate to our alkylation procedure for introducing a carbon at C-9 at an early stage of the synthesis, there was attempted a functionalization of the "indolic" positions of **4** and **5** by a Vilsmeier formylation.[9a,11] In this event, **4** proved inert, but but **5** afforded a new product in 84% yield which had incorporated the required elements of CO. However, its nmr revealed *inter alia* the appearance of a formyl H at δ 8.93, more consistent with a formamide than an aldehyde, and the disappearance of the AB quartet characteristic of the protons of the triazoline ring fusion. Further an ir band at 4.78 μ, characteristic of diazo compounds, was present. We formulate the product as the *N*-formyl-*N*-phenylaminodiazo derivative **15**.



15 G

The formation of **15** can be rationalized by a ring opening of the formylated triazoline G. This behavior has been observed in the chemistry of triazolines; however, N_2 evolution usually takes place when there is no stabilizing group for the diazo function.[17]

To carry the main synthetic pathway forward, the photochemical ring contractions of the triazolines **13** and **14** were required. Our earlier work had shown that direct irradiation of **13a** was not successful in achieving an aziridine synthesis. This is consistent with work of Padwa[18] where irradiation of aziridines such as **16**, upon irradiation, resulted in the formation of products **17** and **18**. Thus we hypothesized that this type of reaction, shown by Padwa to proceed through a triplet excited state, must be quenched in order to maintain the integrity of our desired aziridines. In the event of irradiating triazolines **13a** and **14b,f** in 0.66 *M* solutions of piperylene in ethanol, there were obtained aziridines **19** and **20b,c**. Since **14a** was phenyl substituted, its conversion to **20a** did not require triplet quencher. The nmr spectral properties (Table I) were consistent with their formulation as aziridines, that is, upfield shifts and diminished coupling constants, criteria deduced in our previous paper.[9c,12] At this stage of our synthetic program, when it seemed that our two goals, enunciated at the start of this paper, had been achieved, it was decided to confront the third and fourth problems remaining for a total synthesis. Future reports will deal with this aspect of our work.

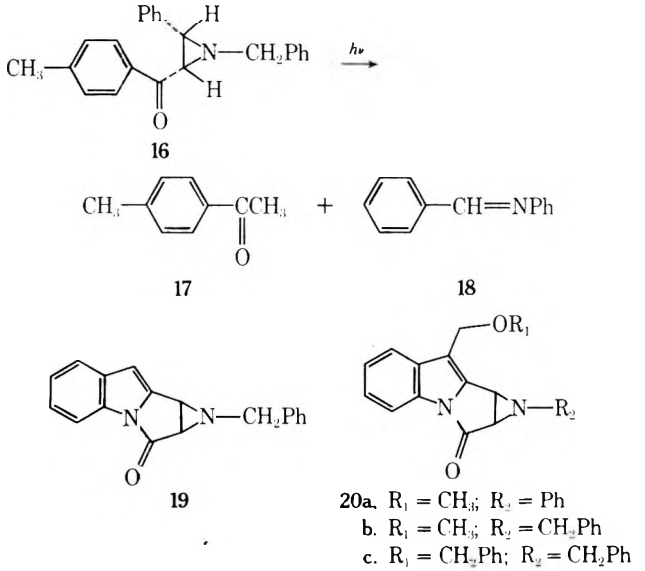


Table I

Aziridine	δ, ppm	J_{AB}, Hz
6	3.80, 4.02	3.7
19	3.17, 3.38	4.3
20a	3.85, 4.20	3.4
20b	3.18, 3.48	4.5
20c	3.10, 3.39	4.5

Experimental Section

Commercially available starting materials were used as supplied, except where noted. Liquids were distilled through a vacuum-jacketed 4-in. Vigreux column; melting points were determined on a Fisher-Johns block, and, like boiling points, are corrected. Thin-layer chromatograms (tlc) in at least two different solvents or solvent pairs were performed on microscope slides coated with silica gel or alumina and were visualized with iodine vapor. Merck acid-washed alumina and Fisher 100–200 mesh silica gel were used for elution chromatography. Woelm fluorescent alumina and silica gel (activity II–III) were used for dry-column chromatography. Solutions were dried by washing with saturated sodium chloride solution (brine) followed by treatment with anhydrous sodium sulfate. Solvents were removed by rotary evaporation. Where noted, an atmosphere of dry nitrogen was maintained by use of the apparatus described by Johnson and Schneider.[20] We thank the Fisher Scientific Co for a generous gift of chemicals.

General Photooxygenation Procedure. Photooxygenations were run in a 500-ml gas washing bottle in a solution of 250 ml of tetrahydrofuran, 200 ml of distilled water, and 50 ml of pyridine with 10 mg of Methylene Blue as sensitizer. All reactions were run at room temperature with magnetic stirring. The reaction vessel was placed in the center of four General Electric cool white fluorescent lamps (15 W per lamp) and the fluorescent bank was surrounded by reflective aluminum foil. The lights were turned on and oxygen gas, passing through the dispersion disk at the bottom, was continually bubbled through the solution. After completion of the reaction, the tetrahydrofuran was removed by evaporation at reduced pressure. The aqueous layer was extracted several times with diethyl ether and the ether was washed successively with distilled water twice 200 ml of 2 *N* hydrochloric acid, a solution of aqueous acidified 1 *N* ferrous sulfate, distilled water, saturated sodium bicarbonate solution, distilled water, saturated sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated to dryness.

Lithium Anion of 9*H*-Pyrrolo[1,2-*a*]indole (7). The lithium anion was prepared in the addition funnel in all experiments. A 10 *M* % excess of a hexane solution of *n*-butyllithium was added by syringe to a magnetically stirred 0.2 *M* solution of 9*H*-pyrrolo[1,2-*a*]indole (**3**) in either anhydrous diethyl ether or anhydrous tetrahydrofuran. The mixture was stirred for 15 min before further reaction, at which time it was a Brunswick green in diethyl ether and a deep red in tetrahydrofuran.

9-Methoxymethyl-9*H*-pyrrolo[1,2-*a*]indole (8). A solution of the anion was prepared from 250 mg (1.6 mmol) of 9*H*-pyrrolo[1,2-*a*]indole (**3**), 1.1 ml (1.76 mmol) of 1.6 *M n*-butyllithium, and 8 ml of anhydrous diethyl ether and then slowly added to an ice-cooled mixture of 3.2 g (0.04 mol, 3.01 ml) of chloromethyl methyl ether in 40 ml of anhydrous diethyl ether. The green anion color was discharged immediately upon addition. The mixture was allowed to warm and was stirred at room temperature for 1.5 hr. A white precipitate of lithium chloride formed, was filtered with suction, and was washed with diethyl ether. Thin-layer chromatography on silica gel eluting with methylene chloride indicated a new component with an R_f of 0.46. Evaporation of the solvent yielded a red oil which turned to a glassy black solid within a few seconds. The black material was no longer soluble in ether or other organic solvents.

9-Methoxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (11). A solution of the anion was prepared from 388 mg (2.5 mmol) of 9*H*-pyrrolo[1,2-*a*]indole (**3**), 1.7 ml (2.72 mmol) of 1.6 *M n*-butyllithium, and 12.4 ml of anhydrous tetrahydrofuran and then added to

1.0 ml (1.06 g, 13.3 mmol) of chloromethyl methyl ether in 7.5 ml of anhydrous tetrahydrofuran. Addition of the anion formed a bright orange solution which was immediately photooxygenated. After 2 hr no more 8 could be detected and the reaction mixture was then worked up as previously described. Evaporation of the ether yielded 440 mg of a dark oil, which was chromatographed on an alumina dry column with benzene. Two distinct yellow bands were visible which were cut and the material was eluted with chloroform, yielding 85 mg (16%) of the desired 9-methoxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (**11**) and 76 mg (18%) of unalkylated 3*H*-pyrrolo[1,2-*a*]indol-3-one (**4**). An analytical sample was prepared by two recrystallizations from hexane to yield 9-methoxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (**11**) as bright yellow needles: mp 89–90°; ir (chloroform) 2916 (w), 2811 (w), 1723, 1611, 1461, 1377, 1355, 1307, 1131, 1091 (b), 1066 cm^{-1}; uv (ethanol) 221 (ϵ 6100), 269 (8600), 275 sh (8100), 359 (8500) nm; nmr (d_1-chloroform) δ 3.45 (s, 3, CH_3), 4.53 (s, 2, CH_2), 5.93 upfield half of AB quartet (d, 1, J_{1-2} = 6 Hz, C-2), 6.90–7.44 (m, 4, C-1, C-6, C-7, C-8), 7.58–7.75 ppm (m, 1, C-5).

Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.02; H, 5.10; N, 6.49.

The above yields were averaged over 11 separate experiments, in which the alkylated product (**11**) was isolated in 8–24% yield and the unalkylated material (**4**) in 9–35% yield. Stirring the anion for 30 min, increasing the molar ratio of chloromethyl methyl ether to anion, or increasing the concentration of chloromethyl methyl ether failed to alter the yields. Addition of chloromethyl methyl ether to the anion gave a 4.3% yield of alkylated product **11** and a 59% yield of unalkylated material **4**. Photooxygenating for a longer period of time also failed to improve the yield.

9-Benzyloxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (12). A solution of the anion was prepared from 264 mg (1.7 mmol) of 9*H*-pyrrolo[1,2-*a*]indole (**3**) 1.43 ml (1.86 mmol) of 1.3 *M n*-butyllithium, and 8.4 ml of anhydrous tetrahydrofuran and then added to 1.33 g (8.5 mmol) of freshly distilled chloromethyl benzyl ether in 5 ml of anhydrous tetrahydrofuran. The entire reaction mixture was then immediately photooxygenated. After 3 hr no more **9** could be detected and the reaction mixture was then worked up as previously described. Evaporation of the ether yielded 1.25 g of a crude black oil. Chromatography on an alumina dry column and eluting with benzene yielded 225 mg (46%) of a yellow oil which was crystallized by dissolving in a minimum amount of ether and triturating with hexane until a cloudiness persisted. After 4 days in the freezer long yellow needles of **12** were obtained. An analytical sample was prepared by two recrystallizations from ether–hexane: mp 61–63°; ir (chloroform) 3016 (w), 2844 (w), 1724, 1611, 1464, 1358, 1311, 1130, 1090, 1065 cm^{-1}; uv (ethanol) 214 (ϵ 11,000), 270 (5600), 276 sh (5100), 360 (5600) nm; nmr (d_1-chloroform) δ 4.65 (s, 2, CH_2), 4.68 (s, 2, CH_2), 5.98 upfield half of AB quartet (d, 1, J_{1-2} = 6 Hz, C-2), 6.95–7.49 (m, 9, C-1, C-6, C-7, C-8, +5 phenyl protons), 7.65–7.82 ppm (m, 1, C-5).

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.73; H, 5.38; N, 4.82.

Maximum yields (42–50%) were obtained by distilling the chloromethyl benzyl ether prior to each reaction. Anhydrous tetrahydrofuran was prepared by distillation from lithium aluminum hydride and stored over sodium. 9*H*-Pyrrolo[1,2-*a*]indole (**3**) was used as pure white needles and dried in a vacuum desiccator prior to use. The molarity of the *n*-butyllithium was checked periodically by the method of Gilman.[4] If these precautions were not taken, the yields dropped to 16–33% and the unalkylated 3*H*-pyrrolo[1,2-*a*]indol-3-one (**4**) was obtained as a side product in 12–24% yield and was isolated as a faster moving component during chromatography of the reaction mixture.

1-Methyl-3a,10b-dihydro-*v*-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (13b). Pyrrolo[1,2-*a*]indol-3-one (**4**) (120 mg), methyl azide (450 mg), and benzene (0.4 ml) were introduced into a tapered 6-in. test tube. The tube was immersed in a Dry Ice–chloroform bath and sealed with a hot flame. After sealing, the tube was removed from the cold bath and sheathed in a section of flexible rubber tubing as a precaution against an explosion as well as to prevent light from entering. After standing at room temperature for 28 days, the tube was cracked open, excess methyl azide was allowed to evaporate off, and hexane was added to the residue. The crystalline product was collected and washed with hexane until the hexane washings were colorless. The yield of the off-white product, which sintered at 170–175° and melted at 189–192° dec with gas evolution, was 94 mg (59%). One recrystallization from THF–hexane gave pure white crystals which sintered at 190° and melted at 197–198.5° dec (gas evolution): ir (KBr) 5.76 μ; uv (CH_3OH) λ_{max} 208, 241, 268 (shd) and 305 nm (ϵ 5540, 21,800, 9030, and 1750); nmr ($CDCl_3$–DMSO-d_6 (3:2)) δ 3.46 (s, 3, N-CH_3), 5.16 (d, 1, J_{10b-3a} = 10.5 Hz, C-10b, showing apparent additional coupling to C-10, J_{10-10b} = 1 Hz), 5.90 (d, 1, J_{3a-10b} = 10.5 Hz, C-3a), 6.75 (bs, 1, J_{10-10b} = 1 Hz, $W_{1/2}$ = 2 Hz, C-10), 7.27–7.78 (m, 3, C-7, 8, 9), 7.92–8.16 (m, 1, C-6 peri proton).

Anal. Calcd for $C_{12}H_{10}ON_4$: C, 63.70; H, 4.46; N, 24.70. Found: C, 63.80; H, 4.47; N, 24.75.

1-Phenyl-10-methoxymethyl-3a,10b-dihydro-*v*-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (14a). A solution of 120 mg (0.56 mmol) of 9-methoxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (**11**), 360 mg (3.03 mmol) of phenyl azide, and 0.72 ml of spectral grade benzene was heated at 75° in a flask covered with aluminum foil. After 24 hr the reaction mixture had become black. The mixture was cooled and evaporated to dryness yielding a crude black solid. The black solid was washed several times with hexane yielding 30 mg (16%) of crude brown material, mp 149–156°, with apparent gas evolution. The crude solid was chromatographed on a silica gel preparative thin layer plate eluting three times with chloroform. A fluorescent band 2–4 cm above the origin was removed and the product was eluted from the silica gel with chloroform. Evaporation of the solvent yielded 18 mg (9.6%) of a tan oil which was crystallized from chloroform–hexane. Four recrystallizations from chloroform–hexane yielded 6 mg (3.2%) of phenyl triazoline (**14a**) as white crystals, mp 150–151°, with apparent gas evolution: ir (chloroform) 2913, 2839, 1756, 1622, 1606, 1461, 1383, 1356, 1317, 1136, 1088 (br), 1064, 1034, 1010, 911 cm^{-1}; uv (cyclohexane) 243 (ϵ 24,000), 276 sh (15,300), 295 sh (11,000) nm; nmr (d_1-chloroform) δ 3.31 (s, 3, CH_3), 4.36 (s, 2, CH_2), 5.70 and 5.93 (AB quartet, 2, J_{10b-3a} = 10.5 Hz, C-10b, C-3a), 7.08–7.65 (m, 8, C-7, C-8, C-9 + phenyl protons), 8.01–8.18 ppm (m, 1, C-6).

1-Benzyl-10-methoxymethyl-3a,10b-dihydro-*v*-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (14b). A solution of 100 mg (0.47 mmol) of 9-methoxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (**11**), 333 mg (2.5 mmol) of benzyl azide, and 1.2 ml of spectral grade benzene was heated at 75° for 20 hr in a flask covered with aluminum foil. The reaction mixture was cooled and triturated with hexane yielding a brown solid. The solid was washed several times with hot hexane to remove the unreacted starting material yielding 46 mg of crude brown triazoline (**14b**), mp 143–147°, with apparent gas evolution. The hexane washings were chromatographed on an alumina dry column eluting with chloroform. Two distinct bands were visible; a broad yellow band of starting material (**11**) with an R_f of 0.50–0.75 followed by a narrow brown band of benzyl triazoline (**14b**) with an R_f of 0.31. The bands were cut and the material was eluted with chloroform yielding 45 mg of unreacted starting material (**11**) and an additional 23 mg of product giving a total yield of 69 mg (42% yield, 77% conversion) of benzyl triazoline (**14b**). An analytical sample was prepared by three recrystallizations from ethyl acetate to yield 22 mg (14% yield, 25% conversion) of benzyl triazoline (**14b**) as white needles, mp 158–159°, with apparent gas evolution: ir (chloroform) 2977 (w), 2911 (w), 1755, 1633, 1461, 1383, 1322, 1135, 1087 (br) cm^{-1}; uv (ethanol) 209 (ϵ 9300), 244 (13,800), 270 sh (6700), 309 sh (1400) nm; nmr (d_1-chloroform) δ 3.46 (s, 3, CH_3), 4.53 (s, 2, CH_2), 4.86 and 5.31 (AB quartet, 2, J_{AB} = 16 Hz, benzyl CH_2), 4.96 and 5.81 (AB quartet, 2, J_{10b-3a} = 10.5 Hz C-10b, C-3a), 7.20–7.65 (m, 8, C-7, C-8, C-9 + 5 phenyl protons), 8.02–8.18 ppm (m, 1, C-6).

Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.24; H, 5.29; N, 16.19.

1-Benzyl-10-benzyloxymethyl-3a,10b-dihydro-*v*-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (14f). A solution of 325 mg (1.12 mmol) of 9-benzyloxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (**12**), 300 mg (2.25 mmol) of benzyl azide, and 1.0 ml of spectral grade benzene was heated at 76–77° for 63 hr. The mixture was cooled and triturated with hexane to crystallize the product. The solid was washed with hexane to remove the unreacted starting material yielding 336 mg (71%) of crude brown triazoline (**14f**). The hexane washings were chromatographed on a silica gel PF preparative thin layer plate eluting with chloroform yielding 22 mg (7%) of recovered 9-benzyloxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (**12**). The crude triazoline (**14f**) was recrystallized twice from ethyl acetate to yield 220 mg (47% yield, 50% conversion) of pure product. An analytical sample was prepared by two additional recrystallizations from ethyl acetate to yield benzyl triazoline (**14f**), as white crystals, mp 165–166° with apparent gas evolution: ir (chloroform) 2914 (w), 2847 (w), 1758, 1628, 1464, 1391, 1364, 1325, 1134, 1086, 1067 cm^{-1}; uv (ethanol) 243 (ϵ 17,100), 271 sh (7900), 304 sh (1700) nm; nmr (d_1-chloroform) δ 4.59 (s, 2, CH_2), 4.63 (s, 2, CH_2), 4.82 and 5.25 (AB quartet, 2, J_{AB} = 16 Hz, benzyl CH_2), 4.91

and 5.82 (AB quartet, 2, $J_{10b\text{-}3a}$ = 10.5 Hz, C-10b, C-3a), 7.13–7.57 (m, 13, C-7, C-8, C-9 + 10 phenyl protons), 8.02–8.18 ppm (m, 1, C-6).

Anal. Calcd for $C_{26}H_{22}N_4O_2$: C, 73.92; H, 5.25; N, 13.26. Found: C, 73.79; H, 5.35; N, 13.27.

1,10-Bis(methoxymethyl)-3a,10b-dihydro-υ-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (14e). A solution of 48 mg (0.23 mmol) of 9-methoxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (11), 132 mg (1.5 mmol) of methoxymethyl azide, and 0.6 ml of spectral grade benzene was heated at 75° for 7 days under an atmosphere of argon. The reaction mixture was cooled and triturated with hexane yielding brown crystals. The crystals were washed several times with hexane to remove the unreacted starting material yielding 31 mg of crude brown triazoline (**14e**). The hexane washings were chromatographed on a silica gel dry column eluting with methylene chloride. Two bands were visible, a broad yellow band of starting material followed by a narrow brown band of triazoline. The bands were cut and the material was eluted with chloroform yielding 11 mg of unreacted 9-methoxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (11) and an additional 7 mg of product giving a total yield of 38 mg (55% yield, 75% conversion) of crude triazoline (**14e**). An analytical sample was prepared by three recrystallizations from ethyl acetate yielding 11 mg (16% yield, 22% conversion) of methoxymethyl triazoline (**14e**) as light brown needles, mp 158–160° with apparent gas evolution: ir (chloroform) 2989, 2928, 2822, 1761, 1639, 1489, 1472, 1389, 1366, 1328, 1316, 1136, 1094, 1071, 1010, 988, 910 cm^{-1}; uv (ethanol) 241 (ε 15,000), 295 (1600), 305 (1400) nm; nmr (d_1-chloroform) δ 3.35 (s, 3, CH_3), 3.55 (s, 3, CH_3), 4.71 (s, 2, CH_2), 5.27 (s, 2, CH_2), 5.29 and 5.96 (AB quartet, 2, $J_{10b\text{-}3a}$ = 10.5 Hz, C-10b, C-3a), 7.30–7.68 (m, 3, C-7, C-8, C-9), 8.03–8.20 ppm (m, 1, C-6).

Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 59.87; H, 5.46; N, 18.60.

1-Methyl-10-methoxymethyl-3a,10b-dihydro-υ-triazolo-[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (14c). A solution of 100 mg (0.47 mmol) of 9-methoxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (11), 0.4 ml of spectral grade benzene, and approximately 0.5 ml of freshly prepared methyl azide was sealed in a test tube, which was protected with a rubber sleeve against possible explosion. The tube was allowed to stand at room temperature for 19 months.[19] The tube was opened and the methyl azide was allowed to evaporate. Removal of the benzene yielded 108 mg (85%) of a crude brown solid which was washed with cold ethyl acetate yielding 32 mg (25%) of light tan crystals of methyl triazoline (**14c**). The ethyl acetate washings were chromatographed on a silica gel PF preparative thin layer plate eluting with ethyl acetate. A fluorescent band with an R_f of 0.67 was removed and the material was eluted from the silica gel with chloroform yielding an additional 38 mg of product giving a total yield of 70 mg (55%) of methyl triazoline (**14c**). An analytical sample was prepared by preparative thin-layer chromatography on a silica gel G prep plate eluting with 2:1 chloroform:ethyl acetate. A fluorescent band 3–5 cm from the origin was cut and the product was eluted from the silica gel with chloroform. Evaporation of the solvent yielded methyl triazoline (**14c**) as white needles, mp 146–147°, with apparent gas evolution: ir (chloroform) 2989, 2922, 1755, 1633, 1460, 1383, 1322, 1169, 1135, 1091, 1013, 987, 921 cm^{-1}; uv (ethanol) 241 (ε 21,000), 270 sh (8600), 295 sh (2400), 305 sh (2000) nm; nmr (d_1-chloroform) δ 3.53 (s, 3, CH_3), 3.57 (s, 3, CH_3), 4.74 (s, 2, CH_2), 5.04 and 5.84 (AB quartet, 2, $J_{10b\text{-}3a}$ = 10.5 Hz, C-10b, C-3a), 7.27–7.63 (m, 3, C-7, C-8, C-9), 8.05–8.22 ppm (m, 1, C-6).

Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.88; H, 5.39; N, 20.40.

1-Benzyloxymethyl-10-methoxymethyl-3a,10b-dihydro-υ-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (14d). A solution of 84 mg (0.39 mmol) of 9-methoxymethyl-3*H*-pyrrolo[1,2-*a*]indol-3-one (11), 330 mg (2 mmol) of benzyloxymethyl azide, and 1.0 ml of spectral grade benzene was heated at 75° for 4 days. The reaction mixture was cooled and evaporated to dryness yielding a crude dark oil which was chromatographed on silica gel G preparative thin layer plates with methylene chloride, giving a tan oil which was crystallized from chloroform–hexane yielding 85 mg (58%) of light brown crystals. An analytical sample was prepared by two recrystallizations from chloroform–hexane to yield 60 mg (41%) of light tan crystals of benzyloxymethyl triazoline (**14d**), mp 126–128° with apparent gas evolution: ir (chloroform) 3000, 2922, 2394, 1750, 1633, 1511, 1478, 1461, 1422, 1378, 1316, 1311, 1130, 1087, 1056, 1007, 919 cm^{-1}; uv (ethanol) 240 (ε 23,900), 268 sh (9700), 298 (2500), 304 (2500) nm; nmr (d_1-chloroform) δ 3.53 (s, 3, CH_3), 4.56 (s, 2, CH_2), 4.65 (s, 2, CH_2), 5.20 and 5.79 (AB quartet, 2, $J_{10b\text{-}3a}$ = 11 Hz, C-10b, C-3a), 5.40 (s, 2, CH_2), 7.24–7.67 (m, 8, C-7, C-8, C-9 + 5 phenyl protons), 8.00–8.18 ppm (m, 1, C-6).

Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 67.02; H, 5.34; N, 14.87.

1a,8b-Dihydro-1-benzylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-2(1*H*)-one (19). A solution of 77 mg (0.25 mmol) of **13a**, 10 ml of freshly distilled piperylene, and 150 ml of freshly distilled 95% ethanol was placed in a water-cooled (15°) photolysis apparatus. After purging with argon for 20 min, the stirred solution was irradiated with a medium pressure mercury arc lamp (Hanovia, 450 W, Pyrex filter) for 2.5 hr. The crude product was absorbed onto 1 g of dry-column silica gel and placed atop a column of the same absorbant (33 × 3.8 cm). The column was eluted with chloroform, the band 10.5 to 14 cm below the top of the column being separated. Work-up of this band yielded 20 mg (29%) of a pale yellow oil. The oil was taken up in ether and after chilling at 0° for several days it gave white crystals: mp 121–123°; ir (KBr) 5.74 μ; uv (MeOH) λ_{max} 218, 249, 310 nm (ϵ_{max} 5480, 15,700, and 2140); nmr ($CDCl_3$) δ 3.17, 3.38 (AB quartet, $J_{8b\text{-}1a}$ = 4.3 Hz, C-8b, C-1a), 3.73 (bs, 2, $W_{1/2}$ = 2 Hz, benzylic CH_2), 6.50 (bs, 1, W 1/2 = 2.5 Hz, C-8), 7.17–7.67 (m, 8, C-5, 6, 7 + 5 phenyl protons), 7.92–8.02 (m, 1, C-4); *m/e* calcd for $C_{18}H_{14}N_2O$, 274.1106, and found, 274.1138.

8-Methoxymethyl-1a,8b-dihydro-1-phenylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-2(1*H*)-one (20a). A solution of 15 mg (0.05 mmol) of 1-phenyl-10-methoxymethyl-3a,10b-dihydro-υ-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (**14a**) and 140 ml of freshly distilled benzene was placed in a photochemical reaction vessel equipped with a water-cooled immersion well. The reaction vessel was covered in the back with reflective foil. The solution was purged with nitrogen for 15 min prior to irradiation with a Sears-Roebuck sun lamp No. 7081 held 2.5 cm from the reaction vessel through two thicknesses of plate glass. The solution was irradiated for 15 min and then evaporated to dryness yielding 14 mg (100%) of a brown oil which was crystallized from chloroform–hexane. Attempts at purification by preparative chromatography on silica gel or alumina were unsuccessful. Three recrystallizations from chloroform–hexane yielded 7 mg (50%) of phenyl aziridine (**20a**) as a light tan solid: ir (chloroform) 3000, 2922, 2844, 1744, 1639, 1600, 1494, 1461, 1378, 1133, 1093, 1019, 924 cm^{-1}; nmr (d_1-chloroform) δ 3.59 (s, 3, CH_3), 3.85 and 4.20 (AB quartet, 2, $J_{8b\text{-}1a}$ = 3.4 Hz, C-8b, C-1a), 4.78 (s, 2, CH_2), 6.93–7.67 (m, 8, C-5, C-6, C-7 + 5 phenyl protons), 7.73–7.92 ppm (m, 1, C-4).

8-Methoxymethyl-1a,8b-dihydro-1-benzylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-2(1*H*)-one (20b). A solution of 42 mg (0.12 mmol) of 1-benzyl-10-methoxymethyl-3a,10b-dihydro-υ-triazolo[4′,5′:3,4]pyrrolo]1,2-*a*]indol-4(1*H*)-one (**14b**), 10 ml of freshly distilled piperylene, and 150 ml of freshly distilled benzene was placed in a photochemical reaction vessel equipped with a water-cooled quartz immersion well. The solution was purged with nitrogen for 15 min prior to irradiation with a Hanovia 679A-36 high pressure quartz mercury-vapor lamp (450 W) through a 2-mm Pyrex filter sleeve. Photolysis was stopped after 1.5 hr even though the starting triazoline had not been completely consumed. Evaporation of the reaction mixture yielded 66 mg of a crude brown oil. Oil (11 mg) was chromatographed on silica gel PF preparative thin layer plate eluting three times with chloroform. A bright orange band was visible with an R_f of 0.25 and a fluorescent band with an R_f slightly less. The bands were removed and the material was eluted from the silica gel with chloroform. The lower band proved to be recovered starting triazoline (**14b**) by ir and comparative thin layer chromatography with authentic material. The orange band yielded 4 mg of an oil whose ir exhibited the desired carbonyl. The remainder of the plate failed to yield any components whose ir contained a carbonyl absorption. The remaining 55 mg of crude reaction mixture was chromatographed similarly. Isolation of the desired component yielded an additional 10 mg giving a total yield of 14 mg (36%) of a crude oil which was crystallized from ether–hexane. The crystals were washed once with cold diethyl ether to remove the dark color. Two recrystallizations from ether–hexane yielded 7 mg (18%) of benzyl aziridine (**20b**): mp 108–111°; ir (chloroform) 3000, 2917, 2839, 1750, 1639, 1461, 1378, 1311, 1133, 1091, 1030 cm^{-1}; nmr (d_1-chloroform) δ 3.18 and 3.48 (AB quartet, 2, $J_{8b\text{-}1a}$ = 4.5 Hz, C-8b, C-1a), 3.33 (s, 3, CH_3), 3.36 and 3.71 (AB quartet, 2, J_{AB} = 3 Hz, benzyl CH_2), 4.63 (s, 2, CH_2), 7.22–7.63 (m, 8, C-5, C-6, C-7 + 5 phenyl protons), 7.88–8.07 ppm (m, 1, C-4); *m/e* calcd for $C_{20}H_{18}N_2O_2$, 318.1368, and found, 318.1340.

8-Benzyloxymethyl-1a,8b-dihydro-1-benzylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]-indol-2(1*H*)-one (20c). A solution of 209 mg (0.5 mmol) of 1-benzyl-10-benzyloxymethyl-3a,10b-dihydro-υ-triazolo[4′,5′:3,4]pyrrolo[1,2-a]indol-4(1*H*)-one (**14f**), 10 ml of

freshly distilled piperylene, and 150 ml of freshly distilled benzene was placed in a photochemical reaction vessel equipped with a water-cooled quartz immersion well. The solution was purged with nitrogen for 15 min prior to irradiation with a Hanovia 679A-36 high pressure quartz mercury-vapor lamp (450 W) through a 2-mm Pyrex filter sleeve. The photolysis was stopped after 6 hr even though the starting triazoline had not been completely consumed. Evaporation of the reaction mixture yielded 418 mg of a dark orange oil, which was chromatographed on a silica gel. Early fractions afforded 45 mg of product; intermediate fractions contained both aziridine and starting triazoline. Later fractions yielded 78 mg of recovered triazoline (**14f**). The impure product was chromatographed on silica gel preparative thin layer plates eluting each three times with chloroform. A broad orange band approximately 5 cm above the origin was visible. The band was removed and the product was eluted from the silica gel with chloroform. Evaporation of the solvent yielded 26 mg of an oil, which was crystallized from ether–hexane. Two recrystallizations from ether–hexane yielded 10 mg (5.1% yield, 8.2% conversion) of benzyl aziridine (**20c**) as light tan crystals; mp 84–85°; ir (chloroform) 2983, 2844, 1744, 1639, 1461, 1389, 1361, 1306, 1136, 1091, 1071, 1028, 921 cm^{-1}; nmr (d_1-chloroform) δ 3.10 and 3.39 (AB quartet, 2, J_{8b-1a} = 4.5 Hz, C-8b, C-1a), 3.60 and 3.66 (lines 2 and 3 of apparent AB quartet, 2, benzyl CH_2), 4.49 (s, 2, CH_2), 4.68 (s, 2, CH_2), 6.68–7.52 (m, 13, C-5, C-6, C-7 + 10 phenyl protons), 7.66–7.99 ppm (m, 1, C-4); *m/e* calcd for $C_{26}H_{22}N_2O_2$, 394.1681, and found, 394.1643.

1-(*N*-Formyl-*N*-phenyl)amino-2-diazo-3*H*-pyrrolo[1, 2-*a*]-indol-3-one (15). To a 50-ml round-bottomed flask containing 4 ml of *N,N*-dimethylformamide (DMF) at 5° was added dropwise 100 mg (0.65 mmol) of phosphorous oxychloride. The resulting solution was allowed to stand for 10 min before a solution of 155 mg (0.54 mmol) of **5** in 4 ml of DMF was introduced over a period of 3 min. The solution was stirred at 5°C for 1 hr, during which time the color changed from an initial pale yellow to a yellow-orange. The contents of the flask were then poured into ice and water and extracted with ether. The ether layer was discarded. The aqueous layer was then made slightly basic by the addition of 2 *N* NaOH and again extracted with ether. The yellow ether layer was washed twice with water, dried over magnesium sulfate, filtered, and evaporated to dryness. The crude yield was 160 mg (84%) of light brown crystals which after two recrystallizations from THF–hexane and one from ethyl acetate gave analytically pure light yellow crystals, mp 173–76° dec, followed by gas evolution at 178°: ir ($CHCl_3$) 3.33, 4.20, 4.78, 5.82,5.99 μ; uv (MeOH) λ_{max} 220, 268, 308 nm (ϵ_{max} 12,280, 17,840, 8000); nmr ($CDCl_3$) δ 6.90 (bs, 1, $W_{1/2}$ = 2.5 Hz, C-9), 7.30–8.10 (m, 9, C-1, 6, 7, 8 + 5 phenyl protons), 8.23–8.50 (m, 1, C-5), 8.93 (s, 1, NCHO).

Anal. Calcd for $C_{18}H_{12}O_2N_4$: C, 68.35; H, 3.82; N, 17.71; mass spectrometer, 316.0960. Found: C, 68.49; H, 3.81; N, 17.88; mass spectrometer, 316.0976.

Registry No.—**3,** 247-66-5; **4,** 24009-76-5; **5,** 24009-77-6; **7,** 52827-13-1; **8,** 52827-14-2; **11,** 52827-15-3; **12,** 52827-16-4; **13a,** 26709-66-0; **13b.** 52827-17-5; **14a,** 52856-34-5; **14b,** 52856-35-6; **14c,** 52827-18-6; **14d,** 52827-19-7; **14e,** 52827-20-0; **14f,** 52827-21-1; **15,** 52827-22-2; **19,** 52827-23-3; **20a,** 52827-24-4; **20b,** 52827-25-5; **20c,** 52827-26-6; chloromethyl methyl ether, 107-30-2; chloromethyl benzyl ether, 3587-60-8; methyl azide, 624-90-8; phenyl azide, 622-37-7; benzyl azide, 622-79-7; methoxymethyl azide, 52827-27-7; benzyloxymethyl azide, 52827-28-8; piperylene, 504-60-9.

References and Notes

(1) (a) We gratefully acknowledge the financial support of the U.S. Public Health Service, Grant CA 11421. (b) Taken from the Ph.D. Theses of R.J.K. and G.J.S., Fordham University, 1974. (c) Presented in part at the 6th Northeast Regional Meeting of the American Chemical Society, Burlington, Vt., August 1974, Paper No. 174.

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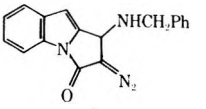

i

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Active Heteromethylene Compounds. I. Hindered Halomethyl Amides

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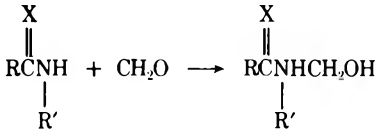
Received May 13, 1974

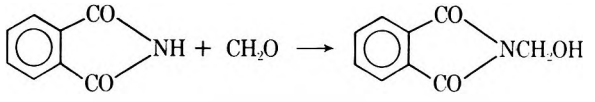
A novel series of hindered *N*-halomethyl- or oxymethyl-α-haloacetanilides (1) have been shown to react *via* sulfuric acid catalysis with nitriles to give *N*-acylaminomethyl-α-haloacetanilides (2). Some of the limitations and scope of this sequence are outlined. Structural implications in these hindered compounds are discussed based on nmr spectra.

N-Halomethyl or oxymethyl amides and imides are readily prepared classes of active heteromethylene compounds which constitute attractive intermediates for a variety of synthetic transformations. Condensation of amides with formaldehyde produces *N*-hydroxymethyl amides in a general sequence as outlined.[1]



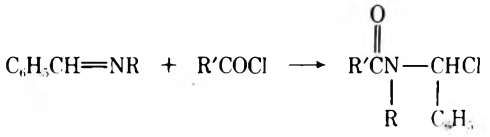
X = O, S
R′ = H, alkyl

Similarly imides condense to give *N*-hydroxymethyl imides, *e.g.*, the reaction of phthalimide and formaldehyde.[1a]



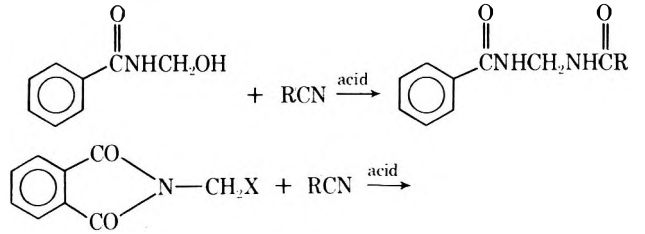
N-Halomethyl derivatives are readily made by hydrogen chloride or thionyl chloride treatment of the corresponding hydroxymethyl compounds mentioned above.[2]

Alternatively such derivatives have, in certain specific instances, been prepared by the addition of acid chlorides to Schiff bases.[3]

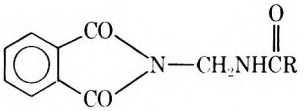


The varied reactivity of *N*-halomethyl or oxymethyl amides and imides is due to activation of the halogen or oxy substituent by the attached amide functionality.[2] Often in such systems the compounds possess this special reactivity due to carbonium ion character which can be induced *via* such systems.[4]

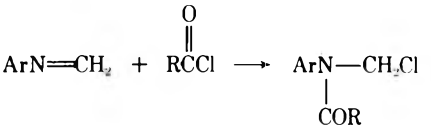
A specific illustration of the above-described reactivity is the reaction of *N*-hydroxymethylbenzamide and phthalimides with nitriles utilizing an acid catalyst.[5]



X = OH, Cl



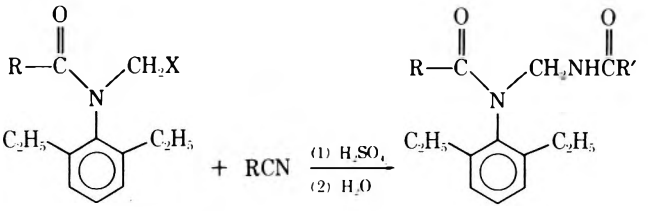
A recently developed procedure for the reaction of hindered azomethines with acid chlorides constitutes a new attractive method of producing a novel series of stable, hindered *N*-halomethyl amides (1).[6]



1

Since compounds of type 1 are hindered chloromethyl amides and as such possess some stability, they are useful intermediates for study.

We wish to describe the utilization of hindered *N*-chloromethyl amides in carbonium ion type reactions similar to those described above. A variety of nitriles, *via* acid catalysis, react with 1 to give methylene bis amides (2) in good yields.



1a, X = Cl
b. X = OCH_3
c. X = $OCOCH_2Cl$

2

A tabulation of the compounds prepared is given in Table I. The replaceable group may be halogen, alkoxyl, or acyloxy, all of which should generate carbonium ion species under acidic conditions. The nitrile can be quite widely varied with the exception of compounds containing acid sensitive groups.

The nmr spectra characteristically exhibit the N–CH_2–NH–methylene at approximately δ 5.0 as a doublet (J = 7 Hz) due to splitting by the adjacent NH proton. Infrared spectra show the presence of two amide carbonyl groups and analytical data are consistent with the proposed structures. Due to the hindered rotation present in such amides two conformations are possible dependent upon the positioning of, for example, the chloromethyl carbonyl over the aromatic ring (A) or away from the ring (B).

A B

In view of the often observed presence of both rotomers in other closely related tertiary substituted α-chloroacetanilides,[6,7] it is perhaps surprising that 2 appears to exist in

Table I
N-Acylaminomethylacetanilides[a]

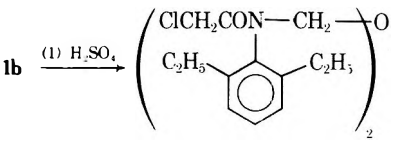
No.	R	R′	Yield, %	Mp, °C	Elemental analysis, % Calcd C	Calcd H	Found C	Found H
2a	Cl	CH_3	79	121–124	59.46	6.77	59.63	6.74
2b	CH_3	CH_3	68	112–115	68.67	8.45	68.88	8.36
2c	CH_3	$ClCH_2$	46	129–130	58.80	7.09	58.79	7.10
2d	$ClCH_2$	H	72	85–89	59.46	6.77	59.64	6.69
2e	$ClCH_2$	CH_3	71	148–149	60.5	7.13	60.68	7.22
2f	$ClCH_2$	n-C_3H_7	72	122–123	62.85	7.76	63.10	7.99
2g	$ClCH_2$	C_6H_5	82	132	66.97	6.46	67.74	6.46
2h	$ClCH_2$	CH_2=CH–	65	174–175	62.23	6.85	62.23	6.72
2i	$ClCH_2$	$ClCH_2$–CH_2–	65	133–136	55.66	6.42	55.55	6.39
2j	$ClCH_2$	C_2H_5S	75	107	56.04	6.76	56.20	6.87
2k[b]	$BrCH_2$	CH_3	57	152–154	54.09	6.53	53.93	6.69
2l[c]	$ClCH_2$	CH_3		145–146	56.58	5.94	56.89	6.10

[a] 2,6-Diethylanilide unless otherwise noted. [b] 6-*tert*-butyl-o-toluidide. [c] *o*-Toluidide.

solution at room temperature, only in form A. This configuration is assigned from the upfield (δ 3.6) shift of the chloromethylene protons arising from their shielding by the aromatic ring.

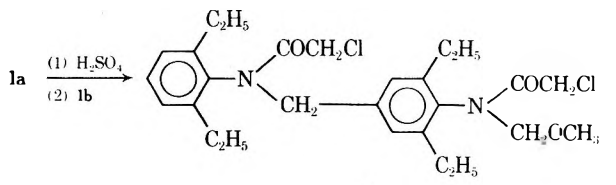
Noteworthy also is the presence of AB coupling observed in the methylene amido protons in **2l** which possesses only one aromatic ortho substituent. Only A_2 character is observed in either symmetrical or asymmetrical (*i.e.*, **2k**) di-ortho-substituted amides. Nonequivalence in this instance may arise from the greater differences in magnetic environments of these two protons when the amide plane is allowed to become nearly coplanar to a single ortho-substituted phenyl ring. Lessened methylene proton nonequivalence might be expected when the more usual orthogonal orientation of these two planes occurs in di-ortho-substituted materials.

Treatment of the derivative **1b** with acid in the absence of nitrile gave the bis ether **3**.[4]



3

The intermediate carbonium ion species may alkylate activated aromatic rings in certain instances if no nitrile is added. Indeed it might be considered somewhat surprising



4

that **1a** does not prefer self condensation even in the presence of other nucleophilic species. These low yield reactions do, however, illustrate alternate reactivity of the "carbonium ion species" with other substrates than nitriles. The mechanism for the above reactions is undoubtedly similar to that for the Ritter reaction with the halo or oxymethylene amide compound **1** serving as a carbonium ion precursor.[2,4,8]

N-Acylaminomethyl-α-haloacetanilides, in particular the formamido compound (**2**, R′ = H), provide a series of intermediates of interest for synthesis of a variety of new compounds. These results will be published in future papers.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Nuclear magnetic resonance spectra were recorded on Varian A-60 and T-60 spectrometers while infrared spectra were recorded on a Perkin-Elmer Infracord. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

The following preparations of materials **2** are illustrative of the procedures used to make the materials appearing in Table I. Minor variations in procedure are not critical for good yields and product purity.

Acetamidomethyl(2′,6′-diethylphenyl)carbamoyl Chloride (2a). Chloromethyl-*N*-(2,6-diethylphenyl)carbamoyl chloride was prepared by the simple addition of equimolar amounts of phosgene to 2,6-diethyl-*N*-methyleneaniline.[9] This adduct (15 g, 0.058 mol) was mixed with acetonitrile (2.5 g, 0.06 mol) and added to 40 ml of 96% sulfuric acid. The mixture was heated to 50° for *ca.* 15 min, then the mixture was stirred at ambient temperatures for a further hour. The material was then poured into *ca.* 300 ml of ice–water and after 15 min the granular solid (12.9 g) filtered off. The material was recrystallized from ethyl acetate to give 4.7 g, with an additional 3.2 g recovered from the mother liquors: nmr ($CDCl_3$) δ 1.30 (t, 6, J = 7 Hz, $ArCH_2CH_3$), 2.0 (s, 3, CH_3CO), 2.60 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 5.06 (d, 2, J = 6 Hz, NCH_2N), 6.92–7.4 (m, 3, ArH), 8.3 (broad, 1, NH).

***N*-Acetamidomethyl-2′,6′-diethylacetanilide (2b).** *N*-Chloromethyl-2′,6′-diethylacetanilide (prepared by procedures described in ref 9, from addition of acetyl chloride to 2,6-diethyl-*N*-methyleneaniline) (8.0 g, 0.0334 mol) in a mixture with 1.47 g of acetonitrile (0.0358 mol) was added to 35 ml of concentrated sulfuric acid, and the whole was heated with stirring at 55° for 1.5 hr. The homogeneous mixture was then poured into 300 ml of ice–water. No product separated; so the aqueous solution was extracted with 300 ml of methylene chloride; the solution was washed twice with water and then dried over magnesium sulfate. After filtering off the drying agent and removing the solvent under vacuum, the residual oil solidified and was recrystallized from heptane to give a 6.0-g yield: nmr ($CDCl_3$) δ 1.20 (t, 6, J = 6 Hz, $ArCH_2CH_3$), 1.68 (s, 3, $CH_3C(O)N$), 1.91 (s, 3, $CH_3C(O)N$), 2.48 (quartet, 4, $ArCH_2CH_3$), 4.80 (d, 2, J = 7 Hz, $-NCH_2NH$), 7.1–7.4 (m, 4, ArH and N–H).

***N*-(α-Chloroacetamidomethyl)-2′,6′-diethylacetanilide (2c).** The adduct used in the preparation of **2b** (10.0 g, 0.042 mol) was mixed with 3.4 g of chloroacetonitrile (0.045 mol) and added with stirring to 40 ml of concentrated sulfuric acid. The mixture was then heated at 50° for 1 hr, cooled to room temperature, and poured into *ca.* 300 ml of ice–water. The material was permitted to stand for 54 hr and the granular solid was filtered off and slurried well with water, filtered, and washed once again with water, followed by air drying. The solid was then recrystallized from heptane to give 5.8 g: nmr ($CDCl_3$) δ 1.20 (t, 6, J = 6 Hz, $ArCH_2CH_3$), 1.68 (s, 3, CH_3CO), 2.45 (quartet, J = 6 Hz, $ArCH_2CH_3$), 3.9 (s, 2, $ClCH_2CO$), 4.86 (d, 2, J = 7 Hz, $HNCH_2N$), 7.1–7.3 (m, 3, ArH), 7.9 (broad, 1, N–H).

2-Chloro-2′,6′-diethyl-*N*-formamidomethylacetanilide (2d). 2-Chloro-*N*-chloromethyl-2′,6′-diethylacetanilide (200 g, 0.73 mol) was placed in 250 ml of concentrated sulfuric acid and 30 g of (1.04 mol) cooled, liquified hydrogen cyanide was added drop-

wise over 15–20 min at 5–20°. The mixture was then allowed to warm, with final heating at 55–60° for 1 hr. The cooled reaction mixture was then poured into 1.2 l. of ice–water with stirring, and the mixture was allowed to stand for 3 hr. The granular precipitate was then filtered off, washed thoroughly with water, air dried, then recrystallized from methylcyclohexane to give 161 g: nmr ($CDCl_3$) δ 1.21 (t, 6, J = 7 Hz, $ArCH_2CH_3$), 2.51 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 3.62 (s, 2, $ClCH_2$), 4.88 (d, 2, J = 7 Hz, NCH_2N), 7.1–7.4 (m, 3, ArH) 7.65 (broad, 1, NH), 8.2 (s, 1, CHO).

N-**Acetamidomethyl-2-chloro-2′,6′-diethylacetanilide (2e).** To 17.7 g (0.104 mol) of chloroacetic anhydride contained in a minimum amount of hot benzene was slowly added 16.8 g (0.104 mol) of *N*-methylene-2,6-diethylaniline in an equal volume of benzene. Concentration and cooling of the mixture gave crystals, mp 57–58°; elemental analysis and nmr and ir spectra were consistent for the adduct **1c** (R = $ClCH_2$). Material **1c** (7.96 g, 0.025 mol) was mixed with 100 ml of acetonitrile and 5 drops of 10% sulfuric acid was added. The mixture was heated on the steam bath for 70 min then permitted to stand overnight. After an additional reflux period of 90 min, the mixture was poured into 900 ml of ice–water. The solid was filtered off and air dried to give 6.0 g, mp 114–125°. Recrystallization of the material from methanol gave 2.4 g (32%) of **2e**. Better yields (see Table I) of **2e** could be obtained from reaction of **1a** (R = $ClCH_2$) with equimolar amounts of acetonitrile in concentrated sulfuric acid, as described for **2d** above: nmr ($CDCl_3$) δ 1.2 (t, 6, J = 7 Hz, $ArCH_2CH_3$), 1.96 (s, 3, CH_3CO), 2.52 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 3.63 (s, 2, $ClCH_2$), 4.95 (d, 2, J = 6 Hz, NCH_2N), 7.0–7.5 (m, 4, ArH and NH).

N-**Acrylamidomethyl-2-chloro-2′,6′-diethylacetanilide (2h).** 2-Chloro-*N*-(methoxymethyl)-2′,6′-diethylacetanilide[9] (0.05 mol, 13.5 g) was mixed with 2.7 g of (0.05 mol) acrylonitrile and then added at 15–20° to 30 ml of concentrated sulfuric acid. The mixture was heated at 55° for 1 hr, cooled, and poured into 300 ml of ice–water. After standing 15 min with occasional stirring, the solid granules were filtered off, washed on the filter with more water, then recrystallized from 2-propanol to give 10.0 g of product. If **1a** (R = $ClCH_2$) was used in place of **1b** (R = $ClCH_2$), addition takes place with the formation of **2i** in good yield: nmr (**2h**) ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz, $ArCH_2CH_3$), 2.51 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 3.62 (s, 2, $ClCH_2$), 5.02 (d, 2, J = 6 Hz, NCH_2N), 5.4–6.3 (m's, 3, =CH), 7.1–7.5 (m, 4, ArH, NH).

S-**Ethyl** *N*-**[2-Chloro-***N*-**(2,6-diethylphenyl)acetamidomethyl]thiocarbamate (2j).** Material **1b** (R = $ClCH_2$) (0.0222 mol, 6.0 g) was mixed with 2.06 g (0.0238 mol) of ethyl thiocyanate to which *ca.* 5 ml of glacial acetic had been added to help effect the dissolution of the amide. The mixture was then added *via* dropping funnel with stirring to 25 ml of concentrated sulfuric acid at 5–10°. After the addition, the material was allowed to warm to 15° and then was poured into *ca.* 200 ml of ice–water. The insolubles thus obtained gradually hardened overnight to a granular solid. This material was filtered off and air dried to give a 5.7 g yield. The technical material could be further purified by recrystallization from methylcyclohexane–toluene (charcoal): nmr ($CDCl_3$) δ 1.22 (t, 9, J = 7 Hz, $-CH_2CH_3$), 2.52 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 2.81 (quartet, 2, J = 7 Hz, SCH_2CH_3), 3.61 (s, 2, $ClCH_2$), 4.92 (d, 2, J = 7 Hz, NCH_2N), 7.2–7.35 (m, 4, ArH and NH).

N-**Acetamidomethyl-2-bromo-6′-***tert***-butylaceto-***o***-toluidide (2k).** 2-Bromo-*N*-(methoxymethyl)-6′-*tert*-butyl-o-acetotoluidide (6.5 g, 0.0197 mol) was mixed with 5 ml of glacial acetic acid and 0.87 g (0.021 mol) of acetonitrile. The mixture was added to 30 ml of concentrated sulfuric acid at 10–20° and then heated at 55° for 1.5 hr. After cooling, the mixture was stirred into 300 ml of ice–water. The granular precipitate was separated by filtration, washed with water, and air dried to give 5.75 g. The material was recrystallized from 2-propanol to give 4.0 g: nmr ($CDCl_3$) δ 1.35 (s, 9, $(CH_3)_3C-$), 1.95 (s, 3, $ArCH_3$), 2.2 (s, 3, CH_3CO), 3.58 (s, 2, $ClCH_2$), 4.90 (d, 2, J = 6 Hz, NCH_2N), 7.1–7.6 (m's, 4, ArH and NH).

N-**Acetamidomethyl-2-chloro-***o***-acetotoluidide (2l).** **1a** (R = $ClCH_2$) (23.6 g, 0.1 mol) was mixed with 4.5 g of acetonitrile, and this mixture was added to 60 ml of cold, concentrated sulfuric acid. After addition, the mixture was heated at 70–80° for 2 hr, cooled, and poured into 600 ml of ice–water. The material was made basic with NaOH and then permitted to stand 2 days. The solid, consisting of product and sodium sulfate, was separated, air dried, and then recrystallized from toluene: nmr ($CDCl_3$) δ 1.95 (s, 3, $ArCH_3$), 2.23 (s, 3, CH_3CO), 3.71 (s, 2, $ClCH_2$), 4.90 (AB quartet, 1, J = 14 Hz), 5.00 (AB quartet, 1, J = 14 Hz) (4.90 and 5.00 for NCH_2N), 7.1–7.7 (m's, 5, ArH and NH). Deuteration of the sample with D_2O to form the N–D material reduced the absorption in this region to a single AB quartet (J = 14 Hz).

N,*N*′-**(Oxydimethylene)bis(2-chloro-2′,6′-diethylacetanilide) (3).** Material **1b** (R = $ClCH_2$) (9.7 g, 0.036 mol) was mixed with 2.9 g of (0.04 mol) *N*-methylacetamide, and the contents were added dropwise to 10 ml of concentrated sulfuric acid at 10–15°. After addition, the mixture was heated 1 hr at 45–48° and then stirred an additional 3 hr at room temperature. The material was poured into 300 ml of ice–water and the sticky solid was extracted with methylene chloride, washed twice with water, filtered through clay, and dried over $MgSO_4$. On evaporation, an oil was obtained which solidified overnight. The material was recrystallized from ethyl acetate to give product, mp 145–147°: nmr ($CDCl_3$) δ 1.15 (t, 12, J = 7 Hz, CH_2CH_3), 2.48 (quartet, 8, J = 7 Hz, $ArCH_2CH_3$), 4.6 (s, 4, $ClCH_2$), 5.11 (s, 4, NCH_2O), 7.2–7.4 (m, 4, ArH and NH). The mass spectra displayed the parent ion at 492 and base peak at 238 (carbonium ion resulting from ether oxygen–carbon cleavage of **3**).

Anal. Calcd for $C_{26}H_{34}Cl_2N_2O_3$: C, 63.28; H, 6.94. Found: C, 62.84; H, 6.93.

N-**[4-[2-Chloro-***N*-**(methoxymethyl)acetamido]-3,5-diethylbenzyl]-2′,6′-diethyl-2-chloroacetanilide (4).** Equimolar amounts of **1a** and **1b** (R = $ClCH_2$) were mixed together and added dropwise to cold, concentrated sulfuric acid. After addition, the material was heated at 50° for 1 hr, cooled, and then poured into ice–water to give a granular solid. This material was then filtered, washed with water, and air dried. Recrystallization was effected first from methylcyclohexane and then from ethyl acetate, mp 153–156°: nmr ($CDCl_3$) δ 1.0 (triplets, 12, J = 7 Hz, $ArCH_2CH_3$), 2.3 (quartets, 8, J = 7 Hz, $ArCH_2CH_3$), 3.61 (s, 2, $ClCH_2$), 4.10 (s, 2, $ClCH_2$), 4.80 (s, 2, $ArCH_2N$), 7.0 (s, 2, ArH), 7.1–7.3 (m, 3, ArH (A_2B)), 7.9 (broad, 1, NH). The mass spectra gave a parent molecular ion at 464.

Anal. Calcd for $C_{27}H_{36}Cl_2N_2O_3$: C, 64.79; H, 6.96; Cl, 15.30; N, 6.04. Found: C, 65.03; H, 6.97; Cl, 15.89; N, 5.84.

Registry No.—**1a** (R = Cl), 35747-79-6; **1a** (R = CH_3), 52920-49-7; **1a** (R = $ClCH_2$), 40164-69-0; **1b** (R = $ClCH_2$), 15972-60-8; **1c** (R = $ClCH_2$), 40164-65-6; **2a**, 52920-50-0; **2b**, 52920-51-1; **2c**, 52920-52-2; **2d**, 40164-72-5; **2e**, 40164-67-8; **2f**, 40164-95-2; **2g**, 40164-97-4; **2h**, 40164-74-7; **2i**, 40164-93-0; **2j**, 52920-53-3; **2k**, 52920-54-4; **2l**, 52920-55-5; **3**, 52920-56-6; **4**, 52920-57-7; acetonitrile, 75-05-8; chloroacetonitrile, 107-14-2; hydrogen cyanide, 74-90-8; *N*-methylene-2,6-diethylaniline, 35203-08-8; chloroacetic anhydride, 541-88-8; ethyl thiocyanate, 542-90-5; 2-bromo-*N*-(methoxymethyl)-6′-*tert*-butyl-o-acetotoluidide, 2163-81-7; acrylonitrile, 107-13-1.

