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AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 20

SEPTEMBER 30, 1977

Nuclear Magnetic Resonance Determination of Enantiomeric Compositions of Oxaziridines Using Chiral Solvating Agents

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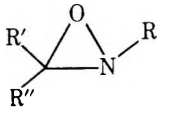
Received March 28, 1977

Addition of chiral arylperfluoroalkylcarbinols to solutions of oxaziridines causes the NMR spectra of the oxaziridine enantiomers to be nonidentical. The resultant chemical shift differences allow direct determination of the enantiomeric composition of the oxaziridine and may ultimately allow assignment of absolute configuration to each enantiomer. Reasons underlying the origin of the spectral nonequivalence are discussed and absolute specific rotations for several oxaziridines are presented.

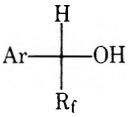
Oxaziridines (**1**) have attracted considerable stereochemical attention as a consequence of the dissymmetric nitrogen and its appreciable barrier to inversion. Optically active oxaziridines have been prepared by the oxidation of achiral imines with chiral peracids,[1] by the oxidation of chiral imines with achiral peracids,[2] by thermal isomerization in a chiral liquid crystal,[3] and by photochemical synthesis in a chiral solvent.[4] The enantiomeric purities of most chiral oxaziridines have been unknown, since only in select instances have partially resolved oxaziridines been crystallized to enantiomeric purity so that absolute specific rotations might be determined. We now report a method employing chiral solvating agents (CSA) for the rapid and convenient NMR determination of the enantiomeric composition of oxaziridines. This method may ultimately allow determination of oxaziridine absolute configuration as well.

When used as CSA, fluoro alcohols of general structure **2** cause the NMR spectra of oxaziridine enantiomers to differ. This behavior was first noted[5] when oxaziridine **1a**, formed by oxidation of *N*-*tert*-butylformimine with (*S*)-(+)-monoperoxycamphoric acid (MPCA), was examined by NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-phenylethanol (**2a**) and separate *tert*-butyl singlets and AB patterns were observed for each oxaziridine enantiomer. Simply by comparing the relative signal intensities, the enantiomeric composition of **1a** was determined.

The differential NMR effect of CSA (**2b**) upon the enantiomers of partially resolved oxaziridine **1b** is shown in Figure 1. Results obtained from the NMR spectra of other partially resolved oxaziridines in the presence of (*S*)-(+)-**2b** and **2c** are shown in Table I. In each instance, enantiomeric composition was determined from the relative intensities of the anisochronous resonances of the enantiomers.



1a, R′ = R″ = H; R = *tert*-butyl
b, R′ = H; R″ = CH_3; R = *tert*-butyl



2a, Ar = phenyl; R_f = CF_3
b, Ar = 9-(10-methylanthryl); R_f = CF_3
c, Ar = 9-anthryl; R_f = CF_3
d, Ar = 9-(10-Bromoanthryl); R_f = CF_3

Type **2** CSA cause enantiomeric spectral nonequivalence for a wide variety of solutes by forming diastereomeric chelate-like solvates, exemplified by generalizations **3a,b.** These diastereomeric solvates have nonidentical time-averaged NMR spectra owing to the stereochemical dependence of the shielding effect exerted by the aromatic substituent of **2** on R_1 and R_2. Typically R_1 and R_2 show opposite senses of nonequivalence. In alkyl oxaziridines there are but two basic sites, the oxygen and the nitrogen. Because of the opposite senses of nonequivalence observed for the nitrogen and carbon substituents of the nonaromatic oxaziridines, we consider it highly probable that the observed nonequivalence stems from solvation of these oxaziridines by **2** as depicted in **3a,b.** Experience has shown that the hydroxyl proton of **2** hydrogen bonds preferentially to the more basic of the two sites. A priori, it is not known for oxaziridines whether oxygen or nitrogen is the site for primary hydrogen bonding. This is important,