References and Notes

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Free-Radical Alkylation of Adamantanes

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Received February 5, 1974

Adamantane and dimethyladamantane were alkylated exclusively at the bridgehead position with olefin in the free-radical chain reaction initiated by di-*tert*-butyl peroxide. *n*-Hexyl-, *n*-octyl-, cyclohexyl-, or cyclooctyladamantane was prepared in moderate yield based on consumed olefin. The major by-product isolated was that of allylic coupling. Treatment of an adamantane with ethylene gave the corresponding bridgehead ethyladamantane in practically quantitative yield when the initial pressure of ethylene was low. With higher ethylene pressure, *n*-butyl- and *n*-hexyladamantanes were also formed.

Adamantane often serves as an excellent probe for the investigation of aliphatic substitution because of its skeletal stability[1] and its resistance to intramolecular rearrangement.[2] Thus, the synthetic applications of many cationic and some free-radical[3-6] substitutions for the functionalization of adamantanes are very successful.

The free-radical alkylation of dimethyladamantane[7] with an olefin in the presence of di-*tert*-butyl peroxide gave the corresponding 1-alkyl-3,5-dimethyladamantane as the major product. Results are summarized in Table I. The important by-products obtained were the corresponding 1:2 adduct and the coupling product derived from the allylic radical. Thus, the radical alkylation was extended to ethylation of 1,3-dimethyladamantane with ethylene, which bears no allylic hydrogen (excluding the possibility of the formation of the allylic coupling product) but has a moderate tendency toward radical telomerization depending on the pressure of ethylene. The results are shown in Table II. Yield of the ethylation of 1,3-dimethyladamantane (based on dimethyladamantane consumed) was excellent (89%) at low ethylene pressure (2 kg/cm^2). The telomerization (higher alkylation) became more important with the increase in ethylene pressure, and 1-*n*-butyl-3,5-dimethyladamantane, 1-*n*-hexyl-3,5-dimethyladamantane, and 1-*n*-octyl-3,5-dimethyladamantane were obtained with moderate ethylene pressure (2–10 kg/cm^2). Similar results were also obtained for adamantane (see Table III).

Thus, the direct free-radical alkylation of 1,3-dimethyladamantane with an appropriate olefin is an excellent procedure. Other alkylation procedures of adamantane in the literature are (1) the Wurtz type synthesis[8] giving alkyladamantanes only in poor yield, (2) the Grignard coupling of adamantyl bromide with alkylmagnesium bromide[9] giving methyladamantane in excellent yield but considerably reduced yields with higher alkyl groups, and (3) the Friedel–Crafts type syntheses[10-14] with moderate to excellent yields, but often accompanied by skeletal rearrangement of an alkyl group.

The characteristics of the present alkylation are its regiospecificity producing almost exclusively bridgehead radical from 1,3-dimethyladamantane or adamantane and the very efficient chain transfer from the growing chain to 1,3-dimethyladamantane or adamantane.

The observed regiospecificity was interpreted by the bulkiness of the attacking (abstracting) radical.[15]

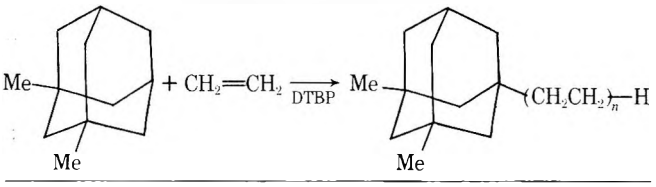
A bulky attacking radical was observed to increase the bridgehead of reduced bridge reactivity ratio as shown in Table IV, because of reduced bridge reactivity, probably by the steric repulsion in a transition state. An intermediate radical derived from adamantyl and an olefin (1) is that of the secondary structure (except for the ethylene addition),

Table I
1:1 Adducts of the Radical Addition of 1,3-Dimethyladamantane with Various Olefins[a]

1:1 adduct R	Olefin used	Registry no.	Molar ratio[c]	Yields of[b] 1:1 adduct, %	Yields of[b] olefin dimer, %
C_6H_{13}	Hexene-1	592-41-6	1	9	0
			10	20	0
C_8H_{17}	Octene-1	111-66-0	5	15	0
			10	17	0
C_6H_{11}	Cyclohexene	110-83-8	10	5	9
C_8H_{15}	Cyclooctene	931-88-4	5	15	1
			10	26	2

[a] Reactions were initiated by DTBP at 150° and kept for 5 hr. [b] Yields were determined based upon the converted olefins. The yield of the 1:1 adduct based on dimethyladamantane was practically quantitative. [c] The ratio of dimethyladamantane to olefin.

Table II
Products of the Radical Addition of Ethylene to 1,3-Dimethyladamantane[a]



	Experiment 1	2	3
Ethylene pressure, kg/cm^2	2	5	10
Conversion of dimethyladamantane (%)	22.5	29.6	25.3
Products	**Yield,[b] mol %**		
1-Ethyl-3,5-dimethyladamantane (n = 1)	89.0	69.7	33.5
1-Butyl-3,5-dimethyladamantane (n = 2)	10.5	17.0	23.9
1-Hexyl-3,5-dimethyladamantane (n = 3)	0.5	1.8	4.8
1-Octyl-3,5-dimethyladamantane (n = 4)	0	0.4	1.1
(n = 5)			

[a] Reactions were initiated by DTBP at 130° and kept at a constant pressure of ethylene for 5 hr. [b] Yields were calculated based upon dimethyladamantane consumed.

Table III
Alkylation of Adamantane with Ethylene in Benzene (50 ml) in the Presence of DTBP (0.73 g) at 150° for 2 hr

	Initial pressure of ethylene, kg/cm²		
	5	10	20
Adamantane, g			
used	13.65	13.61	13.65
recovered	11.63	*a*	*a*
Product, g			
1-ethyladamantane	1.18	0.58	0.25
1-*n*-butyladamantane	0.46	0.51	0.33
1-*n*-hexyladamantane		0.034	0.051

[a] Recovery was practically quantitative.

Table IV
Effect of Bulkiness of an Abstracting Radical in Simple Brominations[6]

Brominating reagent	Abstracting radical	Bridgehead to bridge react. ratio
Br_2	·Br	2.5
CH_2Br_2	·CH_2Br	9
$BrCCl_3$	·CCl_3	27

favoring the hydrogen abstraction from the bridgehead position of 1,3-dimethyladamantane or adamantane.

$$1,3\text{-}R_2AdH + 3,5\text{-}R_2Ad^{(1)}CHR'\dot{C}HR'' \longrightarrow$$
$$3,5\text{-}R_2Ad\cdot^{(1)}\ (major) + 3,5\text{-}R_2Ad^{(1)}CHR'CH_2R''$$
$$1$$
$$R = H \text{ or } CH_3$$

A substituent at the bridgehead (1 position) lowers the reactivity of the 2 position *profoundly* and that of the 4 position *moderately*.[16] While the reactivity of the 3 position was less affected by a substituent, actually a small *acceleration* by methyl was observed for the bromination with NBS or the chlorination with CCl_4.

For 1,3-dimethyladamantane, most of the bridge hydrogens are *doubly* deactivated, so that the reasonable assumption should be made that the abstraction of a bridgehead hydrogen prevails over that of a bridge hydrogen.

Experimental Section

Materials and Apparatus. Commercially available 1,3-dimethyladamantane, adamantane, olefins (ethylene, hexene-1, octene-1, cyclohexene, and cyclooctene), and di-*tert*-butyl peroxide were used. All the materials except ethylene were purified by usual distillation. Commercially available ethylene (99% pure) was used without further purification.

Nmr spectra were measured with a Varian EM 360, 60 MHz, using TMS as an internal standard in CCl_4 solvent. Infrared spectra were measured with a Hitachi 215 spectrophotometer. Glc analysis was performed using a 0.3 × 200 cm column (Apiezon grease L, 5 and 10%).

1-Alkyl-3,5-dimethyladamantane from Ethylene and 1,3-Dimethyladamantane. A mixture of 1,3-dimethyladamantane (16.435 g; 0.1 mol) and di-*tert*-butyl peroxide (0.730 g, 5 mmol) was placed in a 100-ml autoclave. After the replacement of air with ethylene, the initial pressure of ethylene was adjusted to 5 kg/cm² and the mixture was stirred at 130° for 5 hr. After cooling, the reaction products were isolated by distillation *in vacuo* and/or preparative gas chromatography. Four products (determined as 1-ethyl-, 1-butyl-, 1-hexyl-, and 1-octyl-3,5-dimethyladamantane) were obtained, which amounted to 3.976, 1.110, 0.128, and 0.040 g, respectively (mol %: 69.7, 17.0, 1.8, and 0.4) and the combined yield was 89% based on adamantane consumed, determined by analytical glc. A higher homolog ($n \geq 5$) could not be isolated but in some cases was obtained as a white precipitate, probably admixed with high polymer. Similarly, the alkylations of 1,3-dimethyladamantane with higher initial pressures of ethylene were carried out.

Alkylation of Adamantane with Ethylene. Similar alkylation was applied to 13.6 g (0.1 mol) of adamantane dissolved in 50 ml of benzene with ethylene of the initial pressure of 5 kg/cm² in the presence of 0.73 g (5×10^{-3} mol) of di-*tert*-butyl peroxide at 150° for 2 hr. Together with 11.63 g of recovered adamantane, 1.18 g of 1-ethyladamantane (50% based on adamantane consumed) and 0.46 g of 1-*n*-butyladamantane (17% based on reacted adamantane) were obtained. The combined yield of the alkylation based on ethylene was practically quantitative. Higher 1-alkyl homologs were present in the product only in trace amounts under the present condition. 1-Ethyl-, 1-*n*-butyl-, and 1-*n*-hexyladamantanes were identified with those from the relevant syntheses: 1-ethyl- from 1-bromoadamantane and ethylmagnesium bromide,[9] 1-*n*-butyl- from 1-bromoadamantane and thiophene with stannic chloride followed by the Raney Ni hydrogenolysis,[14] and 1-*n*-hexyladamantane from adamantane and 1-hexene in the presence of di-*tert*-butyl peroxide.

Alkylation of adamantane at higher initial ethylene pressure under similar reaction conditions gave the following results: at 10 kg/cm², ethylene, 1-ethyladamantane, 1-*n*-butyladamantane, and 1-*n*-hexyladamantane in a molar ratio of 23:17:1, the combined yield of alkyladamantanes based on reacted adamantane was practically quantitative; at 20 kg/cm², ethylene, 1-ethyladamantane, 1-*n*-butyladamantane, and 1-*n*-hexyladamantane in a molar ratio of 6.5:7.4:1, the combined yield was again practically quantitative.

1-Alkyl-3,5-dimethyladamantanes from 1,3-Dimethyladamantane and Olefins. A mixture of 1,3-dimethyladamantane, an olefin, and di-*tert*-butyl peroxide was placed in a flask and heated at a given temperature (between 110 and 150°). The initial molar ratio of dimethyladamantane to an olefin was in the range of 1–10 and the amount of the initiator added was 5–50 mol % of the olefin. After the usual work-up, the 1:1 adduct was isolated by the preparative gas chromatography. Table I shows the results obtained for hexene-1, octene-1, cyclohexene, and cyclooctene. In the case of cyclooctene, the products consisted of two components (in a ratio of 3:1); the major one was found to be 1-cyclooctyl-3,5-dimethyladamantane, but the structure of the minor one has not yet been determined.

Physical and Spectral Properties of 1-Alkyl-3,5-dimethyladamantanes. 1-Ethyl-3,5-dimethyladamantane: bp 65–67° (5 mm); $n^{25}D$ 1.4804; nmr δ 0.80 (s, 6 H, CH_3, CH_3), 0.80 (t, 3 H, CH_2CH_3), 2.00 (br, 1 H, bridgehead proton), and 0.9–1.7 ppm (m, 12 H, remaining adamantyl protons); mass spectrum, *m/e* (relative intensity) 192 (M^+, 2), 177 (M − 15, 11), 163 (M − 29, 100), 107 (M − 85, 70).

1-*n*-Butyl-3,5-dimethyladamantane: bp 123–124° (9 mm); $n^{25}D$ 1.4813; nmr δ 0.80 (s, 6 H, two CH_3), 0.89 (t, 3 H, CH_2CH_3), 2.00 (br, 1 H, bridgehead proton), and 1.0–1.5 ppm (three sharp peaks centered at 1.09, 1.27, and 1.30, 18 H, remaining alkyl and adamantyl protons); mass spectrum, *m/e* 220 (M^+, 1), 205 (M − 15, 6), 163 (M − 57, 100), 107 (M − 113, 43).

1-*n*-Hexyl-3,5-dimethyladamantane: bp 108–108.5° (0.9 mm); $n^{25}D$ 1.4807; nmr δ 0.80 (s, 6 H, two CH_3's), 2.00 (br, 1 H, bridgehead proton); mass spectrum, *m/e* 248 (M^+, 1), 233 (M − 15, 6), 163 (M − 85, 100), 107 (M − 141, 67).

1-*n*-Octyl-3,5-dimethyladamantane: $n^{25}D$ 1.4802; nmr δ 0.76 (t, 3 H, $(CH_2)_7CH_3$), 0.78 (s, 6 H, two CH_3), 2.00 (br, 1 H, bridgehead proton), 0.9–1.6 ppm (m, 26 H, remaining alkyl and adamantyl protons); mass spectrum, *m/e* 276 (M^+, 1), 231 (M − 15, 1), 163 (M − 83, 100), 107 (M − 169, 34).

1-Cyclohexyl-3,5-dimethyladamantane: $n^{25}D$ 1.5137; nmr δ 0.80 (s, 6 H, two CH_3), 1.73 (br, 1 H, cyclohexyl tertiary proton), 2.00 (br, 1 H, bridgehead proton), 0.9–1.5 ppm (m, 24 H, remaining alkyl and adamantyl protons); mass spectrum, *m/e* 246 (M^+, 1), 244 (M − 2, 1), 231 (M − 15, 1), 163 (M − 83, 100), 107 (M − 139, 34).

1-Cyclooctyl-1,5-dimethyladamantane. This compound was contaminated with a small amount of an impurity assumed to be 1-cyclooctenyl-1,5-dimethyladamantane. Gas chromatographic separation gave the titled compound in a practically pure state: $n^{25}D$ 1.5175; nmr δ 0.80 (6 H, two CH_3), multiplets centered at 1.11, 1.30, 1.56, and 2.08 ppm; mass spectrum, *m/e* 274 (M^+, 2), 272 (M − 2, 2), 244 (M − 30, 5), 163 (M − 111, 100), 149 (M − 125, 5), 135 (M − 139, 25), 107 (M − 167, 34).

Acknowledgments. The authors are very grateful to Professor Yoshida of Kyoto University for his helpful discussions. The authors are also grateful to du Pont de Nemours and Co. for their kind supply of adamantane.

Registry No.—1,3-Dimethyladamantane, 702-79-4; ethylene, 74-85-1; 1-ethyl-3,5-dimethyladamantane, 1687-35-0; 1-*n*-butyl-3,5-dimethyladamantane, 52826-28-5; 1-*n*-hexyl-3,5-dimethyladamantane, 52873-50-4; 1-*n*-octyl-3,5-dimethyladamantane, 52855-93-3; 1-cyclohexyl-3,5-dimethyladamantane, 19385-91-2; 1-cyclooctyl-3,5-dimethyladamantane, 52826-29-6; adamantane, 281-23-2.

References and Notes

(1) Fragmentation is one of the common fates of an intermediate from a chain aliphatic compound.
(2) Even for free-radical reactions, some intramolecular rearrangement was observed. See, *e.g.*, W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N.Y., 1966 p 13, for the 1,2-chlorine shift. But the 1,2-hydrogen shift on the adamantyl radical was not observed although the following indirect intermolecular process was sometimes observed which

$$Ad^{\cdot(2)} \xrightarrow{SH} AdH \xrightarrow{R\cdot} Ad^{\cdot(1)} \xrightarrow{Y\text{-}X} Ad^{(1)}\text{-}X$$

was confirmed in the perester decomposition in biacetyl (I. Tabushi, K. Fukunishi, and S. Kojo, manuscript in preparation).
(3) Unselective chlorination and autooxidation: G. W. Smith and H. D. Williams, *J. Org. Chem.*, **26**, 2207 (1961).
(4) Chlorocarbonylation; I. Tabushi, J. Hamuro, and R. Oda, *J. Org. Chem.*, **33**, 2108 (1968); I. Tabushi, T. Okada, Y. Aoyama, and R. Oda *Tetrahedron Lett.*, 4069 (1969).
(5) Regiospecific photoacetylation; I. Tabushi, S. Kojo, and Z. Yoshida, *Tetrahedron Lett.*, 2329 (1973).
(6) Radical bromination or chlorination with various halogenating reagents; I. Tabushi, J. Hamuro, and R. Oda, *J. Amer. Chem. Soc.*, **89**, 7127 (1967). See also I. Tabushi, Y. Aoyama, S. Kojo, I. Hamuro, and Z. Yoshida, *J. Amer. Chem. Soc.*, **94**, 1177 (1972), and I. Tabushi, Y. Aoyama, and Z. Yoshida, *ibid.*, **93**, 2077 (1971).
(7) This compound is a liquid under the reaction conditions and reaction proceeds much more smoothly by using this than parent adamantane.
(8) S. Landa, *et al.*, *Chem. Listy*, **51**, 2325 (1957).
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(12) An adamantane and an alcohol with sulfuric acid; A. Schneider, U.S. Patent, 3,382,288 (1968); *Chem. Abstr.*, **69**, 35584 (1968); *Amer. Chem. Soc. Div. Petrol. Chem. Prepr.*, 15 (1970); *Chem. Abstr.*, **75**, 109936 (1971).
(13) Dimethyladamantane with boron trifluoride–ether complex and sulfuric acid; R. E. Moore, U.S. Patent, 3,671,600 (1972); *Chem. Abstr.*, **77**, 100938 (1972).
(14) Adamantyl bromide and thiophene with stannic chloride followed by Raney Ni desulfurization; W. Hoek, *et al.*, *Recl. Trav. Chim. Pays-Bas*, **85**, 1045 (1966).
(15) In the case of 1,3-dimethyladamantane, the substituent effect seems to be operative also.
(16) (a) The results of systematic analyses of the reactivities will be published soon. A part of the work was presented; I. Tabushi, Y. Aoyama, and Z. Yoshida, 12th Symposium on Organic Free Radicals, Nagoya, 1971, Abstracts of Papers, p 75; 26th Annual Meeting of Japan Chemical Society, Hiratsuka, 1972, Abstracts of Papers, III, p 1333. (b) The statistically corrected reactivity ratio of bridgehead to bridge position for the chlorocarbonylation of 1-substituted adamantanes amounted to 2.3 for methyl, 5.7 for methoxyl, and 4.4 for carbomethoxy (considerably larger than 1.2 for the unsubstituted); I. Tabushi, T. Okada, Y. Aoyama, and R. Oda, *Tetrahedron Lett.*, 4069 (1969). Similarly, the reactivity ratios for the $BrCCl_3$ bromination were 26.8 for methyl and 22.8 for methoxyl (18.3 for the unsubstituted); P. H. Owens, G. J. Gleicher, and L. M. Smith, Jr., *J. Amer. Chem. Soc.*, **90**, 4122 (1968). However, in the above results, differentiations between 2 and 4 positions were not made.

Stable Carbocations. CLXXII.[1] 2-Adamantyl Cations

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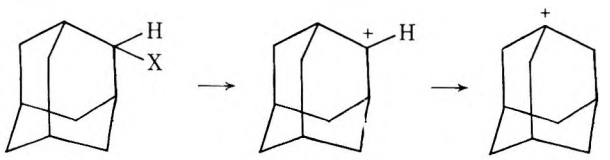
Received May 22, 1974

A series of 2-alkyl-, 2-phenyl-, and 2-halo-substituted 2-adamantyl cations were obtained in FSO_3H, FSO_3H·SbF_5, and SbF_5 (SO_2ClF or SO_2) solutions at −78° and their ^1H and ^{13}C nmr spectra were studied. Tertiary 2-adamantyl cations, unlike the parent secondary 2-adamantyl cation which immediately undergoes intermolecular rearrangement to the bridgehead 1-adamantyl cation, show no skeletal rearrangement in superacidic media. 2p–π conjugation between the phenyl π system and the empty 2p orbital at the carbenium center in 2-phenyl-2-adamantyl cation was found important. Halogen back donation (n–2p conjugation) induced by the halogen unshared electron pairs in 2-halo-2-adamantyl cations was found to increase in accordance with the increasing order of halogen electronegativity Br < Cl < F.

The observation and study of 1-adamantyl cations[2] in strongly acidic media in our laboratory prompted interest in the study of 2-adamantyl cations. These ions have similar rigidity but bear positive charge at the secondary, nonbridgehead position of the adamantane system. The parent 2-adamantyl cation 1–H has thus far not been directly observed. The reason is that fast intermolecular hydride shift takes place immediately after the relatively unstable secondary ion 1–H is formed, giving the more stable tertiary bridgehead 1-adamantyl cation **2**.[3,4]



3 1–H 2

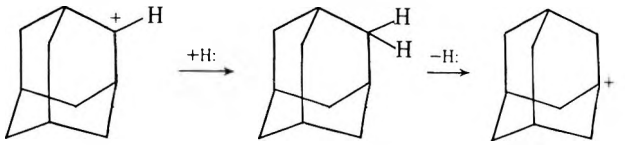
X = OH, Cl, Br or F

2-Methyl-2-adamantyl cation is, however, stable in strong acid solutions (in H_2SO_4, FSO_3H, or FSO_3H–SbF_5) and shows no tendency to interconvert.[5] Many rearrangements involving apparent 1,2-hydride shifts in adamantane systems are now known to take place intermolecularly.[3,4,6] The interconversion of 2-methyl- and 1-methyladamantane, however, was shown to proceed intramolecularly involving rearrangement of 2-methyl-2-adamantyl cation to the 4-protoadamantyl cation followed by a rearrangement back to the adamantyl skeleton.[4b]

Although a series of 1-adamantyl cations have been prepared and characterized,[2] 2-substituted-2-adamantyl cations have not yet been reported in the literature. We, therefore, undertook the preparation of a series of 2-substituted-2-adamantyl cations and the study of their structure and stability in superacidic media. Proton and carbon-13 nmr spectra of 2-adamantyl cations including 2-alkyl-, 2-phenyl-, and 2-halo-substituted ions were obtained.

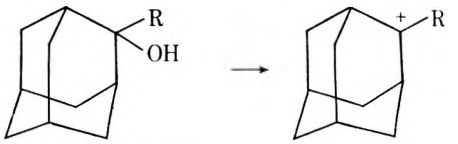
Results and Discussion

2-Adamantyl Cation 1-H. Attempts to prepare the parent secondary 2-adamantyl cation 1-H from various precursors 3 (X = OH, Cl, Br, F) at different temperatures (−78 and −120°) were unsuccessful.[2] The initially formed ion 1-H in SbF_5SO_2ClF solution even at −120° immediately rearranged into the more stable tertiary ion 2. The solvolysis of 2-adamantyl esters gave 2-adamantanol as the sole product after saponification,[4a,6,7] indicating the potential stability of ion 1-H under nucleophilic substitution conditions. The secondary ion 1-H formed under nonnucleophilic, stable ion conditions must undergo facile intermolecular hydrogen transfer to give ion 2 (intramolecular 1,2-hydrogen shift is impossible, because the orientation of the empty p orbital relating to the tertiary C–H bonds prevents it). A possible pathway might be visualized in the following manner.



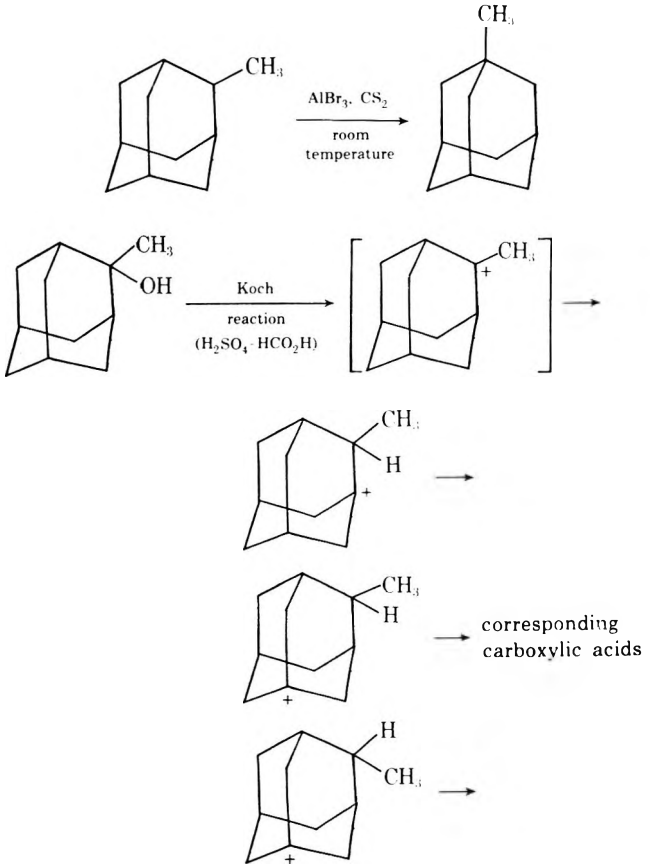
1-H 3 (X = H) 2

2-Methyl- and 2-Ethyl-2-adamantyl Cations. (1-CH_3 and 1-CH_2CH_3). These two ions are formed in fluorosulfuric acid–antimony pentafluoride sulfuryl chloride fluoride solution at −78° from their respective alcohols, 4. Both



4, R = CH_3 or CH_2CH_3 1-R

ions are stable and show no rearrangement in the temperature range studied (−78–+25°). Under the conditions of



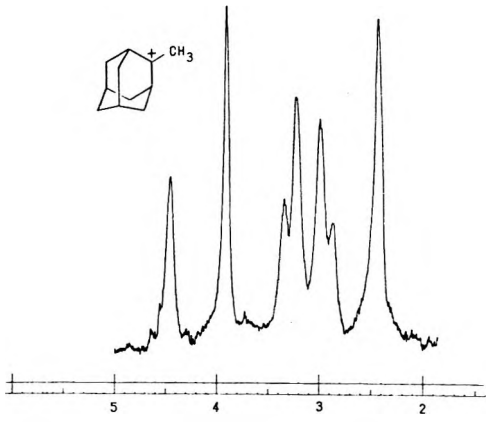


Figure 1. Pmr spectrum (100 MHz) of 2-methyl-2-adamantyl cation.

the Koch reaction,[8] 2-methyl-2-adamantanol is known to give a mixture of isomeric methyladamantylcarboxylic acids, while 2-methyladamantane is known to isomerize to 1-methyladamantane.[8-10] However, under stable ion conditions the 2-methyl-2-adamantyl cation 1-CH_3 is stable and apparently no isomerization takes place. Likewise, ion 1-CH_2CH_3 is also sufficiently stable under these conditions, to be observed as the stable, nonrearranging ion.

Pmr spectra of 2-methyl- and 2-ethyl-2-adamantyl cations (1-CH_3 and 1-CH_2CH_3) are very similar and considerably different from that of the 1-adamantyl cation[2a,b,g] (Figure 1). Pmr spectra of 2-substituted-2-adamantyl cations are summarized in Table I. Four basic proton resonances are observed in all 2-adamantyl cations. The two bridgehead protons resonances in the β positions to the empty p orbital (H_1 and H_3) are observed at δ 4.5 as a singlet; the four equivalent methylene protons show an AB quartet centered at δ 3.12 and 3.08 for 1-CH_3 and 1-CH_2CH_3, respectively; the additional two bridgehead protons (H_5 and H_7) are found at about δ 2.3–2.4; and the C_6 methylene protons usually are overlapping with the H_5 and H_7 signals.

Fourier transform (FT) ^{13}C nmr spectra of 1-CH_3 and 1-CH_2CH_3 are also completely different from that of 1-adamantyl cation.[2c,d] We have now obtained the complete FT ^{13}C nmr spectra for these ions and have summarized cmr parameters in Table II. The carbenium carbon shifts for both ions are found at $\delta_{^{13}C}$ 323.0 and 322.7 (from external capillary TMS), respectively. These values are very close to those found in the *tert*-butyl- ($\delta_{^{13}C}$ 329.1) and 1-methylcyclohexyl ($\delta_{^{13}C}$ 331.5) cations, indicating only a slight shielding due to the electron-releasing alkyl groups attached to the sp^2 center. The two equivalent bridgehead carbons (C_1 and C_3) and the four equivalent methylene carbons (C_4, C_8, C_9, and C_{10}) all show normal deshielded carbon shifts (Table II) experiencing the inductive effect at α and β positions to the positive charge, respectively. One noticeable point is that the two bridgehead carbons (C_5 and C_7) are found to be more shielded (by about 7–8 ppm) than the methylene carbon (C_6) which is the furthest away from the carbenium center. This observation is striking, since carbons γ to the carbenium center are generally more deshielded than those at the δ position. In the parent adamantane molecule, the bridgehead methine carbon atoms are less deshielded ($\delta_{^{13}C}$ 38) than the methylene ones ($\delta_{^{13}C}$ 27). We believe a contributing factor to the deshielding is the strain induced by ionization. If so, the same reasoning can be applied to the unusual observations of cmr shifts of 2-adamantyl cations.

Protonated 2-adamantanone 1-OH has previously been reported and characterized by pmr.[11] Ion 1-OH (in

Table I
Pmr Parameters of 2-Adamantyl Cations[a]

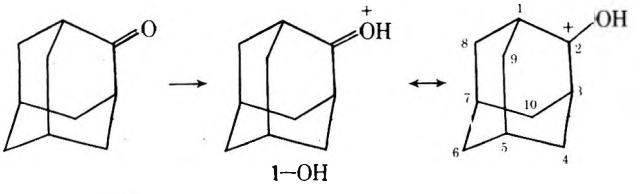
R	Registry no.	H_1, H_3	H_4, H_8, H_9, H_{10}	H_5, H_7	H_6	CH_3	CH_2*CH_3	Other
CH_3	27411-03-6	4.45, s	3.12, ABq	2.45, s	2.45, s	3.90		
CH_2CH_3	52873-72-0	4.48, s	3.08, ABq	2.48, s	2.30, s	1.80, t	4.25, q	
C_6H_5	52873-73-1	4.82, s	3.00 ABq	2.58, s	2.58, s			o: 9.12, d[b] p: 8.96, t m: 8.35, d-d
Br	52873-74-2	5.02, s	3.35, s	2.60, s	2.60, s			
Cl	52873-75-3	4.82, s	3.56, ABq	2.78, s	2.78, s			
F	51608-57-2	4.20, d	3.45, ABq	2.70, s	2.70, s			
OH	52873-76-4	3.50	2.73	2.40	2.30			13.85

[a] Pmr shifts (δ) are relative to external TMS; s = singlet; ABq = AB quartet; t = triplet; d = doublet; d-d = doublet of doublet. [b] Aromatic protons: o = ortho; p = para; m = meta.

Table II
^{13}Cmr Nmr Shifts of 2-Adamantyl Cations[a]

R	C^+	C_1, C_3	C_4, C_8, C_9, C_{10}	C_5, C_7	C_6	CH_3	*CH_2CH_3	Other
CH_3	323.0	66.3	52.6	29.1	36.6	41.2		
CH_2CH_3	322.7	62.5	51.3	28.7	36.0	7.8	49.4	
	271.3	51.4	49.3	29.5	36.3			o: 138.1[b] m: 132.9 p: 154.2 q: 137.1
OH	267.1	47.5	44.2	27.4	35.3			
Br	316.1	76.2	56.2	30.4	37.0			
Cl	313.7	71.6	56.5	30.4	36.9			
F	297.2[c] 286.0	56.1	53.9	29.3	36.4			

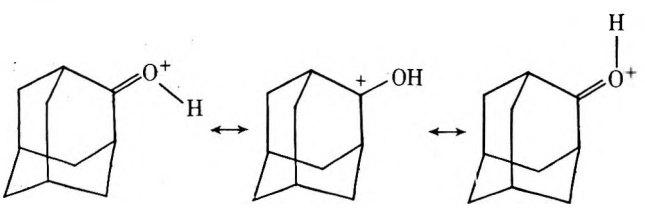
[a] Carbon-13 shifts are in parts per million from external TMS (capillary). [b] Aromatic carbons: o = ortho; m = meta; p = para; q = quaternary. [c] A doublet is observed for 1-F with J_{CF} = 422.6 Hz, and the average carbon shift is 291.6; ^{19}F shift for this ion is −126.4 (triplet, J_{HF} = 17 Hz). ^{19}F chemical shift is in parts per million from external CCl_3F (capillary).



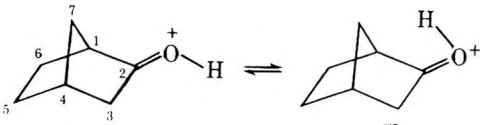
1–OH

FSO_3H–SO_2 or SO_2ClF) is extremely stable and only one OH absorption is observed (Table I) between −125 and 25°. The FTC C nmr spectrum of 1–OH shows five carbon absorptions characteristic to all the 2-adamantyl cations. Again, C_6 is more deshielded than C_5 and C_7.

Protonation of ketones normally gives isomeric species and the energy barrier for interconversion between isomers varies with different systems. The energy barrier for 1–OH seems generally to be low and the interconversion between the two oxonium ion forms must be fast since both ^{1}H and ^{13}C spectra indicate that the ion is symmetrical. If only one of the isomers would be present at low temperature, the two bridgehead carbons (C_1 and C_3) apparently should be different and a more complicated cmr spectrum should



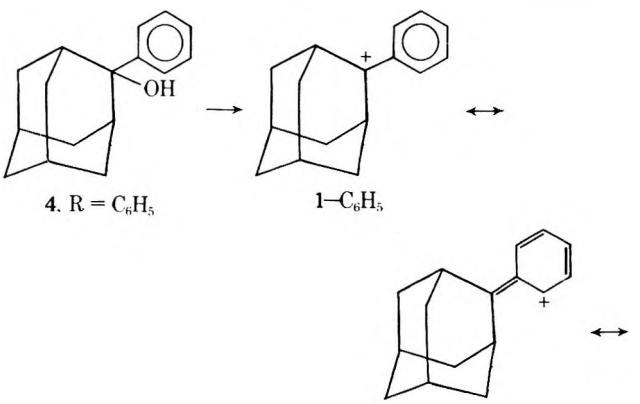
be obtained. An example is seen in the C nmr spectrum of the protonated 2-norbornanone **5**.[1b,10] At low temperature, two isomeric protonated 2-norbornanones are observed in FSO_3H–SO_2ClF. The bridgehead carbon C_1 in **5a** has a different carbon shift than that of C_1 in **5b**, and the C_3 carbon shift in **5a** is different than that in **5b**. At higher temperature (+10°), **5a** and **5b** equilibrate.



5a **5b**

It is surprising that rotation along the C–O bond is very fast in the case of 1–OH. This behavior is quite different from other protonated bicyclic ketones.[10] There must be some yet not understood special factors which enable 1–OH to undergo interconversion through a very low barrier.

The 2-phenyl-2-adamantyl cation 1–C_6H_5 has not been previously obtained. When the corresponding alcohol



4. R = C_6H_5 1–C_6H_5

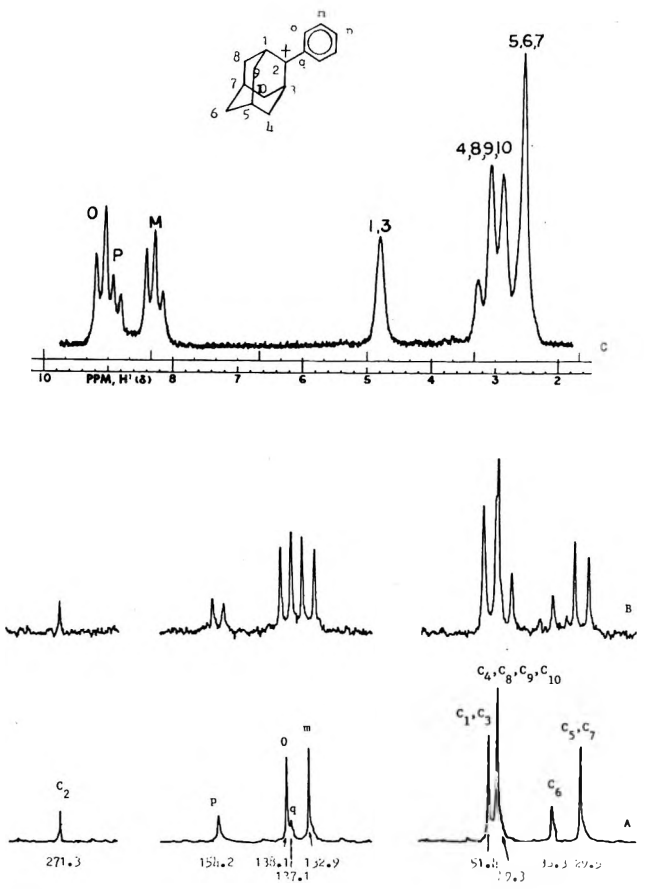
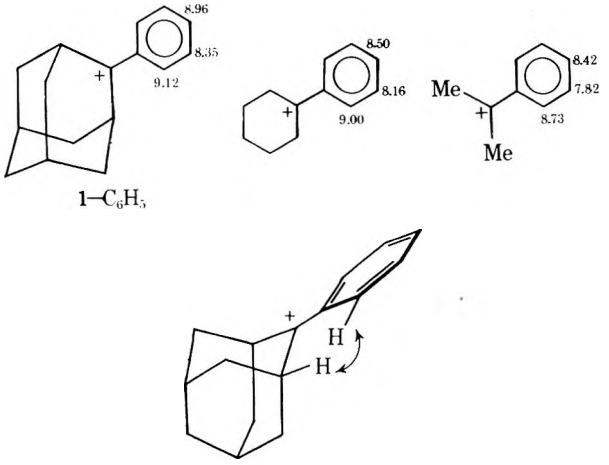
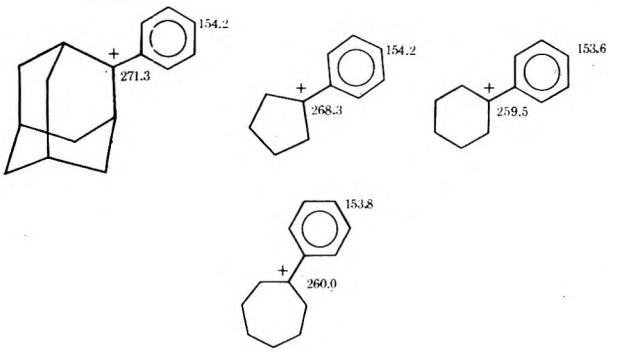


Figure 2. Proton-decoupled ^{13}C nmr (A), off-resonance ^{13}C nmr (B), and ^{1}H nmr (C) spectra of 1-C_6H_5.

4–C_6H_5 is added to FSO_3H–SO_2ClF at −78°, a light colored solution of 1–C_6H_5 is formed, the pmr (60 MHz) spectrum of which (Figure 2) was obtained. Ion 1–C_6H_5 shows the characteristics of classical tertiary phenylcarbenium ion. Both ortho and para protons are deshielded (δ 9.12 and 8.96, respectively) along with the other four proton resonances which are characteristic of a 2-substituted adamantyl cation. The two bridgehead protons (H_1 and H_3) are furthermore more deshielded than those of 1–CH_3 and 1–CH_2CH_3.

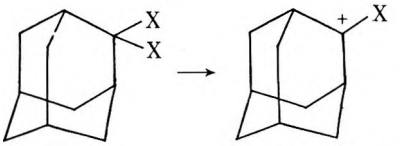


The Fourier-transform C nmr spectrum (Table II) of 1–C_6H_5 also clearly indicates that extensive charge delocalization exists between the adamantyl nucleus and the phenyl ring. The carbon-13 chemical shift of the carbenium center is observed at $\delta_{^{13}C}$ 271.3, which is very close to those of tertiary phenyl carbenium ions.



That the positive charge is extensively delocalized into the phenyl ring is further indicated by the observation of the deshielded para carbon in 1–C_6H_5 ($\delta_{^{13}C}$ = 154.2) whose shift is very similar to those in the model ions shown.[1b] This is also supported by the fact that 2-phenyl-2-adamantanol can be recovered unchanged when this alcohol is treated with 98% sulfuric acid at 0° for 1 hr.[10a] 2-Methyl-2-adamantanol, on the contrary, undergoes extensive rearrangement under the same condition.[3,4,10]

2-Halo-2-adamantyl Cations. In SbF_5–SO_2ClF or FSO_3H–SbF_5–SO_2ClF solutions, 2-halo-2-adamantyl cations 1–Br, 1–Cl, and 1–F were found stable at −78°. They are formed directly from the respective 2,2-dihaloadamantanes **6**. Among the three ions, the 2-bromo-2-adamantyl cation 1–Br is less stable than the other two cations.



6 1–X, X = F, Cl, Br

In the pmr spectra of ions 1–Br, 1–Cl, and 1–F (see data summarized in Table I) the two bridgehead protons (H_1 and H_3) are found most deshielded in 1–Br, and least deshielded in 1–F, while those in 1–Cl fall in between. Two important factors should be considered to interpret the results: (a) different anisotropic effects of the halogen atoms, (b) decreasing n–p conjugation between the halogen atom and the empty p orbital in the order F > Cl > Br. We consider that the shielding of the two bridgehead carbons (H_1 and H_3) in 1–F is caused by effective n–p conjugation between the fluorine lone pairs of electrons and the empty p orbital of the carbenium center. C_2 in 1–F apparently bears less positive charge than those in 1–Br and 1–Cl.

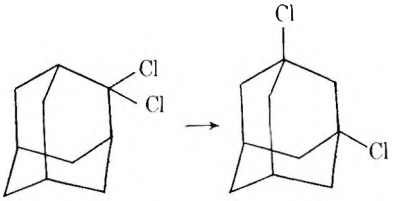
The anistropy effect of halogen atoms in the halocarbenium ions apparently has direct effect toward the deshielding of the neighboring protons. The methylene protons (H_4, H_8, H_9, and H_{10}) in both 1–Cl and 1–F exhibit AB quartets with coupling constants smaller than those of 2-alkyl- (1–CH_3, 1–CH_2CH_3) and 2-phenyl- (1–C_6H_5) 2-adamantyl cations; and those in 1–Br exhibit a singlet absorption (Table I). The difference can, therefore, be attributed to the fact that the size of a bromine atom is considerably larger than those of chlorine and fluorine atoms.

The Fourier transform C nmr spectra of 2-halo-2-adamantyl cations, the cmr parameters, and assignments are summarized in Table II. A consideration of the cmr data reveals several interesting points. (a) The magnitude of the deshielding of the carbenium carbon increases in the order of 1–F < 1–Cl < 1–Br. (b) The two bridgehead carbons (C_1 and C_3) show increasing shielding effect according to the order 1–Br < 1–Cl < 1–F. (c) The methylene carbons (C_6)

fathest from the positive charge are more deshielded than the bridgehead carbons (C_5 and C_7) which are closer to the positive charge.

We have previously discussed the effect of halogen substitution toward the carbenium carbon shifts in halocarbenium ions.[12,13] Fluorocycloalkyl cations show less deshielded carbenium ion centers than those in chloro- and bromocyclocarbenium ions,[12,13] due to the presence of strong fluorine "back-donation." We find this is also true in the case of 2-halo-2-adamantyl cations. The n–p conjugation between the empty p orbital and the fluorine unshared 2p electrons not only places less positive charge on the carbenium center in 1-F but also makes the bridgehead carbons α to the carbenium center less deshielded (see Table II).

2,2-Dichloro- and 2,2-dibromoadamantane (**6**, X = Cl and Br) have recently been found to undergo Lewis acid halide catalyzed rearrangement,[10] similar to the case of 2-methyl-2-adamantanol, when a solution of the dichloride (**6**, X = Cl) in carbon tetrachloride is stirred in the presence of aluminum chloride for 3 days at room temperature. 1,3-Dichloroadamantane is obtained in 70% yield.[10a] The



6, X = Cl 70%

2,2-dibromide (**6**, X = Br) rearranges much more readily than does the dichloride; after 1 hr in carbon disulfide–aluminum chloride the product contains 75% 1,3-dibromoadamantane.[10a] Although the 1-adamantyl and 2-halo-2-adamantyl cations do not show any rearrangement in antimony pentafluoride based superacids, their behavior in general Friedel-Crafts catalyzed systems may be different and tend to show rearrangements.

Experimental Section:

Materials. 2-Methyl-,[7a] 2-ethyl-, and 2-phenyl-2-adamantanols[10a] were prepared from the reaction of 2-adamantanone (Aldrich) with methyl-, ethyl-, and phenylmagnesium bromides, respectively.

2,2-Dichloro- and 2,2-dibromoadamantanes (**6**, X = Cl and Br) were prepared by reaction of 2-adamantanone with the appropriate $PX_5 \cdot PX_3$ mixture.[10a,14] 2,2-Difluoroadamantane (**6**, X = F) was obtained from the reaction of 2-adamantanone with SF_4 at room temperature, mp 195.9°.

Formation of 2-Adamantyl Cations. A cold solution of the 2-adamantane precursors in SO_2ClF (SO_2) was added dropwise, with vigorous stirring, to a solution of FSO_3H, FSO_3H–SbF_5, or SbF_5 in SO_2ClF (SO_2) at −78°.

Proton and Carbon-13 Nuclear Magnetic Resonance Spectroscopy. Pmr spectra were obtained using Varian Associates Model A-56/60A and HA-100 spectrometers, equipped with a variable temperature probe. Tetramethylsilane (external capillary) was used as reference. ^{12}C nmr spectra were obtained using a Varian VFT, XL-100-15 spectrometer equipped with a broad-band proton noise decoupler and a variable temperature probe. The instrument was operated in the pulse Fourier transform mode. Typically 500–2000 (~30°) pulses were needed for the accumulation of satisfactory spectra. No pulse delay was employed. Carbon chemical shifts were measured from the ^{13}C signal of capillary TMS (5% ^{13}C enriched).

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

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Ten-Membered Rings. Transannular Double-Bond Participation in Acid-Promoted Cyclizations[1,2]

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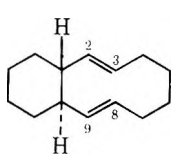
Received June 13, 1974

Acid-promoted cyclizations of **1**, **2**, and **3** are described. They occur with great facility in buffered acetic acid because protonation is accompanied by participation of a transannular double bond and there is consequent relief of medium-ring strain as the *trans,syn,trans*-perhydroanthracene system is generated. Two isomeric *trans,syn,trans*-perhydroanthracenes can be produced from **2** and **3**, the ratio of which depends upon the regioselectivity of protonation. The effects of the methyl substituent of **2** are a 1.5-fold increase in rate of cyclization relative to **1** and a 19:1 regioselectivity of protonation which favors generation of methyl-stabilized tertiary carbocation **9** over secondary carbocation **13**. Cyclization of **3** occurs exclusively *via* protonation of the cyclopropane with participation of the double bond (not *vice versa*) and generation of carbocation **15**.

This article reports synthetic work and results of acid-promoted cyclization studies relating to three compounds: *trans,trans*-2,8-*trans*-bicyclo[8.4.0]tetradecadiene (**1**), 2-methyl-*trans,trans*-2,8-*trans*-bicyclo[8.4.0]tetradecadiene (**2**), and *trans*-9-*trans,anti,trans*-tricyclo[9.4.0.$0^{2,4}$]pentadecene (**3**).



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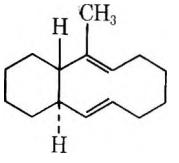

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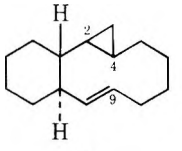

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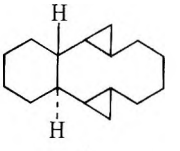
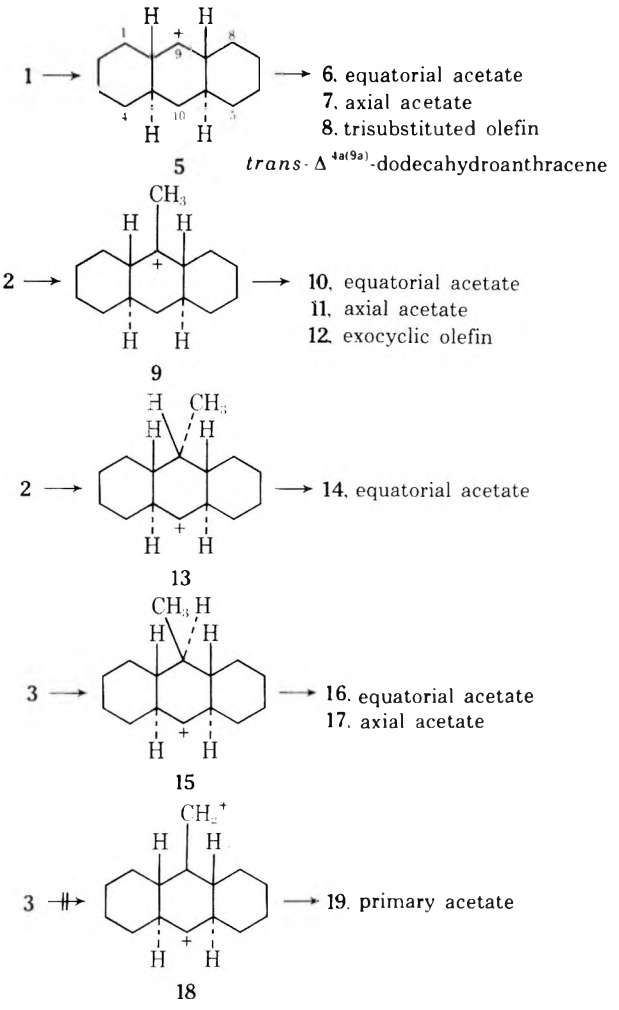


4

Results and Discussion. The high energy of **1** (medium-ring strain) and its locked conformation[3] (chair-chair-chair) are, in combination, highly favorable to reactions involving overlap of the p orbitals of C-3 and C-8 with the development of a σ bond.[4] The distance separating C-3 and C-8 across the ring is only about 3 Å and the p orbitals on these atoms are well aligned for interaction.[5,6] The anticipated acid-promoted cyclization of **1** to carbocation **5** (see Scheme I) should be facilitated, relative to that of acyclic 1,5-dienes, if protonation involves participation of the transannular double bond for, as the *trans,syn,trans*-perhydroanthracene system is developed, there is a gain of at least 12 kcal mol^{-1} with the relief of ring strain.[7] Indeed **1** is tremendously reactive. Cyclization can be effected in buffered acetic acid at 60°, conditions which are without effect on either *trans*-cyclodecene or *cis,trans*-1,5-cyclodecadiene.[8]

An initial series of cyclizations was carried out with acetic acid containing perchloric acid at room temperature and is mentioned here because it was subjected to the most careful analysis which revealed that all products were indeed derivable from carbocation **5**. Products were identified by comparison with authentic samples synthesized as described in the next section. An exemplary analysis yielded the following data: 80.8% of equatorial acetate **6**, 3.0% of axial acetate **7**, 0.4% of trisubstituted olefin **8**, and 15.0% of the tetrasubstituted olefin *trans*-$\Delta^{4a(9a)}$-dodecahydroanthracene which was formed at least in part under the reaction conditions by hydrogen rearrangement of **8**. The yields given are absolute and correspond to quantitative cyclization, a characteristic which sharply distinguishes 1,5-cyclodecadienes from their acyclic counterparts.[9]

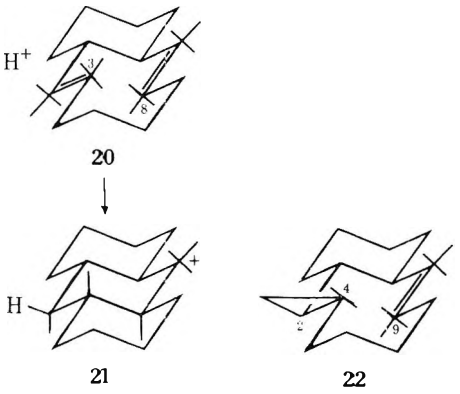
Scheme I



Subsequently, all cyclizations were carried out in buffered acetic acid at 60° and allowed to proceed for approximately 90 hr (close to 6 half-lives). The mixture of equatorial and axial acetates **6** and **7** was produced in at least 81% yield (this yield was obtained after isolation) and in almost the same ratio as in strong acid (94:6 by gc analysis). The olefin fraction was not investigated.

Characterization of the products establishes all stereochemical aspects of cyclization except that of protonation. This was determined by carrying out experiments with deuterium labeling.[10] The synthesis of 1-2,9-d_2 is de-

scribed in the next section. Its cyclization in buffered acetic acid yielded an acetate fraction which was converted to the corresponding ketone (**25**) *via* sequential treatment with lithium aluminum hydride and chromic acid. This procedure retained the deuterium atom which was at the site of protonation but removed the other one. The infrared spetrum of the ketone showed C–D doublet maxima at 2124 and 2145 cm^{-1}. The complementary experiment of cyclizing **1** in buffered acetic acid-*O*-*d* was also carried out. It afforded a monodeuterated ketone with C–D doublet maxima at 2149 and 2170 cm^{-1}. Together the two sets of doublets are diagnostic for axial and equatorial C–D, respectively.[11] Thus protonation occurs with equatorial approach to the open face of the double bond antiparallel to the developing carbon–carbon bond (see **20** → **21**). That the stereospecificity of protonation is absolute is suggested by the fact that 2124 cm^{-1} corresponds to maximum absorption for one ketone but base-line absorption for the other.



There are two alkenyl methyl derivatives of **1** and the synthesis of one of them, **2**, is described in the next section. If the overall nature of the reaction with acetic acid were to remain unchanged[12] the effect of the methyl group might be observable in a rate enhancement and also a regioselectivity of protonation which generates the methyl-stabilized tertiary carbocation **9** in preference to secondary carbocation **13**. Evaluation of these two pathways was facilitated by independent synthesis of the principal products expected to be produced from these cations, as described in the next section.

The half-life of **2** in buffered acetic acid at 60° was found to be 10 hr. For comparison that of **1** is 16 hr. Product composition was found to vary with time because of the solvolytic instability of the initially formed tertiary acetates and the analyses cited refer specifically to work-up after a reaction period of 10 half-lives. Of most interest was the presence of 5% of secondary equatorial acetate **14** formed *via* carbocation **13**. The remaining 95% was, as expected, derived from tertiary carbocation **9** and consisted of 25% of equatorial tertiary acetate **10**, 4% of axial tertiary acetate **11**, and 66% of exocyclic olefin **12**.[13]

The rate ratio for cyclization of **2** *vs.* **1** is 1.6:1 and the rate ratio for generating tertiary carbocation **9** *vs.* secondary carbocation **5** is therefore 1.5:1. In addition to this intermolecular comparison there is the intramolecular comparison of forming tertiary carbocation **9** *vs.* secondary carbocation **13** which is associated with a rate ratio of 19:1. The intramolecular ratio is somewhat higher but some of the difference may well be caused by a steric retardation effect of the methyl group in the formation of **13**.[14]

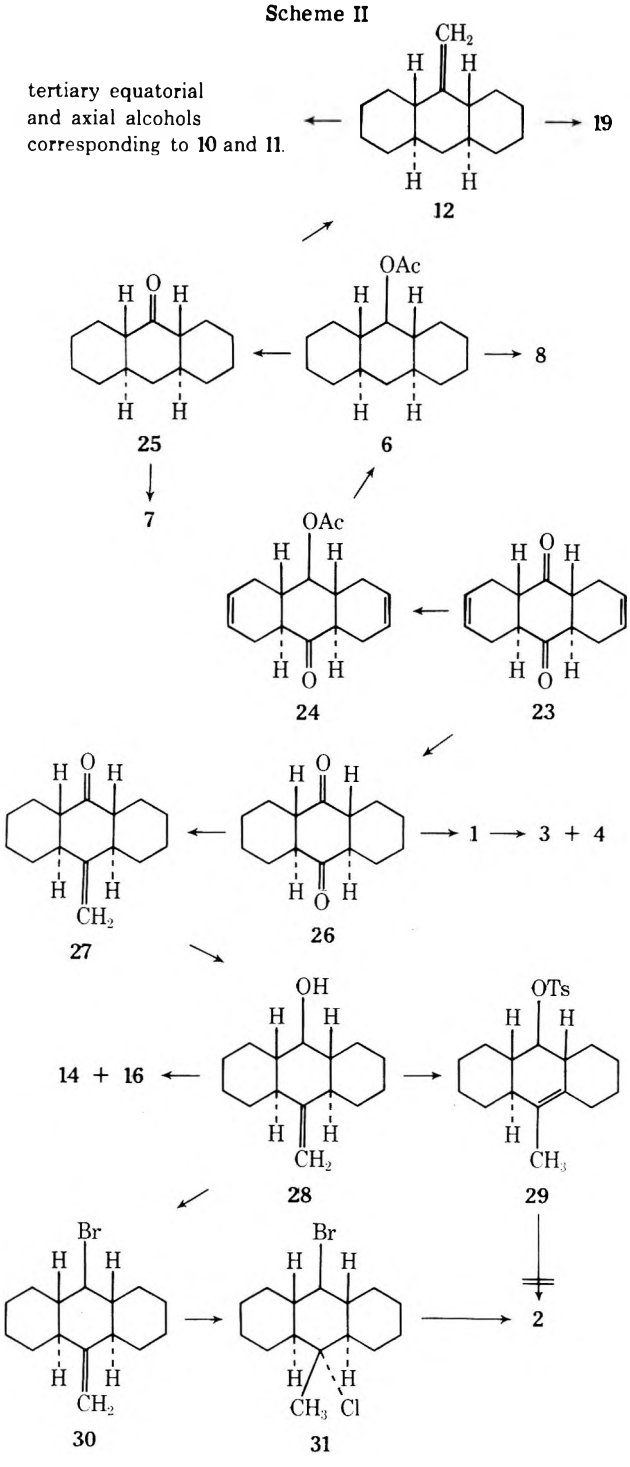
The pattern of reactivity of **2** is described by a large rate increase relative to the corresponding saturated compound (*trans*-cyclodecene) with a small rate increase (2 to 20) for substitution of a methyl group on the participating double bond. In the absence of reference data on protonation of double bonds with acetic acid, a comparison with solvolytic data can be made.[15] The ion pairs formed by solvolytic and protonation routes bear some resemblance. Specifically the transition state for protonation of **1** resembles that of the solvolysis of *trans*-5-cyclodecenyl *p*-nitrobenzoate for which substantial participation of the double bond has been shown (there is a rate increase of 1500 relative to the saturated system).[16] Moreover, several solvolyses involving participation of a double bond show rate increases for methyl substitution of the same order of magnitude found for **2** even though the extents of participation differ greatly. The 2-(3′-cyclohexenyl)ethyl, 2-(3′-cyclopentenyl)ethyl, and 7-*anti*-norbornenyl systems solvolyze with rate increases, relative to the corresponding saturated systems, of 5, 10^2, and 10^{11} but the additional rate increases found upon substituting methyl on the participating double bond are much the same: 7, 7, and 13.[17]

The synthesis of olefinic cyclopropane **3** is described in the next section. The small ring is attached with the stereochemistry shown in **22**. The external cyclopropane bond at C-2 is pseudoequtorial and there is potential interaction of the p-orbital of C-9 with the rear lobe of the external cyclopropane bond of C-4 which should lead to behavior similar to that of **1** and **2**, namely acid-promoted cyclization with generation of the *trans,syn,trans*-perhydroanthracene system. With results of the cyclization of **2** in hand, the more likely of the two pathways leading to the *trans,syn,trans*-perhydroanthracene system was predicted to be protonation of the cyclopropane with participation of the double bond, generating carbocation **15**. The alternative mode of cyclization involving protonation of the double bond with participation of the cyclopropane seemed less likely, not least because of the generation of a less stable (primary) carbocation (**18**).[18] Evaluation of these pathways was assisted by independent synthesis of samples of acetates **16** and **19** as described in the next section. These are the principal acetates which would be produced from carbocations **15** and **18**, respectively.

Reaction of **3** with buffered acetic acid was complete within 6 days at reflux temperature. For comparison, biscyclopropane **4** was unaffected under these conditions. The acetate fraction of the product (58%) was found to consist solely of two components in a ratio of 6:94 with retention times of 12.8 and 15.5 min.[19] Neither component corresponded to **19** which had a coinjection retention time of 14.5 min. Cyclization *via* the pathway leading to carbocation **18** is therefore excluded (it is estimated that 1% of **19** would have been detected). The larger gc peak at 15.5 min corresponded to that of **16** and isolation of the corresponding component and comparison with authentic material established its identity. The smaller gc peak was present in an amount expected for axial acetate **17** produced along with equatorial acetate **16** and this supposition was confirmed indirectly. The acetate fraction obtained from cyclization was subjected to sequential treatment with lithium aluminum hydride, chromic acid, sodium borohydride, and acetic anhydride–pyridine. The expected effect of this sequence on any **16** and **17** originally present is solely to change the ratio in favor of the axial isomer. Experimentally, it was found that, after treatment, the final product still consisted of only two components with retention times unchanged from those of the two components originally present. Their ratio, however, had changed from 6:94 to 79:21. Thus it appears that cyclization of **3** occurs *exclusively via* the pathway with participation of the double bond and generation of carbocation **15**.

Synthetic Work (see Scheme II). Synthesis of **1** was

Scheme II



achieved from **26** using two previously described fragmentation sequences[20] (**26** is derived from the bis adduct of benzoquinone and butadiene *via* **23**). Reduction of **26** with lithium aluminum deuteride gave, by the same sequence, a sample of 1-2,9-d_2.

Simmons–Smith cyclopropanation of **1** afforded **3** as an oil and **4** as a solid. They were readily separated by column chromatography on silica gel impregnated with silver nitrate. In their nmr spectra the vinyl hydrogens of **3** are centered at δ 5.3, downfield from the corresponding signals of **1** which are centered at δ 4.7, and the four external cyclopropane hydrogens of **4** are centered at δ 0.21, downfield from the corresponding two hydrogens of **3** which are centered at δ 0.09. Both differences can be attributed to the shielding effect of the transannular double bond. By contrast, the cyclopropane ring has a negligible effect on the shift of transannular hydrogens.

The synthesis of **2** was more involved. Dione **26** was converted to methylene ketone **27** in 30% yield by treatment with a controlled amount of Wittig reagent. Column chromatography separated **27** from starting dione and the dimethylene compound formed from reaction with 2 equiv of Wittig reagent. Reduction of **27** with sodium in boiling isopropyl alcohol gave a two-component mixture (95:5) from which equatorial alcohol **28** could be crystallized in 70% yield. (Lithium aluminum hydride gave a 60:40 mixture.) Conversion of **28** to a bromo tosylate was readily effected but this compound failed to fragment in the presence of zinc because of rapid 1,2 elimination of hydrogen bromide from the tertiary bromide. The target molecule for fragmentation then became chloro bromide **31**, a molecule in which the degree of substitution of the zinc-reducible bromine has been changed from tertiary to secondary in order to minimize the occurrence of 1,2 elimination. Alcohol **28** was first converted to the corresponding brosylate and the brosylate was treated with potassium bromide in dimethylformamide. This sequence gave a multicomponent mixture from which a pure bromide could be isolated in 30% yield by simple crystallization. Fortuitously, it turned out to be equatorial bromide **30**, presumably formed by two substitutions, the second on the first-formed axial isomer. Bromide **30**, upon treatment with hydrogen chloride in ether, gave a mixture of tertiary chlorides, principally equatorial isomer **31**, which could be isolated by crystallization.

Fragmentation of **31** was effected using Applequist's recipe for the synthesis of spiropentane: zinc dust in boiling aqueous alcohol containing potassium iodide, the disodium salt of ethylenediaminetetraacetic acid, and sodium hydroxide.[21] Pure **31** was first used in the preparation of samples of **2** but it was found that no advantage was thereby gained and subsequently the mixture of equatorial and axial isomers was used. Thereby, with the addition of the appropriate amount of sodium hydroxide,[22] **2** was obtained as an oil in 70% yield after silica gel chromatography. Its nmr spectrum shows a vinyl methyl at δ 1.4 and three vinyl hydrogens in the range 4.5–4.9.

One other synthesis of **2** was attempted but was unsuccessful. The double bond of **28** was isomerized to the endocyclic position, a transformation best carried out on the acetate in liquid sulfur dioxide. Tosylate **29** was then routinely prepared but it failed to fragment to **2** when subjected to Marshall's procedure involving treatment with diborane and then aqueous base[23] and it would appear that diborane does not add in the regiospecific sense which is appropriate for fragmentation. As some slight recompense, reduction of **29** with lithium aluminum hydride yielded an authentic sample of 10-methyl-*trans*-$\Delta^{4a(10)}$-dodecahydroanthracene.

The products formed in acid-promoted cyclizations of **1**, **2**, and **3** were identified by comparison with compounds synthesized as described in the following paragraphs. Hydrogenation of the acetate of **28** yielded a 2:1 mixture of **14** and **16** with the axial methyl isomer **14** predominating as would be expected from delivery of hydrogen to the less hindered side. The major isomer, mp 150–153°, was purified by preparative gc but pure minor isomer, mp 95–96.5°, was obtained only from cyclization of **3**.

Partial reduction of **23** was accomplished with sodium borohydride in pyridine, a combination which afforded a ketol in 19% yield. Acetylation of the ketol gave acetate **24**. Sequential hydrogenation, thioketalization, and desulfurization applied to **24** afforded equatorial acetate **6**. Saponification of **6** and subsequent oxidation gave ketone **25** from

which axial acetate **7** was obtained *via* reduction with sodium borohydride.[24] Careful pyrolysis of **6** afforded trisubstituted olefin **8.** Perchloric acid in acetic acid isomerized **8** to *trans*-$\Delta^{4a(9a)}$-dodecahydroanthracene.

Subjection of ketone **25** to the Wittig reaction afforded exocyclic olefin **12.** Application of the sequence hydroboration–acetylation to **12** yielded a 2:5 mixture of **19** and the more abundant corresponding axial isomer. The individual isomers were separated by preparative gc. Application of the sequence epoxidation–reduction to **12** afforded a 2:3 mixture of axial and equatorial alcohols corresponding to acetates **10** and **11.** The axial alcohol was generated much more selectively by the addition of methyllithium to ketone **25.**

The stereochemical assignments to **14** and **16** are unambigously established by their specific geometric relations to **2** and **3** from which they are respectively formed. The axial methyl of **14** absorbs at δ 0.75 as a doublet with J = 6.5 Hz whereas the equatorial methyl of **16** appears at δ 0.85 as a single broad peak because of a near coincidence of shift of the methyl and C-9 axial hydrogen.

The stereochemical assignments to the acetoxymethyl isomers are well based on nmr coupling data. One of them has acetoxymethyl hydrogens absorbing as a doublet with J = 5 Hz while the corresponding signal of the other isomer (**19**) appears as a single broad peak. A straightforward conformational analysis, based on the effects of 1,3 interactions, reveals that in the equatorial acetoxymethyl isomer the conformer in which the acetate and C-9 axial hydrogen are antiparallel is the most stable (giving a small average J) whereas, in the axial isomer the conformer with the ester and C-9 equatorial hydrogen antiparallel is the least stable (giving a larger average J). Once again the methylene hydrogens which are axial absorb at higher field (δ 3.98) than those which are equatorial (δ 4.16).

The following is a listing of reactions in this series which involve addition to a trigonal carbon at the 9 position and generation of isomers in which a methyl or methylene carbon and a functional group are both present on C-9. The chemical shifts of the methyl or methylene groups of the two isomers are given in δ with that given first corresponding to the major isomer formed. Addition of hydrogen bromide to **12:** 1.49, 1.65. Addition of hydrogen chloride to **30:** 1.30, 1.40. Epoxidation of **12:** 2.46, 2.60. Addition of methyllithium to **25:** 1.06, 0.90. These results, combined with those obtained from the hydroboration of **12** and hydrogenation of **28** which have already been discussed, allow a self-consistent, if not completely satisfactory, set of stereochemical assignments to be made, exemplified by the formulation of **31.** All examples conform to the generalizations that additions to C-9 show a preference for equatorial attack and yield isomers which show a higher field shift for axial methyl or methylene.

Experimental Section

Physical Data. Melting points were determined by the capillary method and are uncorrected. Spectra were recorded using Perkin-Elmer 137 and Beckman IR-8 infrared spectrometers; Cary 11 and 14 ultraviolet spectrometers; Varian A-60 and A-60A nmr spectrometers using tetramethylsilane as an internal reference. Analytical and preparative gas chromatography (gc) were performed on Perkin-Elmer F11 and Varian Aerograph A-90-P units. Peak areas were calculated using a Disc chart integrator.

Materials and Procedures. Solvents were dried and/or distilled before use with the exceptions of ether, methanol, and ethanol. Magnesium and sodium sulfates were used as drying agents. Solvents were removed under reduced pressure using a rotary evaporator. Silica gel used for chromatography was Davison-Grace grade 950, 60–200 mesh. Available procedures for the preparation of special reagents such as Raney nickel, Jones' reagent, activated zinc, and Simmons–Smith reagent were followed.[25] Anhydrous acetic acid was prepared from glacial acetic acid, previously distilled from chromium trioxide, by the sequence: addition of acetic anhydride, reflux, and fractional distillation.

10(e)-Acetoxy-9-keto-$\Delta^{2,6}$-*trans,syn,trans*-decahydroanthracene (24). To a solution of 100.0 g (0.462 mol) of dione **23,** mp 239.0–245.5° dec, in 2500 ml of pyridine, maintained at a water-bath temperature of 75° and in a nitrogen atmosphere, was slowly added, with magnetic stirring, 4.370 g (0.115 mol) of sodium borohydride. After stirring for 7 hr, the resulting yellow-brown reaction mixture was poured into 2500 ml of distilled water and allowed to stand overnight. Filtration of the mixture afforded 5.851 g of recovered dione **23,** mp 211.0–220.0° dec. The filtrate was extracted five times with 500-ml portions of chloroform and the combined organic layers were washed with 500 ml of distilled water and then dried. Evaporation of the solvents under reduced pressure afforded 105.5 g of a yellow-brown gum which contained some suspended crystalline material. Crystallization of the crude product from benzene gave 18.75 g (19%) of light tan crystals, mp 197.5–204.0° dec. Three recrystallizations of 17.18 g from benzene gave 11.80 g of white needles, mp 209.0–212.0° dec, not raised by further crystallization.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.22; H, 8.45.

Oxidation of the ketol regenerated **23,** with mp undepressed upon admixture with authentic dione.

A solution of 11.33 g (0.052 mol) of the ketol, mp 209.0–212.0° dec, in 300 ml of pyridine (distilled from barium oxide) containing 150 ml (1.57 mol) of acetic anhydride was allowed to stand at room temperature for 24 hr. A deposit of white needles separated from solution. The mixture was diluted with 1500 ml of distilled water and allowed to stand at room temperature for 7 hr. The precipitate was collected, washed with several portions of 2% hydrochloric acid, and dried, thereby affording 13.47 g of white solid, mp 204.0–207.0° dec: nmr ($CDCl_3$) δ 5.65 (broad s, 2), 5.07 (t, 1, J = 8 Hz), and 2.11 (s, 3). Sublimation of the recovered nmr sample at 100° (0.1 mm), followed by crystallization from absolute ethanol, gave an analytical sample, mp 206.0–209.0°

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.98; H, 7.78.

9(e)-Acetoxy-*trans,syn,trans*-perhydroanthracene (6). A suspension of 11.94 g of unsaturated ketol acetate **24,** mp 205.5–208.5° dec, in 300 ml of ethyl acetate was hydrogenated over 1.01 g of 5% palladium-on-calcium carbonate at 40 psi and room temperature for 1.9 hr. The reaction mixture was filtered and the solvent evaporated under reduced pressure to give a white crystalline residue. Crystallization from absolute ethanol afforded 11.45 g (94%) of white crystals, mp 157.5–158.5°: nmr (CCl_4) δ 4.86 (t, 1, J = 9 Hz) and 2.04 (s, 3); ir ($CHCl_3$) 5.79, 5.84 μ.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 73.00; H, 9.20.

A suspension of 4.93 g (0.0186 mol) of ketol acetate, mp 157.5–158.5°, in a mixture of 5.0 ml (0.060 mol) of ethanedithiol and 5.0 ml of freshly distilled boron trifluoride etherate, was stirred at room temperature. After a few minutes the mixture became warm and most of the suspended white solid dissolved. Upon continued stirring, the mixture cooled and a white solid separated. After 30 min the mixture was diluted with 20 ml of methanol and cooled to −20°. The resulting solid was collected, washed with several small portions of cold methanol, and dried, thereby giving 6.202 g (98%) of white crystals, mp 141.0–141.5°: nmr (CCl_4) δ 4.36 (m, 1), 3.16 (s, 4), and 1.99 (s, 3); ir ($CHCl_3$) 5.80 μ.

Anal. Calcd for $C_{18}H_{28}O_2S_2$: C, 63.48; H, 8.29; S, 18.83. Found: C, 63.46; H, 8.16; S, 18.71.

A mixture of 5.501 g of thioketal, mp 141.0–141.5°, and *ca.* 70 g of W-4 Raney nickel catalyst in 600 ml of absolute ethanol was heated under reflux for 5 hr. The warm reaction mixture was passed through Filter Cel and the nickel residues were washed with several portions of hot absolute ethanol. Concentration of the filtrate and washings to *ca.* 45 ml followed by cooling to −20° gave 3.520 g of white solid, mp 125.0–179.0°. Sublimation at 60° (0.1 mm) afforded 2.980 g of white powder, mp 123.5–125.0°. Crystallization from absolute ethanol gave 2.658 g (66%) of small white needles, mp 125.5–126.0°: nmr (CCl_4) δ 4.37 (m, 1) and 1.98 (s, 3). Sublimation of the recovered nmr sample at 75° and 0.1 mm, followed by crystallization from absolute ethanol, afforded an analytical sample of **6,** mp 125.5–126.0°.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.62; H, 10.54.

$\Delta^{4a(10)}$-*trans,syn*-Dodecahydroanthracene (8). A 1.003-g sample of acetate **6,** mp 125.0–126.0°, was sealed under vacuum in

a 2.2 × 16 cm Pyrex tube and heated at *ca.* 400° in a furnace for 20 min. The crude product crystallized on standing at room temperature. Chromatography on 100 g of 60–200 mesh silica gel with hexane elution, followed by crystallization from aqueous acetone, afforded 0.573 g (75%) of white solid, mp 49.0–50.0°. Two additional crystallizations from aqueous acetone afforded 0.456 g of white solid, mp 50.5–51.0°, not raised by further crystallization: nmr (CCl_4) δ 5.01 (broad s, 1). Sublimation of the recovered nmr sample at room temperature and 0.1 mm gave an analytical sample of **8**, mp 50.5–51.0°: uv end absorption (95% ethanol) 210 nm (ε 6200); mol wt from the mass spectrum, 190.

Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.23; H, 11.65.

$\Delta^{4a(9a)}$-*trans*-Dodecahydroanthracene. A solution of 0.285 g of **8**, mp 50.5–51.0°, in 35 ml of an anhydrous 0.557 *M* solution of perchloric acid in acetic acid, was stirred magnetically under nitrogen at 27° for 3 hr. The resulting light orange solution was diluted with 70 ml of distilled water and was extracted four times with 35-ml portions of benzene. The combined benzene extracts were washed twice with 70-ml portions of distilled water, twice with 70-ml portions of 10% potassium bicarbonate solution, once with 70 ml of distilled water, and then dried. Capillary gc showed that there were present in the product the desired olefin, starting olefin, and acetate **6** in the ratio 1.4:1.3:1.0. Preparative gc at 165° on a 5 ft × 0.25 in. column of SF-96 on 60–80 firebrick afforded an analytical sample, mp 23–24°: nmr (CCl_4) no olefinic hydrogens; uv end absorption (cyclohexane) 210 nm (ε 4100); mol wt from the mass spectrum, 190.

Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.52; H, 11.45.

9-Keto-*trans,syn,trans*-perhydroanthracene (25). Saponification of 2.448 g of acetate **6**, mp 125.5–126.0°, in 1 *N* methanolic potassium hydroxide afforded, after crystallization from carbon tetrachloride, 1.916 g (94%) of alcohol, mp 169–170°.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.82; H, 11.58.

The alcohol afforded a tosylate in good yield *via* the normal pyridine–tosyl chloride method, mp 116–117° dec.

Anal. Calcd for $C_{21}H_{30}O_3S$: C, 69.57; H, 8.34: S, 8.85. Found: C, 69.73; H, 8.08; S, 8.89.

A solution of 1.669 g (8.00 mol) of alcohol, mp 169–170°, in 500 ml of acetone (distilled from potassium permanganate) was cooled at ice-bath temperature and 2.30 ml of Jones' reagent was added rapidly from a buret with magnetic stirring. After stirring at ice-bath temperature for 8 min, the mixture was diluted with 2500 ml of distilled water. The resulting precipitate was collected, washed well with distilled water, and dried, thereby yielding 1.567 g of white powder, mp 117.0–124.0°. Two crystallizations from absolute ethanol afforded 1.079 g (65%) of small white plates, mp 130.5–131.5°. Two additional crystallizations from aqueous ethanol afforded an analytical sample of **25**, mp 130.5–131.5°.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.76; H, 10.76.

Ketone **25** afforded an oxime by the normal method, mp 221–222° dec. The ketone was converted to *trans,syn,trans*-perhydroanthracene as follows. A mixture of 0.288 g (1.40 mmol) of **25**, mp 130.5–131.5°, 0.30 ml (3.6 mmol) of ethanedithiol, and 0.30 ml of freshly distilled boron trifluoride etherate in a test tube was homogenized with a stirring rod. The mixture became warm and set to a white paste. After 10 min the mixture was diluted with 10 ml of methanol, cooled to −20°, and filtered. The collected solid was washed with several portions of cold methanol and dried, thereby affording 0.392 g (99%) of white solid, mp 202.0–203.0°. Crystallization from ethyl acetate afforded 0.355 g of white needles, mp 202.0–203.0°: nmr ($CDCl_3$) δ 3.17 (s, 4). A single recrystallization from ethyl acetate gave an analytical sample, mp 202.0–202.5°.

Anal. Calcd for $C_{16}H_{26}S_2$: C, 68.02; H, 9.27; S, 22.70. Found: C, 68.31; H, 9.35; S, 22.78.

A mixture of 0.201 g of thioketal, mp 202.0–203.0°, and *ca.* 4 g of W-4 Raney nickel catalyst in 40 ml of absolute ethanol was heated under reflux for 4 hr. The hot reaction mixture was filtered and the nickel residues were washed with several portions of hot absolute ethanol. Evaporation of solvent under reduced pressure gave a white solid residue which was crystallized three times from acetone to yield 0.054 g (40%) of white plates, mp 88.0–89.0°, undepressed on admixture with authentic *trans,syn,trans*-perhydroanthracene.[26] The infrared and nmr spectra of the two compounds were identical.

9(a)-Acetoxy-*trans,syn,trans*-perhydroanthracene (7). A solution of 0.413 g (2.00 mmol) of ketone **25**, mp 130.5–131.5°, in 80 ml of anhydrous methyl alcohol was cooled at ice-bath temperature and 0.145 g (3.82 mmol) of sodium borohydride added with magnetic stirring. A white precipitate formed after 13 min. Stirring at ice-bath temperature was continued for 22 hr. The reaction mixture was then diluted with 250 ml of distilled water and the resulting precipitate collected, washed with several portions of distilled water, and dried, thereby, giving 0.411 g of white powder, mp 115.0–117.5°. Two crystallizations from aqueous ethanol afforded 0.306 g (73%) of fibrous white needles, mp 122.0–123.0°. Repeated recrystallizations from aqueous ethanol and acetonitrile gave an analytical sample, mp 122.0–122.5°. Oxidation of the alcohol with Jones' reagent regenerated ketone **25**.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.70; H, 11.64.

The alcohol afforded a tosylate, but with some difficulty, using a butyllithium–tetrahydrofuran–tosyl chloride procedure, mp 85–85.5 dec.

Anal. Calcd for $C_{21}H_{30}O_3S$; C, 69.57; H, 8.34; S, 8.85. Found: C, 69.75; H, 8.27; S, 8.83.

A solution of 0.160 g (0.766 mmol) of alcohol, mp 122.0–123.0°, in 4.0 ml of pyridine (freshly distilled from barium oxide) was treated with 2.0 ml (21 mmol) of acetic anhydride and allowed to stand at room temperature for 20 hr. The reaction mixture was then diluted with 25 ml of distilled water and allowed to cool at room temperature for 2.6 hr. The precipitate was collected, washed well with 2% hydrochloric acid and then with distilled water, and finally dried, thereby affording 0.176 g of white solid, mp 96.0–103.0°. Preparative gc on a 5 ft × 0.25 in. column of 5% Carbowax 20M on Teflon-6 at 190°, followed by two crystallizations from aqueous ethanol, gave 0.081 g (42%) of white fibrous crystals, mp 109.0–110.0°: nmr (CCl_4) δ 4.91 (broad s, 1) and 2.00 (s, 3). The recovered nmr sample was sublimed at 50° (0.1 mm) and crystallized repeatedly from aqueous ethanol to give an analytical sample of **7**, mp 110.0–111.0°.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.51; H, 10.49.

9(a)-Hydroxy-9-methyl-*trans,syn,trans*-perhydroanthracene. To a stirred solution of 0.113 g (0.549 mmol) of ketone **25**, mp 128.0–129.2°, in 2 ml of ether under nitrogen at room temperature, was added 1.3 ml of commercial (Foote Chemical) 1.62 *M* methyllithium in ether. The resulting mixture of liquid and white precipitate was stirred under nitrogen for 12 hr. Ether and water were added, the mixture was poured into saturated sodium chloride, the resulting mixture was extracted with ether, and the combined ether extracts were washed with saturated sodium chloride and dried. The ether was removed under reduced pressure to yield 0.123 g (100%) of a light yellow solid: nmr (CCl_4) δ 2.2–0.4 complex with an intense singlet at 1.06 (equatorial CH_3) and a small singlet at 0.90 (axial CH_3). Crystallization from 2-methylbutane gave as a first crop 0.051 g (42%) of axial alcohol as clear prisms, mp 69.5–70.2°.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.04; H, 11.66.

9-Methylene-*trans,syn,trans*-perhydroanthracene (12). To a solution prepared from 0.082 g of a 55% oil dispersion of sodium hydride in 1.0 ml of dimethyl sulfoxide was added a solution of 0.647 g (1.81 mmol) of methyltriphenylphosphonium bromide in 2.0 ml of dimethyl sulfoxide. An additional 1.0 ml of dimethyl sulfoxide was used to rinse remaining bromide salt into the reaction flask. The resulting red-green mixture was stirred at room temperature, under nitrogen, for an additional 20 min. Then 4.0 ml of dimethyl sulfoxide and 0.326 g (1.59 mmol) of ketone **25**, mp 128.0–129.2°, were added and the resulting dark amber solution was heated at 50–53° with stirring, for 31 hr. The solution was then cooled and poured into saturated sodium chloride solution. The mixture was extracted with pentane. The combined pentane extracts were thoroughly washed with distilled water and dried. Removal of the pentane yielded 0.405 g of light yellow solid which was chromatographed on 10.6 g of Woelm neutral alumina (activity 1). The use of pentane as eluent afforded 0.187 g of a white solid, mp 52.0–58.0°. Crystallization from anhydrous methanol yielded as a first crop 0.090 g (28%) of olefin **12**, mp 62.5–63.0°: nmr (CCl_4) δ 4.50 (s, 2, $=CH_2$). Ozonolysis of **12** afforded a ketone with properties identical with those of authentic **25**.

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.27; H, 11.71.

Mixture of Isomers of 9-Hydroxy-9-methyl-*trans,syn,trans*-perhydroanthracene. To a stirred solution of 0.229 g of 85% *m*-chloroperoxybenzoic acid in 2.0 ml of chloroform, cooled in an ice-

water bath, was added a solution of 0.151 g (0.740 mmol) of **12**, mp 62.2–63.0°, in 1.0 ml of chloroform. The resulting mixture of clear solution and white precipitate was stirred under nitrogen at room temperature for 12 hr. Ether was added, the solution was poured into water, and the mixture was extracted with ether. The combined ether extracts were washed first with 10% sodium sulfite solution until a negative iodine–starch paper test was observed and then with saturated sodium bicarbonate solution. The ether solution was dried and the ether was removed to yield 0.164 g (100%) of a light yellow solid which was dissolved in 4.0 ml of ether and cooled in an ice–water bath. Solid lithium aluminum hydride, 0.062 g (1.63 mmol), was added and the mixture was stirred under nitrogen at room temperature for 30 min. The mixture was cooled in an ice–water bath, 10 ml of 5% hydrochloric acid was added, and the resulting mixture was extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and dried, and the ether was removed under reduced pressure to yield 0.163 g (99%) of a light yellow solid: nmr (CCl_4) δ 2.70–0.30, complex with singlets at 1.08 (equatorial CH_3) and 0.91 (axial CH_3). Analysis by gc at 140° on a 150 ft × 0.01 in. column of SF-96 showed axial and equatorial alcohols at 15 and 16 min in the ratio of 42:58.

9(e)-Acetoxymethyl-*trans,syn,trans*-perhydroanthracene (19). A solution of 1.225 g (5.52 mmol) of **12** in 10 ml of tetrahydrofuran was subjected to an exhaustive hydroboration treatment (a total of 2.27 g of sodium borohydride and 4.0 g of boron trifluoride etherate was used). Work-up gave 0.842 g (64%) of a solid which was acetylated in a mixture of 5 ml of acetic anhydride, 5 ml of isopropenyl acetate, and 5 ml of pyridine, heated at 95° for 60 min. Work-up afforded 0.707 g (71%) of a pasty solid which was chromatographed on 10 g of silica gel using 5-ml portions of methylene chloride as eluent: fractions 3–10 gave 0.167 g (18%) of an oily solid. Analysis by gc at 215° on a 10 ft × 0.25 in. column of 20% SF-96 on Anakrom showed two main components (92% of total) with retention times of 16 and 18 min in the ratio 1:2.4. These components were separated by preparative gc on the same column, thereby affording samples of **19** (16 min), mp 122–124° (nmr (CCl_4) δ 2.00 (s, 3) and 4.16 (broad s, 2)), and the corresponding axial epimer (18 min), mp 67–69° (nmr (CCl_4) δ 1.92 (s, 3) and 3.98 (d, 2, J = 5 Hz)).

***trans,trans*-2,8-*trans*-Bicyclo[8.4.0]tetradecadiene-2,9-d_2** was prepared by following the procedures published for the unlabeled compound.[20] A suspension of 4.400 g (20.0 mmol) of 9,10-diketo-*trans,syn,trans*-perhydroanthracene (**26**) and 1.495 g (37.4 mmol) of lithium aluminum deuteride in 100 ml of tetrahydrofuran was heated at reflux for 16 hr. The mixture was then cooled and excess hydride destroyed by adding saturated ammonium chloride solution. Dilute hydrochloric acid was also added and the total liquid layer was then removed by decantation from the resulting gum. The gum was extracted with ethyl acetate and the ethyl acetate solutions were combined, washed with water and sodium bicarbonate solution, and dried. Filtration and removal of solvent afforded 3.774 g (83%) of diol. This material was dissolved with warming in 90 ml of pyridine. The solution was then cooled, treated with 11.77 g of mesyl chloride, and stored at 5° overnight. The mixture was then poured into ice–water and the resulting solid was collected, washed with dilute hydrochloric acid and then water, and dried, yielding 5.839 g (92%) of dimesylate, mp 129–133° dec. A portion of this material, 1.515 g (3.84 mmol), was mixed in a three-necked flask under nitrogen with 0.803 g of activated zinc powder, 1.995 g of potassium iodide, and 40 ml of dimethylformamide. After 26 hr at 65° the mixture was cooled and residual zinc removed by decantation. The decanted solution was extracted with hexane–water. Work-up of the combined hexane fractions gave 0.631 g (83%) of a colorless oil which was chromatographed on 40 g of silica gel using hexane as eluent and collecting 25-ml fractions. Fractions 4–9 gave 0.34 g (46%) of oily 1-2,9-d_2: nmr (CCl_4) δ 4.70 (broad d, 2, J = 10 Hz).

9-Keto-10-methylene-*trans,syn,trans*-perhydroanthracene (27). To a solution prepared from 56.5 g of a 50% oil dispersion of sodium hydride (pentane washed to remove the oil) in 700 ml of dimethyl sulfoxide was added a solution of 420.4 g (1.178 mol) of methyltriphenylphosphonium bromide in 1000 ml of dimethyl sulfoxide. An additional 400 ml of dimethyl sulfoxide was used to rinse remaining bromide salt into the reaction flask. The resulting red-yellow-green mixture was stirred at room temperature for 15 min. Then 3000 ml of dimethyl sulfoxide and 178.7 g (0.810 mol) of solid diketone **26** were added and the resulting dark red solution was heated to maintain an internal temperature of 42 to 48°, with stirring for 27 hr. The solution was cooled to about 18° and rapidly poured into a well-stirred mixture of 5000 ml of distilled water and 500 ml of pentane. The resulting mixture was extracted thoroughly with water and dried. The pentane was removed under reduced pressure to yield 198.6 g of yellow solid. This solid was combined with 17.8 g of comparable material from another run and the resulting 216.4 g of material was digested with 2500 ml of pentane. The mixture was filtered and the filtrate was chromatographed on 3600 g of alumina (80–200 mesh), using successively eleven 1000-ml portions of pentane, twelve 1000-ml portions of pentane–ether (97:3), twenty-six 1000-ml portions of pentane–ether (95:5), and twenty 1000-ml portions of pentane–ether (93:7). Removal of solvent under reduced pressure yielded 6.0 g of white solid from fractions 1–6, 28.1 g from fractions 7–11, 27.7 g from fractions 12–21, 19.6 g from fractions 22–25, 15.6 g from fractions 26–29, 16.0 g from fractions 30–35, 15.0 g from fractions 36–49, 3.2 g from fractions 50–58, and 0.96 g from fractions 59–69.

A sample, 3.317 g, of compound comparable to that of fractions 1–11, but obtained in another run, was crystallized from hexane, thereby affording 1.769 g of 9,10-dimethylene-*trans,syn,trans*-perhydroanthracene, mp 132–134°: ir (KBr) 6.10 (C=C) and 11.35 μ (=CH_2); nmr (CCl_4) δ 4.66 (s, 4, =CH_2).

Anal. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.66; H, 11.29.

Crystallization from hexane of the solid obtained from fractions 26–29 and similar fractions from another run afforded 59.02 g (30%) of **27** as hard, white prisms, mp 161.0–162.0°: ir (KBr) 5.90 (C=O), 6.10 (C=C), and 11.35 μ (=CH_2); nmr (CCl_4) δ 4.81 (s, 2, =CH_2).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.13; H, 10.16.

9(e)-Hydroxy-10-methylene-*trans,syn,trans*-perhydroanthracene (28) was made by following a similar preparation.[27] To a stirred, boiling solution of 31.55 g (0.144 mol) of **27**, mp 161.0–162.0°, in 5300 ml of isopropyl alcohol was added, in small portions over a 30-min period, 450 g (19.58 mol) of sodium metal. The mixture was heated at reflux for 5 hr and then 2000 ml of methanol was carefully added and the mixture was poured over 12,000 ml of cracked ice. The resulting mixture was extracted with ether, and the combined ether extracts were washed with water and dried. Removal of solvent yielded 31.8 g of a white solid. This material was combined with 31.1 g of comparable material from another run and the mixture was crystallized from hexane, thereby giving 43.9 g (70%) of white needles, mp 170.0–171.0°: nmr (CCl_4) δ 4.58 (broad s, 2). Repeated crystallizations from hexane yielded an analytical sample of **28**, mp 170.9–171.1°. Oxidation with Jones' reagent gave a ketone identical with starting material.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.70; H, 11.03.

9(e)-Bromo-10-methylene-*trans,syn,trans*-perhydroanthracene (30). A solution of 2.274 g (10.34 mmol) of **28**, mp 169.0–169.3°, and 3.712 g (14.55 mmol) of *p*-bromobenzenesulfonyl chloride in 25 ml of pyridine was allowed to stand under nitrogen at room temperature for 24 hr. Then 0.4 ml of distilled water was added and the resulting solution was allowed to stand at room temperature for 60 min. This solution was poured into a solution of 250 ml of saturated sodium chloride solution and 1000 ml of 5% hydrochloric acid and the mixture was extracted with ether. The combined ether extracts were washed with 5% hydrochloric acid and saturated sodium bicarbonate solution and dried. The ether was removed to yield 4.234 g (94%) of crude brosylate as an off-white solid, mp 108.0–117.0° dec.

From another run a mixture of 88.1 g (0.201 mol) of comparable crude brosylate and 54.3 g (0.456 mol) of dried, finely ground potassium bromide, in 850 ml of dry dimethylformamide, was heated at 55–65° with vigorous stirring under nitrogen for 20 hr. The resulting mixture was cooled, diluted with water, and extracted with ether. The combined ether extracts were washed thoroughly with water and dried, and the ether was removed under reduced pressure to yield 57.2 g (100%) of crude bromide as a light yellow solid, mp 62–104°, with the nmr spectrum showing no aromatic hydrogen signals.

A portion of this crude bromide (10.2 g) was crystallized from 95% ethanol to give 5.827 g of white solid, mp 90.5–105.5°. Further crystallization from ethyl acetate yielded 2.913 g of bromide **30** as hard, white prisms, mp 110.0–112.0°: ir (KBr) 6.10 (C=C) and 11.30 μ (=CH_2); nmr (CCl_4) δ 4.65 (s, 2, =CH_2), 3.54 (t, 1, J = 9 Hz). Repeated recrystallization from 95% ethanol yielded an analytical sample, mp 113.0–113.7°.

Anal. Calcd for $C_{15}H_{23}Br$: C, 63.60; H, 8.18; Br, 28.21. Found: C, 63.60; H, 8.22; Br, 28.20.

9(e)-Bromo-10(e)-chloro-10-methyl-*trans,syn,trans*-perhydroanthracene (31). A solution of 0.9246 g (3.26 mmol) of **30** in 20 ml of ether, cooled in a Dry Ice–acetone bath, was saturated with anhydrous hydrogen chloride gas over a period of 45 min. The mixture was allowed to warm slowly to room temperature and then to stand at room temperature for 4 hr. The solution was poured over crushed ice and the mixture was extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and dried. Removal of the ether yielded 1.024 g (98%) of bromo chlorides as a light yellow solid, mp 103–116°: nmr (CCl_4) δ 1.30 (axial CH_3) and 1.40 (equatorial CH_3), the former signal very much larger than the latter. Repeated crystallization of this material from hexane yielded 0.084 g of analytically pure **31**, mp 123.3–124.5°: nmr (CCl_4) δ 3.39 (t, 1, J = 10 Hz).

Anal. Calcd for $C_{15}H_{24}BrCl$: C, 56.34; H, 7.57; Br, 25.00; Cl, 11.09. Found: C, 56.32; H, 7.54; Br, 25.32; Cl, 11.20.

2-Methyl-*trans,trans*-2,8-*trans*-bicyclo[8.4.0]tetradecadiene (2). To 0.690 g (2.16 mmol) of crude **31**, mp 103–116°, and 0.749 g (11.45 mg-atom) of activated zinc dust was added 65 ml of a solution prepared by dissolving 186.1 g (0.50 mol) of the disodium salt of ethylenediaminetetraacetic acid, 43.0 g (1.07 mol) of sodium hydroxide, and 6.78 g (0.04 mol) of potassium iodide in 3000 ml of 95% ethanol and 1050 ml of water. This mixture was heated at reflux, with vigorous stirring, under nitrogen, for 13 hr. Then 6 ml of 0.4 M sodium hydroxide in 75% ethanol was added, and the mixture was heated at reflux, with vigorous stirring, under nitrogen, for an additional 90 min. The mixture was cooled, poured into water, and extracted with pentane. The combined pentane extracts were washed with saturated sodium bicarbonate solution and then water and dried. The pentane was removed under reduced pressure to yield 0.421 g of a clear oil which was chromatographed on 75.0 g of silica gel using 1015 ml of pentane in 29 fractions of 35 ml each. The solvent was removed from each fraction in a stream of nitrogen. Fractions 1–3 yielded 0.010 g of an oil. Fractions 4–7 yielded 0.045 g of **12** (11%), mp 57.5–62.0°. Fractions 8–15 yielded 0.270 g of oily **2** (70%) which revealed only one component when subjected to gc analysis at 140° on a 150 ft × 0.01 in. column of SF-96: ir (film) 6.03 and 10.30 μ; uv_{max} (2-methylbutane, using 0.1 mm cells) 189 nm (ϵ 16,000) with a slight shoulder at *ca.* 210 nm (ϵ 6300); nmr (CCl_4) δ 5.0–4.4 (complex, 3) and 2.6–0.7, showing a broad methyl singlet at 1.40; mol wt from the mass spectrum, 204.

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.88; H, 12.06.

10-Methyl-$\Delta^{4a(10)}$-*trans,syn*-dodecahydroanthracene. Acetylation of crude alcohol **28** with acetic anhydride in pyridine gave a yellow solid crude acetate in quantitative yield. Crystallization of 9.67 g of crude acetate from absolute ethanol yielded 6.70 g (68%) of white solid, mp 120–121°. Repeated crystallization afforded on analytical sample, mp 121–122°: nmr (CCl_4) δ 4.60 (broad, 3) and 1.97 (s, 3).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.76; H, 10.24.

The double bond of the acetate was isomerized by placing a sample, typically 0.07 g, mp 120–121°, in a cold nmr tube to which was added liquid sulfur dioxide and a trace of tetramethylsilane. The tube was sealed and then heated at 50° with monitoring of the progress of the reaction *via* nmr spectra. Individual runs took variable times (60 hr was not uncommon) and poor results were obtained without nmr monitoring. Combination of the products from three runs afforded 0.200 g of white solid which yielded 0.113 g, mp 97–98°, after crystallization from absolute ethanol: nmr (CCl_4) δ 4.50 (t, 1, J = 9.5 Hz), 1.99 (s, 3), and 1.59 (broad s, 3). One recrystallization gave an analytical sample, mp 98.5–99.5°.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.99; H, 10.19.

A sample of isomerized acetate, 0.420 g (1.60 mmol), mp 96–98.5°, was saponified in 20 ml of 0.50 M ethanolic potassium hydroxide heated at reflux for 5 hr. The resulting light yellow solution was poured into saturated sodium chloride solution, and the mixture was extracted with ether. The combined ether extracts were washed with water and dried. Removal of the ether yielded 0.346 g (85%) of light yellow solid, showing no carbonyl absorption in the ir spectrum. A sample of this crude alcohol, 0.173 g (0.785 mmol), was converted to the corresponding tosylate by mixing with 0.204 g (1.071 mmol) of *p*-tosyl chloride in 2 ml of pyridine and allowing the mixture to stand at 5° for 76 hr. Work-up afforded 0.285 g (97%) of crude tosylate as a viscous tan oil which eventually solidified: nmr (CCl_4) δ 8–7 (4), 4.30 (t, 1, J = 9 Hz), 2.42 (s, 3), and 1.59 (s, 3).

Repeated reduction of a sample of this tosylate, 0.025 g, with lithium aluminum hydride in ether afforded, after work-up, 0.015 g of an oily, tosylate-free material: nmr (CCl_4) δ 1.55 (s, 3). Although the oil failed to crystallize, gc analysis showed it to be relatively pure; at 150° on a 150 ft × 0.01 in. column of Apiezon L one principal component was visible at 32 min (93%) with four minor components apparent at 22 (3%), 27 (1%), 34 (2%), and 36 min (1%).

9(e)-Acetoxy-10(a)-methyl-*trans,syn,trans*-perhydroanthracene (14). A mixture of 0.125 g of **28** acetate, mp 120–121°, and 0.109 g of platinum oxide, in 20 ml of ethyl acetate, was vigorously stirred at room temperature under an atmosphere of hydrogen for 20 hr. The resulting mixture was filtered and the ethyl acetate was removed from the filtrate under reduced pressure to yield 0.126 g (100%) of a light yellow solid: nmr (CCl_4) δ 4.32 (broad, 1) and 1.97 (s, 3). Analysis by gc at 140° on a 150 ft × 0.01 in. column of SF-96 showed the presence of two components at 32 and 36 min in the ratio 32:68. A sample of the major component was obtained by careful preparative gc at 198° on a 5 ft × 0.25 in. column of 20% SF-96 on 60–80 firebrick. The solid thus obtained, 40 mg, was crystallized twice, first from methanol–ethanol (1:1) and then from methanol to yield 16 mg of white crystals, mp 150–152°; nmr (CCl_4) δ 0.75 (d, 3, J = 6.5 Hz).

Cyclization of 1. A solution of 0.73 g of diene **1**, mp 48–49°, in 90 ml of an anhydrous 0.557 M solution of perchloric acid in acetic acid was stirred magnetically under nitrogen at a bath temperature of 26 ± 2° for 3 hr. The resulting light yellow reaction mixture was diluted with 180 ml of distilled water and extracted four times with 35-ml portions of benzene. The combined benzene extracts were washed twice with 100-ml portions of distilled water, twice with 100-ml portions of 10% potassium bicarbonate solution, once with 100 ml of distilled water, and then dried and concentrated to a small volume under reduced pressure. The residue was diluted to a volume of exactly 50 ml with benzene and analyzed by gc at 203° on a 150 ft × 0.01 in. column of UCON Polar. The following products were identified by the peak enhancement technique (retention times in min in parentheses): **8** (7.5), $\Delta^{4a(9a)}$-*trans*-dodecahydroanthracene (8.2), **7** (20.4), and **6** (22.4). Preparative gc at 222° on a 10 ft × ⅜ in. column of 5% Carbowax 20M on Teflon-6 afforded samples of **4**, **5**, and **7** with properties identical with those of previously prepared authentic compounds. The authentic compounds were used as standards in a quantitative gc analysis which thereby accounted for 100.9% of the products in terms of the material balance as follows: **8** (0.4%), $\Delta^{4a(9a)}$-*trans*-dodecahydroanthracene (15.1%), **7** (3.0%), and **6** (81.6%) and 0.8% of an unidentified olefin at 8.0 min. Samples of **6** and **7** were found to be virtually unchanged after being submitted to the same reaction conditions as were used in the cyclization.

The conditions used for cyclization of **1** in buffered acetic acid are exemplified by the following description of one of the experiments involving deuterium labeling.

A mixture of 0.47 g (2.51 mmol) of **1** in 5 ml of acetic acid-*O-d* containing 0.070 g of sodium acetate was stirred at 60° for 95 hr. Extraction with hexane–water afforded after work-up 0.591 g of white solid, mp 115–123°. Crystallization of this solid from hexane afforded 0.265 g, mp 123–124°. The mother liquor was chromatographed on 15 g of acid-washed alumina using 90 ml of hexane and then 90 ml of 3:1 hexane:ether as eluent and collecting 30-ml fractions. Fraction 4 gave 0.239 g of a solid, mp 115–120°, which was combined with the 0.265 g obtained by crystallization (overall, 0.514 g or 81%). This material was treated with 0.304 g of lithium aluminum hydride in 5 ml of tetrahydrofuran first at room temperature for 150 min and then at reflux for 30 min. The mixture was cooled and water was added cautiously and then dilute hydrochloric acid. Extraction with chloroform afforded after work-up 0.390 g (99%) of a white solid, mp 166–168°. A portion of this solid, dized with Jones' reagent. Excess chromic acid was destroyed by adding a drop of methanol. Extraction of the mixture with dichloromethane gave after work-up 0.026 g (90%) of a solid. This was filtered through a column of 3 g of silica gel in 1:1 hexane:ether solution. Removal of solvent afforded 0.026 g of solid **25**-*9-d*, mp 128–130°: ir (KBr) 2149 and 2170 cm^{-1} (equatorial C–D stretching).

Cyclization of **1**-*2,9-d*$_2$ in buffered acetic acid was similarly carried out and the product converted as described above to a sample of **25**-*9-d*, mp 128–129°: ir (KBr) 2124 and 2145 cm^{-1} (axial C–D stretching).

Cyclization of 2. A solution of 75.5 mg (0.57 mmol) of diene **2**, 3.3 mg (0.04 mmol) of sodium acetate, and 39.7 mg (0.27 mmol) of *p*-dichlorobenzene (an internal reference for rate measurements) in 0.25 ml of acetic acid was maintained at 60° for 88 hr. Work-up

afforded 99 mg of a white solid. The nmr spectrum showed that 67% of the product consisted of olefin **12**.

A portion of product, 27 mg, was chromatographed on 2.7 g of acid-washed alumina. One 30-ml fraction of pentane and one 30-ml fraction of ether were collected. Removal of the pentane afforded 17 mg of crude **12**, mp 54–60°, which was homogeneous by gc analysis but by nmr analysis only 90% pure (the remainder absorbing in the saturated C–H region).

Another portion of product, 28 mg, was reduced with lithium aluminum hydride. Gc analysis of the product at 140° on a 150 ft × 0.01 in. column of SF-96 showed four components at 7, 11, 12, and 17 min, identified by coinjection as olefin **12** (66%), the alcohol corresponding to axial acetate **11** (4%), the alcohol corresponding to equatorial acetate **10** (25%), and the alcohol corresponding to equatorial acetate **14** (5%).

Another portion of the product was subjected to preparative gc at 197° on a 5 ft × 0.25 in. column of 20% SF-96 on 60–80 firebrick. Samples of **12** and **14** were thereby obtained and found to be identical with authentic compounds previously prepared.

Synthesis and Cyclization of 3. A mixture of 195 mg (3 mequiv) of activated zinc dust and 63 mg (0.33 mmol) of cuprous iodide in 3 ml of ether was stirred for 30 min at room temperature. Solutions of 142 mg (0.75 mmol) of **1** in 0.6 ml of ether and 405 mg (1.5 mmol) of methylene iodide in 0.6 ml of ether were then added consecutively. Ether was added periodically to compensate for evaporation losses. After 24 hr work-up afforded 161 mg of a pale yellow oil. This oil was passed through a column of 3 g of silica gel in a cold room at 5° with a total of 50 ml of pentane. Removal of the pentane gave 109 mg of a colorless oil which was further purified by chromatography on 5 g of silica gel impregnated with 5% silver nitrate. Seven 5-ml fractions of hexane and five 5-ml fractions of 3:1 hexane:ether were collected. Fraction 2 gave a trace of solid **4**. Fractions 4 and 5 gave 14 mg of an oil shown by gc to contain at least four components. Fractions 9–11 yielded 64 mg (42%) of oily **3**, shown to be homogeneous (>95%) by gc at 200° on a 10 ft × 0.25 in. column of 20% SF-96 on Anakrom: nmr (CCl_4) δ 0.09 (broad, 2, cyclopropane CH_2) and 4.9–5.4 (broad, 2); mol wt from the mass spectrum, 204.

A similar reaction, but using relatively more Simmons–Smith reagent (620 mg (9.5 mequiv) of zinc dust, 182 mg (0.96 mmol) of cuprous iodide, and 1.01 g (7.12 mmol) of methylene iodide to 142 mg (0.75 mmol) of **1**) afforded 156 mg of crude oil which was chromatographed in a cold room at 5° on 13 g of silica gel. Sixteen 10-ml fractions of pentane were collected. Fractions 2–4 gave 99 mg of colorless oil which was crystallized from methanol–ethyl acetate at 5°, thereby yielding 44 mg (27%) of **4** as a white solid, mp 38–39°, shown to be homogeneous by gc at 200° on a 10 ft × 0.25 in. column of 20% SF-96 on Anakrom: nmr (CCl_4) δ 0.21 (broad, 4, cyclopropane CH_2); mol wt from the mass spectrum, 218.

A solution of 64 mg of **3** and 32 mg of sodium acetate in 2 ml of acetic acid was heated to reflux for 6 days. Periodically acetic acid was added to compensate for evaporation losses. Work-up afforded 74 mg of a reddish pasty solid which was chromatographed on 15 g of acid-washed alumina. Four 15-ml fractions of hexane and five 15-ml fractions of 3:1 hexane:ether were collected. Fractions 1 and 2 gave 10 mg of oil which was shown by gc analysis to contain at least three components. Fractions 5 and 6 yielded 48 mg (58%) of solid acetates, mp 82–87°, which consisted of two components in a 6:94 ratio with retention times of 12.8 and 15.5 min according to gc analysis at 213° on a 10 ft × ⅜ in. column of 5% Carbowax 20M on Teflon-6. Crystallization from methanol afforded 16 mg of **16**, mp 95–96.5°: nmr (CCl_4) δ 0.85 (broad s, 3), 1.97 (s, 3), 4.25 (broad, 1). The minor gc component was shown not to be **19** by coinjection analysis (14.5 min). Its characterization as **17** was demonstrated as follows. A sample, 25 mg, of the acetate fraction obtained from cyclization was reduced with lithium aluminum hydride in tetrahydrofuran, work-up affording 24 mg of a colorless solid, mp 141–145°, showing no carbonyl absorption in the infrared spectrum. Oxidation of this solid with Jones' reagent gave 22 mg of a solid ketone mixture, mp 97–102°. Reduction of the ketone mixture with sodium borohydride in ethanol yielded 17 mg of a pasty solid which was acetylated with a mixture of acetic anhydride and pyridine. Work-up afforded 17 mg of a pasty solid which was shown by gc coinjection analysis to consist of the same two acetates obtained in the cyclization but in a ratio which had changed from 6:94 to 79:21.

Registry No.—**1**, 1460-23-7; **1**-2,9-d_2, 52759-82-7; **2**, 32427-44-4; **3**, 52747-13-4; **4**, 52747-14-5; **6**, 52747-15-6; **6** deacetyl derivative, 52747-16-7; **6** tosylate derivative, 52747-17-8; **7**, 52747-18-9; **8**, 52747-19-0; **10**, 52747-20-3; **10** deacetyl derivative, 52747-21-4; **11**, 52747-22-5; **11** deacetyl derivative, 52747-23-6; **12**, 52747-24-7; **14**, 52747-25-8; **16**, 52747-26-9; **17**, 52747-27-0; **19**, 52747-28-1; **23**, 36257-83-7; **23** ketol derivative, 20843-80-5; **24**, 52747-29-2; **24** tetrahydro derivative, 52747-30-5; **24** thioketal derivative, 52747-31-6; **25**, 52747-32-7; **25** ketal derivative, 52747-33-8; **25** tosylate derivative, 52747-34-9; **25** oxime, 52747-35-0; **25** thioketal derivative, 52747-36-1; **25**-9-*d* equatorial, 52759-83-8; **25**-9-*d* axial, 52759-84-9; **26**, 52747-37-2; **26** dimesylate derivative, 32687-23-3; **27**, 52747-38-3; **27** dimethylene derivative, 52747-39-4; **28**, 52747-40-7; **28** brosylate, 52747-41-8; **28** acetate, 52747-42-9; **28** isomerized acetate, 52747-43-0; **29**, 52747-44-1; **30**, 52747-45-2; **31**, 52747-46-3; **31** equatorial CH_3, 52759-85-0; ethanedithiol, 540-63-6; $\Delta^{4a(9a)}$-*trans*-dodecahydroanthracene, 52747-47-4; *trans,syn,trans*-perhydroanthracene, 1755-19-7; *p*-bromobenezenesulfonyl chloride, 98-58-8; 10-methyl-$\Delta^{4a(10)}$-*trans,syn*-dodecahydroanthracene, 52747-48-5; acetic acid-*O*-*d*, 758-12-3; *p*-tosyl chloride, 98-59-9.

References and Notes

(1) The investigation was supported by Public Health Service Research Grants GM 09759, 14133, and 16338 from the Division of General Medical Services, U.S. Public Health Service.

(2) The article is abstracted from the Ph.D. Theses of R.A.K. and R.J.K., University of Wisconsin, and the M.A. Thesis of T.O., Wesleyan University.

(3) The conformations of *trans,trans*-1,5-cyclodecadienes are discussed by P. S. Wharton, Y.-C. Poon, and H. C. Kluender, *J. Org. Chem.*, **38**, 735 (1973).

(4) The facile Cope rearrangement of **1** has already been reported by P. S. Wharton and R. A. Kretchmer, *J. Org. Chem.*, **33**, 4258 (1968).

(5) Dreiding models are useful if account is taken of distortions revealed by X-ray data of related *trans,trans*-1,5-cyclodecadienes. See J. McLure, G. A. Sims, P. Coggon, and A. T. McPhail, *Chem. Commun.*, 128 (1970), and F. H. Allen and D. Rogers, *ibid.*, 588 (1967).

(6) Spectroscopically, an interaction is revealed by a transition which is seen as a shoulder at 204 nm, ϵ 2000. *trans,trans*-1,5-Cyclodecadienes, in general, show similar uv behavior. See F. Sorm, *Progr. Chem. Org. Natur. Prod.* **19**, 1 (1961).

(7) See P. S. Wharton and D. W. Johnson, *J. Org. Chem.*, **38**, 4117 (1973).

(8) Under more vigorous conditions, trifluoroacetic acid at room temperature, *cis,trans*-1,5-cyclodecadiene reacts with quantitative cyclization. See J. G. Traynham and H. H. Hsieh, *Tetrahedron Lett.*, 3905 (1969), and J. G. Traynham, G. R. Franzen, G. A. Knesel, and D. J. Northington, *J. Org. Chem.*, **32**, 3285 (1967).

(9) For example, cyclized products are obtained in less than 50% yield from 2,6-octadienes. See H. E. Ulery and J. H. Richards, *J. Amer. Chem. Soc.*, **86**, 3113 (1964).

(10) The use of deuterium to establish the stereochemistry of protonation of 1,5-dienes has been previously reported by Ulery and Richards[9] and A. Nickon, F. Y. Edamura, T. Iwadare, K. Matsuo, F. J. McGuire, and J. S. Roberts, *J. Amer. Chem. Soc.*, **90**, 4196 (1968).

(11) This diagnostic characterization is documented by E. J. Corey, M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 5036 (1956).

(12) Generation of a methyl stabilized but uncyclized carbocation which would lead to a 6-5-7 tricyclic system is conceivable but no evidence for this pathway was found.

(13) Analytical figures do not take into account 7% of a high molecular weight saturated hydrocarbon fraction which is thought to have been present in starting diene.

(14) See the data of Taft cited in ref 17b.

(15) Whichever comparison is made there is certainly a large rate difference associated with the direct generation of tertiary *vs.* secondary carbocations. A factor of 10^3–10^4 is given for protonation (isobutylene *vs.* propylene; see ref 14) and 10^6 is estimated as the limiting difference for solvolysis.

(16) H. L. Goering and W. D. Closson, *J. Amer. Chem. Soc.*, **83**, 3511 (1961).

(17) (a) H. Felkin and C. Lion, *Chem. Commun.*, 60 (1968); (b) P. D. Bartlett and G. D. Sargent, *J. Amer. Chem. Soc.*, **87**, 1297 (1965); (c) P. G. Gassman and D. S. Patton, *ibid.*, **91**, 2162 (1969). It should be noted that other homoallylic systems are more sensitive to methyl substitution than is the 7-*anti*-norbornenyl as is emphasized in ref 17a.