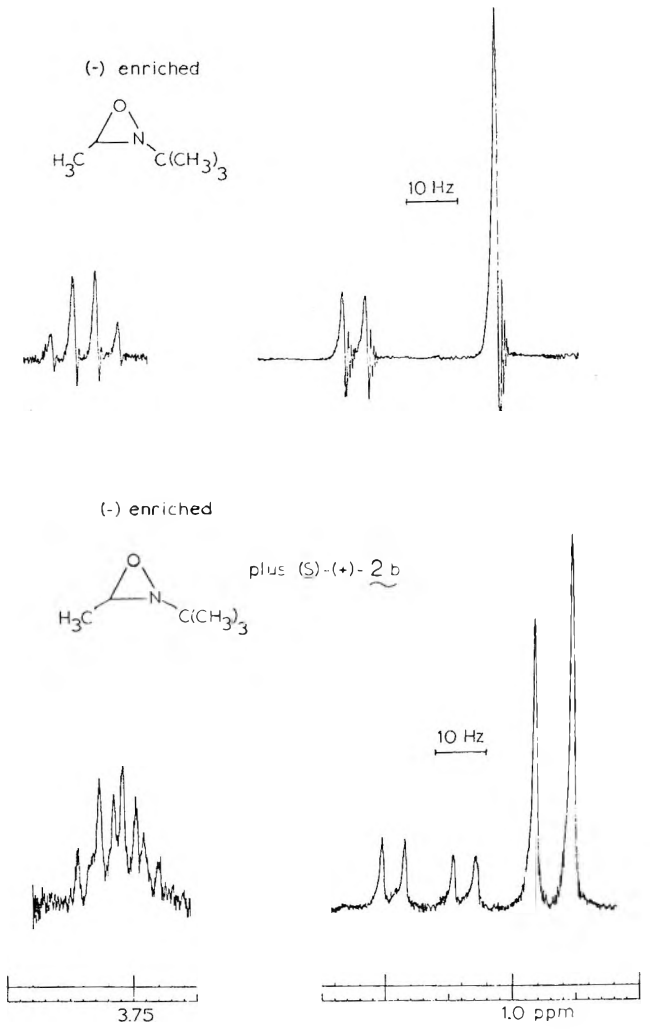
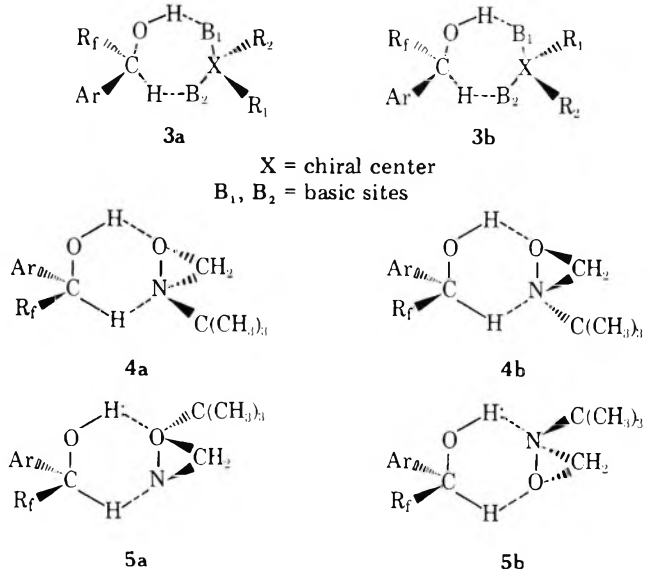


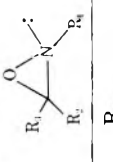
Figure 1. 100-MHz NMR spectrum of (−)-enriched **1b** in the absence (top) and in the presence (bottom) of (*S*)-(+)-**2b**.

since formation of diastereomeric solvates of the type illustrated by **4a,b** as opposed to those illustrated by **5a,b** would



invert the prediction of nonequivalence sense for a given absolute configuration. It is this uncertainty that prevents us from assigning absolute configurations to the oxaziridines in Table I based upon the observed senses of nonequivalence and the known absolute configurations of **2b,c**.

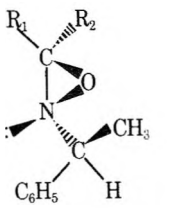
Table I. Properties of Oxaziridines from Percamphoric Acid Oxidation of Imines



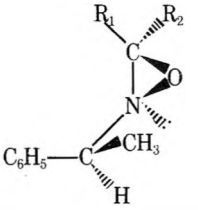
	Registry no.	Chemical shifts, δ CCl_4			Nonequivalence,[a] Hz[b]/sense[c]				% enantiomeric excess by NMR	$[\alpha]^{27}_D$,[d] deg	$[\alpha]^{27}_D$ max, deg
		R_1	R_2	R_3	R_1	R_2	R_3	CSA			
1a	63017-52-7	1.03	3.62 AB	3.62	9.0/H	35.0/H	30.0/L	2b	6	−2.07	−34.5
1b	62107-41-9	1.07	4.00 q	1.37 d	7.5/H	3.0/L	15.0/L	2c	14[f]	−5.19[g]	−37.1
1c	63017-53-8	2.43	1.3–2.0		11.0/H			2b	14	−5.39[g]	−38.5
1d	63087-57-0	1.05	4.63 s	7.1–7.6	6.7/L	0		2b	21[f]	−22.3	−85.6
1e	40264-03-7	2.80	4.25 s	7.27	2.5/L	1.5/H		2c	40[f]		
1f	39345-63-1	2.34	5.02 s	7.32	8.5/H		12.0/L	2c	12		
1g	59905-68-9	1.14	4.62 s	7.84	3.5/L	0	3.0/L	2c	25	−30.9	−124

[a] Nonequivalence was caused by adding ca. a threefold excess of (*S*)-(+)-**2b** or (*S*)-(+)-**2c** to a dilute CCl_4 solution of oxaziridine. [b] At 100 MHz and 25 °C. [c] H refers to high-field sense, L to low-field sense. [d] Rotations were taken in CCl_4 using concentrations of ca. 5%. [e] Obtained as a 1.2:1 mixture of trans/cis isomers. [f] Recrystallized MPCA used. [g] Rotations were taken of the neat liquid.

One approach to the determination of the site of the primary interaction (O vs. N) would be to examine partially resolved oxaziridines of known absolute configuration so as to see which primary interaction site accounted for the observed nonequivalence senses. There are but five oxaziridines (**6**–**10**)



6, R_1, R_2 = C_6H_5
7, R_1 = *p*-BrC_6H_4; R_2 = H
8, R_1 = H; R_2 = *p*-BrC_6H_4



9, R_1 = H; R_2 = *p*-BrC_6H_4
10, R_1 = *p*-BrC_6H_4; R_2 = H

of known absolute configuration[10,11] and, while partially resolved samples of these all show nonequivalence in the presence of **2d**, no consistent or interpretable pattern of nonequivalence was observed. This was not altogether unexpected, since the aromatic rings on these oxaziridines introduce two complications.[12] First, phenyl rings can act as additional "secondary" basic sites, and give rise to solvation modes other than **4a,b** or **5a,b**. For instance, styrene epoxides are known[13] to show nonequivalence in the presence of chiral type **2** alcohols, the senses of nonequivalence being explained best by a solvate in which the epoxide oxygen acts as the primary basic site, while the phenyl ring acts as the secondary basic site. The second complication attending the aromatic groups in **6**–**10** is that the anisotropy of the phenyl rings could possibly give rise to nonequivalence stemming from different conformational behavior of these groups in one diastereomeric solvate than in the other. In this event, "internal" nonequivalence would stem from shielding (or deshielding) by the aryl groups *of the oxaziridine* rather than by the "external" anthryl substituent of **2d**. The time-averaged result of such contributions cannot be predicted.