(18) Other comparisons are interesting. The literature reveals (a) similar reactivities toward protonation of cyclopropane and propylene and (b) relative participatory powers of double bonds and cyclopropanes which are highly dependent on geometry and vary greatly, some comparisons favoring the double bond and others the ring. See (a) C. D. Lawrence and C. F. H. Tipper, *J. Chem. Soc.*, 713 (1955), and (b) J. B. Lambert, J. W. Hamersma, A. P. Jovanovich, F. R. Koeng, S. A. Sweet, and P. J. Kucinski, *J. Amer. Chem. Soc.*, **92**, 6372 (1970), and several examples cited by B. Capon, *Org. React. Mech.*, **44** (1968).

(19) The hydrocarbon fraction was not investigated.

(20) P. S. Wharton, Y. Sumi, and R. A. Kretchmer, *J. Org. Chem.*, **30**, 234 (1965); P. S. Wharton and G. O. Spessard, *ibid.*, **37**, 548 (1972).

(21) D. E. Applequist, G. F. Fanta, and B. W. Hendrickson, *J. Org. Chem.*, **23**, 1715 (1958).

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hydroxide was added, a result which is intriguingly explicable (but unestablished) in terms of fragmentation followed by subsequent cyclization in the weakly acidic medium.

(23) J. A. Marshall and G. L. Bundy, *Chem Commun* 854 (1967).

(24) Several interconversions and cross-checks were carried out in order to make sure that at no stage was the trans,syn,trans stereochemistry of the tricyclic compounds changed. Exemplary is the thioketalization of **25** and subsequent desulfurization to authentic *trans,syn,trans*-perhydroanthracene, the structure of which rests on X-ray evidence. See S. Bog, O. Hassel, and E. H. Vihovde, *Acta Chem. Scand.*, **7**, 1308 (1953).

(25) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N.Y., 1967.

(26) See R. K. Hill, J. G. Martin, and W. H. Storch, *J. Amer. Chem. Soc.*, **83**, 4006 (1961).

(27) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Amer. Chem. Soc.*, **83**, 606 (1961).

Regioselective [4 + 2] and [2 + 2] Cycloadditions of 1-Azirines to Heterocumulenes. Formation and Rearrangements of the Cycloadducts

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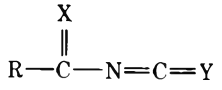
Received June 14, 1974

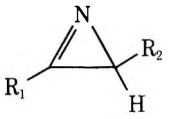
The cycloaddition of 1-azirines to some heterocumulenes is presented. The thermal reaction of representative 1-azirines (**4**) to thiobenzoyl isocyanate (**2**) results in exclusive [4 + 2] cycloaddition. The regiospecificity of the reaction was confirmed by hydrolysis of the cycloadducts **5** to the ureas **6**. Controlled thermolysis of **5a** results in the formation of a novel seven-membered-ring system, a thiadiazepinone (**7**). Compound **7** undergoes a sulfur extrusion reaction thermally to give a pyrimidine ring system (**8**). Benzoyl isocyanate (**1**) also gave [4 + 2] cycloaddition products (**9**). Benzoyl isothiocyanate (**3**), however, gave products (**12**) resulting apparently from a regiospecific [2 + 2] cycloaddition about the C=S bond. The nature of the transition state for the initial [2 + 2] addition is discussed. Structural identification came from mass spectral and nmr studies, particularly ^{13}C nmr.

Heterocumulenes containing a carbonyl or related unsaturation adjacent to the cumulative bonds such as **1**, **2** and **3**, offer the possibility of entry into complex heterocyclic



1, R = Ph; X = O; Y = O
2, R = Ph; X = S; Y = O
3, R = Ph; X = O; Y = S

systems through thermal symmetry-allowed [$_\pi4_s$ + $_\pi2_s$] or [$_\pi2_s$ + $_\pi2_a$] pericyclic reactions. The small ring nitrogen heterocycle, 1-azirine (**4**), may participate as a component in



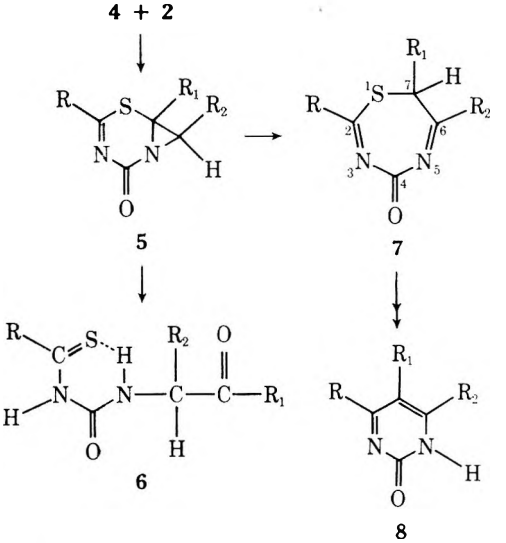
4a, R_1 = Ph; R_2 = Ph
b, R_1 = Ph; R_2 = CH_3
c, R_1 = Ph; R_2 = H

these cycloadditions by utilizing its reactive π bond.[1-4] The possibility of regioselectivity resulting from the inherent polarization in both components enhances the complexity of these reactions. We wish to report on such cycloadditions and to provide evidence that minor structural changes in the heterocumulenes can produce gross changes, not only in the preferred mechanistic pathway for the formation of the adducts, but also in the thermal stability of the final products. A brief announcement of some of our results was made earlier.[11]

Results and Discussion

Thiobenzoyl isocyanate (**2**) can be generated from 2-phenylthiazoline-4,5-dione by thermal extrusion of carbon monoxide.[5-8] When a solution of freshly generated **2** in *p*-xylene was treated with 2,3-diphenyl-1-azirine (**4a**)[9,10] at room temperature for 12 hr, and the reaction mixture after solvent removal was subjected to preparative layer chromatography, a white crystalline compound was obtained, mp 154–155°.[11] Its mass spectral parent ion (*m/e* 356) and fragmentation pattern established the presence of the azirine and thiobenzoyl isocyanate moieties within the structure and that the yield of adduct was high (85%). At least three possibilities exist for the mode of addition:[12] (i) $_\pi4_s$ + $_\pi2_s$ cycloaddition, (ii) $_\pi2_s$ + $_\pi2_a$ adduction, (iii) initial nucleophilic attack by the lone pair of the azirine nitrogen on the highly reactive electrophilic carbon of the carbonyl of the isocyanate and subsequent 1,3-bond scission and cyclization in one or more ways. That the product was actually the result of an exclusive [$_\pi4_s$ + $_\pi2_s$] cycloaddition (**5a**) came from its PFT carbon-13 nmr spectral evidence. The aziridine carbons appeared at δ 53.31 and 56.60, the carbonyl carbon at 173.46, and the imine carbon at 162.94.

The question of the direction or regiospecificity of the cycloaddition and further substantiation of structure was provided in an elegant way by the acid-catalyzed hydrolysis of **5a** to the urea **6a**, yellow plates, mp 199–201°. Dramatic



proof for this mode of ring opening was provided by the observation of three different carbonyl-type carbons (>C=O, N—C(=O)—N, C=S) as suggested by chemical shift correlations in the ^{13}C nmr spectrum. Further confirmation

was provided by the ^1H nmr spectrum of **6a** which showed the two urea N–H absorptions at δ 9.87 (singlet) and 10.47 (doublet, J = 6.9 Hz). A remarkable observation in the ^1H nmr study was the very slow rate of deuterium exchange of the N–H at δ 10.47 suggesting the presence of intramolecular hydrogen bonding. That this was indeed the case was shown by the diagnostic infrared shift of the hydrogen bonded N–H to 2400 cm^{-1} on deuteration.[13,14]

When the cycloadduct **5a** was subjected to thermolysis at 80°, a yellow crystalline compound, mp 165–167°, was isolated after chromatographic purification in 67% yield. Its 70-eV mass spectrum suggested that a rearrangement without fragmentation had occurred. The infrared spectrum showed no N–H absorption but peaks at 1725 and 1650 cm^{-1}. Its ^{13}C nmr spectrum (in $CDCl_3$) suggested the structure **7a** with δ 91.67 (C-7), singlets between 127.44 and 135.42 (phenyl carbons), 139.42 (C-6), 162.94 (C-2), 194.12 (C-4).

Prolonged thermolysis of **5a** at higher temperatures (110°) resulted in the removal of elemental sulfur and the eventual formation of a pyrimidone **8a**. That **7a** was indeed the intermediate in this sulfur extrusion reaction was confirmed not only by its isolation from the reaction mixture but also by its actual quantitative conversion to **8a** at 110°.

The differences in the stability of the cycloadducts derived from the three azirines bear consideration. The reactivity toward hydrolytic cleavage is in the direction **5a** < **5b** < **5c**. Compound **5c** undergoes hydrolysis even on silica gel columns whereas compound **5a** has to be heated at 55° for at least several hours. Whereas this acid-catalyzed hydrolysis proceeds quantitatively for **5b** and **5c** the lower yield (49%) in the case of **5a** is a reflection of the competitive ring opening reaction to **7a**. This rearrangement reaction is relatively unimportant for **5b** and **5c** even at elevated temperatures (138°, *p*-xylene reflux). Thermally **5b** and **5c** are much more stable than **5a**.

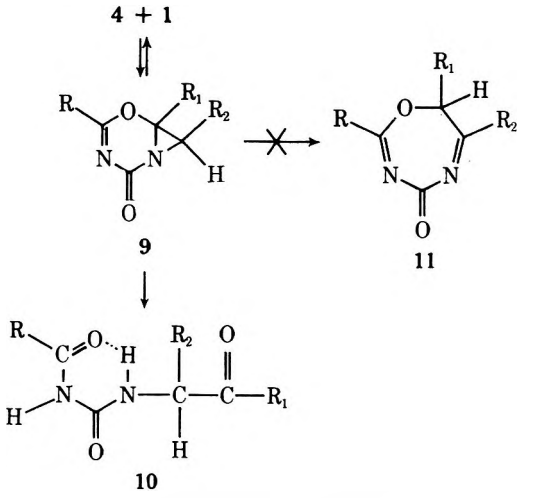
Our results with 2 prompted the investigation of the reaction of benzoyl isocyanate (**1**)[6] with 1-azirines (**4**). We discovered that the behavior of benzoyl isocyanate toward 4 paralleled those of thiobenzoyl isocyanate and [4 + 2] cycloaddition products **9** were isolated.[15] These compounds

Table I
Thermal Decomposition of 0.572 *M* Cycloadduct (9b) at 70°

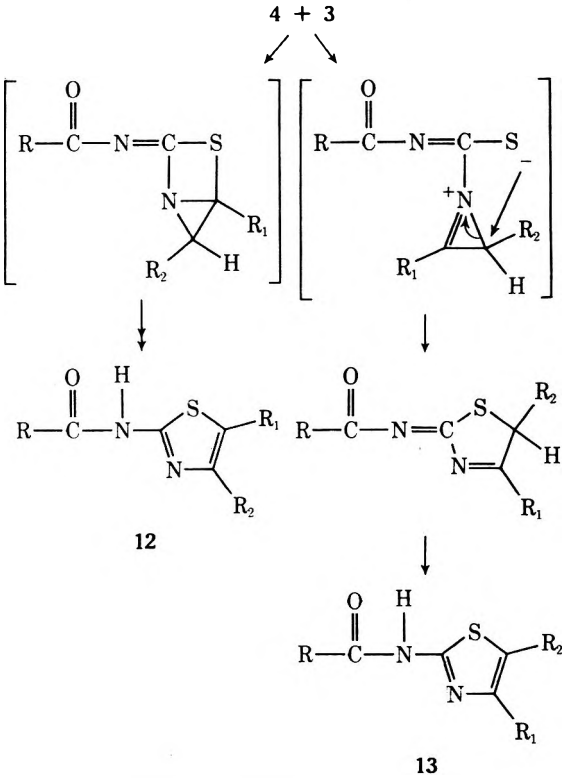
Time, hr	*M* concn of 9b	Dec, %
0	0.572	0
0.5	0.482	15.8
1.0	0.431	24.6
1.5	0.391	31.6
2.0	0.361	36.9
2.5	0.340	40.5
4.5	0.301	47.4
6.5	0.281	50.8
8.0	0.274	51.7
16.0	0.274	51.7

could be hydrolyzed to the ureas **10** under acid-catalyzed conditions. Thermolysis to **11** was not observed. At 70° a clean retro [4 + 2] pericyclic reaction took place and equilibrium was attained after 8 hr with $K = 3.24 \pm 0.20 \times 10^{-1}$.

Benzoyl isothiocyanate (**3**) can be prepared by the reaction of benzoyl chloride and lead thiocyanate.[16,17] A literature search revealed that only a limited amount of work had been done in the area of cycloadditions to **3**. We attempted the reaction of **3** with 1-azirines, not only to establish its preferred mode of addition, but also as a comparison with the behavior of **1** and **2** where exclusive [4 − 2] cy-

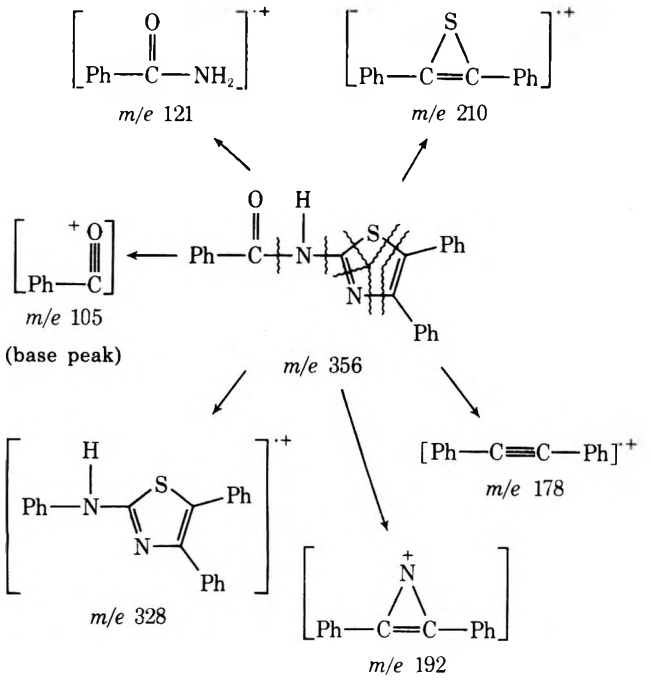


cloaddition was observed. Thus, when 2,3-diphenyl-1-azirine (**4a**) was treated with benzoyl isothiocyanate (**3**) in refluxing benzene for 12 hr, preparative layer chromatography gave a white crystalline cycloadduct in 68% conversion, mp 143–144°. Mass spectral data and elemental analysis were consistent with the molecular formula $C_{22}H_{16}N_2OS$. The infrared spectrum showed diagnostic absorptions at 3270, 1675, and 1550 cm^{-1}. Its ^1H nmr spectrum (in $CDCl_3$) showed aromatic absorptions and a broad singlet (1 H) at δ 11.15 which underwent rapid exchange with D_2O. The PFT ^{13}C nmr spectrum (in $CDCl_3$)[27] showed singlets in the phenyl carbon region and resonances at δ 144.51, 157.46, and 165.33. This inconsistency in the nmr spectral data with a [4 + 2] cycloadduct was also apparent in the mass spectrum. Collectively, the data were consistent with benzamide bearing a thiazole ring system on the amide nitrogen. Two plausible structures are **12** and **13**. Compound **12** is

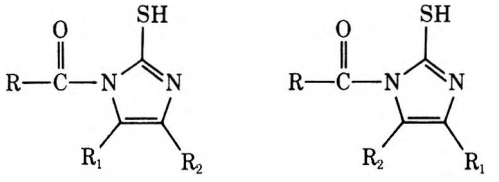


the eventual result of a [$_\pi 2_s$ + $_\pi 2_a$] cycloaddition and hydrogen shift(s). Compound **13** results from initial nucleophilic attack, 1,3-bond scission and cylization, and a 1,5-sigmatropic hydrogen shift. Both structures are consistent with the mass spectral data, *e.g.*, for **12a**[18] (Scheme I).

Scheme I



Mass spectral data, however, rules out structures **14** and **15**, the result of addition across the C=N bond of **3**.



14 **15**

Final structural confirmation came from the ^{1}H nmr spectrum of **12c** which showed the 4-H absorption as a singlet at δ 7.08. From comparison of a number of known thiazole derivatives it is clear that this absorption would be about 0.5 ppm upfield if the structure was **13c**.[19-21]

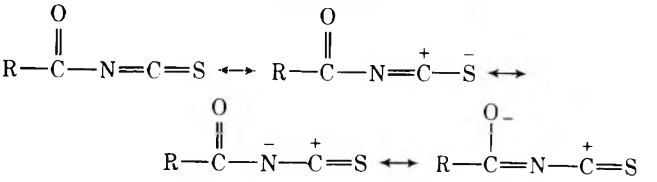
The marked difference in behavior between the exclusive [4 + 2] cycloaddition observed for benzoyl isocyanate (**1**) and thiobenzoyl isocyanate (**2**) and the apparent [2 + 2] cycloaddition in a regiospecific manner to the C=S bond of **3** requires explanation. Orbital symmetry analysis[12,22] reveals a possible concerted $[_\pi 2_s + _\pi 2_a]$ pathway but does not explain why the replacement of O by S produces such a marked change in mechanism. A striking clue to the nature of the transition state came from solvent polarity studies with **4c** at 75° (Table II) which showed a dramatic increase

Table II
Reaction of 2-Phenyl-1-azirine (4c) with Benzoyl Isothiocyanate at 75°

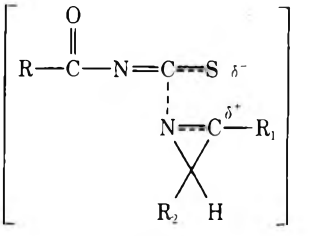
Solvent	Dielectric constant	Reaction time, hr	% yield of 12c
Benzene	2.3	2	13.4 ± 1.5
Ethyl acetate	6.0	2	19.3 ± 1.5
Nitrobenzene	34.8	2	42.7 ± 1.5

in product yield with increase in the dielectric constant of the solvent. We interpret this solvent dependency as reflecting the presence of a polar transition state in the pathway to the formation of the initial cycloadduct. The polarization of **3** (Scheme II) is similar to **1** except for the greater

Scheme II



ability of sulfur to stabilize a negative charge.[17] A dipolar transition state such as **16** could conceivably account not



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only for the solvent dependency but also for the marked difference in behavior between **1**, **2**, and **3**. Whether such a transition state would transform into a relatively stable dipolar intermediate[23] so as to favor a two-step combination is not known.

Experimental Section

General. All melting points are uncorrected. The ir spectra were recorded on a Beckman IR-20A. The nmr spectra were determined at 60 MHz with a Varian A-60 nmr spectrometer with TMS as the internal reference and with a Bruker HX-90E PFT nmr spectrometer interfaced with a Nicolet 1080 computer and disk unit. The mass spectra were obtained on a Hitachi RMU-6E mass spectrometer using direct inlet and an ionization energy of 70 eV. Elemental analyses were performed by the University of Iowa Microanalytical Service.

2,3-Diphenyl-1-azirine (**4a**) and 2-phenyl-1-azirine (**4c**) were prepared by a modification of the literature method.[9,10] 3-Methyl-2-phenyl-1-azirine (**4b**) was prepared by the method of Nair.[24] 2-Phenylthiazoline-4,5-dione was prepared by the method of Goerdeler, *et al.*[5,7,25] Thiobenzoyl isocyanate was generated by thermolysis of 2-phenylthiazoline-4,5-dione in *p*-xylene at 120° for 5 min and used *in situ*. Benzoyl isocyanate was prepared from benzamide and oxalyl chloride by established methods.[8,26] Benzoyl isothiocyanate can be obtained from the reaction of benzoyl chloride and lead thiocyanate.[16]

Reaction of 2,3-Diphenyl-1-azirine (4a) with Thiobenzoyl Isocyanate (2). A solution of thiobenzoyl isocyanate (**2**) in *p*-xylene generated from 2.865 g (15 mmol) of 2-phenylthiazoline-4,5-dione was treated at 25° with 2.42 g (12.5 mmol) of 2,3-diphenyl-1-azirine (**4a**) and the reaction mixture was stirred for 4 hr at 25°. The precipitated material was filtered off and chromatographed using a silica gel column. The product was eluted with ether. Crystallization from ether gave 3.673 g (85% yield based on 1-azirine) of **5a** as white rectangular crystals: mp 154–155°; ir ν_{max} (Nujol) 1720 (C=O), 1550 (C=N) cm^{-1}; ^{1}H nmr δ_{TMS} ($CDCl_3$) 4.46 (s, 1 H), 7.10–8.17 (m, 15 H); ^{13}C nmr δ_{TMS} ($CDCl_3$) 53.31, 56.60, 127.55, 127.82, 128.46, 128.95, 129.22, 129.38, 129.54, 132.94, 134.18, 135.48, 136.93, 162.94, 173.46; mass spectrum *m/e* 356 (M^+), 324 (M^+ − S), 296 (M^+ − S–CO), 253 (M^+ − PhCN), 193 (azirine), 163 (isocyanate), 103 (PhCN).

Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13; H, 4.52; N, 7.86. Found: C, 73.89; H, 4.47; N, 8.05.

Reaction of 3-Methyl-2-phenyl-1-azirine (4b) with Thiobenzoyl Isocyanate (2). The azirine (**4b**) (0.524 g, 4 mmol) was treated with thiobenzoyl isocyanate (**2**) as described above and the reaction mixture was stirred at 25° for 24 hr. The product was separated by column chromatography on silica gel with 50% ether–pentane as the eluent. Crystallization from ether–pentane gave colorless rectangular crystals of **5b** (0.841 g, 72%): mp 96–98°; ir ν_{max} (Nujol) 1719 (C=O), 1560 (C=N) cm^{-1}; ^{1}H nmr δ_{TMS} ($CDCl_3$) 1.15 (d, J = 5.8 Hz, 3 H), 3.42 (q, J = 5.8 Hz, 1 H), 7.18–8.15 (m, 10 H); ^{13}C nmr δ_{TMS} ($CDCl_3$) 14.73, 47.85, 54.16, 127.14, 128.76, 129.35, 134.15, 135.07, 137.39, 171.70, 173.15; mass spec-

trum *m/e* 251 (M^+ − HNCO), 191 (M^+ − PhCN), 163 (isocyanate), 148 ($Ph(C_2S)CH_3$), 131 (azirine), 103 (PhCN) (product partly rearranged under operating conditions).

Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.33; H, 4.79; N, 9.52. Found: C, 69.50; H, 4.90; N, 9.24.

Reaction of 2-Phenyl-1-azirine (4c) with Thiobenzoyl Isocyanate (2). The azirine (**4c**) (0.351 g, 3 mmol) was treated with **2** and chromatographed as described above to give 0.172 g (20%) of **5c** as colorless rectangular crystals: mp 128–129°; ir ν_{max} (Nujol) 1710 (C=O), 1560 (C=N) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 2.80 (s, 1 H), 3.13 (s, 1 H), 7.22–8.20 (m, 10 H); mass spectrum *m/e* 280 (M^+), 248 (M^+ − S), 177 (M − PhCN), 163 (isocyanate), 117 (azirine), 103 (PhCN).

Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.32; N, 9.99. Found: C, 68.21; H, 4.21; N, 9.99.

When the silica gel column was eluted with CH_2Cl_2, 0.344 g (38.5%) of **6c** was obtained as yellow needles: mp 166–167°; ir ν_{max} (Nujol) 3240, 3120 (N–H), 1690 (br) (C=O), 1535 cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 4.87 (d, J = 5.0 Hz, 2 H), 7.25–8.17 (m, 10 H), 10.06 (s, br, 1 H, exchanges in D_2O), 10.69 (t, J = 5.0 Hz, 1 H, very slow D_2O exchange); ^{13}C nmr δ_{TMS} ($CDCl_3$) 47.63, 127.03, 128.06, 128.65, 128.97, 132.16, 134.04, 134.58, 154.00, 193.06, 200.93; mass spectrum *m/e* 298 (M^+), 264 (M^+ − H_2S), 193 (M^+ − PhCO), 177 (M^+ − PhCS), 161 ($PhCOCH_2NCO$), 137 ($PhCSNH_2$), 121 (PhCS), 105 (PhCO).

Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.40; H, 4.71; N, 9.39. Found: C, 64.38; H, 4.81; N, 9.21.

Thermolysis of Cycloadduct (5a) at 80°. Formation and Isolation of Thiadiazepinone (7a). A solution of 0.250 g (0.7 mmol) of **5a** in 10 ml of benzene was heated under reflux for 6 hr. The solvent was removed and the residue was chromatographed on preparative layer silica gel PF_{254} plates with 50% ether–pentane as the developing solvent. The thiadiazepinone (**7a**) crystallized from ether–pentane as yellow prisms (0.163 g, 67%): mp 165–167°; ir ν_{max} (Nujol) 1725 (C=O), 1650 (C=N) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 7.22–8.40 (m, 15 H), 8.62 (s, 1 H); ^{13}C nmr δ_{TMS} ($CDCl_3$) 91.67, 127.44, 128.84, 129.22, 132.02, 135.42, 139.42, 162.94, 194.12; mass spectrum *m/e* 356 (M^+), 324 (M^+ − S), 296 (M^+ − S–CO), 253 (M^+ − PhCN), 193 (azirine), 163 (isocyanate), 121 (PhCS), 103 (PhCN).

Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13; H, 4.52; N, 7.86. Found: C, 73.93, H, 4.43; N, 7.71.

Thermolysis of Cycloadduct (5a) at 110°. Isolation of Pyrimidone (8a). A solution of 0.965 g (2.6 mmol) of **5a** in 20 ml of toluene was heated under reflux for 24 hr. The pyrimidone (**8a**) crystallized directly out of the reaction mixture as yellow needles (0.475 g, 54%): mp 274–278°; ir ν_{max} (Nujol) 3340 (br, N–H), 1645 (C=O), 1590 (C=N) cm^{-1}; ^1H nmr δ_{TMS} (CF_3CO_2H) 7.10–8.20 (m, 16 H); mass spectrum *m/e* 324 (M^+) 296 (M^+ − CO), 193 (azirine), 103 (PhCN).

Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.94; N, 8.64. Found: C, 81.25; H, 5.22; N, 8.33.

Thermolysis of Thiadiazepinone (7a). Isolation of Pyrimidone (8a). A solution of 0.08 g (0.225 mmol) of **7a** in 15 ml of toluene was heated under reflux for 24 hr. The solvent was then removed and the residue was crystallized from dichloromethane–ether to give **8a** as yellow needles (0.063 g, 86.5%): mp 274–278°.

Hydrolysis of Cycloadduct (5a). A suspension of **5a** (0.200 g, 0.56 mmol) in 15 ml of 1 *M* HCl was stirred at 55° for 24 hr. The yellow solid formed was filtered, washed with water, and purified by preparative plates (silica gel PF_{254}) using ether as the developing solvent. The urea **6a** crystallized from ethanol as yellow plates (0.103 g, 49%): mp 199–201°, ir ν_{max} (Nujol) 3240, 3105 (NH), 1700 (C=O), 1690 (C=O) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 6.58 (d, J = 6.9 Hz, 1 H), 6.8–8.17 (m, 15 H), 9.87 (s, br, 1 H, exchanges with D_2O), 10.47 (d, br, J = 6.9 Hz, 1 H, very slow exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 59.44, 127.41, 128.16, 128.81, 131.40, 133.72, 134.04, 136.31, 136.46, 141.97 152.16, 195.11, 202.17; mass spectrum *m/e* 374 (M^+), 340 (M^+ − H_2S), 269 (M^+ − PhCO), 253 (M^+ − PhCS), 163 (PhCSNCO).

Anal. Calcd for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.69; H, 4.90; N, 7.36.

Hydrolysis of cycloadduct (5b) (0.200 g, 0.68 mmol) with 1 *M* HCl gave the urea **6b** (0.195 g, 92%): mp 136–138°; ir ν_{max} (Nujol) 3240, 3145 (NH), 1702 (br, C=O) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 1.51 (d, J = 7.0 Hz, 3 H), 5.53 (m, J = 6.9 Hz, 7.0 Hz, 1 H), 7.12–8.16 (m, 10 H), 10.39 (s, br, 1 H, exchanges with D_2O), 10.78 (d, br, J = 6.9 Hz, 1 H, very slow exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 19.31, 51.89, 127.14, 128.49, 128.76, 130.59, 132.05, 133.88, 142.24, 153.63, 197.86, 201.15; mass spectrum *m/e* 312 (M^+), 278 (M^+ − H_2S), 207 (M^+ − PhCO), 191 (M^+ − PhCS), 163 (PhCSNCO).

Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.21; H, 5.21; N, 8.60.

Reaction of 3-Methyl-2-phenyl-1-azirine (4b) with Benzoyl Isocyanate (1). To a solution of 0.588 g (4 mmol) of benzoyl isocyanate in 5 ml of benzene was added 0.524 g (4 mmol) of the azirine (**4b**) in 5 ml of benzene. The reaction mixture was stirred at 25° for 20 hr and then chromatographed on a silica gel column using 50% ether–pentane as the eluting solvent for the product. The cycloadduct (**9b**) crystallized from ether–pentane as white needles (0.510 g, 45.5%): mp 111–113°; ir ν_{max} (Nujol) 1730 (C=O), 1610 (C=N) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 1.17 (d, J = 5.8 Hz, 3 H), 3.16 (q, J = 5.8 Hz, 1 H), 7.22–8.25 (m, 10 H); ^{13}C nmr δ_{TMS} ($CDCl_3$) 13.59, 44.45, 78.86, 127.14, 128.65, 129.19, 129.52, 129.73, 132.32, 134.48, 163.39, 167.17; mass spectrum *m/e* 147 (PhCONCO), 131 (azirine), 105 (PhCO), 103 (PhCN).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.06. Found: C, 73.07; H, 4.98; N, 10.21.

Reaction of 2-Phenyl-1-azirine (4c) with Benzoyl Isocyanate (1). The azirine (**4c**) (0.588 g, 4 mmol) was treated with 1 in benzene at 25° for 7 hr. Subsequent column chromatography resulted in hydrolysis of the cycloadduct **9c** to the urea **10c**. The urea **10c** was eluted from the column with CH_2Cl_2 and crystallized from ethanol as white needles (0.467 g, 40%): mp 146–147°; ν_{max} (Nujol) 3250 (NH), 1710 (C=O), 1690 (C=O), 1545 (amide II band); ^1H nmr δ_{TMS} ($CDCl_3$) 4.82 (d, J = 5.0 Hz, 2H), 7.16–8.18 (m, 10 H), 9.59 (d, br, J = 5.0 Hz, 1 H, very slow exchange with D_2O), 11.24 (s, br, 1 H, rapid D_2O exchange); mass spectrum *m/e* 282 (M^+), 177 (M^+ − PhCO), 147 (PhCONCO), 121 ($PhCONH_2$), 105 (PhCO).

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.43; H, 5.13; N, 10.09.

Reaction of 2,3-diphenyl-1-azirine (4a) with benzoyl isocyanate (1) was carried out as described above using 0.588 g (4 mmol) of **1** and 0.772 g (4 mmol) of **4a**. The adduct **9a** crystallized from ether–pentane as white needles (0.082 g, 6%): mp 133–134°; ir ν_{max} (Nujol) 1730 (C=O), 1565 (C=N) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 4.23 (s, 1 H), 7.05–8.24 (m, 15 H); mass spectrum *m/e* 193 (azirine), 147 (PhCONCO), 105 (PhCO), 103 (PhCN).

Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.71; N, 8.23. Found: C, 77.50; H, 4.64; N, 8.11.

Hydrolysis of the Cycloadduct 9b. A suspension of **9b** in 10 ml of 1 *M* HCl was stirred at 25° for 18 hr. The white precipitate that resulted was filtered off, washed with water, and recrystallized from ethanol to give white needles (0.183 g, 86%): mp 137–138°; ir ν_{max} (Nujol) 3270, 3140 (NH), 1710 (C=O), 1680 (C=O), 1550 (amide II); ^1H nmr δ_{TMS} ($CDCl_3$) 1.53 (d, J = 6.9 Hz, 3 H), 5.54 (m, J = 6.9 Hz, 7.0 Hz, 1 H), 7.16–8.20 (m, 10 H), 9.63 (d, br, J = 7.0 Hz, 1 H, very slow exchange with D_2O), 10.08 (s, br, 1 H, rapid exchange with D_2O); mass spectrum *m/e* 296 (M^+), 191 (M^+ − PhCO), 147 (PhCONCO), 121 ($PhCONH_2$), 105 (PhCO).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.57; H, 5.41; N, 9.48.

Thermolysis of Cycloadduct 9b. A solution of 0.278 g (1 mmol) of **9b** in 10 ml of toluene was heated under reflux for 2 hr and then separated on a silica gel column. Azirine (**4b**) (0.115 g) was eluted with 50% ether–pentane and benzamide (0.105 g) was eluted with 10% methanol–dichloromethane.

Kinetic measurements for the thermal decomposition of **9b** were done with a 0.572 *M* solution in *dry* $CDCl_3$ at 70° in a sealed (under N_2) nmr tube. The decomposition rate was followed by ^1H nmr. Careful and repeated integrations were done on the methyl groups of **9b** and **4b** (δ 1.17 and 1.36) and an internal cross-check with the aziridine proton of **9b** and the C-3 proton of **4b** (δ 3.19 and 2.28) was also done. These results are shown in Table I.

Reaction of 2,3-Diphenyl-1-azirine (4a) with Benzoyl Isothiocyanate (3). To a solution of 0.489 g (3 mmol) of benzoyl isothiocyanate (**3**) in 10 ml of benzene was added 0.386 g (2 mmol) of 2,3-diphenyl-1-azirine (**4a**) in 5 ml of benzene and the reaction mixture was heated under reflux for 12 hr. The solvent was removed and the residue was chromatographed on preparative plates carrying silica gel PF_{254} with 50% ether–pentane as the developing solvent. The cycloadduct (**12a**) crystallized from ether–pentane as white needles (0.483 g, 67.5%): mp 143–144°; ir ν_{max} (Nujol) 3270 (NH), 1675 (C=O), 1550 (amide II) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 6.85–7.95 (m, 15 H), 11.15 (s, br, 1 H, rapid exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 127.25, 127.57, 128.22, 128.76, 129.51, 131.83, 132.05, 132.54, 134.37, 144.51, 157.46, 165.33; mass spectrum *m/e* 356 (M^+), 328, 210, 192, 178, 165, 121, 105.

Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13; H, 4.52; N, 7.86. Found: C, 74.15; H. 4.64; N, 8.03.

Reaction of 3-Methyl-2-phenyl-1-azirine (4b) with Benzoyl Isothiocyanate (3). The cycloaddition was carried out as described above to give **12b** in 65% conversion as white needles: mp 138–139.5°; ir ν_{max} (Nujol) 3170 (NH), 1680 (C=O), 1545 (amide II) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 1.97 (s, 3 H), 7.24–8.10 (m, 10 H), 12.01 (s, br, 1 H, rapid exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 15.27, 126.28, 127.52, 128.17, 128.81, 129.03, 132.27, 132.80, 141.87, 157.62, 165.98; mass spectrum *m/e* 294 (M^+), 266, 191, 148, 121, 116.

Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.35; H, 5.08; N, 9.34.

Reaction of 2-phenyl-1-azirine (4c) with benzoyl isothiocyanate (3) was carried out as described above but for 48 hr at 25°. The adduct **12c** was obtained in 15% yield as pale yellow needles: mp 212–213°; ir ν_{max} (Nujol) 3165 (NH), 1685 (C=O), 1570 (amide II) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 7.08 (s, 1 H), 7.21–8.15 (m, 10 H), 12.75 (s, br, 1 H, rapid exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 126.12, 127.90, 128.33, 128.87, 129.14, 136.67, 132.80, 133.02, 143.60, 159.51, 166.03; mass spectrum *m/e* 280 (M^+), 252, 134, 121, 105.

Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.32; N, 9.99. Found: C, 68.64; H, 4.63; N, 9.78.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We are indebted to the National Science Foundation for providing funds toward the purchase of a Pulse Fourier Transform nmr spectrometer.

Registry No.—**1,** 4461-33-0; **2,** 3553-61-5; **3,** 532-55-8; **4a,** 16483-98-0; **4b,** 16205-14-4; **4c,** 7654-06-0; **5a,** 52920-29-3; **5b,** 52977-07-8; **5c,** 52920-30-6; **6a,** 52920-31-7; **6b,** 52920-32-8; **6c,** 52920-33-9; **7a,** 52920-34-0; **8a,** 52920-35-1; **9a,** 52920-36-2; **9b,** 52920-37-3; **10b,** 52920-38-4; **10c,** 52920-39-5; **12a,** 52920-40-8; **12b,** 52920-41-9; **12c,** 52920-42-0.

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Di(2-*tert*-butylphenyl) Phosphorochloridate. A New Selective Phosphorylating Agent[1]

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Received April 2, 1974

A procedure for the preparation of 5′-nucleotides is described. 5′-Phosphates of adenosine, cytidine, uridine, guanosine, and thymidine were prepared directly from unprotected nucleosides in good yields by two-step synthesis using a new selective phosphorylating agent, di(2-*tert*-butylphenyl) phosphorochloridate (**1d**). The agent is stable, versatile, and highly selective for a primary hydroxyl in the presence of unprotected secondary hydroxy groups. The *tert*-butylphenyl protective groups are quite resistant toward dilute base and acid hydrolysis and are easily removed by hydrogenolysis in a nearly quantitative yield.

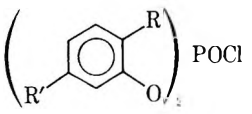
The polyfunctional nature and unique properties of nucleosides and carbohydrates present a considerable problem as to the choice of protective groups to achieve selectivity in phosphorylations. Recently, attention has been focused on the preparation of 5′-phosphates of various natural and synthetic compounds using selective phosphorylating agents.[2] A new phosphorylating agent has been explored, possessing the following properties: (a) ease of preparation, (b) relatively stable, (c) selective for the primary hydroxyl in the presence of unprotected secondary hydroxyls, (d) protective groups are stable under dilute base or acid conditions, and (e) protective groups are easily removable by hydrogenolysis.

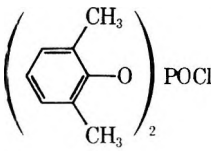
This reagent does not offer any advantage over the phosphoryl chloride–triethyl phosphate procedure for the direct synthesis of 5′-mononucleotides.[2b] However, the presence of an acid and base stable protected 5′-phosphate group allows for further chemical modification of a nucleotide derivative prior to removal of the protective groups by hydrogenolysis.

Results and Discussion

Considering properties of phosphorylating agents studied previously,[2] and the spatial arrangement of various furanosides and pyranosides, it is reasonable to assume that steric hindrance can facilitate selective phosphorylation of the nucleoside primary hydroxy group in the presence of unprotected secondary hydroxy groups. In an effort to investigate this premise we synthesized phenolic esters of phosphate (**1a–f**) as potentially selective phosphorylating agents.

Phosphorochloridates **1a**, **1b**, **1c**, and **1d** were synthe-





1f

1a, R = H; R′ = H
b, R = ethyl; R′ = H
c, R = isopropyl; R′ = H
d, R = *tert*-butyl; R′ = H
e, R = *tert*-butyl; R′ = CH_3

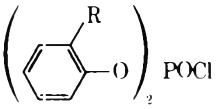
sized by a slightly modified procedure for preparation of diphenyl phosphorochloridate.[3] Although the reaction time was increased the yields were similar to that of diphenyl phosphorochloridate, ranging between 40 and 60%. The isolation of products was based upon removal of the low boiling fraction (unreacted alkylphenol and $POCl_3$) and alkylphenyl phosphorodichloridate. The residue was usually analytically pure dialkylphenyl phosphorochloridate. No further purification was performed because of the high hygroscopicity of product; the corresponding amides were prepared for analytical purposes. Structure assignments were based on nmr and mass spectrometry. Loss of the *tert*-butyl group was observed during the attempted preparation of **1e**, most probably by a retro Friedel–Crafts reaction. A significant amount of *tert*-butyl chloride from reaction of isobutylene with hydrogen chloride generated in the reaction was isolated from the carrier gas (N_2). An attempt to prepare **1f** was unsuccessful; the presence of two methyl groups adjacent to phenolic OH apparently presents a severe steric problem. Loss of the *tert*-butyl group also was observed from di(2-*tert*-butylphenyl) phosphorochloridate (**1d**) after prolonged heating at 160°.

The di(alkylphenyl) phosphorochloridates **1a**, **1b**, **1c**, and **1d** were found to phosphorylate thymidine in pyridine in reasonable yields, ranging between 50 and 75%. The phosphorylation was found to be relatively insensitive to temperature. Although yields of phosphorylated thymidine were highest when the reaction was performed at 0° followed by overnight stirring at room temperature, the yields of reactions at 40 and 70° were only slightly lower. The isolation and purification of products was limited to evaporation and extraction of a chloroform solution of the residue with water, saturated aqueous $NaHCO_3$ removal of solvent, and solidifying the resulting semisolid by washing with ether. No further purification was performed and the products were hydrogenated as such. The alkylphenyl phosphates appear to be quite resistant toward mild alkaline and acidic hydrolysis; however, treatment under rather vigorous conditions (6 *N* NaOH, 4 *N* HCl) gave partial decomposition.

The hydrogenolysis failed to proceed in commonly used solvents such as methanol, ethanol, tetrahydrofuran, or ethyl acetate. However, reduction was rapid in glacial acetic acid, the product forming in nearly quantitative yields.

For analysis of the procedure using **1a–d** (Table I) the overall yields of thymidine phosphates were determined by the following procedure. After evaporation of pyridine, the entire residue was dissolved in glacial acetic acid and hydrogenated in the presence of catalyst. The catalyst was filtered, the solvent evaporated, and the residue washed several times with ether and lyophilyzed from a 2% ammonia water solution. This residue was analyzed by chromatographic resolution, elution of the ultraviolet absorbing spots, and ultraviolet analysis at 262 nm to determine the yield from the ratio thymidine phosphates: thymidine. The percentage of 5′-phosphate with respect to diphosphate and 3′-phosphate respectively was determined by incubation with snake venom 5′-nucleotidase according to standard procedures.[4] The selectivity of 5′-phosphate formation essentially decreased with decreasing bulk of substituent (Table I). Di(2-*tert*-butylphenyl) phosphorochloridate **1d** was found to phosphorylate solely at the 5′ position when used in equimolar quantities. Loss of specificity was observed when an excess of the reagent was used. The phosphates of uridine, cytidine, adenosine, and guanosine were prepared and examined in the manner similar to that of thymidine. Dimethylformamide was used as a cosolvent in order to solubilize guanosine, cytidine, and adenosine.

Table I
Yield and Selectivity of Phosphorylation Using Di(*o*-alkylphenyl) Phosphorochloridates



	R	Ratio[a]	Yield[b]	5′ product[c]
1a	H	1	57	89
1b	Ethyl	1	50	83
1c	Isopropyl	1	62	91
1d	*tert*-Butyl	1	75	100
1d	*tert*-Butyl	1.2	98	96
1d	*tert*-Butyl	1.5	> 100[d]	93[e]

[a] Molar ratio of phosphorochloridate to thymidine. [b] Yield of thymidine di(2-alkylphenyl) phosphates. [c] Calculated as per cent of total thymidine phosphate found. [d] Some diphosphorylated product was found. [e] The remaining 7% is probably a mixture of 3′-mono- and 3′,5′-disubstituted thymidine.

The hydrogenation of purine nucleotides proceeded well without serious side reactions. The situation is more complex in the case of pyrimidines. Hydrogenation of pyrimidines has been studied extensively. Brown and Johnson[5] observed that reduction of the 5,6 double bond of uracil can be effected by colloidal platinum or palladium and 5,6-dihydrouracil can be prepared by direct hydrogenation of uracil in acidic media. Similarly the nuclear reduction of pyrimidines is effected by palladium on charcoal or barium sulfate as well.[6] These authors also note that Adams catalyst seems to be less effective in mediating the nuclear reductions than corresponding palladium catalysts.[6] Cytosine can undergo extensive hydrogenolysis of the 4-amino group in addition to ring reduction reported for uracil.[7] The exocyclic reductions of pyrimidines can be performed with Adams catalyst under controlled reduction conditions. Using Adams catalyst, very little if any side reactions were reported using the preparation of uridine and cytidine phosphates.[8] This observation was confirmed in the hydrogenolysis of *tert*-butylphenyl protective groups which proceeded in preference to nuclear reduction during preparation of 5′-phosphates of uridine and cytidine. For example, quantitative chromatographic resolution on paper and ultraviolet analysis of the eluted uridine and uridine phosphate accounted for all of the starting material.

The yields of 5′-phosphates of adenosine, guanosine, cytidine, and uridine (54–63%) were determined by spectrophotometric comparison of absorbance of eluted spots corresponding to the nucleosides and nucleotides after electrophoresis of the reduction products. The eluted nucleotides were incubated with 5′-nucleotidase and aliquots examined by electrophoresis (Na_2HPO_4–NaOH buffer pH 12) and spectrophotometrically. No phosphates other than 5′ were detected. All synthetic phosphates were compared with an authentic sample of corresponding nucleotide on electrophoresis and paper chromatography.

Experimental Section

Nucleosides and nucleotides used as reagents or standards and 5′-nucleotidase from *Crotalus adamanteus* venon Grade II were purchased from Sigma Chemical Co., St. Louis, Mo. The former were checked for purity by paper chromatography before use. Descending paper chromatography was performed on Whatman No. 1 or 3MM paper using the solvent system 2-propanol:concentrated ammonia:water = 7:1:2. Paper electrophoresis was performed on a Brinkmann Pherograph type Mini 68 apparatus using Whatman No. 1 paper and 0.05 *M* phosphate buffer at pH 8 or 12. Ultraviolet spectra were recorded on Cary 14 spectrometer, absorbance values on a Beckmann DB spectrophotometer, and nmr on a Varian T60 spectrometer.

Di(alkylphenyl) Phosphorochloridates. The alkylphenol (1 mol) was mixed with $POCl_3$ (78 g, 0.5 mol) and heated at 150–160° for 16 hr under nitrogen. The mixture was distilled and forerun to 84° (0.4 mm) consisting of unreacted $POCl_3$, starting material, and alkylphenyl phosphorodichloridate discarded. The residue was used as such.

Di(2-ethylphenyl) phosphorochloridate (**1b**) was used as the distillation residue boiling over 66° (0.03 mm) yielding 45% of relatively pure product as judged from nmr data.

Di(2-isopropylphenyl) phosphorochloridate (**1c**) was obtained in 46% yield: mass spectrum, calcd mol wt 353.8, found 354.

Di(2-*tert*-butylphenyl) phosphorochloridate (**1d**) as the distillation residue (58% yield) was analytically pure: mass spectrum, calcd mol wt 380.8, found 381.

Anal. Calcd for $C_{20}H_{26}O_3PCl$: C, 63.15; H, 6.84. Found: C, 62.84; H, 6.99.

Di(alkylphenyl) Phosphoamidates. Dialkylphenyl phosphorochloridate (1.5 mmol) was dissolved in 40 ml of anhydrous ether and dry ammonia was bubbled through the solution. The white precipitate (NH_4Cl) was filtered. The ether solution was extracted with water and dried ($MgSO_4$). The white solid resulting from evaporation of solvent was recrystallized from ether and petroleum ether (1:4).

Diphenyl phosphoramidate was prepared in 94% yield (recrystallized from ether:petroleum ether), mp 144–145, long white needles.

Anal. Calcd for $C_{12}H_{12}PO_3N$: C, 57.83; H, 4.85; N, 5.62. Found: C, 57.92; H, 5.09; N. 5.62.

Di(2-ethylphenyl) phosphoramidate was prepared in 91% yield (recrystallized from ether:petroleum ether), mp 81.5–82°, long white needles.

Anal. Calcd for $C_{16}H_{20}PO_3N$: C, 62.94; H, 6.60; N, 4.95. Found: C, 62.68; H, 6.62; N. 4.84.

Di(2-isopropylphenyl) phosphoramidate was prepared in 96% yield mp 69.5°.

Anal. Calcd for $C_{18}H_{24}O_3PN$: C, 64.85; H, 7.26; N, 4.20. Found: C, 64.91; H, 7.24; N, 4.08.

Synthesis of Thymidine 5′-Phosphate. Di(2-*tert*-butylphenyl) phosphorochloridate (**1d**, 4 mmol) was dissolved in 25 ml of dry pyridine and 0.9 g of thymidine was (3.75 mmol) added. After stirring at 25° (0. 40, 70°, respectively) for 1 day the pyridine was removed *in vacuo* at 40°. The semisolid residue was dissolved in 70 ml of chloroform, washed with 30 ml of water, 20 ml of a saturated solution of sodium bicarbonate, and again with 30 ml of water, and the chloroform layer was dried. After evaporation, the residue (75% of theoretical) was dissolved in 40 ml of acetic acid and added to 100 ml of acetic acid containing prereduced platinum oxide (0.6 g). The mixture was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen was absorbed (8 equiv of H_2). The catalyst was filtered and the solvent evaporated *in vacuo* at 25°. The semisolid residue was washed several times with ether, dissolved in 30 ml of 2% ammonia solution, filtered, and lyophylized to afford the ammonium salt of thymidine 5′-phosphate in 70% overall yield: the product was identical with an authentic sample by paper chromatography and electrophoresis.

Anal. Calcd for $C_{10}H_{21}N_4O_8P \cdot 4H_2O$: C, 28.04; H, 6.82; N, 13.08. Found: C, 27.76; H, 6.40; N, 13.16.

Confirmation of the 5′-phosphate as the only isomer was by hydrolysis with snake venom 5′-nucleotidase.

This procedure was also used in the synthesis of thymidine 5′-phosphate using the other phosphorochloridates, and with similar yields; however, concurrent formation of some 3′-phosphate was observed (Table I).

Uridine 5′-phosphate was prepared by this procedure in 63% yield.

Guanosine 5′-Phosphate. Guanosine (250 mg, 0.85 mmol) was dissolved in 20 ml of dry pyridine, 12 ml of dry dimethylformamide was added, and the solution was acidified with acetic acid. After cooling to 0°, 380 mg of di(2-*tert*-butylphenyl) phosphorochloridate (1 mmol) was added and the mixture was stirred for a day at 25°. The sequence from this point was identical with that used in the synthesis of thymidine 5′-phosphate. A 55% yield of product was observed; it was identical with an authentic sample of guanosine 5′-phosphate in paper chromatography, electrophoresis, and to snake venom 5′-nucleotidase action.

Similarly, adenosine 5′-phosphate and cytidine 5′-phosphate were prepared in 62 and 53% yield, respectively.

Enzyme Hydrolysis. The enzyme used was the 5′-nucleotidase Grade II from *Crotalus adamanteus* venom with activity of 15–20 μmol of adenosine 5′-phosphate hydrolyzed per minute per milligram of enzyme. The assay, at pH 8.5, contained 0.2 ml of 1 *M* glycine–NaOH buffer, 0.2 ml of 0.1 *M* $MgCl_2$, 0.16 mg of enzyme, and about 15 μM of nucleotide in a total volume of 0.5 ml. After 30 min at 37° the mixture was resolved by electrophoresis and the spots corresponding to the nucleoside and remaining nucleotide were eluted with 10 ml of water and the ratio calculated from the ultraviolet absorbance.

Registry No.—**1a**, 2524,64-3; **1b**, 52555-40-5; **1c**, 52555-41-6; **1d**, 52555-42-7; $POCl_3$, 10025-87-3; 2-ethylphenol, 90-00-6; 2-isopropylphenol, 88-69-7; 2-*tert*-butylphenol, 88-18-6; diphenyl phosphoramidate, 2015-56-7; di(2-ethylphenyl) phosphoramidate, 52555-43-8; di(2-isopropylphenyj)phosphoramidate, 52555-44-9; thymidine, 50-89-5; thymidine 5′-phosphate ammonium salt, 20706-32-5.

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Reaction Pathways in Nucleophilic Displacements with 1-Benzyl-Δ^2-tetrazoline-5-thione and 1,2,3,4-Thiatriazoline-5-thione

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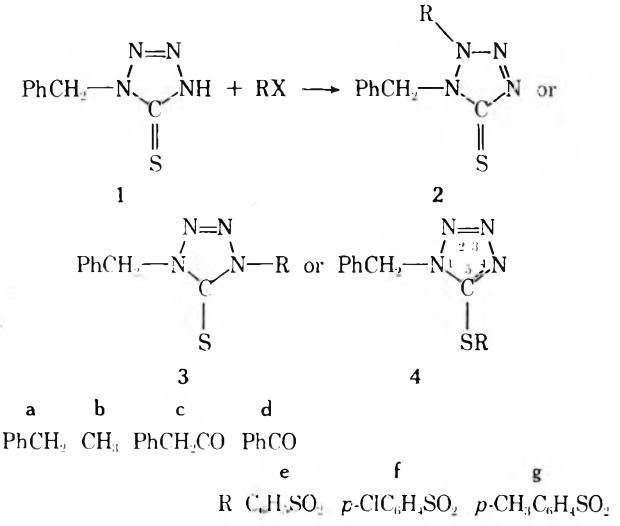
Received June 24, 1974

1-Benzyl-Δ^2-tetrazoline-5-thione (1) reacted with benzyl chloride, methyl iodide, benzoyl chloride, and arylsulfonyl chlorides to give S derivatives (4). Phenylacetyl chloride, on the contrary, furnished the N derivative **3c**. Structure elucidation was based on ^1H and ^{13}C nmr analysis and confirmed by ir in the cases of the acyl derivatives. The structure of the benzoylated product of sodium thiatriazolinethiolate, formulated by Lieber, *et al.*, as the N product **6c**, was reinvestigated by ^{13}C nmr spectroscopy and found to be the S product **7c** in agreement with the findings of Christophersen and Holm.

1-Benzyl-Δ^2-tetrazoline-5-thione (1), prepared from benzyl isothiocyanate and sodium azide,[1] is an ambident nucleophile, and substitution could lead to products **2, 3, or 4.** In fact, treatment of **1** with benzyl chloride, methyl iodide, phenylacetyl chloride, benzoyl chloride, and three different arylsulfonyl chlorides gave a single crystalline product in good yield in each case (see Table I). If substitution occurred at nitrogen, the more stable thiourea structure **3** would be favored over its azo homolog **2** in analogy with other systems.[2]



Although the structure of the alkylated product can be elucidated by ^1H nmr spectroscopy in some favorable cases (see below), we wanted to have at hand more general criteria based on the ^{13}C chemical shifts of the functional groups C=S and C=N occurring in structures **3** and **4.** Since it is well known that the carbonyl carbon atoms absorb over a wide range (*ca.* 40 ppm) in the ^{13}C nmr spectra depending on substituents,[3] we may expect the same situation for the C=S and C=N carbon atoms. To locate their absorptions in our cases, we have therefore utilized model compounds whose structures are unambigously settled by ^1H nmr analysis.

The starting material **1** showed in the ^1H nmr spectrum a broad absorption at δ 14.5 ppm (exchangeable with D_2O) which is indicative of an NH function rather than an SH function (structure **4**, R = H).[4] This is in agreement with the ir findings of Lieber, *et al.*,[5] for the solid state structure of other 1-substituted-Δ^2-tetrazoline-5-thiones. The formulation of Jensen and Pedersen[6] that these compounds have the tetrazole-5-thiol structure is incorrect. The C=S carbon absorption of **1** in the ^{13}C nmr spectrum ($CDCl_3$) was found at δ 164.4 while the methylene carbon absorbed at δ 50.9 ppm.

Treatment of **1** with benzyl chloride did not give the symmetrical structure **3a,** since the ^1H nmr spectrum exhibited two different methylene absorptions at δ 4.50 and 5.30 ppm. The ^{13}C spectrum showed, *inter alia,* an absorption peak at δ 153.9 ppm attributable to the C=N carbon atom of structure **4a.** This shift value is in good agreement with that reported by Weigert and Roberts[7] for the unsubstituted tetrazole (DMSO-d_6, δ 144 ppm), when the expected substituent effects are taken into account. Further evidence for this assignment is provided by the methylated product which exhibited carbon resonances at δ 155.1 (C=N), 51.1 (CH_2N), and 15.4 ppm (CH_3S). The 15.4-ppm peak cannot be attributed to a CH_3N carbon atom which is known to absorb at lower field (δ >20 ppm).[8] On the basis of these considerations we are able to reject structures **2** and **3** for the alkylated products studied in this work.

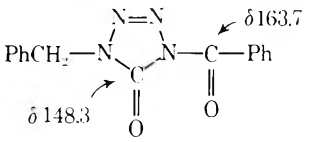
An inspection of the substituted products presented in Table I discloses that N substitution only occurred in one case, namely with phenylacetyl chloride. Indeed, product **3c** showed typical ^{13}C resonances at δ 164.7 (C=S) and

Table I
Reaction Products of 1 with Alkyl Halides, Acyl Chlorides, and Arylsulfonyl Chlorides

No.	R	Yield, %	Mp, °C	^1H nmr (δ values)[a,b]	^{13}C nmr (δ values in ppm from TMS)[b] C$_5$	PhCH$_2$N	Other shift values
4a	$PhCH_2$	99	62.5–63.5	4.50 (s, 2 H, CH_2S), 5.30 (s, 2 H, CH_2N)	153.9	51.1	$PhCH_2S$ at 38.1
4b	CH_3	88	37–38	2.73 (s, 3 H) 5.38 (s, 2 H)	155.1	51.1	CH_3S at 15.4
3c	$PhCH_2CO$	99	63–66	4.44 (s, 2 H, CH_2CO), 5.40 (s, 2 H, CH_2N)	164.7	50.8	$PhCH_2CON$ at 41.2 and 177.9
4d	PhCO	98	99–101	5.56 (s, 2 H)	146.4	52.3	PhCOS at 184.4
4e	$C_6H_5SO_2$	52	85–86	5.76 (s, 2 H)	146.65	52.5	
4f	p-$ClC_6H_4SO_2$	50	113.5–114.5	5.75 (s, 2 H)	146.5	52.6	
4g	p-$CH_3C_6H_4SO_2$	79	125.5–126.5	2.45 (s, 3 H), 5.73 (s, 2 H)	146.8	52.5	

[a] The aromatic proton absorptions are omitted. [b] All the spectra were recorded in $CDCl_3$.