It is evident that enantiomeric compositions of a wide variety of oxaziridines may now be directly determined[14] by using chiral type **2** fluoro alcohols as CSA. The method also appears to have excellent potential for the determination of oxaziridine absolute configuration, although such assignments are presently premature. Determination of the primary site of interaction between oxaziridines and type **2** fluoro alcohols should make such assignments feasible.

Experimental Section

NMR spectra were obtained with Varian Associate A60-A, EM-390, HA-100, and HR-220 spectrometers. Optical rotations were determined in a Zeiss visual polarimeter using a 1.0-dm tube. For nonequivalence measurements spectra were determined at 100 MHz and 27 °C using CCl_4 solutions 0.1–0.2 M in oxaziridine with a one- to twofold excess of **2a**, **2b**, or **2c**.

(*S*)-(+)-Monopercamphoric Acid. This compound was prepared by the method of Miles and McAlevy;[16] a viscous syrup was obtained, which was dissolved in CH_2Cl_2 and titrated for active oxygen by iodometry.

Oxaziridines. Oxaziridines were prepared from the corresponding imines using either the procedure illustrated below or by oxidation at −78 °C in a 3:1 $CHCl_3$–CH_2Cl_2 solution using monopercamphoric acid purified by recrystallization. The use of the purified peracid generally leads to a greater degree of asymmetric induction than does use of the mixed percamphoric acid isomers.[17] Oxaziridines so obtained are designated in Table I.

Synthesis of *trans*-2-*tert*-Butyl-2-phenyloxaziridine (1d). A solution of *N*-*tert*-butylbenzaldimine (8.05 g, 0.05 mol) in CH_2Cl_2 (50 mL) was cooled in a dry ince–acetone bath and monopercamphoric acid (11.9 g, 0.055 mol) in 80 mL of CH_2Cl_2 was added dropwise (30 min) to the stirred solution. The bath and the immersed reaction vessel were allowed to slowly warm to room temperature after stirring overnight. The reaction mixture was extracted once with 100 mL of saturated sodium sulfite, then twice with 10% aqueous potassium carbonate. The organic layer was dried over anhydrous potassium carbonate, the solvent removed under vacuum, and the residual oil purified by molecular distillation to afford a clear liquid: $[\alpha]^{25}_D$ = −22.3° (*c* 10, CCl_4); NMR δ CCl_4 7.1–7.6 (m, 5 H, Ar), −4.63 (s, 1 H, CH), 1.05 (s, 9 H, *tert*-butyl).

Chiral Solvating Agents (2). The fluoro alcohols used in this study were synthesized and resolved by a procedure analogous to that reported previously for **2c**.[18] The syntheses, resolutions, and assignments of absolute configuration of **2a**–**d** have been reported by Pavlin.[19]

Acknowledgments. This work was partially supported by grants from the National Science Foundation and the National Institutes of Health.

Registry No.—$R_2R_3C{=}NR_1$(R_1 = Bu-*t*; R_2, R_3 = H), 13987-61-6; $R_2R_3C{=}NR_1$ (R_1 = Bu-*t*; R_2 = H; R_3 = CH_3), 7020-80-6; $R_2R_3C{=}NR_1$ (R_1 = CH_3; R_2, R_3 = $-(CH_2)_5-$), 6407-35-8; $R_2R_3C{=}NR_1$ (R_1 = Bu-*t*; R_2 = H; R_3 = Ph), 6852-58-0; $R_2R_3C{=}NR_1$ (R_1 = CH_3; R_2 = H; R_3 = Ph), 622-29-7; $R_2R_3C{=}NR_1$ (R_1 = Bu-*t*; R_2 = H; R_3 = $NO_2C_6H_4$) 718-36-5; (*S*)-(+)-monoperoxycamphoric acid, 20696-10-0; **2a**, 10531-50-7.