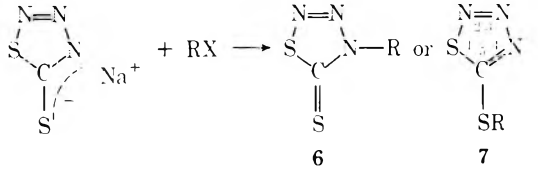
177.9 ppm (CON). The ir spectrum also confirms structure **3c**, showing a high C=O stretching absorption at 1770 cm^{-1} which is typical for azolides.[9] The benzoylated product, on the contrary, has structure **4d** as evidenced by the ^{13}C absorptions at δ 146.4 (C=N) and 184.4 (COS), in addition to the ir C=O thio ester vibration at 1705 cm^{-1} in the ir spectrum.[10] If benzoylation should have occurred at nitrogen, a carbonyl carbon absorption at about δ 165 ppm would be expected in analogy with that found for 1-benzyl-4-benzoyltetrazolin-5-one (**5**). This compound has been prepared in our laboratory[11] from 1-benzyl-4*H*-tetrazolin-5-one and benzoyl chloride (see Experimental Section).



5 (^{13}C nmr taken in C_6D_6)

The data listed in Table I also indicate that the reactions of **1** with arylsulfonyl chlorides have led to thiosulfonic esters **4e–g**. Indeed, the ^{13}C spectra were devoid of C=S peaks at about δ 165 but, instead, showed typical C=N peaks at δ 146–147 ppm.[12]

In view of these results, we are now in a position to reconsider by ^{13}C nmr spectroscopy the structure of the benzoylated product of sodium thiatriazolinethiolate. Lieber, *et al.*,[13] formulated this product as the *N*-benzoyl derivative **6c** because it decomposed to give benzoyl isothiocyanate instead of benzoyl thiocyanate which would result from **7c**. Jensen and Pedersen,[6] however, challenged the value of this argument, stating that an acyl thiocyanate is highly unstable and would easily rearrange to the corresponding acyl isothiocyanate during the degradation experiment. Christophersen and Holm[14] then investigated the thermal decomposition of the benzoylated product by ir techniques and reported the successive appearance and disappearance of an absorption peak at 2170 cm^{-1} which they attributed to the unstable benzoyl thiocyanate. This observation strongly suggests that the starting product would have structure **7c** instead of **6c**.



6 **7**

a b c

R $PhCH_2$ $PhCOCH_2$ PhCO

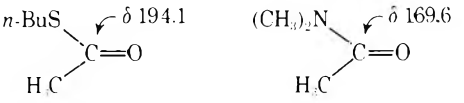
To solve the structure of the benzoylated product by ^{13}C nmr spectroscopy, we have prepared as a model compound for this series the benzyl derivative **7a**, whose structure was previously[13] proven by an unequivocal synthesis starting from benzyl dithiocarbazate ($PhCH_2SCSNHNH_2$) and nitrous acid. In analogy with structure **4a** this compound showed a CH_2S carbon absorption at δ 39.5 ppm. The C=N carbon resonance, however, was shifted to lower field (δ 179.8 ppm) compared with **4a**, due to a modification of the ring structure. Phenacyl chloride also furnished the S derivative **7b** as shown by the ^{13}C nmr values recorded in Table II.

Structure **6c**, formulated by Lieber, *et al.*,[13] for the benzoylated derivative of sodium thiatriazolinethiolate, is now decisively eliminated in favor of **7c** on the basis of ^{13}C nmr analysis. Indeed, the product showed a C=N absorption peak at δ 171.5 in addition to a COS absorption at 185.2 ppm which is comparable with that found for compound **4d**. The ir (KBr) C=O stretching vibration at 1670 cm^{-1} also points to this conclusion.

Table II
^{13}C Nmr Data ($CDCl_3$, δ Values) of the Substitution Products of Sodium Thiatriazolinethiolate

No.	R	C_5	Other shift values
7a	$PhCH_2$	179.8	$PhCH_2S$ at 39.5
7b	$PhCOCH_2$	179	$PhCOCH_2S$ at 191.9 and 43.5
7c	PhCO	171.5	PhCOS at 185.2

From the viewpoint of ^{13}C nmr spectroscopy, it is interesting to note the large difference in C=N shift values ($\Delta\delta$ = 25 ppm) between tetrazoles (δ 145–155) and thiatriazoles (δ 170–180), caused by a change of heteroatom (S *vs.* N) attached to the C=N carbon. This is not unexpected since the C=O carbon absorption undergoes a shift of the same magnitude ($\Delta\delta$ = 22–25 ppm) when a sulfur substituent is replaced by a nitrogen substituent as illustrated below with *n*-butyl thioacetate and *N,N*-dimethylacetamide.[15]



Experimental Section

The ir spectra were taken on a Perkin-Elmer Model 521 spectrometer. Proton nmr spectra were recorded with a Varian A-60 or XL-100 spectrometer using TMS as an internal reference. For ^{13}C nmr spectra, the XL-100 apparatus was equipped with a device for pulsed Fourier transform operation.

The thiatriazole derivatives **7a–c** were prepared as described earlier.[13] 1-Benzyl-Δ^2-tetrazoline-5-thione (**1**), mp 143.5–144° ($CHCl_3$–pentane), was prepared in 47% yield by the procedure of Lieber and Ramachandran.[1]

Substitution Products of 1. These were obtained by combining equimolar amounts (0.01 mol) of **1**, triethylamine, and the electrophilic reagent in ether (50 ml) at reflux temperature for the appropriate reaction time (19 hr for benzyl chloride, 6 hr for methyl iodide and acyl chlorides, and 24 hr for arylsulfonyl chlorides). The precipitated NEt_3·HX was removed by filtration and the filtrates were evaporated partially or completely to give crude products which were crystallized from the appropriate solvents. In the case of **4b**, the ether solution of the crude product was first washed several times with a 5% solution of sodium thiosulfate and dried before allowing it to crystallize at low temperature. In the experiments with arylsulfonyl chlorides, the thiosulfonic esters **4e–f** partially precipitated together with NEt_3·HCl. They were dissolved by adding 100 ml of benzene with stirring prior to isolation of the salt. [Satisfactory analytical data (*m/e* for $M^{\cdot+}$ ±0.002 for **4a,b,d,e** and **3c**; ±0.3% for C, H, N for **4f** and **4g**) have been obtained for the new compounds (Editor).]

Synthesis of 1-Benzyl-4-benzoyltetrazolin-5-one (5). Equimolar amounts (0.02 mol) of benzyl azide and tosyl isocyanate were heated at 90° for 24 hr in the absence of solvent. The reaction mixture was dissolved in CH_2Cl_2 and cooled to give 1-benzyl-4-tosyltetrazolin-5-one in 80% yield; mp 115–117°; ir (KBr) 1760 cm^{-1}. This compound was hydrolyzed in methanol at reflux temperature for 4 days. After removal of the solvent, the crude mixture was crystallized from CH_2Cl_2 to give 1-benzyl-4-*H*-tetrazolin-5-one in 90% yield; mp 136–139°; ir (KBr) 1680–1720 cm^{-1}. This compound (0.01 mol) was dissolved in ether (60 ml) and treated with equimolar amounts of NEt_3 and benzoyl chloride at reflux temperature for 2 hr. The precipitated salt was removed by filtration and the mother liquor was allowed to cool. 1-Benzyl-4-benzoyltetrazolin-5-one (**5**) was thus obtained in 60% yield; mp 92–93°; ir (KBr) 1770 cm^{-1}.

Registry No.—**1**, 33898-72-5; **3c**, 53078-72-1; **4a**, 53078-73-2; **4b**, 53078-74-3; **4d**, 53078-75-4; **4e**, 53078-76-5; **4f**, 53078-77-6; **4g**, 53078-78-7; **5**, 53078-79-8; **7a**, 34930-32-0; **7b**, 53078-80-1; **7c**, 33125-49-4; benzyl chloride, 100-44-7; methyl iodide, 74-88-4; phenylacetyl chloride, 103-80-0; benzoyl chloride, 98-88-4; benzenesulfonyl chloride, 98-09-9; *p*-chlorobenzenesulfonyl chloride, 98-60-2; *p*-methylbenzenesulfonyl chloride, 98-59-9; phenacyl chloride, 532-27-4; sodium thiatriazolinethiolate, 53129-36-5.

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Synthesis of *endo*- and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-Cinnamates

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Received June 10, 1974

The synthesis and separation of *endo*- and *exo*-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-cinnamates *via* 5-(1-keto-2-hydroxyethyl)bicyclo[2.2.1]hept-2-enes are described. The imidazolyl derivatives have a rigid bicyclo[2.2.1]heptane structure; the endo compound was synthesized as a model for α-chymotrypsin and the exo compound was synthesized for purposes of comparison. The mode of 2,5 disubstitution of bicyclo[2.2.1]heptane was determined by a double resonance experiment using nmr.

Enzyme model studies are becoming increasingly important because of interest in enzyme mechanism and the design of synthetic catalysts with enzyme-like activity. However, a difficult problem has been the synthesis of model compounds that can mimic enzyme structure or mechanism, or both. The X-ray structure of α-chymotrypsin has been determined, indicating the spatial alignment of the important functionalities at the active site.[2] Enzyme mechanistic studies have clarified the roles of the functional groups, especially those of the histidine imidazolyl and serine hydroxyl groups in terms of organic reaction mechanisms.[3] Therefore, α-chymotrypsin could be the first enzyme whose catalytic efficiency can be approximated by a synthetic model.

We have approached the synthesis of an enzyme model which has a rigid structure with the correct spatial alignment of the imidazolyl and hydroxyl groups as in α-chymotrypsin (approximately 3 nm from one another). For this purpose we have chosen the bicyclo[2.2.1]heptane ring system as the framework that bears the two functional groups, because its internal free rotations are frozen and its endo-2-, endo-5-disubstituted structure assumes the alignment indicated above. With chymotrypsin, the reaction proceeds in two steps: an acylation of the enzyme on the serine hydroxyl group and a deacylation of the acyl enzyme, an ester.

In this report we describe the synthesis of the titled model compounds which simulate an acyl enzyme in the correct (endo) and incorrect (exo) stereochemistries. In another paper we will report their catalytic effectiveness. *trans*-Cinnamates were used because they are more readily available and have been used before.[3] The endo compound, as expected, was considerably faster than the exo compound, although the former does not have the reactivity of the cinnamoyl enzyme.

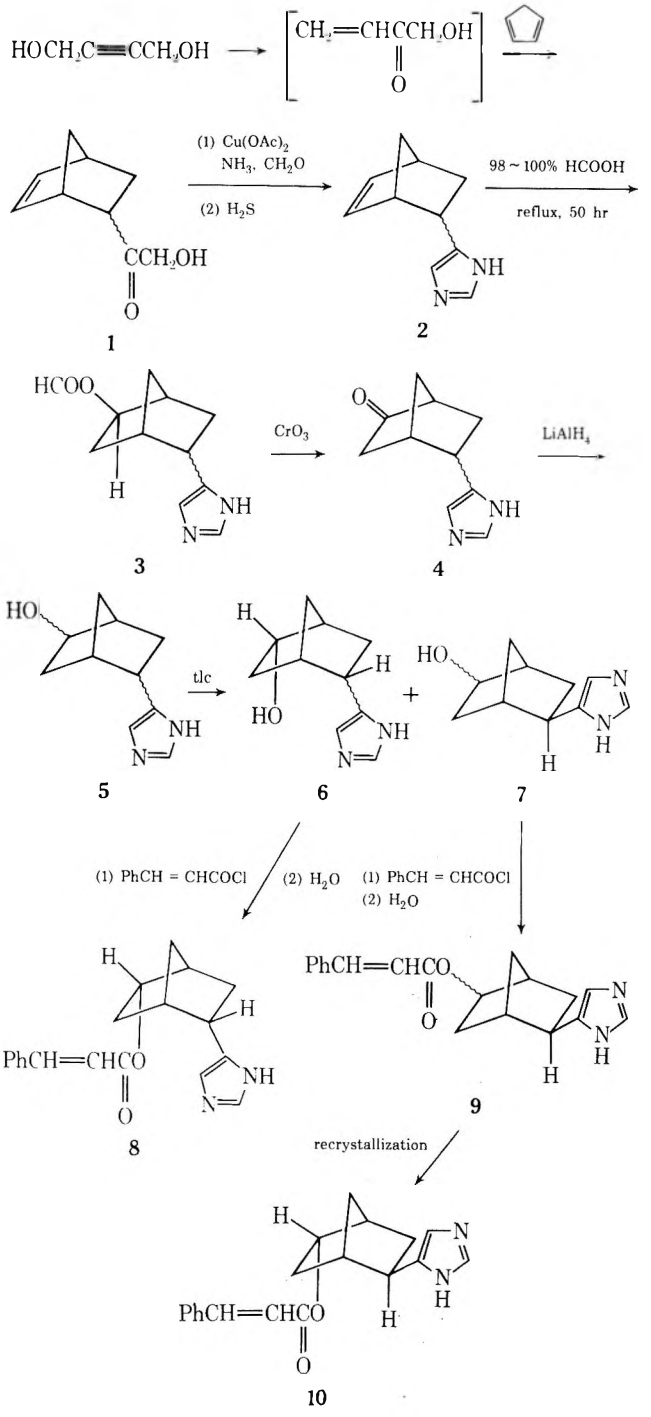
Results and Discussion

Hitherto, only one report concerning cyclic imidazole derivatives has appeared, namely the synthesis of 2- and 3-keto-*endo*-5-(2-imidazolyl)bicyclo[2.2.2]octane.[4a] The synthetic method used for this compound, however, cannot be applied to the present enzyme model, because it does not afford 4(5)-imidazolyl derivatives.

Our synthetic route is shown in Scheme I. At an early stage of this work, the methyl ketone was more easily available and stable than the corresponding hydroxymethyl ketone **1** and was tried as a precursor for the imidazole derivative **2**. But oxidation with selenium dioxide failed to give the glyoxal, which could be converted to **2**. The intermediate hydroxymethyl vinyl ketone is so easily polymerizable[4b] that it was allowed to react with cyclopentadiene without distillation from the reaction mixture, giving the crude Diels–Alder adduct **1** in 18% yield. Since this yield was nearly that reported by Reppe and coworkers for the hydroxymethyl ketone from 2-butyne-1,4-diol,[4b] the Diels–Alder reaction probably proceeded almost quantitatively.

For the determination of the endo:exo ratio, ketone **1** was fractionally distilled through a spinning band column, giving fractions of nearly 100% endo ketone and 85% exo ketone. The nmr spectrum of the endo ketone was consistent with that of methyl *endo*-2-norbornyl ketone.[5] In the spectrum of the exo ketone, a signal with four main peaks appeared at higher field than that of the exo C-5 proton ($\Delta\delta$ = 0.6) and was assigned to the endo C-5 proton.[5] Another important change was seen in the pattern of the olefinic protons. In the endo ketone they appeared as two symmetrical doublets centered at δ 6.16 and 5.81, but in the exo ketone the signal at higher field was diminished and was seen at lower field. Since this difference was adequate for quantitative treatment, this was used for determination of the

Scheme I



endo:exo ratio of the ketone. Separation of the endo and exo ketones on a preparative scale was not preferable at this stage, because endo–exo isomerization took place in subsequent reactions.

Imidazole formation was achieved in good yield (60–70%) according to the method of Weidenhagen.[6] However, this reaction was found to be accompanied by endo–exo isomerization.

When 10 g of the 100% endo ketone was heated to 70–80° with cupric acetate, ammonia water, and formalin, the slightly green cuprous salt began to precipitate in 3 min and after 10 min it was collected by filtration. The filtrate was heated again for 1 hr, and the precipitate was collected. As Table I shows, it is probable that there exists a base-catalyzed equilibration between the endo and exo ketones in basic solution since the longer the ketone is in contact with the basic solution, the higher the exo content of the imidazole derivative.

Table I
Endo:Exo Ratios of *endo*- and *exo*-[4(5)Imidazolyl]bicyclo[2.2.1]hept-2-enes

Starting ketone	Time, min	Endo:Exo **2**
100% endo	10	93:7
100% endo	60	82:18
85% exo	60	26:74
77:23 mixture of endo and exo	60	75:25

The endo:exo ratios of the imidazole derivative **2** were determined by the same method that was used for the ketone **1**, since the signals of the olefinic protons in the nmr spectra of **2** were very similar to those of the ketone.

The imidazole ring C-4(5) proton of **2** was assigned to two somewhat broad singlets at δ 6.83 and 6.63. The former corresponded to the *endo*-imidazole derivative in conjunction with the signal of the exo C-5 proton at δ 3.37 and the latter to the *exo*-imidazole derivative, which had the endo C-5 proton at δ 2.68. The imidazole ring C-2 proton appeared at δ 7.53 and 7.58, corresponding to the endo and exo isomers, respectively. The difference in this case ($\Delta\delta$ = 0.05) was quite small compared with that of the C-4(5) proton ($\Delta\delta$ = 0.20).

Purification of the imidazole derivative **2** proved difficult. Crystallization from hot water or as the picrate or hydrochloride failed to give crystals. Thin layer chromatography using basic alumina or silica gel did not remove the impurity.

After these trials, the number of the olefinic protons relative to the others was found to decrease as indicated by nmr, suggesting the occurrence of polymerization. Therefore, the crude imidazole derivative **2** was used for the next step.

Introduction of a functional group which could be converted to an *endo*-hydroxyl group at the 2 or 3 position of the bicyclic skeleton was tried in various ways. Hydroboration and oxymercuration were unworkable. Palladium chloride oxidation[4a] gave the corresponding ketone in poor yield and thus was unfavorable for synthetic purposes. However, 98–100% formic acid proved excellent. By refluxing in excess formic acid for 50–55 hr, the unsaturated imidazole derivative **2** was converted to the corresponding formate **3** in 80–90% yield, although it required longer reaction time than the 2–3 hr in the case of norbornene.[7] During this reaction period, endo–exo isomerization of the imidazolyl group occurred, a 75:25 mixture of the *endo*- and *exo*-imidazoles **2** being changed to a 60–70:40–30 mixture of the *endo*- and *exo*-imidazoles **3**. The formoxy group was exclusively exo. This stereochemistry was determined by nmr using the signals of the protons attached at the imidazolyl and formoxy carbons. It was not possible to determine whether the formoxy group was introduced at C-2 or C-3 from nmr. But the rather sharp singlet of the formyl proton at δ 7.97 suggested that the group was introduced only at either of the two carbons. The location of the formoxy group at C-2 was firmly deduced from compound **8**.

Oxidation of the crude formic ester **3** to the corresponding ketone **4** was achieved by using chromic acid in aqueous acetone.[7] The use of acetone as a solvent component has the two advantages of high yield (70–80%) and easy separation of the product from the reaction mixture. Ketone **4** has a strong absorption band at 1740 cm^{-1} characteristic for bicyclo[2.2.1]heptan-2-one[8] and was identified by means of

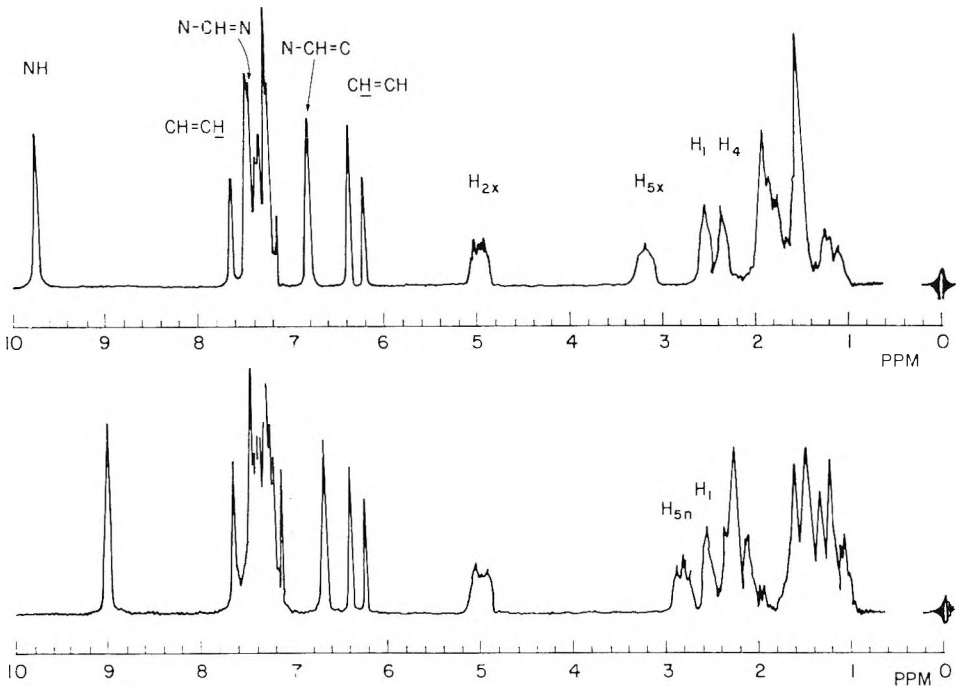


Figure 1. Nmr spectra of *endo*-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-cinnamate (**8**) (upper) and *exo*-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-endo-2-yl *trans*-cinnamate (**10**) (lower). In $CDCl_3$ at 100 MHz, hexamethyldisiloxane as internal standard.

ir, nmr, and mass spectra. Furthermore, ketone **4** was converted to the corresponding 2,4-dinitrophenylhydrazone and identified after recrystallization.

Ketone **4** was a slightly yellow, transparent, and viscous semisolid; its crystallization was not successful. Purification by thin layer chromatography failed. Integration of the C-5 exo proton at δ 3.45 in the nmr spectrum showed that it was a 60–70:40–30 mixture of the endo and exo imidazoles, the endo:exo ratio not having changed from that of the preceding formate **3**. Another important feature of the spectrum was the appearance of the imidazole C-4(5) proton as two singlets ($\Delta\delta$ = 0.03), which seemed to correspond to the endo and exo isomers, although the imidazole C-2 proton appeared as a somewhat broad singlet. The same feature was found in the nmr spectrum of its purified 2,4-dinitrophenylhydrazone derivative.

Reduction of the crude ketone **4** with lithium aluminum hydride in tetrahydrofuran gave the corresponding crude alcohol **5** in 80–90% yield. The endo:exo ratio of the resulting hydroxyl group, which was determined by nmr using the signals of the proton attached to the alcoholic carbon, was found to be about 9:1, similar to that for the hydride reduction product of 2-norbornanone.[9] Lithium trimethoxyaluminum hydride as the reductant gave almost the same endo:exo ratio as above, in sharp contrast to the 98% endo selectivity in the case of 2-norbornanone.[9,10] The endo:exo ratio of the imidazolyl group was found to be lowered to 50:50, indicating endo–exo isomerization during reduction.

Thin layer chromatography using basic alumina proved effective for isolation of *endo*-5[4(5)-imidazolyl]bicyclo-[2.2.1]heptan-*endo*-2-ol (**6**) from the stereoisomeric mixture **5**. The alcohol **6** has a larger R_f value (0.46) than other isomers (0.24); in other words, it traveled further on a thin layer plate. This is quite reasonable because its two functional groups can interact intramolecularly or sterically hinder one another against adsorptive interaction with the basic alumina. Both the imidazolyl and hydroxyl groups were nearly 100% endo as determined by the signals of the protons attached to the carbons which bear those groups. A sharp singlet of the C-4(5) proton of the imidazolyl group, $\Delta\delta$ for the endo and exo isomers being 0.10, was consistent with **6**. Compound **6** was very hygroscopic. When it was dried *in vacuo*, it hardened to an amorphous solid including traces of moisture and methanol.

The fraction of R_f 0.24, from its nmr spectrum, consisted of a compound containing the *exo*-imidazolyl group, with a trace of the endo group with the *endo*- and *exo*-hydroxyl groups in a ratio of 4:1. Thus, the main component in this fraction was probably *exo*-5-[4(5)-imidazolyl]bicyclo-[2.2.1]heptan-*endo*-2-ol, which was isolated later as the *trans*-cinnamate **10** after recrystallization.

O-Acylated compound **8** was obtained from **6** *via* the *O*- and *N*-diacylated intermediate, which was formed in the reaction of **6** with *trans*-cinnamoyl chloride in chloroform. The use of chloroform as solvent is quite important because it completely dissolves the imidazolium hydrochloride generated in the reaction and ensures a homogeneous product. The *O*- and *N*-diacylated intermediate was dissolved in a mixed solvent of chloroform–methanol–water, then partially hydrolyzed, and crystallized to give **8**. Isolation of **8** from the mixture of O-acylated imidazoles derived from **5** was not successful by thin layer chromatography. Compound **10** was obtained from **7** using the same reactions as **8**. However, it required purification by column chromatography and then by fractional crystallization.

Both compounds **8** and **10** were stable, white crystalline materials. The former melts at 130–132° which is 44° lower than the latter, indicating weaker intermolecular interaction in the former as anticipated by its endo,endo orientation.

Significant differences were not found in the ir spectra of **8** and **10**. The nmr spectra of these compounds, however, gave valuable information about their structures. The spectra obtained at 100 MHz are shown in Figure 1. These spectra clearly indicate the endo or exo orientation of each functional group. The chemical shifts of the protons attached to the acyloxy-bearing carbons are in good agreement with literature values.[5] The carbocyclic part of the spectrum of **6** or **8** is very similar to that of *endo*-2-norbornanol or its acetate, except for the existence of the signals due to the *endo*-imidazolyl group.

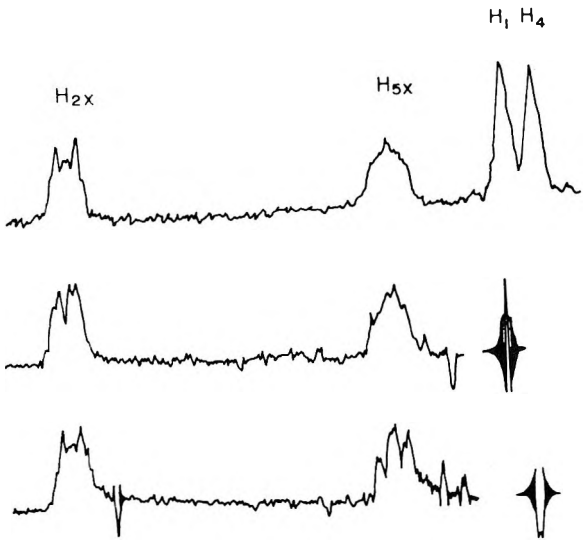


Figure 2. A double resonance experiment for *endo*-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-cinnamate (8). In $CDCl_3$ at 100 MHz.

The question of 2,5 or 2,6 disubstitution was answered definitively by a double resonance experiment at 100 MHz. The spectrum is shown in Figure 2, indicating that H_1 couples with H_{2x} but not with H_{5x}, and H_4 couples with H_{5x} but not with H_{2x}. This result indicates unequivocally 2,5 disubstitution. Since only one mode of disubstitution was observed in the intermediates **3** and **4**, the addition of formic acid to **2** must have been regiospecific, giving only the 2,5-disubstituted bicyclo[2.2.1]heptane.

Experimental Section

All melting points and boiling points are uncorrected. Nmr spectra were obtained on a Hitachi Model R-24 spectrometer (60 MHz). In $CDCl_3$ solutions, TMS was used as internal standard; in DMSO-d_6 or CD_3OD solutions the solvent signal at δ 2.50 or 3.35, respectively, was used as internal standard. A double resonance experiment was carried out on a Varian HA-100 spectrometer. Mass spectra were obtained on a Hitachi RMS-4 spectrometer (70 eV). Elemental analyses were carried out by Mr. Ei-ichiro Amano at Okayama University.

***endo*- and *exo*-5-(1-Keto-2-hydroxyethyl)bicyelo[2.2.1]-hept-2-enes (1).** According to the procedure of Reppe and coworkers,[4b] 100 g (1.16 mol) of 2-butyne-1,4-diol was isomerized to hydroxymethyl vinyl ketone in 500 ml of reagent grade ethyl acetate with mercuric oxide (red), boron trifluoride etherate, and trichloroacetic acid as catalysts. After isomerization, the clear yellow solution was decanted, washed with a dilute aqueous sodium carbonate solution, and evaporated *in vacuo*. To the resulting viscous, orange liquid, 30 g (0.45 mol) of freshly distilled cyclopentadiene was added with stirring. Vigorous heat evolution was observed within a few minutes and the reaction mixture was cooled in an ice bath so that the temperature did not exceed 40°. Heat evolution continued for about 10 min. The solution was allowed to stand overnight at room temperature and then distilled *in vacuo*, yielding 31 g (18%) of the crude product. This was fractionally distilled through a spinning band column (6 mm × 60 cm, 30 plates), giving 2.1 g of a 30:70 mixture, bp 85–88° (8.5 mm), and 12 g of a 71:29 mixture, bp 91–92° (8.5 mm), of the endo and exo ketones **1**, and 3.5 g, bp 92° (8.5 mm), of the endo (>98%) ketone **1**. About 10 g of a liquid that solidified remained in the still pot. The second and third fractions were combined, giving 15.5 g of a 77:23 mixture of the endo and exo ketones **1** for further use: ir (neat) 3430 (OH), 3060 (=C—H), 1710 (C=O), 1570 (C=C), 1080 cm^{-1} (C–O).

Nmr (endo > 98%) ($CDCl_3$) δ 6.16 (1 H, dd, J = 3 and 6 Hz, CH=CH), 5.81 (1 H, dd, J = 3 and 6 Hz, CH=CH), 4.22 (2 H, s, CH_2O), 3.22 (1 H, s, OH), 3.19 (1 H, m, H_4), 2.96 (3 H, m, H_1 and H_{5x}). Nmr (exo 85%, endo 15%[11] $CDCl_3$) δ 6.15 (1.85 H, m, *exo*-CH=CH and *endo*-CH=CH), 5.83 (0.15 H, dd, J = 3 and 6 Hz, *endo*-CH=CH), 4.33 (s, *exo*-CH_2O), 4.25 (s, *endo*-CH_2O), 3.22 (1 H, s, OH), 2.95 (*ca.* 2 H, m, H_1, H_4, and H_{5x}), 2.35 (*ca.* 1 H, m, H_{5n}).

***endo*- and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-2-enes (2).** In 150 ml of ethanol 15.5 g (0.103 mol) of the mixed ketones **1** was dissolved and then diluted with 80 ml of warm water. To this warm solution were added 42 g (0.21 mol) of cupric acetate monohydrate in 180 ml (2.5 mol) of 28% ammonia water and 32 ml (0.43 mol) of 37% formalin. The solution was heated on a water bath to 70–80°. In about 5 min a copious, slightly green precipitate began to form and the reaction mixture was heated for 2 hr. Then the mixture was left to stand at room temperature overnight and filtered. The collected precipitate was washed repeatedly with water, then with acetone, and finally with water. The wet precipitate (about 40 g) was suspended in 500 ml of water, and hydrogen sulfide gas was passed into the suspension with stirring at 40–50° for 3 hr, during which period the suspension was adjusted to pH 3–5 by the addition of concentrated hydrochloric acid. The black precipitate was filtered and washed with water. The combined orange filtrate and washings were concentrated to one-half volume and made alkaline (pH 9) with an aqueous sodium carbonate solution until an oil deposited. The oil was extracted three times with 100 ml of chloroform. After drying over anhydrous magnesium sulfate, the orange extract was concentrated using a rotary evaporator, and then the solvent was removed *in vacuo*, giving 11.5 g (70%) of the crude imidazole compound **2**. It was a very viscous, transparent, orange oil, a 75:25 mixture of the *endo*- and *exo*-imidazoles as indicated by nmr analysis: ir (neat) 3500–2200 (NH), 1580–1560 cm^{-1} (C=C and imidazole ring); nmr ($CDCl_3$) δ 12.4 (1 H, s, NH), 7.58, 7.53 (1 H, two s, N=CH—N), 6.83 (0.25 H, s, *exo*-N—CH=C), 6.63 (0.75 H, s, *endo*-NCH=C), 6.18 (1.25 H, m, CH=CH), 5.80 (0.75 H, dd, J = 3 and 6 Hz, CH=CH), 3.37 (m, H_{5x}), 3.14 (m, H_4), 2.94 (m, H_1), 2.68 (m, H_{5n}), 3.6–0.9 (7 H, m, alicyclic protons except for H_2 and H_3).

***endo*- and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-*exo*-2-yl Formates (3).** The crude 75:25 mixture (11.5 g; 0.072 mol) of the *endo*- and *exo*-imidazoles **2** was dissolved in 115 ml (3.1 mol) of freshly distilled 98–100% formic acid and refluxed for 50 hr. After the excess formic acid was removed using a rotary evaporator, the viscous, dark red liquid was dissolved in 100 ml of water and neutralized (pH 6) with an aqueous sodium carbonate solution. A precipitated black solid was filtered through activated carbon, and the transparent amber-colored filtrate was adjusted to pH 9. The resultant oil was extracted three times with 50 ml of chloroform, and the extract was dried over anhydrous magnesium sulfate. The solution was filtered and concentrated *in vacuo* with heating and gave 13.1 g (88%) of an orange glassy solid **3**: ir (KBr) 3500–2200 (NH), 1715 (C=O), 1570 (imidazole ring), 1170 cm^{-1} (C–O); nmr ($CDCl_3$) δ 12.40 (1 H, s, NH), 7.97 (1 H, s, CHO), 7.62 (1 H, s, N=CH—N), 6.77 (1 H, s, N—CH=C), 4.74 (1 H, m, H_{2n}), 3.12 (0.6–0.7 H, m, H_{5x}), 2.7 (m, H_{5n}), 2.45 (m, H_1 and H_4), 3.4–0.9 (9 H, m, carbocyclic ring protons except for H_{2n}); mass spectrum *m/e* 206 (M^+), 177 (M^+ − CHO).

Nmr analysis indicates the imidazolyl group to be 60–70% endo and 40–30% exo and the formoxy group to be 100% exo.

***endo* and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]heptan-2-ones (4).** In 130 ml of reagent grade acetone 13.1 g (0.063 mol) of the crude formates **3** was dissolved together with 25 ml (H^+, 0.063 mol) of 2.5 *N* sulfuric acid. To this solution 33 ml of 8 *N* chromic acid which was prepared by the procedure of Kleinfelter and Schleyer[7] was added over 20 min with stirring at 20–25°. The reaction mixture was stirred further for 2.5 hr. On addition of 0.2 g of sodium bisulfite, no appreciable color change was observed. The mixture was diluted with 30 ml of reagent grade acetone, and the supernatant was decanted. The remaining dark solids were washed twice with acetone and the combined organic solutions were stored in a refrigerator overnight. After filtering a small amount of a yellow precipitate, the acetone solution was concentrated to about 50 ml and extracted four times with 50 ml of chloroform, and the extract was dried over anhydrous magnesium sulfate. After filtration, the solvent was removed and the residual, very viscous, and slightly orange solid was dried *in vacuo* with gentle heating, giving 8.4 g (75%) of the crude product **4**: ir (neat) 3500–2200 (NH), 1740 (C=O), 1570 cm^{-1} (imidazole ring); nmr ($CDCl_3$) δ 11.72 (1 H, broad s, NH), 7.61 (1 H, s N=CH—N), 6.85, 6.82 (1 H, two s, N—CH=C), 3.45 (0.6–0.7 H, m, H_{5x}), 3.0 (m, H_{5n}), 2.9–2.6 (m, H_1 and H_4), 3.7–1.1 (9 H, m, carbocyclic ring protons); mass spectrum *m/e* 176 (M^+).

Nmr analysis indicated it to be 60–70% endo and 40–30% exo for the imidazolyl group. For identification, the ketone was reacted with 2,4-dinitrophenylhydrazine in ethanol using concentrated hydrochloric acid as the catalyst. The mixture was boiled for 10 min, neutralized (pH 3), evaporated to dryness, and extracted with ethanol. After removal of the solvent, the crude crystals were recrys-

tallized from ethanol, giving yellowish-orange crystals of the 2,4-dinitrophenylhydrazone of **4**: mp 137.5–140.5°; ir (KBr) 3600–2200 (s), 1650 (w), 1620 (s), 1590 (s), 1510 (m), 1420 (m), 1335 (s), 1310 cm^{-1} (s); nmr (DMSO-d_6) δ 8.75 (1 H, dd, J = 1 and 3Hz, benzene ring proton), 8.25 (dd, J = 3 and 10 Hz, benzene ring proton), 7.75 (1 H, d, J = 10 Hz, benzene ring proton), 7.60 (1 H, s, N=CH—N), 6.86, 6.80 (1 H, two s, N—CH=C), 3.3 (0.6–0.7 H, m, H_{5x}), 8.5–5.5 (2 H, broad s, 2 NH).

Anal. Calcd. for $C_{16}H_{16}N_6O_4$: C, 53.93; H, 4.53; N, 23.58. Found: C, 53.78; H, 4.62; N, 23.61.

Nmr analysis indicated that the endo:exo ratio of the recrystallized hydrazone was almost unchanged from that of the crude ketone **4**.

***endo* and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]heptan-*endo*- and *exo*-2-ols (5).** In a four-necked flask were placed 40 ml of anhydrous tetrahydrofuran and 1.1 g (29 mmol) of lithium aluminum hydride; the mixture was stirred at room temperature for 2 hr under a nitrogen atmosphere. The slurry was cooled to 0° and 3.4 g (19 mmol) of ketone **4** in 7 ml of anhydrous tetrahydrofuran was added dropwise during the course of 45 min at 2°. After stirring was continued further for 80 min at 2°, 0.6 ml of water was added to destroy the excess hydride, and then 10 ml of saturated sodium chloride solution was added. Then the mixture was adjusted to pH 9 with concentrated hydrochloric acid. The precipitated white powder was filtered and washed with tetrahydrofuran, and the combined filtrate and washings were evaporated to dryness *in vacuo* with gentle heating, giving 3.0 g (87%) of a white brittle solid of the crude alcohol **5**: ir (KBr) 3400 (OH), ~2200 (NH), 1570 cm^{-1} (imidazole ring); nmr (DMSO-d_6) δ 7.50, 7.46 (1 H, two s, N=CH—N), 6.78, 6.68 (1 H, two s, N—CH=C), 6.4 (4 H, broad s, NH, OH, and moisture), 4.02 (*ca.* 0.9 H, m, H_{2x}), 3.6 (m, H_{2n}), 3.2–2.7 (m, H_{5x} and H_{5n}).

The endo:exo ratios of the hydroxyl and imidazolyl groups were determined from the nmr spectrum of the *O*-acetoxy derivative, because it was difficult to analyze the nmr spectrum of the crude alcohol **5** quantitatively. The *O*-acetoxy derivative was prepared using acetic anhydride according to the method of Bruice and Sturtevant:[12] ir (neat) 3400–2200 (NH), 1730 (C=O), 1570 cm^{-1} (imidazole ring), 1250 cm^{-1} (C–O); nmr ($CDCl_3$) δ 12.70 (1.5 H, broad s, NH and moisture), 7.63, 7.62 (1 H, two s, N=CH—N), 6.90, 6.76 (1 H, two s, N—CH=C), 4.96 (0.9 H, m, H_{2x}) 4.60 (0.1 H, m, H_{2n}), 3.5–2.7 (*ca.* 1 H, m, H_{5x} and H_{5n}), 2.03 (3 H, s, CH_3CO).

***endo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]heptan-*endo*-2-ol (6).** The isolation of **6** from **5** was achieved by preparative tlc. About 240 g of basic alumina from Merck (HF_{254} type E) was coated on ten glass plates (20 × 20 cm) and activated as indicated by Merck. To these plates 1003 mg of the reduction product **5** dissolved in a small amount of anhydrous methanol was applied and developed three times using a 20:1 mixture of dichloromethane and methanol (by volume) as eluent. Four bands were observed and their R_f values and band widths were as follows: 0.09 (2.5 cm), 0.24 (1.5 cm), 0.46 (1.8 cm), and 0.55 (0.3 cm). They were extracted three times with anhydrous methanol, and the components obtained after drying *in vacuo* weighed 30, 449, 276, and 30 mg, respectively. The third component (276 mg, R_f 0.46) was identified as **6**: ir (neat) 3500–3000 (OH), ~2200 (NH), 1570 cm^{-1} (imidazole ring); nmr (DMSO-d_6) δ 7.52 (1 H, s, N=CH—N), 6.78 (1 H, s, N—CH=C), 6.5 (broad s, NH, OH, and moisture), 4.05 (1 H, m, H_{2x}), 3.10 (1 H, m, H_{5x}), 2.25 (2 H, m, H_1 and H_4), 2.4–0.8 (8 H, m, alicyclic protons except for H_{2x} and H_{5x}). The first and fourth components were mixtures of the imidazole compounds and impurities. The second (449 mg, R_f 0.24) was identified as **7**: ir (neat) 3500–3000 (OH), ~2200 (NH), 1570 cm^{-1} (imidazole ring); nmr (DMSO-d_6) δ 7.52 (1 H, s, N=CH—N), 6.82 (trace, s, *endo*-NCH=C), 6.72 (1 H, s, *exo*-N—CH=C), 6.6 (broad s, NH, OH, and moisture), 4.07 (*ca.* 0.8 H, m, H_{2x}). 3.60 (*ca.* 0.2 H, m, H_{5x}), 3.10 (trace, m, H_{5x}), 2.70 (1, H, m, H_{5n}), 3.0–0.8 (9 H, m, carbocyclic protons except for H_2).

***endo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-Cinnamate (8).** In 4 ml of chloroform, which was washed with water and distilled to remove ethanol as stabilizer, 204 mg (1.12 mmol) of **6** was dissolved. To this solution 450 mg (2.7 mmol) of *trans*-cinnamoyl chloride was added, and the solution was refluxed for 90 min at 80–90°. The homogeneous solution was diluted with chloroform, washed with aqueous potassium hydrogen carbonate solution, and evaporated *in vacuo*. An attempt was made to dissolve the residual solid in dilute hydrochloric acid with gentle warming, but only a small amount of the solid dissolved. This dissolved solid was recovered after neutralization (52 mg) and found to contain traces of *exo*-imidazolyl and *exo*-acyloxy groups. The insoluble crystalline solid was recrystallized from chloroform–ether, giving 330 mg of white crystalline material, mp 274–275.5°. Nmr and ir spectra indicated it to be the *O*- and *N*-diacylated compound (both 100% endo). It was dissolved in a mixture of 15 ml of chloroform and 55 ml of methanol. After addition of 20 ml of water, the solution was acidified (pH 3) with hydrochloric acid and allowed to stand at 0° overnight. The hydrolyzed solution was evaporated to about 20 ml and the residual milky mixture was washed twice with ether. The clear solution was adjusted to pH 9 with an aqueous sodium carbonate solution and extracted twice with chloroform. After drying over anhydrous magnesium sulfate, the solvent was removed *in vacuo*, giving 211 mg of a colorless brittle solid. It was crystallized from a minimum volume of chloroform by addition of ether and scratching, giving 186 mg of white crystalline material (dried *in vacuo* at 80° for 2 hr), mp 130–132°; ir (KBr) 3400–2200 (NH), 1703 (C=O), 1635 (C=C), 1575 (imidazole ring), 1185 cm^{-1} (C–O); nmr ($CDCl_3$) δ 9.7 (1 H, s, NH) 7.67 (1 H, d, J = 16 Hz, CH=CH), 7.54 (1 H, s, N=CH—N), 7.7–7.2 (5 H, m, phenyl ring protons), 6.92 (1 H, s, N—CH=C), 6.38 (1 H, d, J = 16 Hz, CH=CH), 5.09 (1 H, m, H_{2x}), 3.28 (1 H, m, H_{5x}), 2.53 (2 H, m, H_1 and H_4), 2.2–0.9 (6 H, m, H_{3x}, H_{3n}, H_{6x}, H_{6n}, $H_{syn\text{-}7}$, and $H_{anti\text{-}7}$).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.92; H, 6.45; N, 9.14.

***exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-Cinnamate (10).** In 8 ml of the purified chloroform, 382 mg (2.15 mmol) of **7** was dissolved. To this solution 860 mg (5.1 mmol) of *trans*-cinnamoyl chloride was added, and the solution was refluxed for 60 min at 75–80°. The homogeneous solution was evaporated, and the residual solid was dissolved in 5 ml of water with gentle warming. A remaining oil was extracted with chloroform and the aqueous solution was adjusted to pH 9 with potassium hydrogen carbonate. The deposited material was extracted with chloroform, giving a slightly yellow solution. After drying over anhydrous magnesium sulfate, the solvent was removed to give 755 mg (theory, 660 mg) of residual material. It was dissolved again in dilute hydrochloric acid, and the insoluble material was filtered through activated carbon. The slightly yellow clear filtrate was treated as before, giving 541 mg of a colorless brittle solid. Nmr analysis indicated it to be the *O*-acylated derivative of **7**. Onto a column containing 125 g of basic alumina (Merck, activity I) (2.4-cm diameter, 30-cm height), 412 mg of the above ester was poured and eluted with a 3:10 mixture of methanol and dichloromethane. The first 70 ml of the eluent contained nothing. The second 32-ml portion of the eluent contained 40 mg, the third 12-ml portion 16 mg, the fourth 16-ml portion 50 mg, the fifth 20-ml portion 53 mg, the sixth 80-ml portion 81 mg, and the seventh 112-ml portion 63 mg of the solute. Further, 16 mg of a solid was recovered from 185 ml of a 1:1 mixture of the two solvents. Nmr analysis indicated that the first and last components were (unidentified) impurities. The third component was discarded because it had a higher percentage of the *endo*-imidazolyl and *exo*-acyloxy groups than the others. Therefore, the fourth, fifth, and sixth portions were combined (197 mg). Almost the same combined material (59 mg) was obtained from 129 mg of the ester using a column of 1.3-cm diameter and 18.5-cm height containing 25 g of alumina. Both the components were combined and crystallized as in the case of **8**, giving 198 mg of white crystalline material. Recrystallization was repeated twice, and finally, 127 mg of white crystals was obtained from chloroform–carbon tetrachloride (dried *in vacuo* at 80° for 4.5 hr):[13] mp 174–176° dec; ir (KBr) 3400–2200 (NH), 1718 (C=O), 1640 (C=C), 1578 (imidazole ring), 1185 cm^{-1} (C–O); nmr ($CDCl_3$) δ 8.75 (1 H, s, NH), 7.68 (1 H, d, J = 16 Hz, CH=CH), 7.57 (1 H, s, N=CH—N), 7.7–7.2 (5 H, m, phenyl ring protons), 6.77 (1 H, s, N—CH=C), 6.42 (1 H, d, J = 16 Hz, CH=CH), 5.12 (1 H, m, H_{2x}), 2.93 (1 H, m, H_{5n}), 3.1–1.0 (9 H, m, carbocyclic protons except for H_{2x}).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08 (same as **8**). Found: C, 73.98; H, 6.55; N, 9.32.

Registry No.—*endo*-**1**, 52747-94-1; *exo*-**1**, 52747-95-2; *endo*-**2**, 52747-96-3; *exo*-**2**, 52747-97-4; *endo*-**3**, 52747-98-5; *exo*-**3**, 52759-86-1; *endo*-**4**, 52747-99-6; *endo*-**4** 2,4-DNP, 52748-00-2; *exo*-**4**, 52748-01-3; *exo*-**4** 2,4-DNP, 52748-02-4; **6**, 52748-03-5; **6** *O*-acetoxy derivative, 52748-04-6; *exo*-**7**, 52748-05-7; *exo*-**7** *O*-acetoxy derivative, 52748-06-8; *endo*-**7**, 52759-87-2; *endo*-**7** *O*-acetoxy derivative, 52759-88-3; **8**, 52748-07-9; **10**, 52759-89-4; formic acid, 64-18-6; *trans*-cennamoyl chloride, 17082-09-6.

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(13) It was imperative to use ethanol-free chloroform for recrystallization.

Notes

Selective Chemical Ionization Mass Spectrometry as an Aid in the Study of Thermally Labile Three-Membered Ring Sulfones

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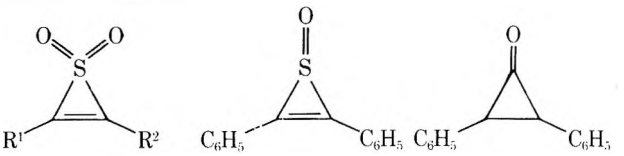
Received April 29, 1974

Recently a theoretically interesting group of compounds has been synthesized in which a sulfur has been incorporated in a three-membered ring.[1] The structures of these unusual compounds have been established by a combination of spectroscopic and chemical data. However, verification of the molecular weight of the sulfones **1a–1c** by mass spectrometry, employing the conventional electron impact (EI) ionization method, has been unsuccessful because of the absence or insignificant intensity of molecular ion peaks in their mass spectra. The base peak in the electron impact mass spectra of **1a–1c**, as well as the related compounds **2** and **3**, corresponds to the formation of the disubstituted acetylene ion $[(R^1{-}C{\equiv}C{-}R^2){\cdot}^+]$.



1a, $R^1 = R^2 = C_6H_5$
b, $R^1 = C_6H_5$, $R^2 = CH_3$
c, $R^1 = R^2 = CH_3$

2 **3**

No molecular ion peaks could be detected in the EI mass spectra of **1a** or **1b**, although very weak ones were observed in the mass spectra of the other compounds (see Table I).

Decomposition of the molecular ions in the EI spectra of **1–3** is particularly favorable because of the facile expulsion of the neutral species SO_2, SO, and CO, respectively. Indeed, in the sulfone case, considerable thermal decomposition may precede ionization as suggested by the fact that only the most volatile of the sulfones examined (**1c**) gave any evidence for a molecular ion. These sulfones generally undergo thermal fragmentation at approximately 100–125°

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Table I
Relative Abundance of Molecular Ionic Species in the EI and CI Spectra of 1–3.

Compd	EI	CI CH_4	CI isobutane	CI NH_3	CI $NHMe_2$
1a				0.2,[b] 2.9[c]	23[d]
1b				2,[b] 21[c]	42[d]
1c	0.12[a]	16[b]	42[b]	0.5,[b] 86[c]	70[d]
2	0.25[a]	26[b]	49[b]	24,[b] 3[c]	69[d]
3	0.10[a]	15[b]	81[b]	45,[b] 9[c]	75[d]

[a] Refers to %Σ of $M{\cdot}^+$. [b] Refers to %Σ of $(M + H)^+$ ion. [c] Refers to %Σ of $(M + NH_4)^+$ ion. [d] Refers to %Σ of $(M + NH_2Me_2)^+$ ion.

at atmospheric pressure, and consequently we decided to investigate the mass spectrometry of these compounds under carefully controlled experimental conditions.

Results and Discussion

Lowering of the ionizing energy to ~10 eV in combination with lower ion source and inlet probe temperatures (<100°) failed to enhance significantly the relative abundance of the molecular ion in the EI spectra of **1–3**, and thus it became apparent that alternative ionization methods had to be considered. In view of the relatively lower energy processes involved in chemical ionization (CI) mass spectrometry,[2,3] we have explored the application of this technique as a means of determining the molecular weights of such unstable compounds. Chemical ionization spectra of **1–3** were obtained with various reagent gases and they are partially summarized in Table I. As a representative example, the complete EI and CI mass spectra of **1a** are compared in Figure 1. In all cases, the ion source temperature was kept at the lowest possible level required for sample vaporization to minimize possible thermal decomposition effects. The heat transmitted from the ion source of the CEC 21-110B mass spectrometer was sufficient for vaporization of the samples, and consequently no further heating of the solid inlet probe was necessary.

The methane CI spectra of **1a–1c** and **2** are dominated by the $(R^1C{\equiv}CR^2 + H)^+$ ion which carries approximately 55, 57, 60, and 26% of the total ion current in the case of **1a**, **1b**, **1c**, and **2**, respectively. As was the case with electron impact ionization, no molecular ion species were detected in the methane CI spectra of **1a** and **1b** at *m/e* values corresponding to $(M + H)^+$. The presence of the SO_2 function in the sulfones **1a–1c** is evident, however, from the intense *m/e* 65 peak corresponding to $(SO_2 + H)^+$, and which carries 22, 23, and 9% of the total ion current in **1a**, **1b**, and

1c, respectively. It is significant that distinct molecular ion species at *m/e* values corresponding to $(M + H)^+$ were observed in the methane CI mass spectra of both **1c** (16% Σ_{40}), **2** (26% Σ_{40}), and **3** (15% Σ_{40}). The higher thermal sta-

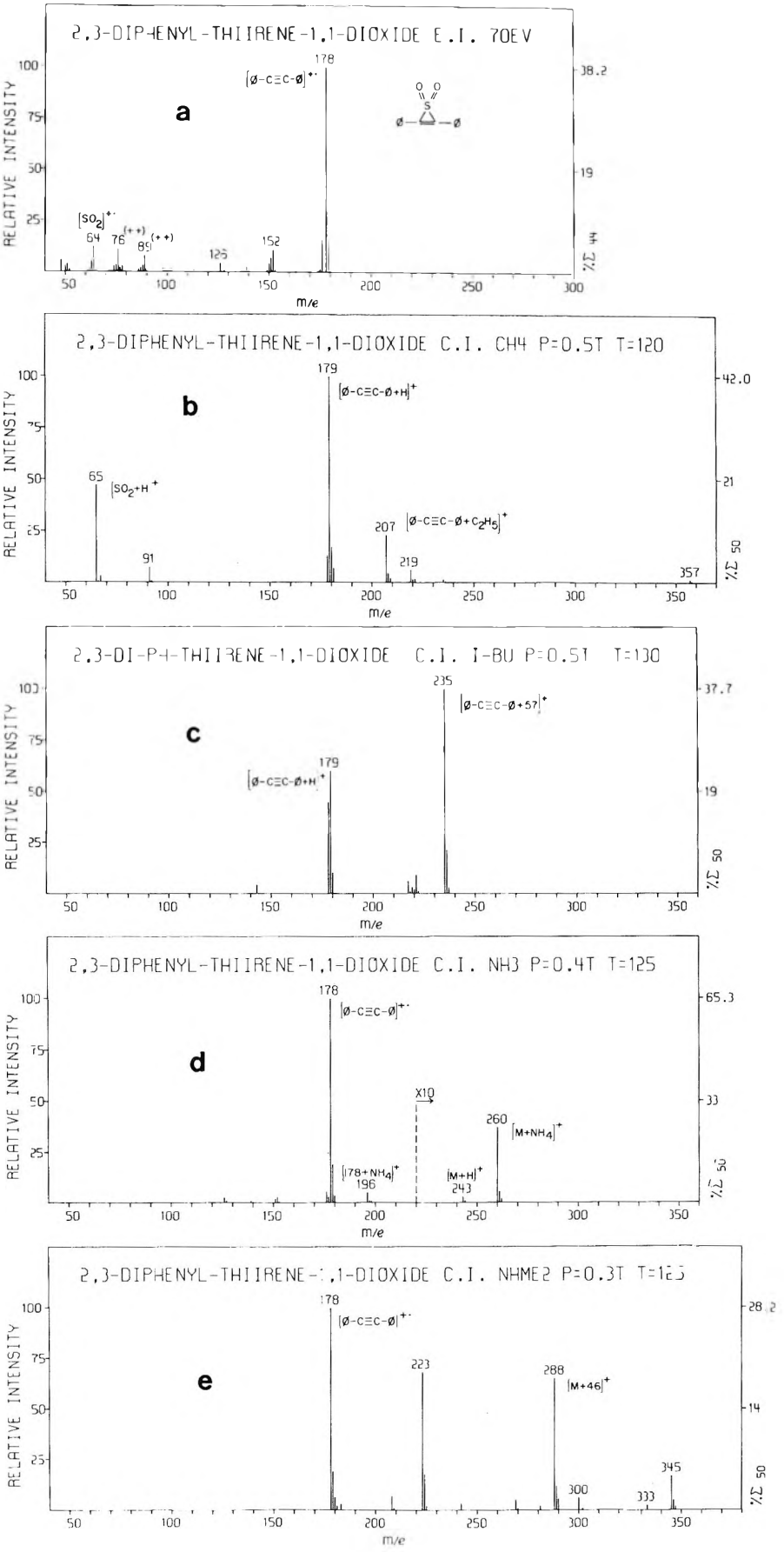


Figure 1. Mass spectra of 2,3-diphenylthiirene 1,1-dioxide: (a) Electron-impact spectrum (70 eV); (b) CI spectrum in methane; (c) CI spectrum in isobutane; (d) CI spectrum in ammonia; (e) CI spectrum in dimethylamine.

bility of the sulfoxide (2) over the sulfone (1a)[1] is further reflected in the comparison of the relative intensities of their ionic species at $M\cdot^+$ or $(M + H)^+$ (Table I). The EI spectrum of 2 exhibits a weak but discernible molecular ion peak while its methane CI spectrum shows an abundant $(M + H)^+$ ion (25% Σ_{40}). It might be noted that while the $(SO + H)^+$ ion was the predominant ionic species (35% Σ_{40}) in the spectrum of **2**, it was not possible to assess the contribution of $(CO + H)^+$ to the peak at *m/e* 29 in the spectrum of **3** because of the interfering reagent gas ion of the same nominal mass.

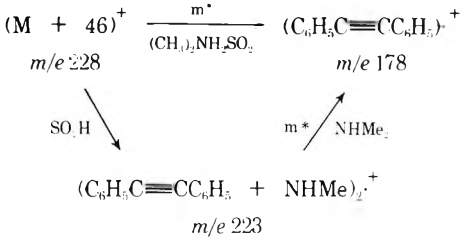
Assuming no thermal decompositions in the ion source or during sample vaporization, formation of $(R^1C{\equiv}CR^2 + H)^+$ and $(SO_2 + H)^+$ in the spectra of **1–2** occurs *via* elimination of SO_2 (SO in the case of **2**) respectively from $(M + H)^+$. In the absence of metastable transitions and because of the generally low thermal stability of thiirene dioxides, it is, of course, impossible to differentiate between thermal and ionic decompositions from the electron impact and methane CI spectra alone.

Proton transfer in isobutane reagent gas is accomplished by the *tert*-butyl carbonium ion and is accompanied by release of less energy than protonation in methane which is carried out by the highly acidic CH_5^+ ion.[4] Nevertheless, the CI spectra of compounds **1–3** in isobutane were similar to their methane counterparts, in that compounds **1a** and **1b** exhibited no $(M + H)^+$ or $(M + C_4H_9)^+$ adduct ions. The lower energy associated with this reaction is reflected in the increased relative intensity (Table I) of the $(M + H)^+$ peak in the spectra of **1c** (42% Σ_{40}), **2** (49% Σ_{40}), and **3** (81% Σ_{40}). On the other hand, in the case of **1a** or **1b** the amount of energy transferred during reaction with $C_4H_9^+$ is enough to cause complete decomposition of the initial molecular adducts formed. It is interesting to note that, as in the methane CI spectra, the adduct ion $[(R^1C{\equiv}CR^2 + H)^+]$ was also highly abundant in the isobutane CI spectra of **1–3** but, in addition, at the ion source temperatures employed, intense peaks were observed at $(R^1C{\equiv}CR^2 + 57)^+$, corresponding to formation of a dialkyl acetylene–$C_4H_9^+$ complex ion. The latter, of course, can be formed either by decomposition of the molecular adduct ion $(M + C_4H_9)^+$ and/or direct reaction of $C_4H_9^+$ with dialkyl acetylene produced by thermal decomposition of the sulfone.

The use of ammonia as a reagent gas in chemical ionization mass spectrometry was first demonstrated in the investigation of the mass spectra of nucleosides.[5] An enhancement in the abundance of the $(M + H)^+$ ions was noted as compared to CI in methane due to the lower acidity of the prevalent ammonium ion and the resulting lower exothermicity of the proton transfer reaction. In view of the above, we determined the mass spectra of compounds **1–3** in this system and, as indicated in Table I, there is a greatly enhanced abundance of the molecular ionic species. In the case of the sulfone **1a**, it is significant that although still weak, the molecular adduct ion peaks at $(M + H)^+$ and $(M + NH_4)^+$ are clearly detectable. The distinct preference for the formation of $(M + NH_4)^+$ rather than $(M + H)^+$ ions in the spectra of the sulfones **1a–1c** indicates a lower proton affinity for the sulfone function than for NH_3 under the experimental conditions. It should be noted that in an analogous fashion the ammonia CI spectrum of diphenyl sulfone ($C_6H_5SO_2C_6H_5$) showed a 100:1 abundance ratio of $(M + NH_4)^+$ to $(M + H)^+$ ions.

In a recent paper, Dzidic has suggested the use of alkylamine reagents for selective chemical ionization based on the relative proton affinities of the reagent gas and the sample.[6] In view of the apparent low proton affinity of the sulfone function, it was expected that no $(M + H)^+$ ions could be formed in the dimethylamine CI mass spectra of **1a–1c**, since $NHMe_2$ is a stronger base than NH_3.[6,7] Indeed, this was the case as indicated in Table I, but in the relatively low ion source temperatures required for mass spectrometry of the thiirene dioxides **1a–1c**, the conditions appear highly favorable for the formation of stable $(MNH_2Me_2)^+$ ion clusters. The greatly enhanced abundance of the molecular ion adducts in the mass spectra of the sulfones **1a** and **1b** provides unequivocal mass spectrometric evidence for the molecular weights of these compounds. Metastable defocusing experiments[8] confirmed that the decompositions *m/e* 288 → *m/e* 178 and *m/e* 223 → *m/e* 178 in the Me_2NH CI spectrum of **1a** are at least in part ionically induced and support the postulated fragmentation sequence (Scheme I). The relatively intense peak at *m/e* 345 in Figure 1e corresponds to $(M + 103)^+$. An ion of *m/e* 103 was always present in the spectrum of the reagent gas and is due to some undetermined impurity.

Scheme I



The data presented above point out the usefulness of chemical ionization techniques for the mass spectrometric study of thermally unstable small ring unsaturated heterocyclic compounds. Selective chemical ionization by employment of different reagent gases can help enhance the relative abundance of molecular adduct ions and thus establish the molecular weight of the compounds investigated. Furthermore, since all chemical ionization mass spectra were obtained with the same instrument and at similar ion source temperature conditions, it is reasonable to assume that the observed decompositions to $(R^1C{\equiv}CR^2)\cdot^+$ or $(R^1C{\equiv}CR^2 + H)^+$ are not necessarily thermally, but at least in part ionically, induced.

Experimental Section

Electron impact ionization mass spectra were obtained with an LKB-9000 mass spectrometer, as well as a CEC 21-110B mass spectrometer operating in a low resolution mode. Samples were introduced into the ion source *via* the direct inlet probe and recorded at various ion source temperatures in the range 25–250°. The ionizing voltage unless otherwise specified was 70 eV. Chemical ionization mass spectra were obtained with a modified CEC 21-110B mass spectrometer,[9] at ion source temperatures ranging from 100–130°. Samples were introduced *via* the standard solid probe inlet provided with the instrument. The reagent gas pressures were 0.5 Torr for methane and isobutane, 0.4 Torr for ammonia, and 0.3 Torr for dimethylamine.

Acknowledgment. Financial assistance to the Institute for Lipid Research by the National Institutes of Health (GM-13901) is gratefully acknowledged.

Registry No.—**1a**, 5162-99-2; **1b**, 30503-83-4; **1c**, 30646-57-2; **2**, 31247-21-9; **3**, 52730-95-7.

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Thermally Labile Ketenimines from Triphenylphosphinalkylimines

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Received July 9, 1974

A recent study in our laboratory of a 1,3-nitrogen to carbon rearrangement (ketenimine → nitrile)[1] required routes to thermally labile and chiral ketenimines in which the asymmetric center was directly attached to the nitrogen. We wish to report our experience with the synthetic sequence shown in Scheme I. The key step is the reaction of

Scheme I

$$Ph_3P \xrightarrow[\text{benzene}]{1\text{ equiv }Br_2} Ph_3PBr_2 \xrightarrow[1\text{ equiv }(C_2H_5)_3N,\ \text{benzene}]{1\text{ equiv }RR'R''CNH_2}$$

1 → 2

$$[Ph_3PNHCRR'R'']^+Br^- \xrightarrow[\text{ether}]{\text{excess KOH}}$$

3

$$Ph_3P{=}NCRR'R'' \xrightarrow[\text{Ether}]{Ph_2C{=}C{=}O}$$

4

$$Ph_2C{=}C{=}NCRR'R'' + Ph_3PO$$

5

diphenylketene with a triphenylphosphinalkylimine, first reported many years ago by Staudinger and Hauser.[2] We believe our present procedures offer some advantages over those previously described. Further, we demonstrate that optically active ketenimines can be prepared by this route with no measurable racemization at the asymmetric center directly attached to the nitrogen.

Nearly stoichiometric yields of the phosphonium bromides (3) were obtained by the addition of a primary amine and 1 equiv of triethylamine[3] to the *in situ* prepared triphenylphosphine dibromide (2). Deprotonation to the phosphinalkylimine (4) was readily accomplished by simply stirring 3 over excess potassium hydroxide in anhydrous ether for 20–40 hr. Previous workers used sodamide.[3] It is our experience that excellent yields are obtained by our procedure.

Slow addition of an ether solution of 4 at room temperature to an ether solution of diphenylketene under nitrogen gives diphenyl-*N*-(substituted)ketenimines in good to excellent yields. It is important to note that thermally labile ketenimines, which cannot be prepared by the more vigorous dehydration and dehydrohalogenation procedures[4] are easily prepared by Scheme I. Some difficulties encountered tered in separating the last traces of triphenylphosphine oxide from the ketenimine were overcome by chromatographing the product mixture over basic alumina.

By this reaction sequence, we have successfully prepared the diphenylketenimines having N-substituents of *tert*-butyl (6), benzyl (7), and 1-phenylethyl (8). The diphenyl-*N*-(diphenylmethyl)ketenimine (9) apparently also is formed *via* Scheme I, but is too labile toward rearrangement[1] at room temperature for isolation since 2,2,3,3-tetraphenylpropionitrile is recovered.

A synthetic sequence starting with (*S*)-(−)-1-phenylethylamine ($\alpha^{25}D$ −37.0°, neat) *via* (*S*)-(−)-triphenylphosphin-*N*-(1-phenylethyl)imine ($[\alpha]^{25}D$ −62.4°, *c* = 14.4, CCl_4) yielded (*S*)-(−)-diphenyl-*N*-(1-phenylethyl)ketenimine ($[\alpha]^{25}D$ 35.3°, c = 5.21, CCl_4). This synthetic sequence proceeds with complete retention of configuration since mild hydrolysis[5] of (*S*)-(−)-8 gives a 95% yield of (*S*)-(−)-diphenyl-*N*-(1-phenylethyl)acetamide showing the same specific rotation as amide directly prepared from starting (*S*)-(−)-1-phenylethylamine and diphenylacetyl chloride ($[\alpha]^{25}D$ −39.6°, *c* = 1.2, $CHCl_3$).

The scope of Scheme I is limited by (i) the thermal lability of the resulting ketenimines and (ii) the availability of reasonably stable ketenes. As a guide for point (i), we observed that the thermal thresholds for reaction of the diphenylketenimines in Table II are 6, ~125°; 7, ~70°; 8, 50°; 9 ≳ 25°. With regard to (ii), it should be possible to extend this synthesis to ketenimines derived from other ketenes if the self-reactions of the latter do not interfere.

Table I
Properties of the Alkylaminotriphenylphosphonium Bromides and Triphenylphosphinalkylimines

			$[Ph_3PNHCRR'R'']^+Br^-$ [a]			$Ph_3P{=}NCRR'R''$ [b]		
R	R′	R″	Mp, °C	Registry no.	Nmr (CD_3Cl, δ)	Mp, °C	Registry no.	Nmr (CCl_4, δ)
Ph	H	H	195–197	52826-42-3	4.33 (2 H) q, 7.2–8.1 (20 H) m, 2.03 (1 H) s	137–138	52826-45-6	4.43 (2 H) d,[c] 7.0–8.0 (20 H) m
Ph	CH_3	H	156–157[d] 116–117[e]	52826-43-4 52918-35-1	1.87 (3 H) q, 4.13 (1 H) m, 2.17 (1 H) s, 7.1–8.1 (20 H) m	67–68[d] oil[e]	52826-46-7 52882-00-5	1.43 (3 H) q,[f] 4.37 (1 H) m,[c] 7.0–8.0 (20 H) m
Ph	Ph	H	267–269	52826-44-5	2.10 (1 H) s, 5.07 (1 H) q, 7.1–8.1 (25 H) m	129–131	52826-47-8	5.33 (1 H) d,[c] 7.0–8.0 (25 H) m
CH_3	CH_3	CH_3	165–167	799-51-9	1.33 (9 H) s, 7.2–8.2 (15 H) m, 2.37 (1 H) s	146–147	13989-64-5	1.17 (9 H) d,[f] 7.0–8.0 (15 H) m

[a] All isolated yields are in excess of 95%. [b] All isolated yields are in excess of 75%. [c] *J* (P = N-CH-) ~20 Hz. [d] Racemic modification. [e] *S*-(−) compound. [f] *J* (P = N-C-CH_3) ~1 Hz.

Table II
Important Data on the Diphenyl-*N*-(substituted)ketenimines

Ketenimines	Isolated Yield,[a] %	Nmr (CCl_4, δ)	Ir (cm^{-1})
6[b]	75–80	1.40 (9 H) s, 7.1–7.4 (10 H) m	2020
7[c]	65–70	4.73 (2 H) s, 7.0–7.4 (15 H) m	2020
8[d]	80–85	1.65 (3 H) d, 4.88 (1 H) q, 7.0–7.4 (15 H) m	2020

[a] After chromatography on alumina. [b] See ref 6 for combustion data. [c] Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94. Found: C, 88.94; H, 6.14; N, 4.90. [d] Calcd for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.74; H, 6.52; N, 4.65.

Experimental Section[7]

Alkylaminotriphenylphosphonium Bromides. Into a 300-ml three-necked flask equipped with a pressure-equalized addition funnel, a reflux condenser with a drying tube and an efficient electric stirrer was added 100 ml of benzene (reagent) and 0.1 mol of triphenylphosphine. The solution was cooled in an ice bath and 0.1 mol of bromine was added dropwise to the stirred solution over 0.5 hr. The mixture was stirred for an additional 0.5 hr (bromine color discharged), and a mixture of 0.1 mol of triethylamine and 0.1 mol of primary amine was added dropwise at ice bath temperature over 0.5 hr. The mixture was stirred for 1 hr at ice bath temperature, and the resulting precipitate was collected, washed with ether, and then water. The solid was dissolved in 50 ml of chloroform and crystallized by addition of 500 ml of ethyl acetate. Isolated yields were in excess of 95% in all cases.

Triphenylphosphinalkylimines. Into a 500-ml flask equipped with a reflux condenser fitted at the top with a nitrogen inlet tube, and arranged for magnetic stirring, was placed 20 mmol of the above prepared alkylaminophosphonium bromide, 50 mmol of potassium hydroxide pellets, and 250 ml of anhydrous ether. The mixture was stirred under nitrogen for 20–40 hr at room temperature. The mixture was then filtered and the ether removed *in vacuo*. The resulting solid was crystallized from cyclohexane. The isolated yields of the triphenylphosphinalkylimines were in excess of 75% in all cases.

Diphenyl-*N*-(substituted)ketenimines. Into a 500-ml three-necked flask equipped with a pressure-equalized dropping funnel fitted at the top with a nitrogen inlet tube and an efficient electric stirrer was placed 7 mmol of the above prepared triphenylphosphinalkylimine in 200 ml of anhydrous ether. Diphenylketene[8] dissolved in 30 ml of anhydrous ether was added dropwise to the stirred solution over 0.5 hr at room temperature. The mixture was stirred an additional 1 hr and the ether solution was washed three times with ice–water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting residue was chromatographed on basic alumina (Woelm) which had been dried at 125° for 2 hr. The ketenimine was recovered in an early fraction by eluting with ether–petroleum ether (4:1). Ketenimines **6**, **7**, and **8** were prepared in this way.

In the case of the preparation of diphenyl-*N*-(diphenylmethyl)ketenimine (**9**), the characteristic ketenimine band at 2020 cm^{-1} was noted in the ir of the crude reaction mixture. However, after concentration of the ether solution, the 2020-cm^{-1} band was gone. Chromatography yielded a material identified as 2,2,3,3-tetraphenylpropionitrile by comparison with a sample independently prepared by a phase transfer reaction.[9]

(*S*)-(−)-Diphenyl-*N*-(1-phenylethyl)ketenimine. (*S*)-(−)-**8** was prepared by the above procedures starting from (*S*)-(−)-1-phenylethylamine (Norse Chemical Co., Santa Barbara, Calif.). The optical purity of (*S*)-(−)-**8** was demonstrated as follows. (*S*)-(−)-**8** was hydrolyzed to the corresponding amide by a slight modification of a procedure described by Stevens and Singhal.[5] To a solution of 100 mg of (*S*)-(−)-**8** in 5 ml of acetone was added 0.5 ml of 4 *N* hydrochloric acid. The mixture was allowed to stand at room temperature for 2 hr. The solution was then cooled to 5° and water was added slowly until no further white precipitate formed. The mixture was placed in a refrigerator (5°) overnight and then filtered. The solid was collected, dried, and recrystallized from cyclohexane–hexane to give a 95% yield of amide, mp 116.0–116.5°, $[\alpha]^{25}D$ −39.6° (c = 1.2, $CHCl_3$). Amide showing the same properties and specific rotation was prepared by conventional procedures from (*S*)-(−)-1-phenylethylamine and diphenylacetyl chloride.

Registry No.—**6**, 26149-14-4; **7**, 52826-48-9; (*S*)-(−)-**8**, 52826-49-0; (*S*)-(−)-**8** amide derivative, 52826-50-3; **9**, 52826-51-4; benzylamine, 100-46-9; (±)-1-phenylethylamine, 618-36-0; (*S*)-(−)-1-phenylethylamine, 2627-86-3; diphenylmethylamine, 91-00-9; *tert*-butylamine, 75-64-9; triphenylphosphine, 603-35-0; bromine, 7726-95-6; diphenylketimine, 52826-52-5.

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(7) Melting points are uncorrected. Combustion analyses were done by Elek Microanalysis Laboratory, Torrance, Calif. All nmr spectra were obtained on a Varian T-60 NMR Spectrometer. All infrared spectra were recorded on a Perkin-Elmer 337 spectrometer. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter. Concentration units are g/100 ml.
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A New Route to 2-Vinylaziridines and an Unusual Intramolecular Analog of the SN2′ Reaction Leading to Aziridine Ring Formation

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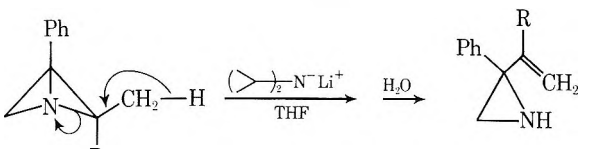
Received July 22, 1974

N-Unsubstituted 2-vinylaziridines have been obtained from butadiene[1a] and isoprene[1b] by modification of the Wenker aziridine synthesis, and as by-products in hydride reductions of isophorone oxime.[1c] N-Substituted 2-vinylaziridines have been synthesized *via* nitrene precursors and butadienes[2]

We report here a new method for the synthesis of certain N-unsubstituted 2-vinylaziridines by treatment of 2-methyl-substituted 1-azabicyclobutanes with strong base. Thus we have obtained 2-phenyl-2-vinylaziridine (**1**) and 2-phenyl-2-(2-propenyl)aziridine (**2**) from the reaction of *exo*-2-methyl-3-phenyl-1-azabicyclobutane[3] and 2,2-dimethyl-3-phenyl-1-azabicyclobutane,[3] respectively, with lithium diisopropylamide in THF.



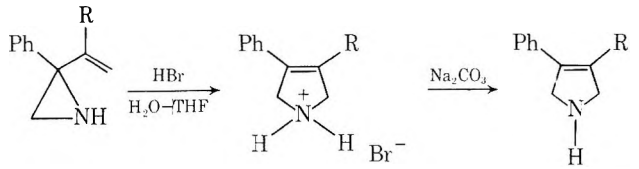
R = H, CH_3

1, R = H
2, R = CH_3

The E2 or E1cB type of elimination which is occurring here involves the formation of an aziridinamide anion as a leaving group. It is noteworthy that such loss of a strongly basic amide anion is probably unknown to occur in elimination reactions.[4] The concommitant relief of ring strain is probably an important factor which allows the above reaction to proceed; in addition, coordination of Li^+ to the N of the azabicyclobutane may play an important role in giving the nitrogen more leaving-group character akin to that of the positively charged N in ammonium salts which can undergo Hofmann-type elimination.

2-Vinylaziridines are of interest as possible substrates for conversion to Δ^3-pyrrolines *via* thermal isomerization[5]

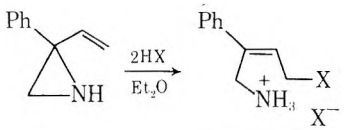
in analogy to the vinylcyclopropane–cyclopentene rearrangement.[6] Hence we examined the pyrolysis of **1** and **2** in high-boiling solvents. Heating **1** in decalin at 160–170° for periods of 1–3 hr led to partial decomposition of **1**, but no peaks corresponding to Δ^3-pyrroline **3** were observed in the nmr spectrum of the crude product. Similarly, heating **2** in decalin at 175–180° (2 hr under N_2) and in refluxing phenetol [bp 171–174° (3 hr, N_2)] led to complete decomposition of **2**, but no formation of Δ^3-pyrroline **4** was observed as evidenced by lack of absorption for $-CH_2N-$ in the δ 2.5–4.0 region of the nmr spectra of the crude products. No change occurred when **2** was heated in refluxing xylene (~140°) for 2 hr.



1, 2 3·HBr, R = H 3, R = H; 4, R = CH_3

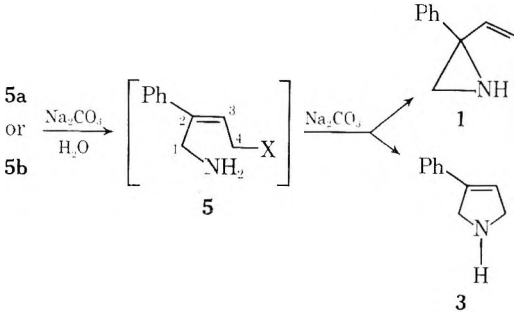
A simple procedure was finally developed whereby **1** could be converted to **3** in fairly high yield. Treatment of **1** with HBr–H_2O in THF for 6 hr at 25–30° led to the formation of the hydrobromide salt of **3** in 70% yield. Treatment of **3** · HBr with Na_2CO_3 afforded the free Δ^3-pyrroline **3**. Attempts to develop a similar route to **4** by way of a clean conversion of **2** to **4** · HBr or **4** · HCl came to naught.

In considering the reaction of **1** with HBr–H_2O–THF which led directly to **3** · HBr, it was presumed that **5a** was a likely intermediate. Indeed, in subsequent work it was found that when **1** is treated with gaseous HBr (or HCl) in anhydrous ether, it is possible to isolate **5a** (or **5b**) directly.



1 5a, X = Br; b, X = Cl

Neutralization of **5a** with Na_2CO_3 in H_2O led, surprisingly, to a mixture of **1** and **3** in a ratio of 1:1. Similarly, **5b** gave a 6:5 mixture of **1** and **3**.



The formation of **3** is taken as proof of the *Z* stereostructures drawn for **5a** and **5b**. The concommitant formation of **1** as a major product suggests that the approach of N in bonding to C-2 from above the plane of the carbon skeleton of **5** can be, with the aid of the C-2–C-3 π system, synchronous with the departure of X^- from above or below the plane of the carbon skeleton. Whereas the π system can be intimately involved in the stabilization of the transition state of this process leading to **1**, which has its intermolecular analogy in the SN2′ reaction, it is orthogonal to the collinear N---C---X system involved in the transition state leading to **3** which has its intermolecular analogy in the SN2 process. Hence, the stabilization afforded by the involvement of the π system in the former SN2′-like process apparently can compensate for the appreciable strain energy which must be introduced during the simultaneous formation of the three-membered ring system, and thus allows this SN2′-like process leading to aziridine ring formation to compete effectively with five-membered pyrroline ring formation which would normally appear to be the transformation more likely to occur.[7,8]

Experimental Section[9]

2-Phenyl-2-vinylaziridine (1). *n*-Butyllithium (0.036 mol; 15.3 ml of a 21.3% solution in hexane; Alfa Inorganics) was added dropwise to a solution of *exo*-2-methyl-3-phenyl-1-azabicyclobutane[3] (3.0 g, 0.021 mol) and diisopropylamine (3.6 g, 0.036 mol) in 65 ml of anhydrous THF during a period of 6–10 min under N_2 while stirring vigorously. The temperature of the reaction was maintained at 35° for 5 hr. Water (40 ml) was added and the resulting mixture was extracted with CH_2Cl_2; the extracts were combined and dried over anhydrous K_2CO_3. Evaporation of the solvent *in vacuo* left an orange oil. Distillation afforded 1.45 g (48%) of 2-phenyl-2-vinylaziridine (**1**), bp 58–60° (0.4 mm), which was pure enough for most purposes. A sample of analytically pure **1** was obtained by evaporative distillation: bp 55–60° (0.4 mm); nmr ($CDCl_3$) δ 0.90 (br s, 1), 2.07 (s, 1), 2.13 (s, 1), 4.93 (dd, 1, J = 17, 1.5 Hz), 5.12 (dd, 1, J = 10, 1.5 Hz), 5.85 (dd, 1, J = 17, 10 Hz), 7.33 (m, 5); ir (CCl_4) 3310, 1632, 1220, 1139, 1108, 918, 890, 692 cm^{-1}; uv max (cyclohexane) 198 nm (ϵ 24,000), 243 (1300 sh). *Anal.* Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.80; H, 7.62; N, 9.62.

2-Phenyl-2-(2-propenyl)aziridine (2). *n*-Butyllithium in hexane (0.038 mol; 16.2 ml of a 21.3% solution) was added dropwise to a solution of 2,2-dimethyl-3-phenyl-1-azabicyclobutane[3] (3.0 g, 0.019 mol) and diisopropylamine (3.8 g, 0.038 mol) in 40 ml of anhydrous THF during a period of 6–10 min at room temperature and under N_2 while stirring vigorously. Stirring was continued for 7 hr at 47°. Workup as described for **1** afforded 1.55 g (52%) of 2-phenyl-2-(2-propenyl)aziridine (**2**) [bp 60–63° (0.3 mm)]. Redistillation afforded analytically pure **2**: bp 60–63° (0.3 mm); nmr ($CDCl_3$) δ 0.98 (br s, 1), 1.74 (m, 3), 2.05 (s, 1), 2.18 (s, 1), 4.98 (m, 1), 5.05 (m, 1), 7.33 (m, 5); ir (CCl_4) 3310, 1645, 1230, 1190, 1140, 910-870, 690 cm^{-1}; uv max (cyclohexane) 198 nm (ϵ 26,000), 215 (8600sh), 258 (366). *Anal.* Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.65; H, 8.29; N, 8.78.

Δ^3-3-Phenylpyrroline Hydrobromide (3 · HBr). A solution of 48% HBr (sp. gr. 1.5; 0.42 g, 0.0025 mol) in 10 ml THF was slowly added during *ca.* 30 min to a solution of 2-phenyl-2-vinylaziridine (**1**) (0.30 g, 0.00207 mol) in 15 ml of THF while stirring under N_2. Stirring was continued for 6 hr at 25–30° under N_2. Upon reduction of the volume of the solution to *ca.* 8 ml, small needle-like crystals separated. The crystals were filtered and washed with THF–ether (1:1). Reduction of the volume of the combined mother liquor and washings and addition of ether caused further precipitation. The total yield of crystalline **3** · HBr was 0.32 g (70%) which was pure by nmr assay. Recrystallization from acetonitrile gave analytically pure **3** · HBr: mp 159.5–160.5°; nmr (D_2O) δ 4.18 (m, 2), 4.32 (m, 2), 6.13 (quintet, 1, J = 2 Hz), 7.32 (s, 5); ir (KBr pellet) 3000–2580, 1575, 1400, 1150, 1040, 750, 690 cm^{-1}; uv max (EtOH) 250 nm (ϵ 13,300). *Anal.* Calcd for $C_{10}H_{12}NBr$: C, 53.12; H, 5.35; N, 6.19. Found: C, 52.95; H, 5.31; N, 6.17.

Δ^3-3-Phenylpyrroline (3). A solution of **3** · HBr (140 mg, 0.62 mmol) in 5 ml of H_2O was added dropwise to a stirred solution of Na_2CO_3 (0.3 g) in 25 ml of H_2O. Extraction of the resulting white suspension with CH_2Cl_2 followed by drying (K_2CO_3) and evaporation of the extracts afforded **3** (76 mg; 85% yield) as a pale yellow solid. Sublimation [50° (0.2 mm)] gave small crystals of **3**: mp 120–125°; nmr ($CDCl_3$) δ 2.66 (br s, 1), 3.77–4.22 (symmetrical m, 4), 6.16 (quintet, 1, J = 2 Hz), 7.27 (m, 5); ir (KBr) 3440, 1600, 1575, 1400, 1050, 750, 698 cm^{-1}; ir (CH_2Cl_2) 3360, 1603, 1578, 1500, 1410, 1070, 1040, 820 cm^{-1}; uv max (EtOH) 254 nm (ϵ 11,800). The results of three analyses (two of sublimed material) were erratic and not in good agreement with theory; the combined C, H, and N percentages in each case totaled less than 100% suggesting that some air oxidation of the samples had occurred before analysis.

(*Z*)-1-Amino-4-bromo-2-phenyl-2-butene Hydrobromide (5a). Gaseous HBr was rapidly passed through a solution of 2-phenyl-2-vinylaziridine (200 mg, 1.4 mmol) in 20 ml of ether. A pale purple precipitate (350 mg) formed. Recrystallization from aceto-

nitrile yielded 140 mg (34%) of **5a** as a white amorphous solid. An additional recrystallization afforded analytically pure **5a:** mp 148.5–150° (uncor.); nmr (DMSO-d_6) δ 4.10 (br s, 2), 4.46 (d, 2, J = 8.5 Hz), 6.35 (t, 1, J = 8.5 Hz), 7.47 (m, 5), 8.13 (broad peak, 3); nmr (D_2O) δ 4.34 (br s, 2), 4.40 (d, 2, J = 8.5 Hz), 6.43 (t, 1, J = 8.5 Hz), 7.56 (s, 5); ir (KBr) 3020–2600, 1595–1580, 1490, 1200, 1110, 760, 690 cm^{-1}; uv max (EtOH) 252 nm (ϵ 11,700). *Anal.* Calcd for $C_{10}H_{13}NBr_2$: C, 39.12; H, 4.27; N, 4.56. Found: C, 39.24; H, 4.26; N, 4.51.

(*Z*)-1-Amino-4-chloro-2-phenyl-2-butene Hydrochloride (5b). Gaseous HCl was rapidly passed through a solution of 2-phenyl-2-vinylaziridine (**1**) (200 mg, 1.4 mmol) in 20 ml of ether. A pale orange precipitate (200 mg) which was obtained afforded 120 mg (40%) of **5b** upon recrystallization from acetonitrile. One additional recrystallization gave analytically pure **5b:** mp 154–155° (uncor); nmr (DMSO-d_6) δ 4.03 (br s, 2), 4.56 (d, 2, J = 8 Hz), 6.24 (t, 1, J = 8 Hz), 7.46 (m, 5), 8.45 (broad peak, 3); nmr (D_2O) δ 4.18 (br s, 2), 4.35 (d, 2, J = 8 Hz), 6.18 (t, 1, J = 8 Hz), 7.43 (s, 5); ir (KBr) 3000–2610, 1590, 1210, 1110, 1000–990, 770, 696 cm^{-1}; uv max (EtOH) 245 nm (ϵ 11,600). *Anal.* Calcd for $C_{10}H_{13}NCl_2$: C, 55.06; H, 6.01; N, 6.42. Found: C, 54.56; H, 5.95; N, 6.40.

Neutralization of 5a. The hydrobromide **5a** (60 mg, 0.20 mmol) was dissolved in DMSO and treated with Na_2CO_3 as described below for **5b.** Following the usual workup procedure, the nmr spectrum of the crude product showed that **1** and **3** were present in a ratio of 1:1. Approximately 10% of other impurities were also present.

Neutralization of 5b. A solution of **5b** (60 mg, 0.28 mmol) in 0.6 ml of DMSO (or alternatively, 2 ml of H_2O) was rapidly added to a solution of 0.4 g of Na_2CO_3 in 20 ml of water with stirring. Stirring was continued for 10 min. The mixture was extracted with CH_2Cl_2. The extracts were combined, dried over K_2CO_3, and evaporated *in vacuo*. An nmr spectrum of the crude product showed the presence of only two compounds, **1** and **3**. The ratio of **1** to **3** was 6:5 by nmr assay.

Acknowledgments. We thank the Alfred P. Sloan Foundation, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support.

Registry No.—**1,** 52906-57-7; **2,** 52906-58-8; **3,** 52906-59-9; **3** HBr, 52906-60-2; **5a,** 52951-32-3; **5b,** 52906-61-3; *exo*-2-methyl-3-phenyl-1-azabicyclobutane, 35903-66-3; 2,2-dimethyl-3-phenyl-1-azabicyclobutane, 35903-67-4; diisopropylamine, 108-18-9.

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(9) All melting points and boiling points are uncorrected. The following spectrometers were used: nmr, Varian A-60A; ir, Perkin-Elmer 457; uv, Cary 14. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Bridgehead Nitrogen Heterocycles. VIII. Dimroth Rearrangement of 3*H*-1,2,4-Thiadiazolopyrimidines[1]

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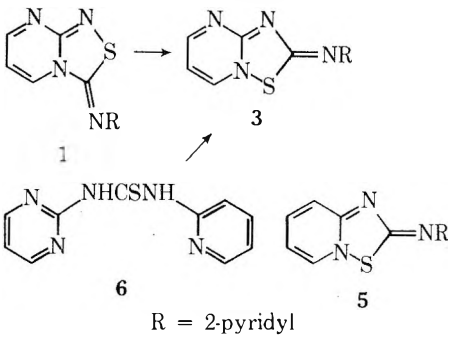
Received July 22, 1974

In a recent publication[2] the reaction of perchloromethyl mercaptan with 2- and 4-aminopyrimidines to give derivatives of the 3*H*-1,2,4-thiadiazolo[4,3-*a*]- and -[4,3-*c*]pyrimidine systems **1** (R = substituted-2-pyridyl or aryl) and **2** was described. Ring closure to the isomeric 2*H*-1,2,4-thiadiazolo[2,3-*a*]- and -[2,3-*c*]pyrimidine systems **3** (R = substituted-2-pyridyl or aryl) and **4** was excluded on the basis of the similar spectral characteristics of **1** and **2** and the 3*H*-1,2,4-thiadiazolo[4,3-*a*]pyridine[3] system. Confirmation of the initial structural assignments has now been obtained by the isolation and characterization of systems **3** and **4** by Dimroth-type rearrangement[4a] of **1** and **2** and by the independent synthesis of **3.**

Dimroth-type rearrangements have been reported[4b] in a variety of ring-fused pyrimidine systems and the *s*-triazolo[4,3-*a*]- and -[4,3-*c*]pyrimidine systems have been found to undergo facile rearrangement in either acid or alkaline medium.[5,6] It was therefore anticipated that systems **3** and **4** could be prepared by the Dimroth-type rearrangements of **1** and **2** and, indeed, treatment of 3-(2-pyridylimino)-3*H*-1,2,4-thiadiazolo[4,3-*a*]pyrimidine (**1,** R = 2-pyridyl) with either 10% ethanolic HCl or 10% ethanolic NaOH resulted in the formation of 2-(2-pyridylimino)-2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine (**3,** R = 2-pyridyl).



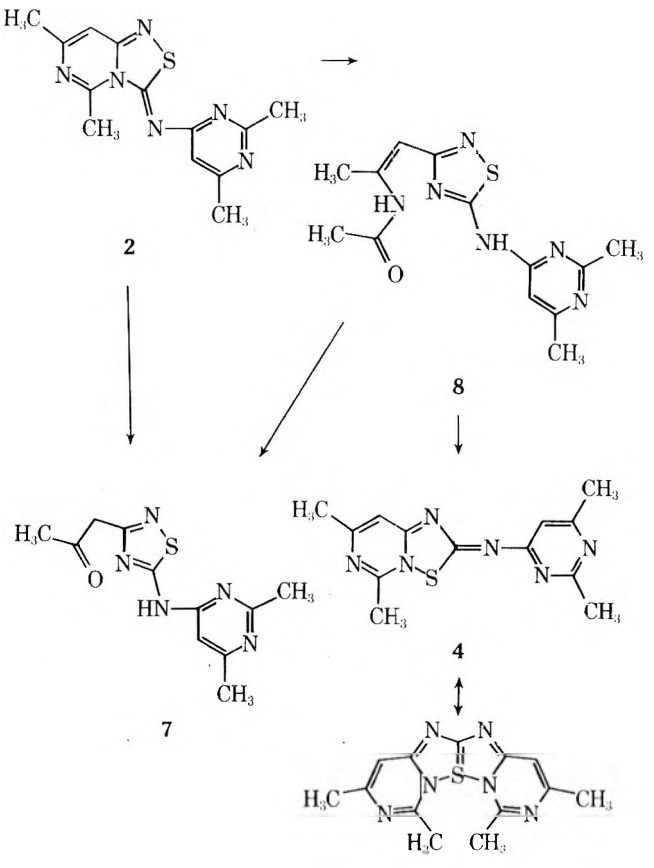
R = 2-pyridyl

The structure of **3** is based on the close relationship of its spectral data[7] to that of **5** (R = 2-pyridyl) and on its alternative synthesis by the sulfuryl chloride oxidation of thiourea **6.**

Under similar conditions 5,7-dimethyl-3-(2,6-dimethyl-4-pyrimidylimino)-3*H*-1,2,4-thiadiazolo[4,3-*c*]pyrimidine (**2**) gave no rearranged products; with 10% ethanolic HCl a product for which structure **7** is best in accord with the spectral and analytical data was obtained. Similar results have been obtained[6,8] in the Dimroth rearrangement of the *s*-triazolo[2,3-*c*]- and -[4,3-*c*]pyrimidine systems. Attempted rearrangement in 10% ethanolic NaOH gave a product which corresponded to the addition of water to the starting material. All available data are in agreement with its formulation as Dimroth intermediate **8** and the isolation of such intermediates, although rare, is not without precedent.[9] Hydrolysis of **8** in 10% ethanolic HCl again resulted in the formation of ketone **7** (Scheme I).

Refluxing **8** in $POCl_3$ for 1 hr resulted in the formation of 5,7-dimethyl-2-(2,6-dimethyl-4-pyrimidylimino)-2*H*-1,2,4-thiadiazolo[2,3-*c*]pyrimidine (**4**). It is particularly interesting to note that the nmr spectrum of **4** showed only two signals for the four methyl groups and a single signal for the two aromatic protons suggesting that structure **4**

Scheme I



may best be represented as a resonance hybrid (4 ↔ 4a) reminiscent of the 1,6,6a-S^{IV}-trithiapentalenes.[10] Similar conclusions have been drawn[7] in order to explain the properties of 5 (R = 2-pyridyl).

Experimental Section[11]

2-(2-Pyridylimino)-2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine[12] (3, R = 2-pyridyl). 3-(2-Pyridylimino)-3*H*-1,2,4-thiadiazolo[4,3-*a*]pyrimidine (0.23 g) was suspended in a stirred solution of 10% HCl (10 ml) and ethanol (20 ml). The reaction mixture quickly achieved homogeneity and was stirred for 3 hr before being neutralized with $NaHCO_3$. The solvent was removed from the reaction mixture and the residue was extracted with a $CHCl_3$–H_2O mixture. Drying of the $CHCl_3$ layer over Na_2SO_4 and subsequent evaporation to dryness gave a yellow solid which, when treated with acetone (*ca.* 3 ml), gave pale yellow, irregular prisms: 0.20 g (87%); mp 254–255° dec; ir (KBr) 3000 (CH), 1620 (C=N) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 344 nm (log ϵ 4.28), 293 (4.26), 247 (4.16), 235 (4.18), 215 (4.17); nmr (D_2O) δ 6.47–8.25 (m, 7, aromatic); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 229 (100).

Anal. Calcd for $C_{10}H_7N_5S$: C, 52.38; H, 3.08; N, 30.55. Found: C, 52.15; H, 2.99; N, 30.32.

***N*-(2-Pyridyl)-*N'*-(2-pyrimidyl)thiourea (6).** *S*-Methyl *N*-(2-pyridyl)dithiocarbamate[13] (14.7 g), 2-aminopyrimidine (7.6 g), and toluene (200 ml) were refluxed for 18 hr. Filtration of the cooled reaction mixture gave a cream solid which crystallized from ethanol as colorless, matted needles: 9.1 g (49%), mp 203–204° dec; ir (KBr) 3200 (NH), 3000 (CH) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 287 nm (log ϵ 4.44), 270 (4.38); nmr ($CDCl_3$) δ 7.20, 7.83, 8.85 (3 m, 7, aromatic), 8.50, 9.60 (2 broad s, 2, NH); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 231 (100).

Anal. Calcd for $C_{10}H_9N_5S$: C, 51.93; H, 3.92; N, 30.28. Found: C, 51.70; H, 3.76; N, 30.47.

Alternative Synthesis of 3. Sulfuryl chloride (2.80 g) in dry $CHCl_3$ (10 ml) was added to a stirred solution of 6 (4.60 g) and dry $CHCl_3$ (100 ml). After refluxing for 15 min the reaction mixture was cooled and filtered. The precipitate was dissolved in H_2O and neutralized with $NaHCO_3$. The aqueous solution was extracted with $CHCl_3$ which was separated and dried over Na_2SO_4. Evaporation to dryness gave a yellow solid which, when treated with acetone, gave pale yellow, irregular prisms, identical in all respects with 3: 1.0 g (22%), mp 254–255° dec, mmp 254–255° dec.

3-Acetonyl-5-(2,6-dimethyl-4-pyrimidylamino)-1,2,4-thiadiazole (7). The thiadiazolopyrimidine 2 (0.20 g) was stirred for 3 hr in 10% HCl (10 ml) and ethanol (10 ml). Neutralization with $NaHCO_3$ and filtration of the resulting precipitate gave a colorless solid which crystallized from aqueous ethanol as colorless, matted needles: 0.17 g (92%), mp 185–186°; ir (KBr) 3350 (NH), 3000 (CH), 1700 (CO), 1620 (C=N) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 290 nm (log ϵ 4.29), 260 sh (3.82); nmr ($CDCl_3$) δ 2.22, 2.40, 2.58 (3 s, 9, CH_3), 3.40 (broad s, 1, NH), 3.95 (s, 2, CH_2), 6.78 (s, 1, aromatic); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 263 (56).

Anal. Calcd for $C_{11}H_{13}N_5OS$: C, 50.17; H, 4.97; N, 26.60. Found: C, 50.34; H, 5.02; N, 26.58.

3-(2-Acetylamino-1-propen-1-yl)-5-(2,6-dimethyl-4-pyrimidylamino)-1,2,4-thiadiazole (8). The thiadiazolopyrimidine 2 (0.20 g) and 10% NaOH solution (10 ml) and ethanol (10 ml) were stirred for 2 hr at room temperature. Subsequent neutralization with 10% HCl and filtration gave a colorless solid which crystallized from $CHCl_3$ as colorless, irregular prisms:[14] 0.20 g (94%); mp ~270° dec; ir (KBr) 3250 (NH), 3000 (CH), 1680, 1670, 1610 (CO, NC=C, C=N) cm^{-1}; $\lambda_{max}^{CHCl_3}$ 287 nm (log ϵ 4.64); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 304 (100).

Anal. Calcd for $C_{13}H_{16}N_6OS$: C, 51.29; H, 5.30; N, 27.61. Found: C, 51.14; H, 5.21; N, 27.41.

Hydrolysis of 8. The acetyl derivative 8 (0.10 g) was stirred for 2 hr in 10% HCl (5 ml) and ethanol (5 ml). Neutralization with $NaHCO_3$ and subsequent reduction in volume gave a colorless solid identical in all respects with 7: 0.08 g (92%); mp 185–186°, mmp 185–186°.

5,7-Dimethyl-2-(2,6-dimethyl-4-pyrimidylimino)-2*H*-1,2,4-thiadiazolo[2,3-*c*]pyrimidine (4). The acetyl derivative 8 (0.20 g) and $POCl_3$ (20 ml) were refluxed for 1 hr. The reaction mixture was evaporated and the residue was triturated with methanol in order to decompose any residual $POCl_3$. After the methanol had been removed, the concentrate was dissolved in H_2O and neutralized with $NaHCO_3$. The aqueous solution was extracted with $CHCl_3$ and the $CHCl_3$ extract was separated and dried over Na_2SO_4. Evaporation to dryness gave a cream solid which crystallized from ethanol as colorless needles: 0.06 g (32%); mp ~370° dec; ir (KBr) 3050 (CH), 1620 (C=N) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 344 nm (log ϵ 4.63), 255 sh (4.07), 237 (4.22); nmr ($CDCl_3$) δ 2.52, 2.83 (2 s, 6, CH_3), 7.08 (s, 1, aromatic); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 286 (100).

Anal. Calcd for $C_{13}H_{14}N_6S$: C, 54.52; H, 4.93; N, 29.35. Found: C, 54.10; H, 4.93; N, 29.07.

Registry No.—1 (R = 2-pyridyl), 40899-19-2; **2**, 40899-28-3; **3** (R = 2-pyridyl), 52856-33-4; **4**, 52906-78-2; **6**, 52827-10-8; **7**, 52827-11-9; **8**, 52827-12-0; *S*-methyl-*N*-(2-pyridyl)dithiocarbamate, 13037-46-2; 2-aminopyrimidine, 109-12-6.

References and Notes

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(3) K. T. Potts and R. Armbruster, *J. Org. Chem.*, **35**, 1965 (1970).
(4) (a) Several reviews of the Dimroth Rearrangement are available: D. J. Brown in "Mechanisms of Molecular Migrations," B. S. Thyagarajin, Ed., Wiley-Interscience, New York, N.Y. 1968, p 209; M. Wahren, *Z. Chem.*, **9**, 241 (1969); (b) P. Guerret, R. Jacquier, and G. Maury, *J. Heterocycl. Chem.*, **8**, 643 (1971).
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(12) The procedure for the alkaline rearrangement of **1** (R = 2-pyridyl) differed only in that neutralization was effected after ~10 min and gave a 73% yield of **3** (R = 2-pyridyl).
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(14) Compound **8** was too insoluble for nmr characterization.

A Mechanistic Study on Elimination Reactions over Solid Acid and Base Catalysts

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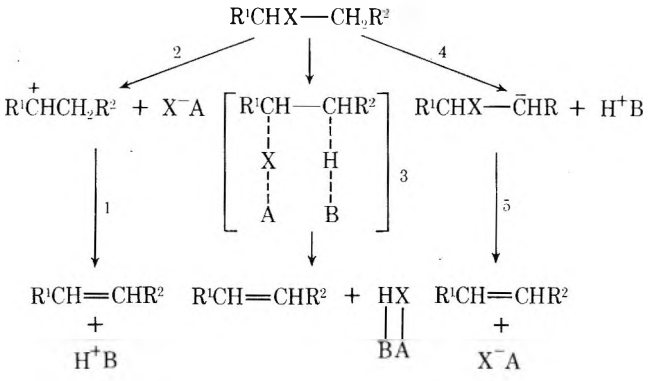
Received February 13, 1974

Possible mechanisms[2,3] of ionic HX elimination from haloalkanes over solid catalysts are summarized in Scheme I. By taking account of the rate-determining step, five

Scheme I



(A catalyst consists of acidic (A) and basic (B) sites.)

Type of Elimination Mechanism

Rate-determining step	Intermediate	Abbreviation of mechanisms
1	Carbonium ion	E1
2	Carbonium ion	$E2_{Ca}$
3	Simultaneous cleavage of C–H and C–X bonds	E2 concerted
4	Carbanion	$E2_{Cb}$
5	Carbanion	$E1_{Cb}$

kinds of mechanisms are conceivable. The abbreviations are defined based on the following concept. Suffixes Ca and Cb in the abbreviation of the mechanism mean that carbonium ions and carbanions, respectively, are involved in the elimination process as intermediates. The rate-determining step distinguishes E1 and E2. That is, the step of intermediate formation is rate determining in E2 (except for E2 concerted, which is a one-step reaction), whereas the following step is in E1. E1, E2 concerted, and $E1_{Cb}$ need no comment, although conjugated acid or base of the catalyst might play some roles in $E1_{Cb}$ or E1 over the solid catalyst. $E2_{Ca}$ and $E2_{Cb}$ seem to be possible mechanisms over solid catalysts at elevated temperatures. The differences in these mechanisms can be considered to be present in the degree of C–H or C–X bond fission of the intermediate,[4] so that these mechanisms should change continuously according to the strength of interaction between a substrate and a catalyst. For elimination reactions of a certain reactant over a series of solid catalysts, the reaction may proceed *via* an $E2_{Ca}$ mechanism on a catalyst of moderate acidity, whereas with a basic catalyst it may occur *via* an $E2_{Cb}$ process. The

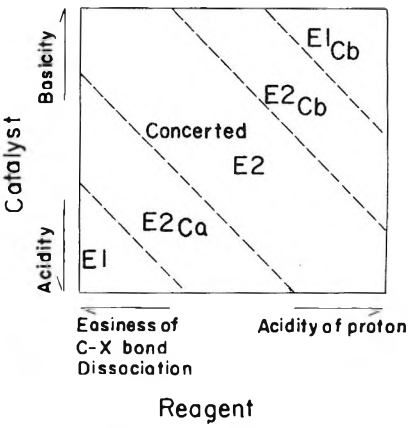


Figure 1. Schematic diagram of mechanism transitions according to the acid–base properties of catalysts and substrates. Abbreviations of mechanisms refer to the text.

E2 concerted mechanism may be possible on a catalyst which is neutral or consists of binary sites of acidity and basicity like alumina.[5] On a catalyst of which acidity or basicity is strong enough, the E1 or $E1_{Cb}$ mechanism may be realized. As for reactants, the same situation should occur. That is, a highly acidic reactant prefers a carbanion-type intermediate and a reactant in which halide is easily eliminated favors a carbonium ion-type intermediate. Continuous changes in acidity or basicity of catalysts and/or substrate structure[2c] may bring about continuous transitions of elimination mechanisms, as schematically described in Figure 1.

In an attempt to study the transitions of elimination mechanisms, the kinetic isotope effects in dehydrohalogenation of 1,2-dibromoethane and 1,1,2,2,-tetrachloroethane and product distributions from 1,1,2-trichloroethane and 1,2-dihalopropanes over some solid catalysts have been investigated. The product distributions from 1,1,2-trichloroethane and reactivity orders of some chloroalkanes over solid catalysts have been explained in terms of $E2_{Ca}$ on solid acids, $E2_{Cb}$ on solid bases, and E2 concerted on alumina in previous papers.[6] Product distributions were found to change continuously according to the acidity of the catalysts.[6] An object of the present study is to understand such a continuous change from a mechanistic aspect.

Experimental Section

Reagents. Haloethanes used were obtained from Tokyo Kasei Co. Deuterated 1,2-dibromoethane ($C_2D_4Br_2$) and 1,1,2,2-tetrachloroethane ($C_2D_4Cl_4$) (Merck) were used without further purification.

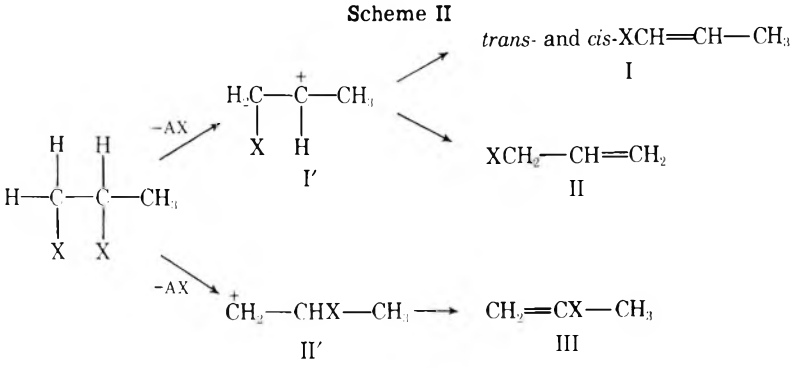
Catalysts. Silica–alumina (13% Al_2O_3), alumina, and KOH–SiO_2 were described in previous papers.

Apparatus and Procedures. Elimination reactions were observed by means of microcatalytic gas chromatography with a column of TCP (4m) at 60°. All reactions were carried out at 300° under a helium gas flow of atmospheric pressure. No occurrence of elimination was observable over the glass-wool packing, implying small contribution of simple pyrolysis. The elimination reaction was of first order under the experimental conditions, and the conversion was verified to be a linear function of the reciprocal space velocity (RSV) at low conversions. Thus, the slope of conversion/RSV gives the apparent rate constant, k (ml/g min). Experimental details have been described in previous papers.[8]

Results and Discussion

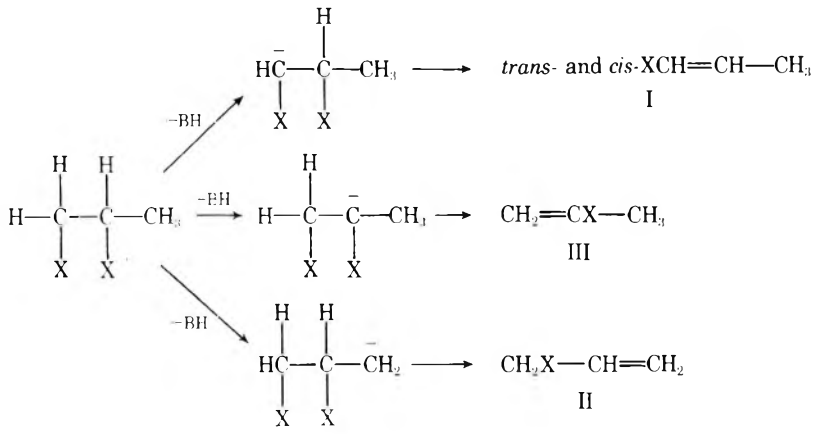
Product Distributions in Eliminations of Haloalkanes over Solid Catalysts. 1,2-Dihalopropane may give *trans*- and *cis*-1-halopropene (I), allyl halide (II), and 2-halopropene (III) through HX elimination over solid acids and bases. The reaction paths depicted in Schemes II–IV may explain formation of these products by various mecha-

Scheme II



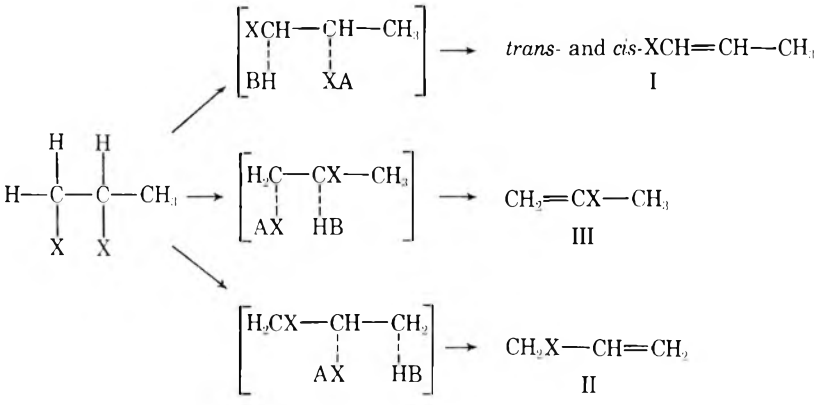
over a solid acid

Scheme III



over a solid base

Scheme IV



over alumina

nisms. Over the solid acid (Scheme II), secondary carbonium ion (I′) is more stable than a primary one (II′), leading to preferential formation of I and II relative to III. Schemes III and IV represent mechanisms for eliminations over solid base and alumina. Limited formation of II for the reaction with the solid base might be anticipated because of the lesser acidity of methyl proton compared with that of other protons. A positive charge on the secondary carbon of the intermediate assumed in the scheme may result in the preferential formation of I to that of III over alumina, although the ratio may not be so little as that over the solid acid because of the participation of protons in the reaction.

The relative proportions of unsaturated products derived from reactions of 1,2-dichloropropane, 1,2-dibromopropane, and 1,1,2-trichloroethane with silica–alumina, alumina, and KOH–SiO_2 are summarized in Table I. The selectivities calculated from Table I are shown in Table II. In Table II, one notices appreciable changes in the selectivity due to change of substituent groups. Such changes can be explained in terms of a transition of the reaction mechanism which corresponds to the change along with abscissa in Figure 1.

A marked change is observed in the III/(I + II) selectivities over silica–alumina by substitution of chlorine with bromine. The order of preferential production is I > II > III from 1,2-dichloropropane whereas it is II > I > III from 1,2-dibromopropane. Such changes can be attributable to less acidity of the proton and a weaker C–X bond in 1,2-dibromopropane which may facilitate easy formation of carbonium ion, provoking a shift from a typical $E2_{Ca}$ to an E1. For an E1 elimination from 1,2-dibromopropane, bridging structures (IV, V) would be expected to the intermediate and increase the III/(I + II) ratio because stability difference between IV and V would be decreased by bridging.

Table I
Relative Proportions of Unsaturated Products[a] from Reactions of 1,2-Dichloropropane, 1,2-Dibromopropane, and 1,1,2-Trichloroethane (%)

	Catalyst											
	Silica–alumina				Alumina				$KOH–SiO_2$			
	Product											
Reactant	*trans*-I	*cis*-I	II	III	*trans*-I	*cis*-I	II	III	*trans*-I	*cis*-I	II	III
1,2-Dichloropropane	7	54	38	0.1	2	74	14	10	46	28	Very small	26
1,2-Dibromopropane	5.5	14.4	75.0	4.5	6.8	50.7	36.5	6.0	34.9	29.6	0.1	35.5
1,1,2-Trichloroethane	7	93		0.1	19	58	23		7	2		9.1

[a] Products I, II, III refer to the text.