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(7) (a) W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **90**, 6250 (1968); (b) W. H. Pirkle, S. D. Beare, and R. L. Muntz, *Tetrahedron Lett.*, 2295 (1974); (c) W. H. Pirkle and D. L. Sikkenga, *J. Org. Chem.*, **40**, 3430 (1975).
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(12) The departure of the C-aryl-substituted oxaziridines in Table I from the "opposite sense of nonequivalence" generalization made for C and R substituents presumably has its origin in such effects.
(13) (a) F. Montanari, I. Moretti, and G. Torre, *Gazz. Chim. Ital.*, **104**, 7 (1974); (b) F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 135 (1969).
(14) A referee has raised the question of the precision of NMR determinations of enantiomeric purity. The precision with which the relative intensities of two NMR signals may be determined will be influenced by experimental parameters such as signal to noise ratio, instrument stability, and chemical shift differences between the signals. We routinely attain precision of ±1%. The accuracy of the enantiomeric purity measurements cannot yet be independently checked for oxaziridines. Such checks have been made, however, for methyl esters of α-amino acids and agreements of ±1–2% were observed.[15]
(15) W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **91**, 5150 (1969).
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(19) M. S. Pavlin, Ph.D. Thesis, University of Illinois, 1977.

Reactions of α-Halo Acid Chlorides with Diisopropylcarbodiimide. 5-Oxazolidinones

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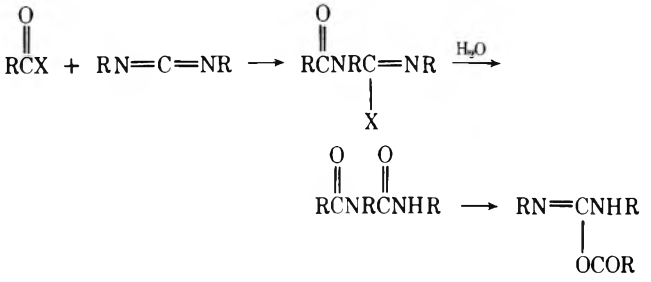
Department of Chemistry, North Texas State University, Denton, Texas 76203

Received April 4, 1977

The reaction of diisopropylcarbodiimide with chloroacetyl, α-chloropropionyl, and α-bromoisobutyryl chlorides yields the corresponding acylchloroformamidines. Hydrolysis of the formamidines yields the acylureas, which under the acid conditions of the hydrolysis rearrange to the *O*-acylureas, which undergo ring closure to the 5-oxazolidinones upon heating. Chloroacetylchloroformamidine undergoes ring closure in the presence of triethylamine and water to yield the 4-oxazolidinone. The hydrolysis and rearrangement of the 5-oxazolidinones as well as the mechanism of ring formation are discussed.

Acid halides react with carbodiimides to form *N*-acylhaloformamidines, which readily hydrolyze to form *N*-acylureas.[1,2] These ureas may also be formed by the controlled reaction of acids and carbodiimides and by the reaction of an acid halide and an appropriately substituted urea.[3-9] *N*-

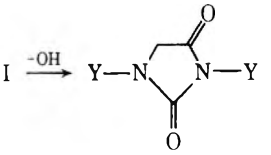


Acylureas rearrange to *O*-acylisoureas under appropriate conditions; i.e., the *N*-acylureas are favored under basic conditions and the *O*-acylisoureas are predominant under acid conditions[4,5,9]

We would like to describe a study of the reactions of some α-halo acid chlorides and diisopropylcarbodiimides to yield *N*-acylchloroformamidines, hydrolysis to the corresponding ureas, and subsequent formation of 5-oxazolidinones and 4-oxazolidinones. We have recently described the conversion of acylchloroformamidines derived from α-halo acid halides and diisopropylcarbodiimide to 2-azetidinones.[11]

The α-halo acid chlorides were reacted with diisopropylcarbodiimide to yield the acylchloroformamidines, which were hydrolyzed to the acylureas. The acylureas apparently rearranged to the *O*-acylisoureas under the acid conditions of the hydrolysis and either on standing or upon heating underwent ring closure to the 3-isopropyl-2-isopropylimino-5-oxazolidinones (I–III). The solid acylureas did not undergo oxazolidinone formation until molten. If the acylureas were heated rapidly, sublimation occurred instead of ring closure.