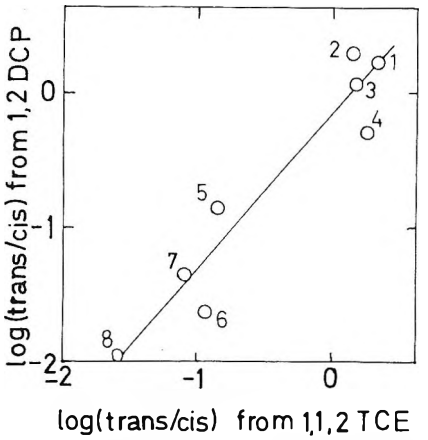


Figure 2. Continuous changes of trans/cis selectivities in elimination reactions of 1,2-dichloropropane and 1,1,2-trichloroethane: 1, $KOH–SiO_2$; 2, $NaOH–SiO_2$; 3, SrO; 4, MgO; 5, silica–alumina; 6, alumina; 7, $NiSO_4–SiO_2$; 8, $NiSO_4$.

The preferential formation of allyl bromide from IV (large II/I selectivity) is also explained by a facile elimination of methyl protons in the intermediate IV.

IV V

Decreasing III/I selectivity of 1,1,2-trichloroethane in comparison with that of 1,2-dihalopropanes on alumina may be due to a shift from a typical concerted E2 to $E2_{Ca}$ induced by the decrease of proton acidity. In $E2_{Ca}$ the stability difference of primary and secondary carbonium ions may principally govern the value of III/I selectivity. Increased II/I selectivity of 1,2-dibromopropane may also be due to the increased $E2_{Ca}$ nature because of the weaker C–Br bond, being consistent with the decreased III/I value.

Similar explanations are also applicable to reactions over the solid base. A decrease of III/I selectivity of 1,2-dihalopropanes in comparison with that of 1,1,2-trichloroethane is explained in terms of a shift in the mechanism from $E2_{Cb}$ to E2 concerted which is produced by decreased acidity of proton.

A linear relation between trans/cis selectivities of 1,2-dichloropropane and 1,1,2-trichloropropene over some solid catalysts is shown in Figure 2. Although factors influencing the trans/cis selectivity in the elimination reactions could not be discussed in the present study, the linear relation may suggest that the mechanisms shown as Schemes II–IV play important roles in the decision of this selectivity. Then, such a continuous change of the trans/cis selectivity may also be explained by the continuous change of the elimination mechanism as shown by the change along the ordinate axis in Figure 1.

Table II
Elimination Selectivities of 1,1,2-Trichloroethane, 1,2-Dichloropropane, and 1,2-Dibromopropane

	Catalyst					
	Silica–Alumina		Alumina		$KOH–SiO_2$	
	Selectivity					
Reactant	III/(I + II)[a]	II/I[a]	III/I[a]	II/I[a]	III/I[a]	II/I[a]
1,2-Dibromopropane	4.7×10^{-2}	3.86	0.10	0.64	0.53	10^{-3}
1,2-Dichloropropane	10^{-3}	0.61	0.14	0.18	0.35	Very small
1,1,2-Trichloroethane	10^{-3}[b]		0.30[b]		10^{b}	

[a] Products I, II, III from dihalopropanes refer to the text. [b] The ratio of 1,1-dichloroethylene/*trans*- and *cis*-1,2-dichloroethylene. 1,1,2-Trichloroethane (VI) has a similar structure to those of the 1,2-dihalopropanes except for their methyl groups substituted by chlorine, so that product distributions were arranged by a similar way in this table.

Table III
Kinetic Isotope Effects in the Elimination Reaction of 1,2-Dibromoethane and 1,1,2,2-Tetrachloroethane

	k_H/k_D	
Catalyst	1,2-Dibromoethane[a]	1,1,2,2-Tetrachloroethane[a]
Silica–Alumina	1.0 ± 0.1	1.5 ± 0.1
Alumina	1.0 ± 0.1	1.2 ± 0.1
KOH–Silica	1.6 ± 0.2	1.2 ± 0.1

[a] Reagent.

Changes in Kinetic Isotope Effect (k_H/k_D). Kinetic isotope effects in dehydrohalogenation of 1,2-dibromoethane and 1,1,2,2-tetrachloroethane over the solid acid and the base are summarized in Table III. Primary and secondary effects are included in these values because all hydrogens were replaced by deuteriums. The limiting value of the primary isotope effect at 300° is estimated to be 2.7.[7] On silica–alumina, the value as for 1,2-dibromoethane is unity, whereas it clearly increased for 1,1,2,2-tetrachloroethane. A similar change was also observable on alumina although the values were near unity. In contrast, the situation is reversed on KOH–silica.

Although definite mechanisms cannot be deduced from these values of kinetic isotope effect near unity, their changes are reasonably explained in terms of continuous transitions of the elimination mechanism (Figure 1) due to the acid–base character of the reagents, taking account of the relation of the kinetic isotopic effect with the elimination mechanism extensively reviewed by Fry.[8]

The acid–base natures of 1,2-dibromoethane and 1,1,2,2-tetrachloroethane concerning the ionic elimination

can be summed up as follows: (1) acidity of proton, 1,1,2,2 > 1,2 and (2) strength of C–X bond, 1,1,2,2 > 1,2 (all protons and C–X bonds of each reagent are equivalent). These factors may contribute to a shift of the mechanism from $E2_{Ca}$ of 1,2-dibromoethane to concerted E2 of 1,1,2,2-tetrachloroethane on the solid acid, increasing the value of the kinetic isotope effect. The same situation may occur on the alumina catalyst where the low acidity of the proton and a weak C–Br bond may facilitate an $E2_{Ca}$ mechanism for 1,2-dibromoethane in spite of binary sites on the catalyst. The value of the isotope effect may, thus, increase for 1,1,2,2-tetrachloroethane because the mechanism is nearer to the typical concerted E2 than that of 1,2-dibromoethane. In the case of solid base, more $E1_{Cb}$ nature of 1,1,2,2-tetrachloroethane compared with 1,2-dibromoethane gives a low value for the kinetic isotope effect for the former. Thus, changes in the selectivity and the kinetic isotopic effect in the elimination due to the change of reactants are consistently explained in terms of continuous transitions of the reaction mechanism according to the acid–base nature of reagents as described in Figure 1.

The changes in Table III may correspond to the transitions of the mechanism according to the acid–base nature of the catalyst. As for 1,2-dibromoethane, increasing the basicity of the catalyst should shift the mechanism from $E2_{Ca}$ to $E2_{Cb}$ *via* E2 concerted, as indicated by the isotope effect. Alternatively, elimination from 1,1,2,2-tetrachloroethane proceeds by an E2 concerted mechanism with acidic catalysts but shifts to an El_{Cb} mechanism *via* an $E2_{Cb}$ mechanism with basic catalysts.

Registry No.—1,2-Dichloropropane, 78-87-5; 1,2-dibromopropane, 78-75-1; 1,1,2-trichloroethane, 79-00-3; 1,2-dibromoethane, 106-93-4; 1,1,2,2-tetrachloroethane, 79-34-5; silica, 7631-86-9; alumina, 1344-28-1; KOH, 1310-58-3.

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Photolysis of 1-Methoxy-1,2,3-benzotriazole

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Received August 1, 1974

Recent experiments in our laboratory regarding the derivatives of 1-methoxy-1,2,3-benzotriazole (1) as potential pesticides prompted us to consider the photolytic decomposition of these molecules to see what harmful products would result upon the absorption of ultraviolet light. The photolysis of 1,2,3-benzotrizole (2) and several of its 1-substituted derivatives had been reported,[1-5] but the photochemistry of 1 had not been studied. Thus, we decided to photolyze 1 in several solvents in order to (a) obtain information regarding the photolytic reaction pathway and (b) determine whether a solvent effect was operative in the photolysis.

1 was prepared by treating 1-hydroxy-1,2,3-benzotriazole with sodium ethoxide and methyl iodide. Solvents ranging in polarity from cyclohexane and benzene to methanol and acetonitrile were used. All samples were 0.005 *M* in 1 degassed using a freeze–vacuum–thaw sequence and irradiated under a helium atmosphere at 300 nm for 6 hr, after which the solution had darkened to such an extent that further irradiation proved fruitless. The major products were isolated by chromatography on alumina and silica gel and identified by comparison of their spectral properties with those of known samples. The minor products were identified by comparison of their glpc retention times and tlc R_f values with those of known compounds. The results of the photolyses are listed in Table I.

Table I
The Photolysis of 1 at 3000 Å (Per Cent Yields)

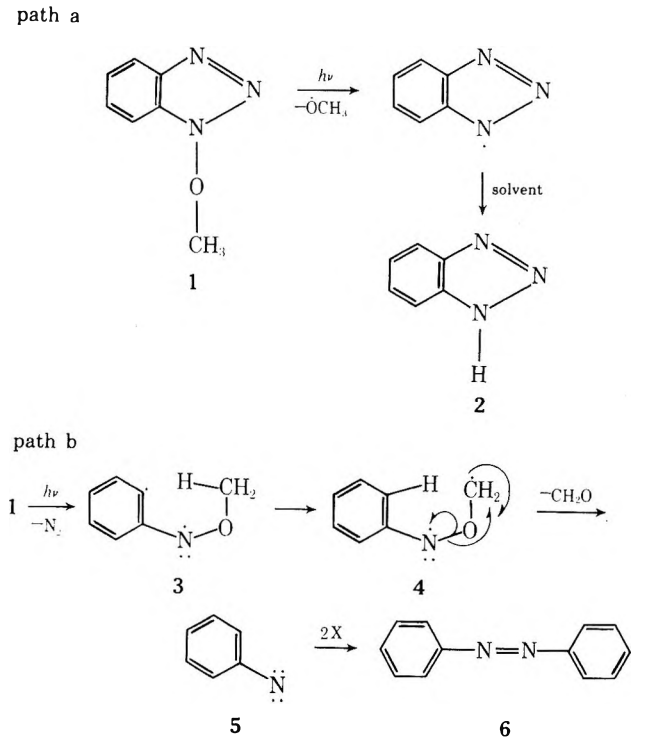
Product	In benzene	In methanol	In cyclohexane	In acetonitrile
1-Methoxy-1,2,3-benzotriazole (**1**)	13	9	15	6
Aniline		4	4	8
Benzotriazole (**2**)		9	28	
Azobenzene (**6**)	63	61	11	81
2-Aminobiphenyl	8			
Biphenyl	6			
Bicyclohexyl			8	
N-Cyclohexylaniline			24	

From Table I it is readily apparent that the 1-methoxy group is lost during the photolyses in all the solvent systems studied. The formation of 2 in the methanol and cyclohexane photolyses can most easily be pictured as forming *via* a homolytic cleavage of the N–OCH_3 linkage followed by abstraction of a hydrogen atom from the solvent (Scheme I, path a). Supporting evidence for the occurrence of this pathway came from the isolation of bicyclohexyl from the cyclohexane photolysis. The dimer expected from the methanol photolysis, ethylene glycol, was also detected. Although no 1,2,3-benzotriazole was isolated from the benzene photolysis, its initial formation by the path mentioned above is strongly suggested by the isolation of 2-aminobiphenyl and biphenyl, both of which were found in the reported photolysis of 1,2,3-benzotriazole in benzene.[2]

An interesting feature of the photolyses was the isolation of azobenzene **6** as the major product in all the solvent systems studied with the exception of cyclohexane. The absence of any product containing the N–OCH_3 linkage together with the previously reported isolation of **6** from azidobenzene *via* phenylnitrene[6] **5** suggested path b (Scheme I) as a possible way of accounting for the formation of **6** from the photolysis of **1**. **1** upon irradiation can lose a molecule of nitrogen to yield the diradical **3**, which intramolecularly or intermolecularly abstracts a hydrogen to give the new diradical **4**. **4** in turn undergoes a homolytic cleavage of the N–O bond to eliminate a molecule of formaldehyde and generate **5**. Dimerization of **5** could then yield azobenzene. The isolation of formaldehyde *via* its 2,4-dinitrophenylhydrazone in acetonitrile lent credence to the proposed path b mechanism.

It was noted above that cyclohexane was the only solvent in which **6** was not found to be the major product. How-

Scheme I



ever, the product *N*-cyclohexylaniline has been reported to be a principal product resulting from the thermal decomposition of azidobenzene in cyclohexane, where a triplet nitrene was pictured as the intermediate.[7] Thus, if both **6** and *N*-cyclohexylaniline are assumed to be formed *via* **5**, a summation of the yields of these two products would indicate that the generation of the nitrene intmediate in cyclohexane is the principal reaction pathway in cyclohexane as it is in all the other solvents studied.[8]

To check the veracity of the path b mechanism and to attempt to gain some insight into the intramolecularity or intermolecularity of the proposed H shift, **1** was photolyzed in CD_3OD. Mass spectral analysis of the azobenzene isolated from the reaction revealed that the product contained no excess deuterium. The failure of the **6** produced to have incorporated any deuterium from the solvent lends support to the proposed mechanism and strongly suggest that the hydrogen abstraction proposed in path b proceeds intramolecularly.

Using 3-methoxyacetophenone E_T = 72 kcal/mol,[9] the photolysis of **1** could be sensitized at 350 nm in all solvent systems examined. Solutions of **1** in the solvents of interest showed no reaction when irradiated at 350 nmin the absence of sensitizer. Quenching experiments were attempted using 1,3-cyclohexadiene E_T = 52.5 kcal/mol.[10] Solutions of **1** containing 1,3-cyclohexadiene, when irradiated at 300 nm, showed a definite decrease in product formation compared to equimolar solutions of **1** containing no 1,3-cyclohexadiene. The reaction, however, could not be totally quenched.

In conclusion, it appears that the photolysis of **1** in the solvent systems studied proceeds *via* two pathways. The principal pathway involves the loss of N_2 (path b). A minor mode of reaction involves cleavage of the N–OCH_3 linkage (path a).

Experimental Section

Photolyses were conducted in a Rayonet photochemical reactor at 300 or 350 nm as indicated. The infrared spectra were obtained on a Beckman IR-4 spectrophotometer. High-resolution mass spectra were obtained on a CEC-21-110 instrument. Glpc was performed on a Varian Model 1200 HYFI.

Materials. 1-Hydroxy-1,2,3-benzotriazole was prepared according to procedure of Macbeth and Price.[11] **1** was prepared by the method of Brady and Reynolds.[12]

Irradiation of 1. In a quartz vessel 80 ml of a solution (0.005 *M* in **1** in the appropriate solvent) was degassed using a freeze–vacuum–thaw sequence and irradiated at 300 nm for 6 hr. The reaction was then analyzed by glpc (6 ft, 3% SE-30 column) and thin-layer chromatography (tlc). The products were identified by comparing their retention times with those of known samples. Infrared spectra of the products isolated by column chromatography were superimposable with the infrared spectra of known samples. The major products and their per cent yields are listed in Table I. A trace of ethylene glycol was also established by glpc.

Isolation of Formaldehyde-2,4-dinitrophenylhydrazone. In a quartz vessel 80 ml of a solution of **1** (0.005 *M* in acetonitrile) was degassed and irradiated at 300 nm for 6 hr as described above. The photolysis vessel was then cooled in a chlorobenzene slush bath (−45°). The photolysis vessel was then cracked and its contents was placed in a flask containing 25 ml of a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* HCl. The solution was then brought to room temperature and refluxed for 30 min. Upon cooling platelets formed which were collected and crystallized from ethanol, mp 165–166° (lit.[13] 166°). A mixture melting point of the platelets with an authentic sample of formaldehyde-2,4-dinitrophenylhydrazone showed no melting point depression.

Irradiation of 1 in CD_3OD. In a quartz vessel a 0.005 *M* solution of **1** in CD_3OD was degassed by a freeze–vacuum–thaw sequence and irradiated at 300 nm for 6 hr. The azobenzene isolated from the reaction by column chromatography was subjected to high-resolution mass spectral analysis. The mass peaks at 182, 183, and 184 corresponding to **6** containing 0, 1, and 2 deuteriums, respectively, showed no added deuterium had been incorporated.

Sensitization of the Photolysis of 1. A solution (10 ml) 0.005 *M* in **1** in the appropriate solvent was divided into two equal parts. To one portion 0.01 ml of 3-methoxyacetophenone was added. Both samples were then placed in Pyrex vessels, degassed, and irradiated at 350 nm for 76 hr. At the end of that period glpc analysis showed that in the vessel containing the 3-methoxyacetophenone reaction had occurred while in the vessels containing no sensitizer, no product had formed.

Attempted Quenching of the Photolysis of 1. A 10-ml sample of a 0.005 *M* solution of **1** in the appropriate solvent was divided into two equal parts. To one part 0.01 ml of 1,3-cyclohexadiene was added. Both solutions were placed in quartz vessels, degassed, and irradiated at 300 nm for 3 hr. During that time aliquots were removed from each photolysis vessel and analyzed by glpc. In all the solvents investigated, the photolysis of the solution containing the 1,3-cyclohexadiene was significantly retarded relative to the solution containing no quencher. However, in no case could the reaction be completely quenched.

Registry No.—**1**, 22713-34-4.

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Halogenated Ketenes. XXVII. The Mechanism of the Dehydrohalogenation of α-Halo Acid Halides[1]

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Received May 28, 1974

The triethylamine dehydrohalogenation of α-chloropropionyl chloride produces an enolate salt which has been suggested as being an intermediate in the formation of methylchloroketene.[2] Isobutyryl chloride reacts with triethylamine to yield an acylammonium salt which is apparently the precursor to dimethylketene.[2-5] However, in the synthesis of *tert*-butylhaloketenes, we have discovered some new evidence which has prompted us to further examine the dehydrohalogenation of α-halo acid halides.

The reaction of 2-bromo-3,3-dimethylbutanoyl chloride or 2-chloro-3,3-dimethylbutanoyl chloride with triethylamine in chloroform at room temperature did not yield any detectable amount of vinyl ester, but does produce *tert*-butylbromo- and *tert*-butylchloroketenes which are stable in the reaction solution as evidenced by infrared bands at 2121 and 2110 cm^{-1}, respectively. Efforts to trap an enolate with the more effective acylating agent, trichloroacetyl chloride, were also unsuccessful. Attempts to observe either the enolate or acylammonium salt at −78° by infrared absorption were also unsuccessful. Triethylamine reacted with 2-chloro-3,3-dimethylbutanoyl chloride at −73° to produce a strong ketene absorption. This data suggest that as the steric bulk increases about the α carbon, the α proton becomes less accessible and the ketene is formed from the acylammonium salt.

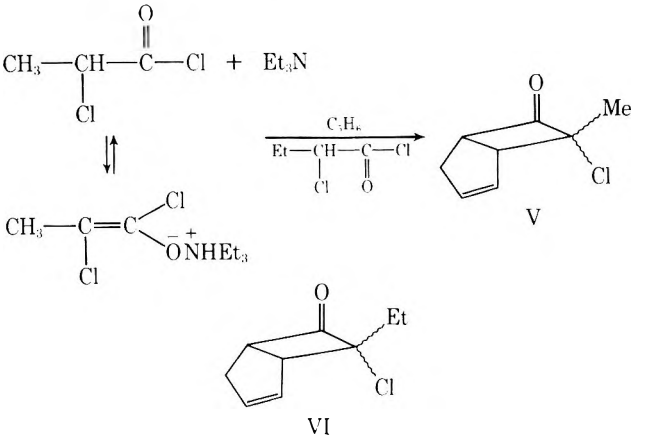
The reaction of α-chloropropionyl chloride in chloroform at −78° with triethylamine yields the enolate salt.[2] Treatment of this salt with an equimolar amount of α-chlorobutyryl chloride produced four products (Scheme I) as evidenced by vpc and confirmed by nmr. The vinyl esters were produced in a ratio of 1:1:0.7:0.6 respectively.

Vinyl esters I and II are expected to be produced by acylation of the enolate by either of the two acid halides. However, the formation of III and IV indicates that the enolate derived from α-chlorobutyryl chloride has been formed which dictates that enolate formation is reversible.

To ensure that enolate formation from α-chloropropionyl chloride and triethylamine had gone to completion, the enolate salt was isolated and washed with hexane as had previously been reported.[2] The addition of an equimolar amount of α-chlorobutyryl chloride in chloroform again produced all four vinyl esters in the same ratio as before.

When the enolate salt of α-chlorobutyryl chloride was formed at −78° and treated with an equimolar amount of α-chloropropionyl chloride, the same four vinyl esters, I–IV, were also produced but in a ratio of 1:6:5:3. This difference in vinyl ester ratios on reversing the order of addition dictates that equilibration is not the most rapid reaction and indicates that a reaction other than enolate formation is occurring at low temperature prior to equilibration. This reaction is probably ketene formation through the acylammonium salt.

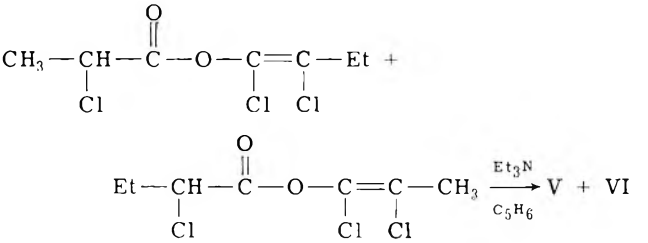
The addition of equimolar amounts of α-chlorobutyryl chloride and cyclopentadiene to the enolate salt derived from α-chloropropionyl chloride and triethylamine at −78° produced approximately equal amounts of the methylchloro- and ethylchloroketene cycloadducts with cyclopentadiene upon warming to room temperature.[6,7] There was no evidence of any vinyl ester formation.



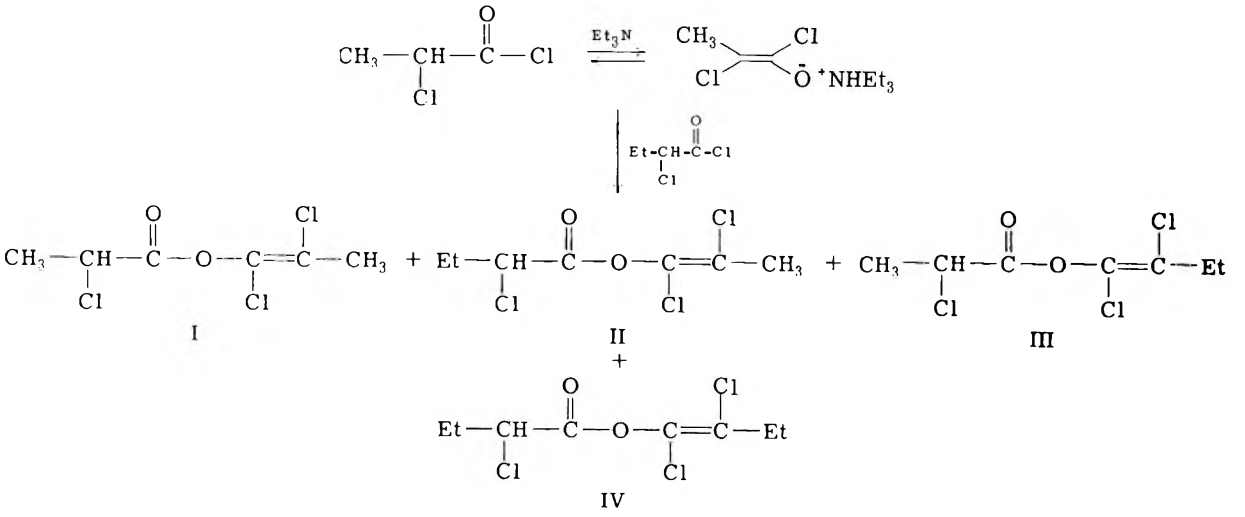
V

VI

Also, it has been found that a synthetic mixture of vinyl esters II and III in a 2:1 ratio, respectively, react with triethylamine in the presence of cyclopentadiene to yield equal mixtures of the two cycloadducts from methylchloro- and ethylchloroketenes. This elimination reaction could



Scheme I

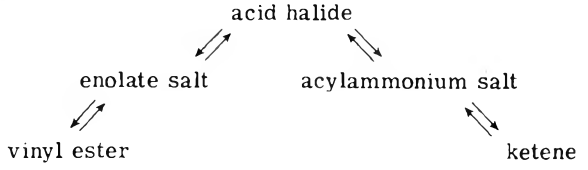


I II III IV

also take place either by nucleophilic attack on the ester carbonyl, or by formation of the vinyl ester enolate and loss of carboxylate. In either case an equal mixture of the two cycloadducts would be expected.

These results clearly demonstrate to us that the enolate forming step in the triethylamine reaction with α-halo acid halides is reversible and furthermore suggests the precursor to halogenated ketenes is the acylammonium salt.

Consequently, it has become clear that a complex series of equilibria are involved in the dehydrohalogenation of α-halo acid halides. The data are consistent with a single pathway to ketene through the acylammonium salt as illustrated.



Experimental Section

Proton nmr spectra were recorded on a Jeolco Minimar 60-Mhz and a Jeolco PS-100 nmr spectrometers employing tetramethylsilane as an internal standard and CCl_4 as a solvent. Solvents and triethylamine were distilled from sodium and stored over Linde type 4-A molecular sieve. Vpc was performed on an F & M Scientific Model 700 gas chromatograph with a 10 ft × 0.25 in. column packed with 10% SE-30 on acid washed chromosorb W (80/100).

***tert*-Butylbromo- and *tert*-Butylchloroketenes.** To a stirred solution of 0.1 mol of triethylamine in 90 ml of chloroform was added dropwise 0.1 mol of 2-bromo-3,3-dimethylbutanoyl chloride or 2-chloro-3,3-dimethylbutanoyl chloride in 10 ml of chloroform at room temperature. The ketene was observed by ir: *tert*-butylbromoketene, 2121 cm^{-1}, and *tert*-butylchloroketene, 2110 cm^{-1}. *tert*-Butylbromoketene persisted in the reaction mixture for 3 days while *tert*-butylchloroketene was observable for only 4 hr. Numerous attempts to isolate the *tert*-butylbromoketene were unsuccessful.

Attempts to trap an enolate from 2-halo-3,3-dimethylbutanoyl chloride with the starting acid halide as previously described were unsuccessful.[8] Efforts to trap an enolate with the more effective acylating agent, trichloroacetyl chloride, are described.

To a stirred solution of 0.05 mol of triethylamine in 40 ml of chloroform was added dropwise 0.05 mol of 2-chloro-3,3-dimethylbutanoyl chloride in 10 ml of chloroform at room temperature. After the addition was complete, 0.05 mol of trichloroacetyl chloride was added and the reaction mixture stirred overnight. No evidence of the mixed vinyl ester, 1,2-dichloro-3,3-dimethyl-1-butenyl trichloroethanoate, was found, only nonvolatile polymeric products.

Vinyl Ester from α-Chlorobutyryl Chloride and the Enolate of α-Chloropropionyl Chloride, I, II, III, and IV. A solution 0.05 mol of α-chloropropionyl chloride in 10 ml of chloroform was added dropwise to a stirred solution of 0.05 mol of triethylamine in 75 ml of chloroform at −78°. Stirring was continued for 0.5 hr after the addition was complete and then 0.05 mol of α-chlorobutyryl chloride in 10 ml of chloroform was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred overnight. A 100-ml portion of hexane was then added to precipitate the amine salt. Filtration, concentration on a rotatory evaporator, and distillation afforded 6 ml, 49–73° at 0.25 mm, of the four vinyl esters in a ratio of 1:1:0.7:0.6 for I, II, III and IV, respectively, as evidenced by vpc and nmr. Geometrical isomers of the four vinyl esters were not separated under these vpc conditions. The simple vinyl esters, I and IV, have been previously described.[8] The two mixed vinyl esters, II and III, could not be separated by distillation nmr, δ (for the mixture), 1.0 (m, 3 H), 1.65 (d, 1.4 H), 2.0 (s, 0.9 H), 2.15 (s, 0.7 H), 2.10 (m, 2 H), and 4.25 (m, 1 H).

Anal. Calcd for $C_7H_9Cl_3O_2$: C, 36.28; H, 3.98. Found: C, 36.52; H, 3.91.

Generation of Methylchloro- and Ethylchloroketenes from α-Chlorobutyryl Chloride and the Enolate of α-Chloropropionyl Chloride. The enolate salt of α-chloropropionyl chloride was prepared at −78° as described above. To this solution were added with stirring 0.05 mol of α-chlorobutyryl chloride and 0.05 mol of freshly cracked cyclopentadiene. The reaction solution was allowed to warm to room temperature and stirring continued overnight. The amine salt was precipitated by the addition of 100 ml of hexane and removed by filtration. Concentration on a rotatory evaporator and vacuum distillation afforded 3.2 g (40%) of an equal mixture of 7-chloro-7-methylbicyclo[3.2.0]hept-2-en-6-one and 7-chloro-7-ethylbicyclo[3.2.0]hept-2-en-6-one as determined by vpc and comparison with known samples of the two cycloadducts.

Generation of Methylchloro- and Ethylchloroketenes from 1,2-Diehloro-1-butenyl 2-Chloropropanoate and 1,2-Dichloropropenyl 2-Chlorobutanoate. The mixed vinyl esters, II and III, were collected in a 2:1 ratio respectively by preparative vpc. A 50-μl portion of this mixture was added to 0.5 ml of chloroform and 150 μl of freshly cracked cyclopentadiene and 100 μmol of triethylamine. The mixture was stirred at room temperature overnight. Both 7-chloro-7-methylbicyclo[3.2.0]hept-2-en-6-one and 7-chloro-7-ethylbicyclo[3.2.0]hept-2-en-6-one were formed in equal amounts as determined by vpc and comparison with known samples of the cycloadduct.

Acknowledgments. The authors wish to express appreciation to the Robert A. Welch Foundation and the North Texas State University Faculty Research Fund for support of this investigation.

Registry No.—I, 52920-13-5; II, 52920-14-6; III, 52920-15-7; IV, 23649-91-4; V, 33471-78-2; VI, 52920-16-8; *tert*-butylbromoketene, 29264-48-0; *tert*-butylchloroketene, 52920-17-9; 2-bromo-3,3-dimethylbutanoyl chloride, 29336-30-9; 2-chloro-3,3-dimethylbutanoyl chloride, 52920-18-0; α-chloropropionyl chloride, 7623-09-8; triethylamine, 121-44-8; α-chlorobutyryl chloride, 7623-11-2; α-chloropropionyl chloride enolate salt with triethylamine, 50635-68-2.

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Synthesis of 5-Ethynyl-2,2′-bithienyl and Related Compounds[1]

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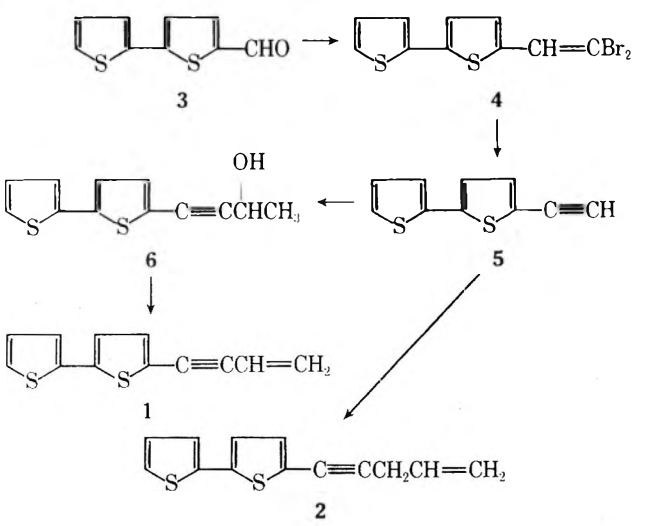
Received July 8, 1974

Because of the potential importance of certain 5-substituted-2,2′-bithienyls in the study of nematode control,[3] we were prompted to synthesize 5-(3-buten-1-ynyl)-2,2′-bithienyl (**1**), a highly potent naturally occurring nematicide. Even though **1** has been previously synthesized,[4] we desired an economical synthesis which would provide a better supply of **1** and related compounds for physiological testing. Also, we required a synthesis of 5-(3-penten-1-ynyl)-2,2′-bithienyl (**2**) for comparison of its ultraviolet spectrum with that of **1**.

The synthesis of **1** was accomplished as shown in Scheme I. A key step in this synthesis is the high yield preparation of 5-ethynyl-2,2′-bithienyl (**5**) using the Corey and Fuchs method.[5] Vapor phase dehydration of 5-(3-hydroxy-1-butynl)-2,2′-bithienyl (**6**) over alumina at 540° (0.18 mm) produced a mixture containing **5**, **6**, and **1**. The low yield of **1** (30%) in this step may partially be due to the competitive retro aldol reaction which produces **5**. Attempted dehydra-

Scheme I



tion of 6 in acidic aqueous medium is reportedly unsuccessful.[4a] Pyrolysis of 5-(3-acetoxy-1-butynyl)-2,2′-bithienyl furnished impure 1 in very low yield. Compound 1 was not produced when coupling of 5 with vinyl bromide was attempted.[6] The improved preparation of 5 provides facile entry into the synthesis of potential nematicides. For example, coupling of the acetylenic Grignard reagent from 5 with 3-bromopropene in the presence of cuprous chloride[7] afforded 2 in 99% yield (77% overall from 3).

Ultraviolet spectroscopy is used extensively for the identification of naturally occurring acetylenes. The ultraviolet absorption is shifted 15–30 nm higher on conjugation with an olefin.[7] The ultraviolet spectrum of the naturally occurring nematicide showed λ_{max} 340 nm (isooctane).[3b] This absorption when compared with the λ_{max} of 335 nm (hexane) for 5-(1-butynyl)-2,2′-bithienyl led to the suggestion of structure 2 for the natural product.[9] Synthesis later proved the correct structure 1.[4a] We have found λ_{max} (*n*-hexane) for 1 at 344 and 256 nm and λ_{max} (*n*-hexane) for 2 at 336, 255, and 240 (sh) nm. The anticipated wavelength increase is absent in the enyne 1. Thus, in the 2,2′-bithienyl series, ultraviolet spectroscopy is not always a reliable method for providing correct structural assignments.

Experimental Section

5-Formyl-2,2′-bithienyl (3). A. Formylation of 2,2′-bithienyl[10] according to Uhlenbroek and Bijloo furnished 3 in 85% yield, mp 54.5–55.5° (lit.[3a] mp 56°). B. Metalation of 2,2′-bithienyl followed by formylation with *N,N*-dimethylformamide after the method of Wynberg and Bontjes[11] afforded 3 in 68% yield, mp 57–57.5°, and 5,5′-diformyl-2,2′-bithienyl (13%), mp 210–212° (lit.[12] mp 217°). Method A proved to be the better procedure for preparing 3.

5-(2,2′-Dibromoethenyl)-2,2′-bithienyl (4). Triphenylphosphine, (20.98 g, 0.08 mol), 5.23 g (0.08 mol) of zinc dust, and 26.54 g (0.08 mol) of carbon tetrabromide were placed in a flame-dried, 500-ml, three-necked, round-bottom flask equipped with magnetic stirrer and gas inlet valve. Anhydrous dichloromethane (100 ml) was added under nitrogen pressure, and the system was closed to the atmosphere after spontaneous refluxing ceased. More dichloromethane was added as required to compensate for loss by evaporation. The mixture was stirred at room temperature for 28 hr and then 6.13 g (0.032 mol) of 5-formyl-2,2′-bithiophene was added under a nitrogen atmosphere and stirring was continued for 2 hr. The reaction mixture was extracted with five 100-ml portions of petroleum ether. Dichloromethane was added when the reaction mixture became too viscous for further extraction. The extracts were filtered and evaporated under reduced pressure, leaving a green residue. Crystallization from hexane produced 9.09 g (82%) of 4; mp 112–112.5°; ir (KBr) 3070, 3000 (aromatic), 1600 (C=C), 840, 795, 700 (5-monosubstituted-2,2′-bithienyl[12]), 821 (trisubstituted alkene), 535 cm^{-1} (C–Br); nmr ($CDCl_3$) δ 7.5 (s, 1 H, HC=C), 6.8–7.3 (m, 5 H, aromatic).

Anal. Calcd for $C_{10}H_6S_2Br_2$: C, 34.3; H, 1.7; S, 18.3; Br, 45.6. Found: C, 34.1; H, 1.8; S, 18.4; Br, 45.5.

5-Ethynyl-2,2′-bithienyl (5). A solution of 3.50 g (0.01 mol) of 4 in 100 ml of dry ether was cooled to −78° under dry nitrogen. *n*-Butyllithium (15.5 ml, 2.01 *M*, 0.03 mol) was diluted with 15 ml of dry ether and added dropwise to the cold solution. After stirring 1 hr at −78°, the mixture was allowed to warm to room temperature and stirring was continued 1 additional hr. The mixture was poured into water and extracted with ether. Drying ($MgSO_4$) followed by concentration on a rotary evaporator produced 1.9 g (100%) of pure 5[4a] (nmr determination) as an oil: ir (neat) 3290 (C≡CH), 2100 cm^{-1} (C≡C); nmr ($CDCl_3$) δ 6.8–7.2 (m, 5 H, aromatic) and 3.35 (s, 1 H, C≡C*H*). Compound 5 was too unstable to attempt elemental analyses. *Anal.* Calcd: mol wt, 194. Found (mass spectrum): mol wt 194.

5-(3-Hydroxyl-1-butynyl)-2,2′-bithienyl (6). To a solution of 9.8 ml (0.52 *M*, 5.1 mequiv) of ethylmagnesium bromide in 10 ml of dry ether was added 0.95 g (5.0 mequiv) of 5 in 20 ml of dry ether. The mixture was heated at reflux for 0.5 hr. After cooling to 5°, 0.44 g (0.01 mol) of acetaldehyde in 20 ml of cold dry ether was added during 10 min. The mixture was heated at reflux for 0.5 hr, cooled, and poured into 100 ml of 1 *N* ammonium chloride solution. The organic layer and two 150-ml ether extracts of the aqueous layer were combined, dried ($MgSO_4$), and concentrated on a rotary evaporator. The remaining yellow oil (1.08 g, 92%) was shown pure by nmr spectroscopy. Chromatography of a small sample on Florisil using hexane–ether eluent furnished 6 as yellow crystals, mp 58–58.5° (lit.[4a] mp 59°), with little loss of material: ir (KBr) 3340 cm^{-1} (OH), 2200 (C≡C); nmr ($CDCl_3$) δ 6.9–7.3 (m, 5 H, aromatic), 4.75 (q, 1 H, J = 6 Hz, CHOH), 2.1 (broad, 1 H, OH), 1.5 (d, 3 H, J = 6 Hz, CH_3).

5-(3-Buten-1-ynyl)-2,2′-bithienyl (1). A 4 in. by 0.5 in. Pyrex tube was loosely packed with 0.31 g of neutral alumina and 0.24 g of Pyrex wool. The tube was placed in a Sargent-Welch horizontal oven and phenol (2 g) was vaporized at 540° (0.18 mm) through the tube. A mixture of 0.21 g (0.9 mmol) of 6 and 0.1 g of anhydrous sodium carbonate was placed in a 25-ml round-bottomed flask. The flask was connected to the pyrolysis tube and heated to 230° (0.18 mm). The vapors were passed through the pyrolysis tube at 540° (0.18 mm) and collected in an exit flask at −70°. The product (140 mg) consisted of a mixture of 52 mg of 6 (0.22 mmol), 49 mg of 1 (33% based on 0.68 mmol of 1 consumed), and 39 mg of 5 (30% based on 0.68 mmol of 1 consumed) as determined by nmr spectroscopy.

Chromatography on alumina (hexane-ether) furnished 44 mg (30%) of pure 1 as a yellow oil. The ir and nmr spectra of 1 were identical with published spectra.[3b,4a] Compound 1 is converted to a gum on long exposure to light or air.

5-(4-Penten-1-ynyl)-2,2′-bithienyl (2). To 24 ml of 0.38 *M* (8.3 mmol) of ethylmagnesium bromide under a dry nitrogen atmosphere was added 1.57 g (8.3 mmol) of 5 in 25 ml of dry ether during 10 min. Addition of 5 caused a gentle reflux. After complete addition, the mixture was heated at reflux for 1 hr. Dry freshly prepared cuprous chloride (0.41 g, 4.1 mmol) was added and the contents were cooled to 25°. Freshly distilled 3-bromopropene (1.08 g, 9 mmol) in 10 ml of ether was added dropwise during 5 min. The reaction mixture was stirred for 12 hr and then poured into 100 ml of 1 *M* ammonium chloride solution. The organic layer was separated and combined with three 100-ml ether extracts of the aqueous layer. The organic solution was dried ($MgSO_4$) and concentrated on a rotary evaporator to give 1.56 g of a brown oil which nmr analysis showed to contain 0.78 g (99% based on consumed 5) of 2 and 0.79 g of 5. Pure 1 was obtained by preparative gas chromatography using a 5 ft by 0.25 in. 20% SE-30 column at 210°: ir (neat) 3110, 3080 (aromatic), 2240 (C≡C), 990, 917 cm^{-1} (vinyl); nmr ($CDCl_3$) δ 6.8–7.2 (m, 5 H, aromatic), 5.0–6.2 (m, 3 H, vinyl), 3.2 (d, 2 H, J = 5 Hz, CH_2).

Anal. Calcd for $C_{13}H_{10}S_2$: C, 67.8; H, 4.4; S. 27.8. Found: C, 68.0; H, 4.4; S, 27.6

Acknowledgment. This research was supported by the Office of Research and Projects, Southern Illinois University.

Registry No.—1, 1134-61-8; 2, 52906-76-0; 3, 3779-27-9; 4, 52906-77-1; 5, 4743-21-9; 6, 6522-33-4.

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A Practical Synthesis of the Sex Pheromone of the Pink Bollworm

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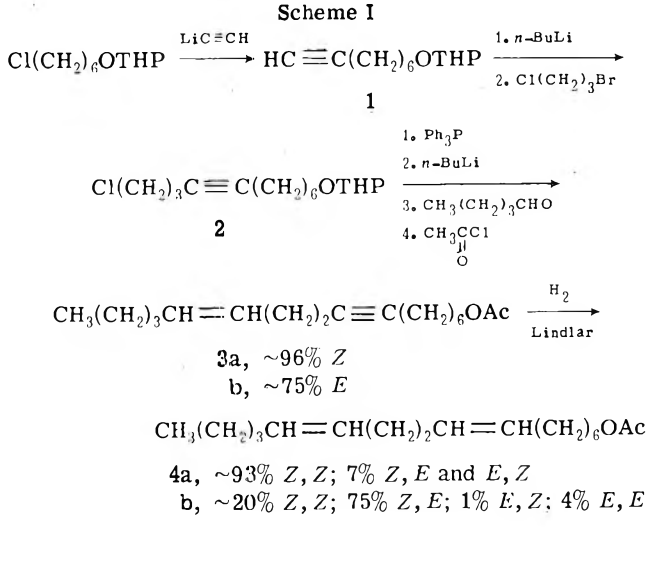
The sex pheromone of the pink bollworm moth, *Pectinophora gossypiella*, is a 1:1 mixture of (*Z,Z*)- and (*Z,E*)-7,11-hexadecadien-1-ol acetates.[1] The presence of the other two isomers of this diene, or a distinctly different ratio of the two natural isomers, causes a loss in potency of the mixture.[2] We sought to develop a route to the two desired isomers, or mixtures thereof, that would be sufficiently free of the other isomers, and that could be used to prepare the quantities of material required for testing and for subsequent control efforts. Preferably such a route would require no more than simple or fractional distillations for purification of intermediates and would avoid column chromatography. Our earlier efforts to synthesize the dienes involved the coupling of allylic Grignard reagents[2,3] and the elaboration of 1,5-hexadiyne[2] and were only partially successful. Another synthesis has been recently reported, but overall yields are low and isomer composition was determined only by infrared data.[4] We report here a useful route that starts with hexamethylene chlorohydrin (see Scheme I).

Scheme I



The tetrahydropyranyl ether (THP) of the chlorohydrin was treated with lithium acetylide ethylenediamine complex to give the THP of 7-octyn-1-ol (**1**)[5] in 84% yield. The lithium salt of this acetylene was added to a solution of 1-bromo-3-chloropropane in HMPA–THF to obtain the γ-chloropropylated acetylene, **2** (53% yield); unreacted **1** could be recovered (36%). The triphenylphosphonium salt of **2** was converted to an ylide with *n*-butyllithium in HMPA–THF and allowed to react with valeraldehyde. The use of HMPA as a cosolvent in Wittig condensations has been shown to produce olefins that are ≃96% cis.[6] The resulting THP of (predominantly) (*Z*)-11-hexadecen-7-yn-1-ol was transformed directly to the acetate, **3a** (58% yield from the phosphonium salt). Although **3a** was not resolved by capillary gas chromatography, the diene acetate, **4a**, obtained by hydrogenation of **3a** over Lindlar catalyst was separated into two peaks (7:93). The major peak was identical with a previously prepared sample of the *Z,Z* isomer.[2] The *Z,E* and *E,Z* pair were not distinguishable. Since catalytic hydrogenation of the acetylene was expected to produce about 3–4% (*E*)-7 double bond and the directed Wittig reaction was expected to produce about 4% (*E*)-11 double bond, the minor peak was assumed to be a composite of the *Z,E* and *E,Z* isomers in roughly equal proportions.

Attempts to produce (*E*)-11-hexadecen-7-yn-1-ol THP from **2** by Schlosser's modification to the Wittig reaction[7] failed. Also, the use of a less polar solvent (toluene) increased the proportion of trans, but the cis linkage still predominated. Isomerization of **3a** with aqueous nitrous acid at 70–75°[8] isomerized the 11 double bond to a mixture in which trans predominated, **3b**. This treatment does not shift the double bond;[9] also the gas chromatograms of the diene acetate, **4b**, resulting from hydrogenation of **3b** gave no indication of position isomerization. The *Z,Z* glc peak constituted 20% of the mixture; hence the *E,Z* content could only be ~1%, and the major peak, 75%, must be almost entirely *Z,E*. The *E,E* isomer, ~4%, was due to that proportion of the hydrogenation of **3b** that produced the 7 trans double bond.

Although the synthesis does not produce either desired isomer absolutely pure (to date no reported synthesis does), it is clear that **4a** and **4b** may be relatively easily prepared and that a combination of the two preparations will give the desired isomer ratio with only a few per cent of the unwanted *E,Z* and *E,E* isomers. Preliminary tests revealed that a blend of these preparations is as attractive to male pink bollworm moths as those preparations currently available.[10]

Experimental Section

Boiling points are uncorrected. Ir spectra were determined in CCl_4 using a Perkin-Elmer Model 457A grating spectrophotometer.[11] Nmr spectra were taken in CCl_4 on a Varian Associates T-60 spectrometer and chemical shifts are reported in parts per million (δ) downfield relative to TMS as internal standard. Glc analyses were performed with an Aerograph 1520 instrument employing an SE-30 column (0.92 m × 0.63 cm 5% on Anakrom ABS), and the analyses of the diene acetates were performed with a Hewlett-Packard 5720A instrument employing an EGGS-X SCOT column (15 m × 0.05 cm). Elemental analyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn.

7-Octyn-1-ol Tetrahydropyranyl Ether (1). This compound was prepared as described:[5] yield from hexamethylene chlorohydrin THP, 84%: bp 83–90° (0.25 mm); $n^{25}D$ 1.4580 [lit.[4] $n^{25}D$ 1.4590].

11-Chloro-7-undecyn-1-ol Tetrahydropyranyl Ether (2). Compound **1** (80 g, 0.38 mol) was converted to a lithium salt by adding *n*-butyllithium (206 ml of 2.04 *M* in hexane) to a solution of **1** in THF (200 ml) that was kept under nitrogen and at 0–5° with an ice bath. The resulting solution was transferred to a dropping funnel and then added dropwise to a solution of 1-bromo-3-

chloropropane (48.5 ml, 0.45 mol) in HEMPA–THF (200 ml of each) under nitrogen and kept at −20° with a Dry Ice–methanol bath. The bath was allowed to attain room temperature, and the mixture was kept overnight. The mixture was diluted with cold H_2O and worked up in the usual manner. Distillation (short path) provided 28.5 g of recovered **1** (36%) and 57.8 g of **2** (53%): bp 155–165° (0.8 mm); $n^{25}D$ 1.4757; nmr δ 3.3–4.0 (m, 6, CH_2O, CH_2Cl), 4.50 (bs, 1, OCHO).

Anal. Calcd for $C_{16}H_{27}ClO_2$: C, 66.99; H, 9.49; Cl, 12.36. Found: C, 66.97; H, 9.29; Cl, 12.28.

(*Z*)-11-Hexadecen-7-yn-1-ol acetate (3a). Triphenylphosphine (43.3 g, 0.165 mol) and **2** (45 g, 0.157 mol) were heated at 145° under nitrogen for 16 hr. Magnetic stirring was required because the mixture became heterogeneous for a time during the course of the reaction. The cooled mixture was agitated with ether several times. The ether washes, which contained unreacted starting materials, were stored for subsequent salt preparations. The oily salt (72.2 g, 84% yield) was dissolved in THF (260 ml) and transferred to a 1-l. three-neck round-bottom flask for the Wittig reaction. The solution was placed under nitrogen and cooled to ~ −5° (ice–methanol bath). Conversion to the ylide was effected by adding *n*-butyllithium (64.5 ml, 2.04 *M*) beyond the permanent coloration point. HMPA (130 ml) was added to this solution (no difference in product was noted if *n*-butyllithium was added to a salt solution in both solvents). Valeraldehyde (14.0 ml, 0.131 mol) was added to the mixture at one time. The bath was removed, and the mixture was stirred for 1 hr. The crude product was obtained by dilution of the mixture with H_2O and extraction with petroleum ether. Replacement of the tetrahydropyranyl group by acetyl was effected by warming the crude product at 35–40° for 16 hr in a mixture of acetyl chloride (13.9 ml) and HOAc (140 ml). The presence of triphenylphosphine oxide (TPO) was not deleterious. The acetate, **3a**, was isolated by dilution of the mixture (H_2O) and extraction (petroleum ether). Filtration of the crude acetate through 85 g of alumina with petroleum ether removed most of the TPO. Distillation (short path) afforded 21 g (58%) of **3a**: bp 145–150° (0.7 mm); $n^{25}D$ 1.4628; ir 1740, 975 cm^{-1} (trans, optical density extrapolatd to a 1.0 *M* solution, 0.12); nmr δ 1.93 (s, CH_3CO), 3.97 (bt, 2, CH_2O), 5.32 (bt, 2, CH=).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.42 H, 10.70.

(*Z,Z*)-7,11-Hexadecadien-1-ol Acetate (4a). Hydrogenation of **3a** (5.6 g, 20 mmol) was carried out in pentane (60 ml) with 5% Pd on $BaSO_4$ (250 mg) and quinoline (0.25 ml).

The product was worked up in the usual manner and distilled (short path) giving **4a** (4.7 g, 84%): bp 137–146° (0.5 mm); $n^{25}D$ 1.4578; ir 1740, 975 cm^{-1} (trans, optical density extrapolated to a 1.0 *M* solution, 0.20); nmr δ 1.95 (s, CH_3CO), 3.97 (bt, 2, CH_2O), 5.28 (bt, 4, CH=); analysis by capillary glc discussed in text.

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.00; H, 11.32.

Isomerization of 3a to 3b and Subsequent Reduction to 4b. Compound **3a** (5.0 g, 17.9 mmol) was warmed under nitrogen to 70–75°. Aqueous $NaNO_2$ (1.25 ml of 2 *M*) and HNO_3 (0.85 ml of 6 *M*) were added. The mixture was stirred vigorously for 0.5 hr. The crude product was diluted with petroleum ether, washed with H_2O, dried ($MgSO_4$), and concentrated. Filtration through alumina (20 g) with petroleum ether was followed by distillation to give **3b** (3.7 g, 74%): bp 150–160° (0.5 mm); $n^{25}D$ 1.4601; ir 1740, 975 cm^{-1} (much more intense).

Hydrogenation of **3b** (5.6 g, 19.5 mmol) as described for **3a** gave **4b** (4.5 g, 80%): bp 125–135° (0.3 mm); $n^{25}D$ 1.4564; ir 1740, 975 cm^{-1} (trans, optical density extrapolated to a 1.0 *M* solution, 1.30); nmr, virtually identical with **3b**; analysis by capillary glc discussed in text.

Registry No.—**1**, 16695-31-1; **2**, 53042-77-6; **3a**, 53042-80-1; **3b**, 53042-78-7; **(*Z,Z*)-4**, 52207-99-5; **(*Z,E*)-4**, 51607-94-4; **(*E,Z*)-4**, 53042-79-8; **(*E,E*)-4**, 53042-81-2; 1-bromo-3-chloropropane, 109-70-6; triphenylphosphine, 603-35-0; valeraldehyde, 110-62-3.

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(10) We express our appreciation to Dr. R. H. Staten, APHIS, USDA, Phoenix, Arizona for field bioassays.
(11) Mention of a proprietary product does not constitute an endorsement by the USDA.

Proton Nuclear Magnetic Resonance Spectra of 1,2-Disubstituted Acenaphthenes

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Received May 6, 1974

In conjunction with the study[2] of the nmr spectra of 1-substituted acenaphthenes, and as an extension of our earlier examination[3] of the additivity of substituent effects on chemical shifts, we have analyzed the benzylic portions of the nmr spectra of several 1,2-disubstituted acenaphthenes. The results are shown in Table I. It can be seen that in the five-membered ring of acenaphthene chemical shift relationships are found to be similar to those observed previously[5a] in a limited range of compounds with three-membered rings and in several multiring structures. That is, where a substituent (*e.g.*, Cl, CH_3, OH, OAc) deshields a trans proton (dihedral angle ≈120°) with respect to an eclipsed proton in the fragment **1**, the signal resulting from

1

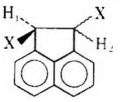
the trans isomer of the related 1,2-disubstituted compound is upfield of the signal resulting from the cis isomer. Where a substituent (*e.g.*, COOH, COOMe) shields a trans proton with respect to an eclipsed proton in the fragment **1** the reverse applies. It follows that stereochemical assignments (*i.e.*, cis–trans relationships) in a 1,2-disubstituted compound, incorporating a flat five-membered ring, may be made from chemical shift data alone, although it can be seen (Table I) that in most cases this relationship is of limited diagnostic utility because the actual differences of chemical shifts may be very small.

If $\Delta\delta_x$(gem), $\Delta\delta_x$(cis), and $\Delta\delta_x$(trans) are defined as the differences between the chemical shifts of the geminal, cis-vicinal, and trans-vicinal protons, respectively, in a 1-substituted acenaphthene,[2] and the chemical shift of the corresponding proton in acenaphthene (X = H), then if the principle of simple additivity[3] applies, a value $\Delta\delta_x$(calcd) may be calculated for the benzylic protons in a cis-disubstituted acenaphthene by summing $\Delta\delta_x$(gem) and $\Delta\delta_x$(trans), and for a trans-disubstituted acenaphthene by summing $\Delta\delta_x$(gem) and $\Delta\delta_x$(cis).

It can be seen (Table II) that there is a fair additive relationship between data based on 1-substituted acenaphthenes[2] [$\Delta\delta_x$(calcd)] and experimental data obtained in this work for 1,2-disubstituted acenaphthenes ($\Delta\delta_x$(exptl)). In most cases, the predicted deshielding by the two substituents is slightly more than that observed.

An obvious source of discrepancy between the calculated and experimental results is the possibility of steric distortion in 1,2-disubstituted acenaphthenes.

Table I
Nmr Data[a] for 1,2-Disubstituted Acenaphthenes



X	Registry no.	E_s[b]	Chemical shift, ppm from TMS[c] $H_{1,2}$	Chemical shift, ppm from TMS[c] Others	Chemical shift from parent	Coupling constants $J_{1,2}$	Coupling constants $J_{C_{13}-H_1}$
cis-H	83-32-9	1.9	3.36		0.0	9.2	129 ± 1
trans-H			3.36		0.0	3.8	129 ± 1
cis-Me	18210-58-7	2.2	3.68	1.22 (CH_3), 7.0–7.6	0.32	7.70 ± 0.03[h]	
trans-Me	51921-69-8		3.13	1.42 (CH_3), 6.9–7.7	−0.23	3.97 ± 0.03[h]	
cis-COOMe	5673-22-3	2.6	4.82 (4.75)	3.7 ($COOCH_3$), 7.3–8.0	1.46		
trans-COOMe	5673-04-1		5.10 (5.04)	3.7 ($COOCH_3$), 7.5–8.0	1.74		
cis-COOH[d]	5673-06-3	2.6	4.74	8.9 (COOH), 7.3–7.9	1.38		
trans-COOH[d]	5673-03-0		5.00	7.8 (COOH), 7.3–7.8	1.64		
cis-Ph	52522-93-7	2.8	5.22	6.5–7.8	1.86		156 ± 1
trans-Br	25226-58-8	3.0	5.95 (5.95)	7.4–7.8	2.59		159 ± 1
cis-Cl	49601-80-1	3.2	5.70 (5.76)	7.2–7.8	2.34	6.3	158 ± 1
trans-Cl	35468-33-8		5.66 (5.69)	7.2–7.7	2.30	1.0 ± 0.1	162 ± 1
cis-OH[e]	2963-86-2	3.4	5.32 (5.35)	4.12 (OH), 7.4–7.9	1.96	6.20 ± 0.05	156 ± 1
trans-OH[e]	2963-87-3		5.32	3.33 (OH), 7.4–7.9	1.96	1.2 ± 0.1	154 ± 1
cis-OBz[f]	52522-94-8	~3.2	6.50				
trans-OBz[f]	52522-95-9		6.46				
cis-ONO_2	17668-54-1		6.73				
trans-ONO_2	17668-53-0		6.54				
cis-OAc	5810-80-0	3.7	6.62	2.1 ($COCH_3$), 7.3–7.8	3.26	6.2	156 ± 1
trans-OAc	52522-96-0		6.60	2.1 ($COCH_3$), 7.4–7.9	3.24	1.40 ± 0.03	158 ± 1
cis-F[g,i]	6671-55-2	3.9				5.1	
trans-F[g,i]	6671-54-1					0.7	

[a] The data refer to 10% solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are in parts per million from TMS and are believed to be significant to ±0.2 ppm and coupling constants to ±0.2 Hz unless otherwise indicated. [b] See ref 2 for definition and data for acenaphthene (X = H). [c] Figures in parenthesis refer to chemical shifts in 1–3% solutions in CCl_4. [d] Approximately 5% solution in $CDCl_3$ (90%) and DMSO (10%). [e] Approximately 10% solution in DMSO. [f] Ref 8. [g] Ref 4. [h] $J_{CH_3,H}$(cis) = 7.42 ± 0.02 Hz and $J_{CH_3,H}$(trans) = 7.15 ± 0.02 Hz. [i] Note Added in Proof. For new data on fluorinated acenaphthenes see L. D. Hall and D. L. Jones, *Can. J. Chem.*, 51, 2902 (1973).

Table II
Comparison of $\Delta\delta_x$(calcd)[a] and $\Delta\delta_x$(exptl)[a] for 1,2-Disubstituted Acenaphthenes

X	$\Delta\delta_x$ (gem)[b]	$\Delta\delta_x$ (trans)[b]	$\Delta\delta_x$ (cis)[b]	$\Delta\delta_x$ (calcd)	$\Delta\delta_x$ (exptl)
cis-Me	−0.17	−0.09		−0.26	−0.32
trans-Me	−0.17		0.62	0.45	0.23
cis-COOMe	−1.13	−0.16		−1.29	−1.46
trans-COOMe	−1.13		−0.46	−1.59	−1.74
cis-COOH	−1.19	−0.21		−1.40	−1.38
trans-COOH	−1.19		−0.46	−1.65	−1.64
cis-Ph	−1.35	−0.46		−1.81	−1.86
trans-Br	−2.35		−0.29	−2.64	−2.59
cis-Cl	−2.31	−0.46		−2.77	−2.34
trans-Cl	−2.31		−0.16	−2.47	−2.30
cis-OH	−2.23	−0.28		−2.51	−1.96
trans-OH	−2.23		0.25	−1.98	−1.96
cis-OAc	−3.14	−0.32		−3.46	−3.26
trans-OAc	−3.14		0.18	−2.96	−3.24

[a] In parts per million. $\Delta\delta_x$(calcd) = $\Delta\delta_x$(gem) + $\Delta\delta_x$(trans) for cis isomer and $\Delta\delta_x$(calcd) = $\Delta\delta_x$(gem) + $\Delta\delta_x$(cis) for trans isomer. $\Delta\delta_x$(exptl) = $\delta_x - \delta_H$ where δ_x and δ_H are the chemical shifts of the benzylic protons in the 1,2-disubstituted acenaphthene and acenaphthene, respectively. [b] See text for definition. Negative sign indicates deshielding with respect to unsubstituted case. Data are derived from ref 2.

However, the agreement between $\Delta\delta_x$(calcd) and $\Delta\delta_x$(exptl) in the cis isomer, where such distortions are more likely is much the same as in the trans isomer (except for the dichloro and diol cases). Some of the above discrepancies may result from the spectra of several 1,2-disubstituted acenaphthenes being recorded in a different solvent than that used for the corresponding 1-substituted derivative.

The results in Table I show that, as in the case of 1-substituted acenaphthenes,[2] and as predicted by the Karplus rule,[6] J_{cis} is always significantly larger than J_{trans}. Firm stereochemical assignments (cis–trans relationships) are therefore possible, on the basis of coupling constant in 1,2-disubstituted acenaphthenes, and presumably also in other five-membered rings which do not deviate appreciably from planarity.

A decrease in both J_{cis} and J_{trans} in 1,2-disubstituted acenaphthenes is observed as the electronegativity of the substituent increases, a result also noted for 1-substituted acenaphthenes,[2] although here the decrease is more dramatic (J_{trans} = 3.8–0.7 Hz and J_{cis} = 9.2–5.1 Hz).

If ΔJ_x(cis) and ΔJ_x(trans) are the decreases, respectively, that occur in J_{cis} and J_{trans} on monosubstitution of acenaphthene at the 1-position, then ΔJ_x(cis)(calcd) and ΔJ_x(trans)(calcd) may be determined for 1,2-disubstituted acenaphthenes by doubling ΔJ_x(cis) and ΔJ_x(trans), respectively. These calculated values and the experimentally determined ΔJ values for the 1,2-disubstituted compounds are compared in Table III. It can be seen that there is good agreement between ΔJ_x(trans)(calcd) and ΔJ_x(trans)(exptl) in all cases except X = F (unless J_{trans} for fluorine

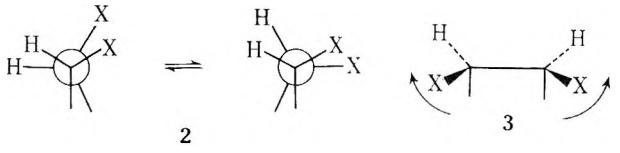
Table III
Comparison of ΔJ_x(calcd)[a] with ΔJ_x(exptl)[a] for 1,2-Disubstituted Acenaphthenes

X	ΔJ_c[b]	ΔJ_x (calcd)	ΔJ_x (exptl)	ΔJ_x(calcd) - ΔJ_x(exptl)
cis-Me	1.1	2.2	1.5	0.7
trans-Me	0.0	0.0	−0.2	0.2
cis-Cl	1.3	3.6	2.9	0.7
trans-Cl	1.36	2.7	2.8	0.1
cis-OH	2.1	4.2	3.0	1.2
trans-OH	1.2	2.4	2.6	−0.2
cis-OAc	1.95	3.9	3.0	0.9
trans-OAc	1.3	2.6	2.4	0.2
cis-F[b]	2.5	5.0	4.1	0.9
trans-F[b]	2.3	4.6	3.1	1.5

[a] In hertz. ΔJ_x(calcd) = $2\Delta J_x$. [b] ΔJ_x is the difference between $J_{1,2}$ in acenaphthene and the corresponding coupling constant in 1-X substituted acenaphthene.[2] [b] See footnote in Table I.

is negative,[5c] in which case the agreement is exact), but a much poorer agreement between ΔJ_x(cis)(calcd) and ΔJ_x(cis)(exptl) in every compound. This cannot be easily rationalized in terms of distortions of the expected type **2** because X-ray diffraction studies[7] on *cis*-1,2-acenaphthenediol (where J_{cis} shows a very large deviation from additivity) showed that distortions from perfect eclipsing due to nonbonded interactions between the cis-vicinal oxygen atoms was of the order of 10°. The nature of the Karplus curve indicates that a change of 10° in the interproton dihedral angle in a 1,2-disubstituted acenaphthene would only cause a small change in the value of J_{cis} (~0.3).

Distortion of the type **3** would, however, cause a diminution in the H-C-C angles resulting in an increase in J_{cis}[5d].



2 **3**

Experimental Section

Analyses of Nmr Spectra. The nmr spectra (100 MHz) of several 1,2-disubstituted acenaphthenes consisted of a singlet between δ 4.7 and 6.7, and a broad multiplet at δ 7.0–8.0. The ^{13}C satellites of the resonance assigned to the benzylic protons (δ 4.7–6.7) were analyzed as an AX system with $\nu_{AX} = \frac{1}{2}J_{^{13}CH}$ after decoupling of the aromatic protons. Each satellite was a doublet with splitting J_{AX}. *cis*-1,2-Diphenylacenaphthene, *cis*-1,2-acenaphthenediol, and *cis*- and *trans* 1,2-acenaphthenedicarboxylic acid were too insoluble in chloroform or dimethyl sulfoxide to give observable satellite resonances. However satisfactory satellite spectra of the first two compounds were obtained using multiple scans (CAT).

Analyses were not carried out for the signals assigned to the aromatic protons (δ 7.0–8.0) although several of these multiplets have been analyzed previously as ABC systems by Hayward and Csizmadia.[8] The methyl and benzylic proton regions of the nmr spectra of *cis*- and *trans*-1,2-dimethylacenaphthene were analyzed as $X_3AA'X_3'$ spin systems ($J_{XX'} = 0$) according to the method of Anet.[9] Analyses were performed using the iterative computer program LAME[10] executed on an IBM 7040/1401 in the Basser Computing Laboratory, School of Physics, University of Sydney. Trial parameters were calculated by the use of interval rules[9] for the $X_3AA'X_3'$ spin system as well as estimates from related compounds whose nmr spectra had been analyzed previously.[2]

Preparation of Compounds. *cis*- and *trans*-1,2-dichloroacenaphthene,[11] *trans*-1,2-dibromoacenaphthene,[12] *cis*- and *trans*-1,2-acenaphthenediol,[12] *cis*- and *trans*-1,2-diacetoxyacenaphthene,[8] *cis*-1,2-diphenylacenaphthene,[13] *cis*- and *trans*-acenaphthenedicarboxylic acid,[14] dimethyl *cis*- and *trans*-1,2-acenaphthenedicarboxylate,[14] and *cis*-1,2-dimethylacenaphthene[15] were prepared as described previously. Physical constants and spectral data were consistent with those reported.

***cis*- and *trans*-1,2-Dimethyl-1,2-acenaphthenediol.** Acenaphthenequinone (15.0 g) was added in small portions to the Grignard reagent prepared from magnesium (8 g), methyl iodide (50 g) and diethyl ether (100 ml). The reaction mixture was heated under reflux for 3 hr, cooled, and poured into a mixture of ice (200 g) and 3*N* sulfuric acid (100 ml). Extraction with diethylether (50 ml) left a large amount of the diol as a suspension in the aqueous phase. This was filtered and the crystals obtained were washed with water and recrystallized from ethanol to give 3.1 g (18%) of *cis*-1,2-dimethyl-1,2-acenaphthenediol: mp 202–203° (lit.[16,17] 187–189°); nmr ($CDCl_3/d_6$-DMSO) δ 1.58 (s, 6, CH_3), 4.63 (br s exch, 2, OH), 5.32 (s, 2, benzylic), 7.40–7.85 (m, 6, aromatic). The ether extract was washed with saturated $NaHCO_3$ solution (20 ml), dried, and the solvent evaporated to give a solid product of mp 156–165°. Successive recrystallizations from methanol and chloroform yielded 6.3 g (36%) of *trans*-1,2-dimethyl-1,2-acenaphthenediol: mp 182–183° (lit.[16,17] 182–183°); nmr ($CDCl_3/d_6$-DMSO) δ 1.61 (s, 6, CH_3), 4.36 (br s, exch, 2, OH), 5.32 (s, 2, benzylic), 7.30–7.80 (brm, 6, aromatics).

***cis*-1,2-Dimethylacenaphthene.** A suspension of *cis*-1,2-dimethyl-1,2-acenaphthenediol (1.0 g) in ethanol (10 ml) was shaken at room temperature, under 4 atmospheres of hydrogen for 3 hr with 10% palladium/charcoal (200 mg) and 10 *N* hydrochloric acid (0.3 ml). The reaction mixture was filtered and the solvent evaporated. The crystalline product was washed with light petroleum (2 × 5 ml) and the washing chromatographed on neutral alumina. The first component eluted by light petroleum was rechromatographed. *cis*-1,2-Dimethylacenaphthene (0.120 g, 14%) was obtained as a colorless oil which became crystalline when cooled with a few milliliters of ethanol, mp 52–54° (lit.[15] 53–54°).

***trans*-1,2-Dimethylacenaphthene.** A solution of *trans*-1,2-dimethyl-1,2-acenaphthenediol (2.0 g) in ethanol (15 ml) was shaken at room temperature under 4 atmospheres of hydrogen for 3 hours with 10% palladium/charcoal (400 mg) and 10 *N* hydrochloric acid (0.4 ml). The mixture was filtered and the solvent evaporated to give a solid product. This was washed with light petroleum (3 × 5 ml) and the washings were chromatographed on neutral alumina. Light petroleum eluted a colorless liquid which was distilled under reduced pressure to yield *trans*-1,2-dimethylacenaphthene (0.14 g, 17%): bp 92–94° (0.6 mm); ir ($CHCl_3$) 3010, 2970, 2940, 2876, 1603, 1448, 1371, 820 cm^{-1}; uv (ethanol) λ_{max} 228 (52,000), 288 (4400) nm.

Anal. Calcd for $C_{14}H_{14}$: C, 92.3; H, 7.7. Found: C, 91.9; H, 8.0.

Acknowledgment. This work was supported by the Australian Research Grants Committee, Grant No. C 65/15567 to S.S.

Registry No.—*cis*-1,2-Dimethyl-1,2-acenaphthenediol, 6566-38-7; *trans*-1,2-dimethyl-1,2-acenaphthenediol, 6566-39-8; acenaphthenequinone, 82-86-0.

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Studies on Vitamin D and Its Analogs. VI.[1,2] 3-Deoxy-*A*-homovitamin D_3, a Model Synthesis

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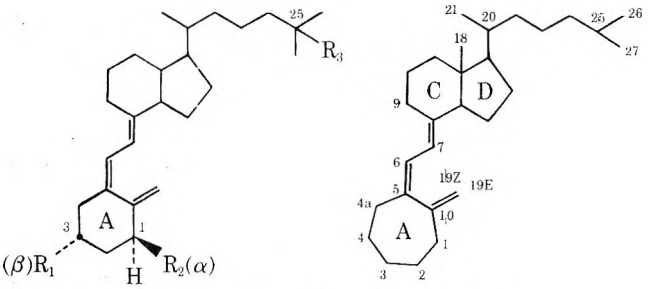
Received July 12, 1974

Vitamin D_3 (**1a**) undergoes an obligatory two-step metabolism to produce its biologically active form, 1α,25-dihydroxyvitamin D_3 (**1b**),[3] which acts biomechanistically like other classical steroid hormones.[4,5] The 1α-hydroxyl in **1b** appears to be critical for biological activity. Significant in this respect is the recent observation of the high biopotency of 3-deoxy-1α-hydroxyvitamin D_3 (**1c**), which we recently reported.[1b,6] In fact, **1c** was able to elicit a greater maximum in intestinal calcium transport than the natural metabolite **1b**. We rationalized this phenomenon in terms of a refined topological model for vitamin D_3 activity, which has, as a necessary requirement, an equatorial orientation of the 1α-hydroxyl group.[1a,6] In order to further probe this structure–function relationship, we have more recently directed our attention toward the synthesis of *A*-homo- and *A*-norvitamin D_3 analogs. This note describes the preparation of 3-deoxy-*A*-homovitamin D_3 (**2**).

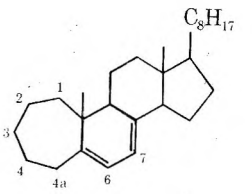
Because the synthesis of hydroxyl-substituted derivatives of **3** entails considerable effort, and since it was not obvious that **3** would isomerize by the well-known[7,8] (in the six-membered ring A series) two-step process to **2**, this model synthesis was carried out. This paper also demonstrates the conversion of the Δ^6-olefin **5** to the provitamin ($\Delta^{5,7}$-diene) **3**. Previously, only Δ^5-olefins had been used to obtain such provitamins.[9]

Diazomethane[10] was reacted with 5α-cholest-6-en-3-one[11] (**6**) in ether–methanol using the *ex situ* method[12] to afford the *A*-homo ketone mixture **7** in 58.5% yield. Nmr (300 MHz) analysis showed the mixture to contain a 60:40 ratio of **7a** to **7b**. Preparative high-pressure liquid chromatography resolved the mixture into pure **7a** and pure **7b**. Catalytic hydrogenation of **7a** afforded the known *A*-homo-5α-cholestan-3-one (**8a**)[13–15] and similar reduction of pure **7b** afforded the known 4-ketone (**8b**).[13] Catalytic hydrogenation of **7** followed by Wolff–Kishner reduction gave the known *A*-homo-5α-cholestane (**9**).[16,17] Similar Wolff–Kishner reduction of mixture **7** afforded 83% **5**.



1a, R_1 = OH; R_2 = R_3 = H
b, R_1 = R_2 = R_3 = OH
c, R_2 = OH; R_1 = R_3 = H

2



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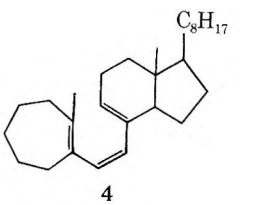

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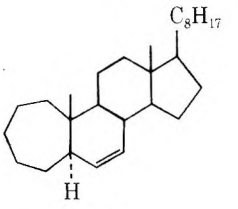

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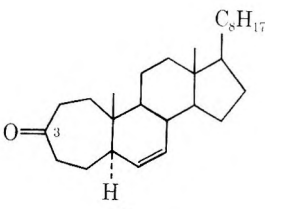
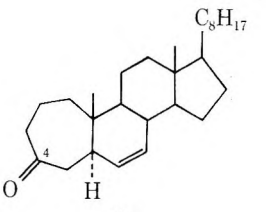


7a



7b

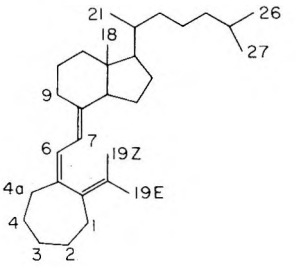


Figure 1. The 300-MHz nmr spectrum of 3-deoxy-*A*-homovitamin D_3 in $CDCl_3$ containing $CHCl_3$ and TMS as internal standards 2180 Hz apart.

The Δ^6-olefin **5** was treated successively with 1,3-dibromo-5,5-dimethylhydantoin and then trimethyl phosphite[9b] to afford a 39% yield of the provitamin **3** along with lesser amounts of *A*-homocholesta-4,6-diene (**10**). The structures of **3** and **10** were particularly evident from their nmr and uv spectra. Finally, it was gratifying to observe that after some experimentation, the *A*-homoprovitamin **3** could be isomerized to 3-deoxy-*A*-homovitamin D_3 (**2**). It is interesting that previtamins in the six-membered A-ring series are usually isolated when provitamins are irradiated under the conditions specified in the Experimental Section. In fact, it has been our usual practice to heat such previtamins for several hours at ~70° to effect isomerization to the vitamins. However, in the case of **3**, the initially formed previtamin was not observed even though a temperature of <30° was maintained. The 300-MHz nmr spectrum of **2** (Figure 1) is in accord with the assigned structure.[18] Studies now in progress are directed toward preparing *A*-homovitamins hydroxylated in the A ring.

Experimental Section

General. Infrared (ir) spectra were obtained with a Perkin Elmer 137 or 621 spectrophotometer and ultraviolet (uv) spectra with a Cary Model 14 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded with a Varian spectrometer[2] with deuteriochloroform as solvent and tetramethylsilane (TMS, τ 10.00) and chloroform (τ 2.74) as the internal standards. Mass spectra were obtained with a Hitachi-Perkin-Elmer RMU-6D spectrometer. Microanalyses were performed by C. F. Geiger, Ontario, Calif. Melting points (mp, Thomas Hoover capillary melting point apparatus) are uncorrected. Low boiling petroleum ether (30–60°) is designated as lbpe.

***A*-Homo-5α-cholest-6-en-3- and -4-one (7).** The starting material **6** was prepared by previously described methods from cholesterol.[11] An ether solution of diazomethane, prepared from a mixture of ether (320 ml), diglyme (220 ml), aqueous sodium hydroxide (30%, 19 ml), and *N,N'*-dinitroso-*N,N'*-dimethylterphthalamide (70% suspension, 17.7 g, 0.12 mol),[10] was distilled over a 2.5-hr period into an ice cooled magnetically stirred solution of **6** (6.645 g, 0.0173 mol) in a mixture of ether (200 ml) and methanol (320 ml).[12] The solution was maintained at 0° for 3.5 hr and then at room temperature overnight. The colorless ether solution, upon concentration, afforded 7.2 g of crude, white solid. Column chromatography (120 g, Woelm neutral III alumina) was carried out by eluting with lbpe and ether–lbpe mixtures. Early fractions contained material (1.96 g) which was tentatively identified as an epoxide (ir, no C=O stretch; nmr), but this material was not investigated further. Later fractions afforded material (5.19 g) which upon crystallization from methanol (175 ml) gave the homo ketone mixture **7** (4.03 g, 58.5%) with mp 97–98° [ir (CCl_4) ν_{max} 1705 cm^{-1}; mass spectrum (80 eV) *m/e* 398 (parent ion)]. In other runs, the yield of pure ketone mixture varied between 45 and 60%. The mixture consisted of a 40:60 ratio of **7b/7a** as determined by examining the ratio of olefinic resonances and C_{19} angular methyl group resonances in the 300-MHz nmr spectrum.

Isolation of Pure 7a and 7b. The purified mixture **7** was subjected to preparative high-pressure liquid chromatography (hplc) (Waters Associates model ALC-202-401; 8 ft. × ⅜ in. porasil A preparative column; diisopropyl ether as solvent using a refractive index detector; 200 mg of **7** in 2 ml of diisopropyl ether injections) and two fractions were collected [faster eluting component (**7b**, minor) and more slowly eluting component (**7a**, major)]. Each fraction after concentration afforded residues which were individually recrystallized from methanol. The properties of pure **7a** and **7b**, each homogeneous to analytical hplc, were as follows.

7a (major): white needles; mp 91.0–92.0° (lit.[15] mp 91–92°); mass spectrum *m/e* 398 (parent ion); nmr (300 MHz) τ 4.51 and 4.79 ($H_{6,7}$, AB q, J_{AB} ~ 10.0 Hz), 9.09 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), 9.18 (C_{19}–CH_3, s), and 9.31 (C_{18}–CH_3, s); **7b** (minor), white needles, mp 123.5–124.0° (lit.[15] mp 126–27°); mass spectrum *m/e* 398 (parent ion); nmr (300 MHz) τ 4.42 and 4.87 ($H_{6,7}$, AB q, J_{AB} ~ 10.0 Hz), 9.09 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), 9.28 (C_{19}–CH_3, s), and 9.31 (C_{18}–CH_3, s).

Reduction of Pure 7a and 7b. The 3-one **7a** (40 mg) and 10% Pd/C (5 mg) in ethanol (10 ml) were subjected to hydrogenation. After work-up and recrystallization of the product, pure **8a** with mp 80.5–82.0° (lit.[13c] mp 83–85°) was obtained.

Identical reduction of pure 4-one **7b** afforded pure **8b** with mp 94.0–95.5° (lit.[13c,14] mp 96–97°).

Conversion of Mixture 7 to *A*-Homo-5α-cholestane (9). The ketone mixture **7** (0.500 g, 0.0125 mol) and 10% palladium on charcoal (100 mg) in absolute ethanol (125 ml) absorbed 40 ml of hydrogen (0.016 mol, 24° (733 mm)) over a 4-hr period. The catalyst was removed by filtration and thoroughly washed with ether. The filtrate upon evaporation afforded 470 mg of crude white solid which was identical with a mixture of *A*-homo-5α-cholestan-3-one and -4-one (**8**)[17] prepared by diazomethane ring expansion of 5α-cholestan-3-one.

The entire crude white solid was dissolved in diethylene glycol (30 ml) in a 100-ml three-necked round-bottom flask fitted with a condenser, thermometer, and a nitrogen inlet. Hydrazine (5 ml) and potassium hydroxide (0.85 g) were added and the mixture was refluxed at 135° for 1 hr. The condenser was replaced with a distillation head and the reaction temperature was allowed to rise to 235°. After 3.5 hr, the mixture was cooled and water (50 ml) was added. The mixture was extracted with ether (2 × 75 ml) and then the ether solution was washed with water (2 × 50 ml), dried (sodium sulfate), and then concentrated to a yellow oily residue. Chromatography (15 g, Woelm neutral I) with lbpe afforded 230 mg of a white solid. Crystallization from methanol (50 ml) afforded pure *A*-homo-5α-cholestane (**9**) with mp 87.5–89.0° (lit.[16] mp 92–94°): nmr (300 MHz) τ 9.11 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), 9.26 (C_{19}–CH_3, s), and 9.36 (C_{18}–CH_3, s).

***A*-Homo-5α-cholest-6-ene (5).** The Wolff–Kishner reduction of ketone mixture **7** was carried out in the same manner as described in the immediately preceding section[16] (**7**, 2.0 g, 0.0050 mol; diethylene glycol, 120 ml; KOH, 3.6 g; hydrazine 20 ml). After work-up and chromatography (50 g of Woelm neutral I with lbpe), the crude product (2.0 g) was crystallized (absolute ethanol) to afford 1.60 g (83%) of pure **5**: mp, 96.0–97.5°; nmr (300 MHz) τ 4.53 and 4.79 ($H_{6,7}$, AB q, J_{AB} ~ 10.0 Hz), 9.10 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), 9.26 (C_{19}–CH_3, s), and 9.32 (C_{18}–CH_3, s).

Several recrystallizations afforded the sample submitted for analysis.

Anal. Calcd for $C_{28}H_{48}$: C, 87.42; H, 12.58. Found: C, 87.15; H, 12.88.

***A*-Homo-5α-cholesta-5,7-diene (3) and *A*-Homo-5α-cholesta-4,6-diene (10).** To a refluxing solution of **5** (1.935 g, 0.00503 mol) in 1:1 benzene–lbpe (80 ml) was added powdered 1,3-dibromo-5,5-dimethylhydantoin (1.0 g, 0.0035 mol) at once. The refluxing solution turned pale yellow immediately and then lemon yellow within 5 min. After a total of 15 min at reflux, the mixture was ice cooled and then filtered to remove the precipitated 5,5-dimethylhydantoin (ice cold lbpe washings). The solution was concentrated to a yellow oily residue under vacuum at below room temperature.

The residue in xylene (20 ml) was added dropwise under nitrogen to a magnetically stirred, refluxing solution of trimethylphosphite (3.0 ml) in xylene (60 ml). After 1.5 hr of reflux, the mixture was cooled and then concentrated to dryness under high vacuum. The resulting yellowish brown semisolid was chromatographed over 100 g of 10% silver nitrate impregnated Woelm neutral alumina. The elution was carried out successively with lbpe and ether–lbpe mixtures. Earlier fractions afforded 1.079 g of crude $\Delta^{5,7}$-diene **3** which upon crystallization afforded 750 mg (39%) of material with mp 75.5–77.0°. Later fractions afforded 435 mg of a mixture of **10** (mainly) and starting material **5**. Crystallization of the mixture afforded pure **10**.

The $\Delta^{5,7}$-diene **3** exhibited the following: nmr (300 MHz) τ 4.46 and 4.63 ($H_{6,7}$, AB q, J_{AB} ~ 6.0 Hz; B further split into t, J ~ 2.8 Hz), 9.06 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.10 (C_{19}–CH_3, s), 9.13 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), and 9.40 (C_{18}–CH_3, s); uv (ether) λ_{max} (ϵ) 255 sh (5660), 266 sh (9870), 274 (13,800), 285 (14,100), 297 (7790) nm. Several recrystallizations afforded the sample submitted for analysis.

Anal. Calcd for $C_{28}H_{46}$: C, 87.88; H, 12.12. Found: C, 88.12; H, 12.27.

The $\Delta^{4,6}$-diene **10** exhibited the following: nmr (300 MHz) τ 4.13 (H_7, dd, J ~ 10.0, 2.5 Hz), 4.48 (H_{4a}, t, J ~ 6.4 Hz), 4.53 (H_6, d, J ~ 10.0 Hz), 9.03 (C_{19}–CH_3, s), 9.09 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.13 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), and 9.29 (C_{18}–CH_3, s); uv (ether) λ_{max} 238 nm.

Repeated recrystallization of this material afforded the sample submitted for analysis, mp 88.5–89.5°.

Anal. Calcd for $C_{28}H_{46}$: C, 87.88; H, 12.12. Found: C, 87.49; H, 12.45.

3-Deoxy-*A*-homovitamin D_3 (2). The photochemical apparatus consisted of a Hanovia quartz immersion well (Cat. No. 19434) fitted with a 125-ml reaction vessel (equipped with a condenser and nitrogen inlet) and a Hanovia 200-W medium-pressure mercury arc (Cat. No. 654A-36) with a No. 9700 Corex filter sleeve. The lamp was prewarmed for 15 min before exposing the ice cooled reaction solution to irradiation for 3.0 min. The solution was purged thoroughly with nitrogen prior to and during the irradiation. Four irradiation mixtures (125 mg of 3/100 ml of ether each; 500 mg total) were pooled and concentrated at <30° under vacuum to afford an oily semicrystalline residue. Nmr and uv analysis indicated the residue to contain mainly a mixture of **3** and **2**. Chromatographic separation (140 g, 10% silver nitrate impregnated Woelm neutral alumina prepared with lbpe, 28-mm diameter column) was carried out using lbpe and lbpe–ether combinations.

Early fractions afforded starting material **3** (256 mg, 51%) while later fractions proved to be the homovitamin D **2** (90 mg, 18%; 37% based on recovered **3**). The semicrystalline homovitamin is exceedingly air-sensitive. Prior to measuring any of its physical properties, it was purified by rechromatography (with lbpe on a 15-g Woelm neutral I column) and the single fraction obtained was evacuated to dryness. The nmr spectrum (300 MHz) shown in Figure 1 revealed the following: τ 3.74 and 3.97 ($H_{6,7}$, AB q, $J_{AB} \sim 11.0$ Hz), 4.93 H_{19Z}, br with a fine structure, $W \sim 6$ Hz), 5.12 (H_{19E}, d, $J \sim 2.2$ Hz; $W \sim 5$ Hz), 7.18 ($H_{9\beta}$, d, $J \sim 12$ Hz), 7.67 ($H_{1\alpha,1\beta,4a\alpha,4a\beta}$, br s, $W \sim 13$ Hz), 9.08 (C_{21}–CH_3, d, $J \sim 6.5$ Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, $J \sim 6.5$ Hz), and 9.46 (C_{18}–CH_3, s); uv (95% ethanol) ϵ_{max} (ϵ) 244 sh (14,000), 252 (16,300), 261 (16,400), 275 br sh (15,100) and λ_{min} 230 (10,700) nm; mass spectrum (80 eV) *m/e* 382 (parent ion).

Registry No.—**2,** 52920-82-8; **3,** 52920-83-9; **5,** 52920-84-0; **6,** 52949-49-2; **7a,** 35569-96-1; **7b,** 35569-95-0; **9,** 24366-12-9; **10,** 52920-85-1; diazomethane, 334-88-3; 1,3-dibromo-5,5-dimethylhydantoin, 77-48-5.

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Oxidation of 4-Phenylurazole with Activated Isocyanates and Dimethyl Sulfoxide

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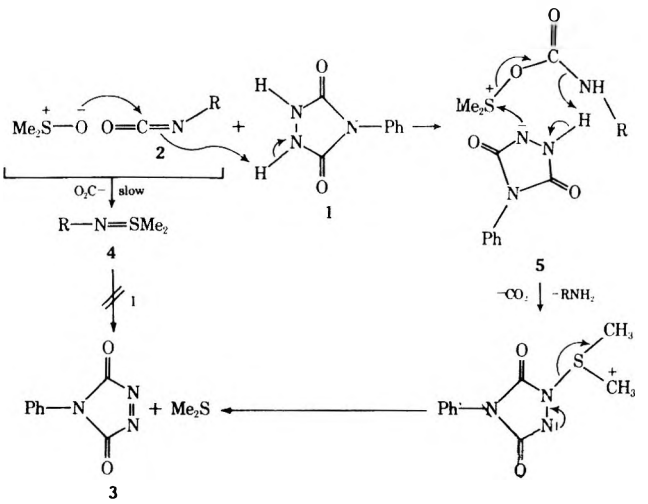
Received November 20, 1973

During an investigation of the chemical reactivity of 4-phenyl-1,2,4-triazoline-3,5-dione (**3**), we observed that reaction mixtures in dry (molecular sieves) dimethyl sulfoxide (DMSO) containing 4-phenylurazole (**1**) turned bright red and emitted an unpleasant odor upon addition of trichloroacetyl isocyanate[11] (**2a**). DMSO has been used in a number[1] of oxidizing systems in recent years, *e.g.*, DMSO–dicyclohexyl carbodiimide–H_3PO_4,[2] DMSO–acetic anhydride[3a] (and similar systems **3b**), DMSO–ketenimine,[4] and DMSO–SO_3–pyridine.[5] The rapidity with which the reaction occurred, the intensity of the characteristic red color of **3** which formed, and the increased usage of **3** as a dieneophile and as a chemical reagent in the current literature prompted us to investigate the utility of this pathway as an easy and rapid route to **3**.[6–10]

Purified acetonitrile was found to be the ideal solvent for a spectrophotometric assay for **3** (λ_{max}^{525}, ϵ 157). Under controlled conditions, the products observed when **2a** was reacted with **1** in DMSO were carbon dioxide (as barium carbonate), dimethyl sulfide (trapped at −80° and characterized as trimethyl sulfonium iodide), trichloroacetamide[12] (essentially insoluble in cold $CHCl_3$), and **3** (isolated by sublimation and characterized by spectroscopic comparisons with an authentic sample).[9] The average yield, determined spectrophotometrically, was 98% with **2a**. Difficulty was encountered in isolating pure **3** from this reaction (~20% yield by sublimation) but this is the only respect in which this new reagent suffers in comparison with the other methods. The chemical reactivity of **3** was shown to be unaffected by the system by isolation of its adduct with cyclobutadiene. The major advantage of this approach lies in the rapidity with which **3** may be generated *in situ*. At room temperature, the reaction is over almost instantaneously. Since the isocyanates used and **1** are indefinitely stable, this provides an instantaneous source of **3** in a highly polar solvent (DMSO). N_2O_4 and *t*-BuOCl are relatively unpleasant materials to work with while the isocyanates used herein can be readily transferred in measured amounts with a hypodermic syringe.

Only isocyanates activated by strongly electron-withdrawing substituents were effective. The reaction with *p*-toluenesulfonyl isocyanate (**2b**) was essentially indistinguishable from that with **2a**, benzoyl isocyanate (**2c**) gave 88% of **3**, while phenyl and *n*-butyl isocyanates gave less than 10% conversion in very slow reactions which stopped

within 15 min. Related heterocumulenes, PhNCS and PhNSO, were completely unreactive in this system. For the purpose of comparison, **1** was oxidized using DMSO–DCC–H_3PO_4 (maximum yield, 33% after 30 min), DMSO–Ac_2O (86% yield after 2 hr), and DMSO–P_2O_5 (yield uncertain because of turbid solutions which could not be clarified; no further increase in absorbance was noted after 5–10 min). The reaction appeared to proceed as well in benzene, toluene, chloroform, carbon tetrachloride, 1,2-dichloroethane, ethyl acetate, acetone, neat DMSO, dioxane, tetrahydrofuran, and 1,2-dimethoxyethane but not in diethyl ether or pyridine. The interference of ether in the course of this reaction remains a puzzle. Considering the similarities between this system and the Pfitzner-Moffatt-type systems, we propose the following mechanistic scheme to rationalize our results.



3 was not formed when **1** was treated with dimethyl sulfilimine **4b**.[13] Furthermore, the reaction between DMSO and isocyanate alone required 3–5 hr for the formation of the sulfilimine to be complete. Thus the initial adduct between DMSO and **2** is effectively trapped before it can eliminate CO_2. This is in keeping with the observed acidity of **1** (soluble in 50% NH_4OH) and with the inhibitory effect of pyridine on the oxidation.

Experimental Section[14]

General Procedure for *in situ* Generation of 4-Phenyl-1,2,4-triazoline-3,5-dione (3). To 1.77 g (0.01 mol) of 4-phenylurazole[10] dissolved in 5 ml of dry DMSO (molecular sieves), cooled to 0° in an ice–water bath, in a magnetically stirred 25-ml round-bottom flask, sealed with a serum cap, was added 1.33 ml (0.01 mol) of *p*-toluenesulfonyl isocyanate (Upjohn Chemical Co.). Care was taken to avoid freezing of the DMSO solution. The isocyanate addition was made slowly to avoid overheating which leads to formation of the corresponding sulfilimine (**4**). Gas evolution was allowed to subside between additions of drops of isocyanate. After the addition of isocyanate was completed the cooling bath was removed and the mixture was stirred at room temperature until gas was no longer evolved (~15 min). The chosen diene can be injected into the solution of **3** if it is a liquid, or a DMSO solution of the solid diene can be added. Evidence of the completion of the reaction is the discharge of the characteristic color of **3**. The reaction mixture is poured into 100 ml of chloroform and the resulting solution is extracted with 5% aqueous sodium hydroxide solution and then distilled water. The chloroform layer is dried over calcium chloride, filtered, and concentrated to an oil on a rotary evaporator. Ethanol is added to the oil and the solution is warmed to dissolve suspended solid, if any is present. The product is precipitated by addition of water to the ethanol solution and may generally be recrystallized from alcohol.

***N*-Phenyl-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide.** This compound was obtained from 0.82 g (0.01 mol) of freshly prepared[15] cyclopentadiene, according to the general procedure given above, yield 1.42 g (59%), melting point 138–39° (lit.[8] 131–133°, 142–144°,[16] 142–144°). The nmr spectrum of the product was in accord with that reported in the literature.[16] If a 1 equiv excess of isocyanate was added along with 5 ml more of DMSO, the yield rose to 79%.

***N*,1,4-Triphenyl-1,2,3,4-tetrahydro-1,4-epidioxo-2,3-diazanapthalene-2,3-dicarboximide.** This compound was obtained from 2.70 g (0.01 mol) of diphenylisobenzofuran,[17] according to the general procedure given above, yield 2.4 g (54%), mp 144°.

Acknowledgment. We wish to acknowledge the assistance, in the form of advice and encouragement, of Professors K. T. Potts and J. P. Anselme, and a generous gift of *p*-toluenesulfonyl isocyanate from the Upjohn Co., Kalamazoo, Mich.

Registry No.—**1**, 15988-11-1; **2a**, 3019-71-4; **2b**, 4083-64-1; **2c**, 4461-33-0; **3**, 4233-33-4; *N*-phenyl-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide, 15971-63-8; cyclopentadiene, 542-92-7; *N*,1,4-triphenyl-1,2,3,4-tetrahydro-1,4-epidioxo-2,3-diazanaphthalene-2,3-dicarboximide, 52950-79-5; diphenylisobenzofuran, 5471-63-6.

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Medium Effects on the Electron Spin Resonance Hyperfine Splitting Constants of *tert*-Butyl Nitroxide in Mixed Aqueous Solvents

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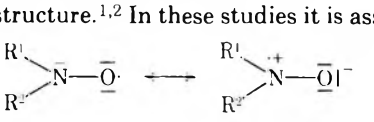
Received August 2, 1974

The substantial variation of the nitrogen hyperfine splitting constants (hfc), A_N, of nitroxide free radicals as a function of substitution pattern or solvent medium has commonly been attributed to a change in spin distribution in the nitroxide π system. In many cases these effects have been rationalized by considering the relative contributions of the two main resonance structures, A and B, to the actual molecular structure.[1,2] In these studies it is assumed that



A B

Table I
Medium Effects on A_N and A_H Values of Nitroxide 1 in Aqueous Solutions (25°)

Solvent	Range of ϵ	A_N^S		A_H^S		
		$a \times 10^2$	b	$c \times 10^2$	d	K
H_2O–MeOH	31.5[a]–78.5	17.3	13.24	27.9	11.72	0.84
H_2O–EtOH	26.0–78.5	17.5	13.22	24.4	11.97	0.51
H_2O–*i*-PrOH	20.0–78.5	14.7	13.39	22.6	12.12	0.31
H_2O–*t*-BuOH	15.5–78.5	12.7	13.56	19.3	12.41	0.21
H_2O–*p*-dioxane	17.5–78.5	15.4	13.47	23.2	12.14	0.39

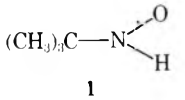
[a] Pure methanol.

A_N is (nearly) isotropic and is determined by the unpaired spin density at the nitrogen nucleus ($|\psi(0)^2|$) by eq 1 in which g and g_N are the electron and nuclear g factors, respectively, β is the electron Bohr magneton, and β_N is the

$$A_N = \frac{8\pi}{3} g g_N \beta \beta_N |\psi(0)^2| \quad (1)$$

nuclear magneton. Effects that favor structure B relative to A will then be associated with an increase in the magnitude of A_N. For substituent effects on A_N this treatment may be a serious oversimplification since bending from planarity around the nitrogen atom is ignored.[3,4] The above rationale seems to be more justified for a semiquantitative treatment of the environmental perturbations of A_N values. However, now the question arises as to the nature of the solvent effect: *a priori* both solvent polarity as well as hydrogen bonding capability may play an important role. Both effects will exert a similar influence on the relative contributions of A and B because hydrogen bonding is expected to occur predominantly with an oxygen lone pair in structure B.[5] Insight into the solvation process is desirable because nitroxides have been frequently used as spin-label in studies on molecules of biological interest.[6]

Previous investigations of the solvent-induced redistribution of spin density in nitroxides have been mainly limited to pure solvents and there exists considerable controversy regarding which solvent parameter is most suitable for correlation with A_N. Thus, A_N has been linearly correlated with bulk dielectric constant,[7] Kosower's Z values,[8] Reichardt's E_T parameters,[9] and dipole moments of the solvents.[10] Correlation coefficients are sometimes poor[7,9b] and there is at least one case in which an excellent correlation with dielectric constant has been overlooked.[11] Only very few studies have been performed on nitroxide radicals in mixed solvents.[11] Since we anticipated that measurements of A_N in binary solvent systems as a function of solvent composition could have a considerable potential in delineating A_N solvent sensitivity, we have measured both A_N as well as A_H values of *tert*-butyl nitroxide (1) in some



1

mixed aqueous solvents and in some aqueous salt solutions.

This nitroxide was chosen because of the expected propensity for hydrogen bonding interaction, both at oxygen (as a H-bond acceptor) and at N–H (as a H-bond donor).

We find that in mixtures (S) of water with methanol, ethanol, 2-propanol, *tert*-butyl alcohol, and *p*-dioxane, both A_N and A_H values are linearly correlated with bulk dielectric constant (ϵ) through eq 2 and 3. The correlation

$$A_N^S = a\epsilon + b \quad (2)$$

$$A_H^S = c\epsilon + d \quad (3)$$

has a surprisingly great precision (correlation coefficients >0.98) provided that ϵ is not too low. The magnitudes of *a*,*b*,*c*, and *d*, which are characteristic for the particular solvent mixture, are given in Table I. A high dielectric constant clearly favors the polar resonance structure B relative to A. The observed linear correlation of A_N and A_H with ϵ is difficult to reconcile with the assumption that solute–solvent hydrogen bonding is the dominating solvation factor in determining how the hfc's vary with solvent composition.[12] Especially in highly aqueous *tert*-butyl alcohol (mole fraction of water between 1.00 and 0.90; ϵ 78.5–52.0; 25°) there exists a definite trend toward a discontinuous variation in solute–solvent H-bond interaction.[13] This is not revealed in our data. In fact the medium dependency of the hfc's may be analyzed in terms of a simple model assuming localized complexes between the N–O π system of 1 and the organic solvent (S_A) or water (S_B). Fraenkel and his associates[14] have proposed that the average observed nitrogen splitting ($\bar{A}_N$) under conditions of fast exchange (on the esr time scale) will be given by

$$\bar{A}_N = \tfrac{1}{2}(A_{S_A} + A_{S_B}) + \tfrac{1}{2}[(K\alpha - 1)/(K\alpha + 1)]\Delta \quad (4)$$

where A_{S_A} and A_{S_B} are the A_N values in the pure solvents S_A and S_B, α is the ratio of solvent concentrations ($\alpha = [S_A]/[S_B]$), Δ is ($A_{S_B} - A_{S_A}$), and K is the equilibrium constant for the solvation equilibrium (eq 5). K values obtained by

$$\mathbf{1}(S_A) + S_B \overset{K}{\rightleftharpoons} \mathbf{1}(S_B) + S_A \quad (5)$$

this procedure are also given in Table I. They indicate that there is a clear tendency for preferential solvation by the organic solvent of low charge-solvating ability, resulting in a reduced sensitivity of A_N (and A_H) for bulk dielectric constant.

The hydrophobic nature of 1 is confirmed by the low perturbation of A_N and A_H in aqueous salt solutions at 25°. For example, A_N varies from 14.55 G in pure water (ϵ 78.5) to 14.68 G in 6 *N* NaBr (ϵ 42.0) or to 14.26 G in 6 *N* $(CH_3)_4NCl$ (ϵ ca. 38). Apparently, incorporation of 1 in the hydration shells of the ions is very unfavorable and consequently A_N scarcely responds to the considerable variation in the macroscopic dielectric constant of the solution.

As noted before, the solvent-induced variation of A_N and A_H in the mixed solvents only fits the linear correlation lines (eq 2 and 3) above a critical value of ϵ (see Table I). For example, in pure dioxane A_N = 12.96 G while eq 2 predicts a value of 13.50 G. Apparently, in the strongly apolar media the local electrostatic fields induced by the solvent in the cybotactic region around the nitroxide function are no longer described by a macroscopic solvent parameter like the dielectric constant of the bulk solvent. Under these conditions, water can hardly compete with organic solvent for solvation of 1 and the spin distribution will now respond to highly specific dipole–dipole and van der Waals interactions.

Finally, we emphasize that A_N or A_H values will be no

adequate probes for solvent dielectric constant around bonding sites of nitroxide spin-labels since the constants a–d in eq 2 and 3 are dependent on the nature of the particular medium. However, A_N and A_H values may have some potential for comparative studies of effects due to changes in solvent polarity on solvation phenomena in these molecules.

Experimental Section

Esr hfc's (in gauss) were determined on a Varian E-4 apparatus fitted with a Varian A 1268 variable-temperature controller. Using optimal machine operating conditions, A_N and A_H could be measured to within ±0.04 G. Nitroxide 1 was prepared *in situ* by oxidation of *N*-*tert*-butylhydroxylamine[15] with PbO_2. The small amount of PbO_2 introduced into the solution had a negligible effect on the magnitudes of A_N and A_H. The solutions were deoxygenated with a nitrogen purge. The hfc's of 1 were measured at at least nine solvent compositions in the range of ϵ given in Table I. The correlation lines were obtained by least-squares analysis. The estimated error in the K values is *ca.* 30%. These values have been calculated for the solvent composition range where A is most sensitive for variation of α.

Supplementary Material Available. Esr hfc's of nitroxide 1 as a function of solvent composition will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N. W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3800.

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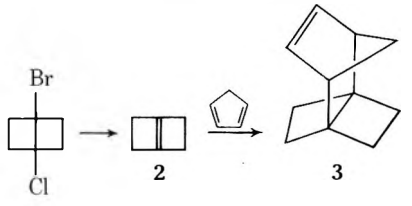
Electroorganic Chemistry. IV.[1] $\Delta^{1,4}$-Bicyclo[2.2.0]hexene

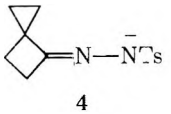
Summary: Controlled current electroreduction of 1-bromo-4-chlorobicyclo[2.2.0]hexane (**1**) in dimethylformamide at −20° on a mercury cathode gave $\Delta^{1,4}$-bicyclo[2.2.0]hexene (**2**) as the only organic product, identified as the Diels–Alder adduct (**3**) with cyclopentadiene.

Sir: The theoretically interesting $\Delta^{1,4}$-bicyclo[2.2.0]hexene (**2**) represents one of the most highly strained olefins conceivable. Examination of its physical and chemical properties would constitute a valuable contribution to a study of the bonding properties of strained molecules. Convincing evidence has been presented[2] for the presence of **2** during the thermolysis of tosylhydrazone salt **4**. The Diels–Alder adduct (**3**) of olefin **2** was isolated and characterized by Wiberg and coworkers, who also reported the low temperature ^{1}H nmr spectrum of the olefin itself. Subsequently the



1 2 3

same research group has reported[3] that **2** can be isolated as the bis(triphenylphosphine)ethylene)platinum π complex (**5**) from which it could be freed by treatment with carbon disulfide.



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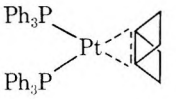

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6

We wish to report that, when bromochloride **1**[4] [$E_{1/2}$ −2.50 V *vs.* saturated calomel electrode in dimethylformamide (DMF)] was electroreduced at −20° in a compartmented cell similar to one described elsewhere[1,5] and the reaction product treated with excess cyclopentadiene, the only volatile organic product (excepting dicyclopentadiene) was adduct **3**. The yield was nearly quantitative, and the crude reaction mixture was free from the Diels–Alder adduct of 1,2-dimethylenecyclobutane (**6**) and olefin **2**, an adduct reported to be formed during the thermolysis of **4**.[2] That the primary product of the reaction was olefin **2** could be demonstrated in two ways. Controlled current electroreduction was conducted at a stirred mercury cathode at 200 mA and −20° using DMF as solvent and tetraethylammonium fluoborate[6] as supporting electrolyte. Following the passage of 2.0 F, excess cyclopentadiene was added to the cold catholyte. The catholyte was worked up in the usual way[1] after it has stood overnight at room temperature. Compound **3** was separated from dicyclopentadiene by preparative glpc. Alternatively, if the reduction was carried out at −20° under 0.6-Torr pressure in a very gentle stream of dry nitrogen and the volatiles were collected directly on the vacuum line in a trap at −200° which contained excess cyclopentadiene, the same result was obtained after the trap was allowed to warm to room temperature as had been obtained by adding cyclopentadiene directly to the cold reaction mixture. The continuous removal of **2** as it was formed prevented its subsequent thermal decomposition. Such a technique was employed previously by us.[7]

Compound **3** showed ^{1}H nmr signals at τ 3.82 (s, 2 H), 7.46 (s, 2 H), and 7.55–8.75 (m, 10 H), in excellent agreement with the values reported previously.[2] The mass spectrum (rel intensity) *m/e* 146 (M^+, 10%), 131 ($C_{10}H_{11}^+$, 22%), 117 ($C_9H_9^+$, 26%), 91 ($C_7H_7^+$, 100%), 90 ($C_7H_6^+$, 42%), 77 ($C_6H_5^+$, 32%), 66 ($C_5H_6^+$, 35%), 61 ($C_5H_5^+$, 23%), supports earlier structural assignment. With a direct convenient synthesis of this unusual olefin now available, work is in progress directed toward the isolation and study of the physical properties of the pure olefin.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

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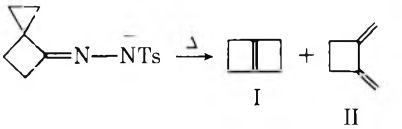
Received August 28, 1974

A Convenient Synthesis of $\Delta^{1,4}$-Bicyclo[2.2.0]hexene[1]

Summary: The electrochemical dehalogenation of 1-chloro-4-bromobicyclo[2.2.0]hexane gives an almost quantitative yield of $\Delta^{1,4}$-bicyclo[2.2.0]hexene.

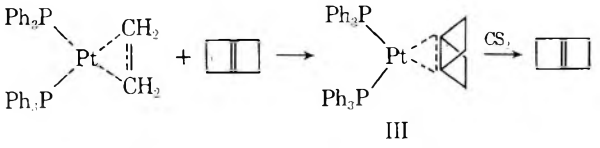
Sir: The synthetically and theoretically interesting hydrocarbon, $\Delta^{1,4}$-bicyclo[2.2.0]hexene (I), has been prepared by the thermolysis of the anion derived from spiro[2.3]hexanone-4 tosylhydrazone.[2] 1,2-Dimethylenecyclobutane (II) was formed in similar amount, and, because of the rapid



I II

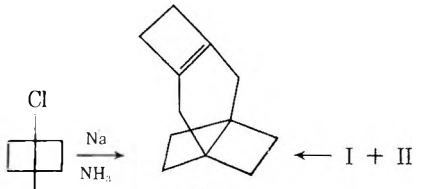
Diels–Alder reaction between I and II even at −60°, it was not possible to isolate I in pure form.

Subsequently, we have shown that I may be separated from II by reaction with bis(triphenylphosphine)(ethylene)platinum.[3] The complex, III, on reaction with carbon disulfide, liberated I. Although this made it possible to obtain a pure sample of I, it cannot be considered a convenient preparative method.

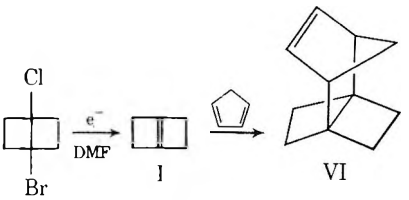


III

Dehalogenation of 1-chloro-4-bromobicyclo[2.2.0]hexane (IV)[4] using 8 molar equiv of sodium in liquid ammonia[5] affords an almost quantitative yield of dimer, $\Delta^{3,6}$-tetracyclo[6.2.2.0^{1,8}.0^{3,6}]dodecene (V), identical in all respects with the product of the Diels–Alder reaction between I and II.[2] A small amount of I (up to ~18%) is produced by the dehalogenation of IV when less sodium is employed, as evidenced by the isolation of the well-characterized Diels–Alder adduct, VI, when the reaction mixture is treated with excess cyclopentadiene. A short reaction time (2–3 min, incomplete reduction) does not improve the yield of I.[6]



While this procedure offers a route to I, it is not attractive on a preparative scale. Therefore we have examined the electrochemical reduction of IV in dimethylformamide at a platinum electrode with tetraethylammonium bromide as the supporting electrolyte. When a potential of −2.50 V *vs.* a mercury pool at −20° was used, the current dropped rapidly when 2 equiv of charge had been transferred. The DMF solution was added to a cold mixture of brine and pentane, and the pentane solution was washed with water. Addition of cyclopentadiene followed by removal of solvent gave a quantitative yield of the Diels–Alder adduct of I with cyclopentadiene (VI, mp 79.5–80°). None of the Diels–Alder product derived from I and II was found, indicating that II was not a by-product in the reaction.



The use of butane as the extracting solvent permits facile separation of I from the electrolysis mixture. Treatment of a butane solution of I with ozone at −78°, followed by reductive work-up with dimethyl sulfide, afforded 1,4-cyclohexanedione. Isolation of I from the butane solution was unsuccessful.

One of the more interesting of the properties of I is its thermal stability. A dilute solution of I was prepared by extracting it from the electrolysis mixture with heptane and washing the heptane layer several times with water. Triethylamine was added, and the solution was sealed in several small ampoules. Kinetic points were taken by quenching the contents of an ampoule with cyclopentadiene and then analyzing the decrease in Diels–Alder adduct VI and the increase in Diels–Alder dimer V by glc. At 14.85°, the concentration of I was found to decrease by a process second order in I, $k_{14.85°} = 2.2 \times 10^{-2}$ l. mol^{-1} sec^{-1}. The amount of V present did not increase. Thus, I is stable at this temperature toward unimolecular isomerizations, but in solution readily undergoes a reaction with itself, possibly by an "ene" reaction as has been observed with cyclopropene.[7]

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Received September 23, 1974

2,2,2-Trichloroethanol

Carboxylic acids are conveniently protected as their 2,2,2-trichloroethyl esters, readily formed by reacting 2,2,2-trichloroethanol with a carboxylic acid and dicyclohexylcarbodiimide. The protecting group is easily removed by stirring the esters with zinc and acetic acid at room temperature.[1] 2,2,2-Trichloroethyl esters have been used extensively in the synthesis of Cephalosphorin C[1] and oligonucleotides,[2,3] in prostaglandin work[4] and in penicillin chemistry.[5] In addition 2,2,2-trichloroethanol is used in the production of anthelmintics, herbicides, hypnotics and insecticides.

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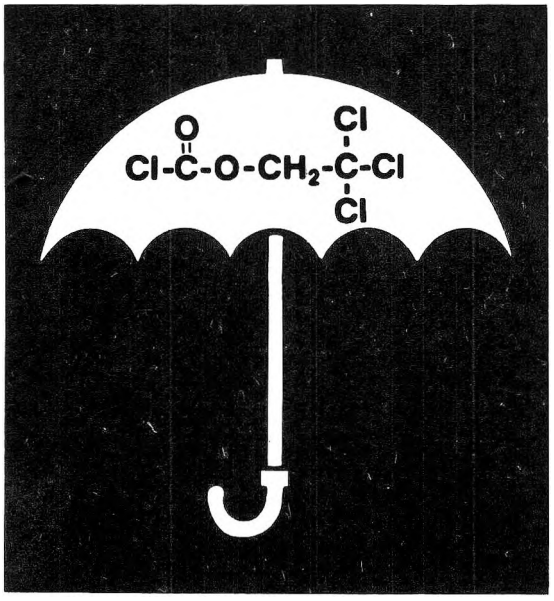
T5480-1 2,2,2-Trichloroethanol
100 g $5.00; 500 g $16.00; 10 kg $270.00

D8000-2 Dicyclohexylcarbodiimide
20.6 g† $3.00; 25 g $3.00; 100 g $10.00; 10 kg $320.00

TWO Useful Reagents from Aldrich for PROTECTING Carboxyl Groups and Alcohols or Amines



2,2,2-Trichloroethyl chloroformate

2,2,2-Trichloroethyl chloroformate is an excellent protecting agent for both aliphatic and aromatic hydroxy and amino groups.[1] The 2,2,2-trichloroethoxycarbonyl group is easily removed by stirring for 1-3 hours at room temperature with zinc and acetic acid or by brief reflux with zinc in methanol, yet is unaffected by mild hydrogenation conditions, Sarett and Jones oxidations, treatment with hydrochloric acid in dioxane or brief treatment with trifluoroacetic acid. This protecting group has been used, for example, in a convenient synthesis of unsymmetrical 1,2-diacylglycerols.[2] Also, tertiary methylamines have been readily demethylated to the corresponding secondary amines, using 2,2,2-trichloroethyl chloroformate.[3]

References

1) T. B. Windholz and D. M. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).
2) F. R. Pfeiffer *et al.*, Unchecked Procedure. *Org. Syn.*, **50**, 1970.
3) T. A. Montzka, J. D. Matiskella and R. A. Partyka, *Tetrahedron Lett.*, 1325 (1974).

14,207-7 2,2,2-Trichloroethyl chloroformate
21.2 g† $8.50; 100 g $26.70

† Deci-mole units

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