Upon washing I with a suspension of ether and dilute potassium hydroxide solution for 5 min, 1,3-diisopropyl-1,3-diazolidine-2,4-dione (IV) was recovered from the ether layer.

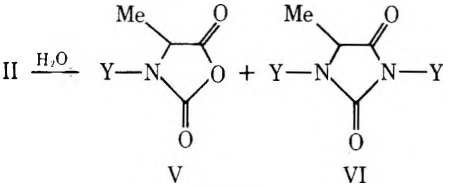


IV

Y = *i*-Pr

This rearrangement apparently involves a nucleophilic attack by base at the carbonyl carbon with subsequent ring opening forming a resonance stabilized oxyanion involving the imino group. A subsequent ring closure would yield the diazolidinedione. When the reaction was allowed to proceed for more than 5 min, the diazolidinedione was hydrolyzed further, in which case the products were not identified.

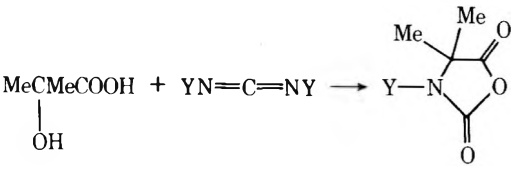
The 5-oxazolidinones are sensitive to moisture and undergo rearrangement and hydrolysis upon exposure to the atmosphere. A sample of II was allowed to stand in air for 2 weeks. The initially solid 5-oxazolidinone reacted with the moisture in the air and was converted to a viscous oil. This oil was dissolved in ether and analyzed by VPC and identified as 4-methyl-3-isopropyl-2,5-oxazolidinedione (V) and 4-methyl-1,3-diisopropyl-1,3-diazolidine-2,5-dione (VI). The diazolidinedione is the rearrangement product and the oxazolidinedione is the result of hydrolysis of the carbon–nitrogen double bond of the 5-oxazolidinone. A similar 3-cyclohexyl-4,4-dimethyl-2,5-oxazolidinedione was obtained by Robba and Maume from the reaction of α-hydroxyisobutyric acid with dicyclohexylcarbodiimide.[12]



V VI

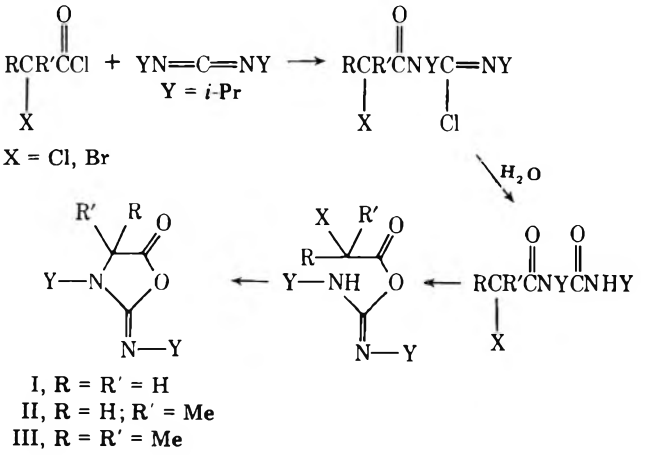
Y = *i*-Pr

In an effort to verify the intermediacy of the *O*-acylisourea



Y = C_6H_{11}

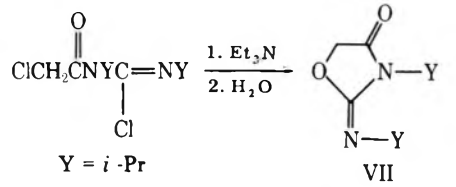
Scheme I



I, R = R′ = H
II, R = H; R′ = Me
III, R = R′ = Me

in the formation of the 5-oxazolidinones, chloroacetic acid and diisopropylcarbodiimide were allowed to react in carbon tetrachloride. The 5-oxazolidinone was isolated along with some disubstituted urea, which is the by-product of chloroacetic anhydride formation. The 5-oxoazolidinone formation from the *O*-acylisourea is the result of a nucleophilic displacement of the α-chloro substituent on the acyl group by the imino group of the isourea with the subsequent loss of hydrogen chloride as illustrated in Scheme I.

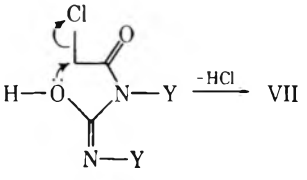
The treatment of the acylchloroformamidine derived from chloroacetyl chloride and diisopropylcarbodiimide in hexane with triethylamine at room temperature followed immediately by the addition of water resulted in the formation of 3-isopropyl-2-isopropylimino-4-oxazolidinone (VII). The acyl-



Y = *i*-Pr VII

chloroformamidine will react slowly with the triethylamine at room temperature to yield the 2-azetidinone, so the addition of water is critical. The presence of the amine scavenges the hydrogen chloride that is eliminated from both the hydrolysis of the acylchloroformamidine and the ring closure, thus inhibiting the formation of *O*-acylisourea, which is favored under acid conditions, and preventing the formation of the 5-oxazolidinone. Mironova and Dvorko have reported a similar reaction of chloroacetic anhydride or chloroacetyl chloride with dicyclohexylurea in benzene in the presence of pyridine.[10]

The 4-oxazolidinone ring formation arises from the nucleophilic displacement of the α-chloro substituent on the acyl group by the oxygen of the carbonyl of the urea with subse-



Y = *i*-Pr

quent loss of hydrogen chloride. There was no evidence for the formation of the diazolidinedione, which would arise from the nitrogen of the amino group of the urea displacing the chloride ion.

While there are several reports in the literature on the reaction of carboxylic acids, acid halides, and other acid derivatives with carbodiimides, there are very scattered reports whereby the acid derivative contains an α-halo substituent. This feature enables a facile ring closure of the α-haloacylurea or the corresponding *O*-acylisourea to 5-oxazolidinones and 4-oxazolidinones, respectively. Therefore, in summary, the reaction of α-halo acid halides with carbodiimides, hydrolysis to the ureas, spontaneous rearrangement to the *O*-acylisourea, and subsequent ring closure provides an excellent general synthesis for 5-oxazolidinones.

Experimental Section

Proton NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B spectrometer employing tetramethylsilane as an internal standard. VPC separations were achieved using a 10 ft × ½ in. outside diameter glass column packed with 10% SE-30 on Chromosorb WAW, 60/80 mesh, in a Varian 1525-B gas chromatograph with a thermal conductivity detector. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E double focusing mass spectrometer. The infrared spectra were recorded on a Perkin Elmer Model 237 and Beckman Model 33 grating infrared spectrometers.

Solvents were dried and purified by distillation from sodium–potassium alloy under a nitrogen atmosphere prior to use. Commercially available triethylamine was dried over sodium metal and distilled prior to use.

N-tert-Butylbenzylimine was prepared from benzaldehyde and *tert*-butylamine according to standard procedure.[13] *N,N'*-Diisopropylcarbodiimide was commercially available and used without further purification.

General Procedure for Acylformamidines. A 0.05-mol portion of the α-haloacid halide was added with stirring to 0.5 mol of diisopropylcarbodiimide in 100 mL of ether at room temperature. After about 30 min, the ether was evaporated to yield the *N*-(α-haloacyl)-*N,N'*-diisopropylformamidine.

Chloro-*N*-chloroacetyl-*N,N'*-diisopropylformamidine. This formamidine decomposed upon distillation: IR 1670 and 1695 cm^{-1}; NMR (CCl_4) δ 1.23 (d, 6 H), 1.35 (d, 6 H), 3.90 (h, 1 H), 4.15 (s, 2 H), and 4.46 (h, 1 H).

Chloro-*N*-(α-chloropropionyl)-*N,N'*-diisopropylformamidine. This adduct distilled at 34 °C (0.025 Torr): 1665 and 1700 cm^{-1}; NMR (CCl_4) δ 1.23 (d, 6 H), 1.35 (d, 6 H), 1.58 (d, 3 H), 3.90 (h, 1 H), 4.45 (h, 1 H), and 4.67 (q, 1 H).

Anal. Calcd for $C_{10}H_{18}Cl_2N_2O$: N, 11.06. Found: N, 11.39.

General Procedure for Acylureas. An ether solution containing 0.05 mol of acylformamidine was prepared as described above. A 10-mL portion of water was added with stirring and stirring was continued for 1 h. The ether layer was separated, dried over anhydrous $CaCl_2$, and evaporated to yield the urea.

***N*-Chloroacetyl-*N,N'*-diisopropylurea.** A viscous oil was obtained which was unstable at room temperature: IR 1670, 1720, and 3300 cm^{-1}; NMR (CCl_4) δ 1.15 (d, 6 H), 1.25 (d, 6 H), 4.0 (m, 2 H), 4.18 (s, 2 H), and 7.50 (br d, 1 H).

***N*-(α-Chloropropionyl)-*N,N'*-diisopropylurea.** This urea was recrystallized from petroleum ether (100%): mp 92 °C; IR 1660, 1695, 1740, and 3260 cm^{-1}; NMR (CCl_4) δ 1.25 (d, 6 H), 1.35 (d, 6 H), 1.62 (d, 3 H), 4.2 (m, 2 H), 4.54 (q, 1 H), and 6.95 (s, 1 H).

Anal. Calcd for $C_{10}H_{19}ClN_2O_2$: C, 51.17; H, 8.16; N, 11.93. Found: C, 51.37; H, 8.29; N, 12.07.

***N*-(α-Bromoisobutyryl)-*N,N'*-diisopropylurea.** This urea was recrystallized from petroleum ether (75%): mp 87–89 °C, slowly decomposed at room temperature; IR 1640, 1675, 1700, and 3300 cm^{-1}; NMR (CCl_4) δ 1.30 (d, 6 H), 1.45 (d, 6 H), 2.05 (s, 6 H), 4.02 (h, 1 H), 4.62 (h, 1 H), and 6.98 (br d, 1 H).

General Procedure for 5-Oxazolidinones. A 0.01-mol portion of the acylurea prepared as described above was heated slightly above the melting temperature until the solid 5-oxazolidinone had formed.

3-Isopropyl-2-isopropylimino-5-oxazolidine (I). This oxazolidinone was obtained at room temperature upon standing overnight. Purification was accomplished by sublimation (77%): mp 192 °C; IR 1670 and 1795 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 6 H), 1.44 (d, 6 H), 4.10 (h, 1 H), 4.58 (h, 1 H), and 5.05 (s, 2 H); mass spectrum parent peak at *m/e* 184 (theory 184).

4-Methyl-3-isopropyl-2-isopropylimino-5-oxazolidinone (II). The acylurea was heated at 100 °C for 1 h (98%): mp 110 °C; IR 1665 and 1790 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 6 H), 1.40 (d, 6 H), 1.55 (d, 3 H), 4.05 (h, 1 H), 4.93 (h, 1 H), and 5.17 (q, 1 H); mass spectrum parent peak at *m/e* 198 (theory 198).

4,4-Dimethyl-3-isopropyl-2-isopropylimino-5-oxazolidinone (III). The acylurea was heated at 95 °C for 1 h and sublimed in vacuo (90%): mp 185 °C; IR 1695 and 1785 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 6 H), 1.44 (d, 6 H), 1.62 (s, 6 H), 4.03 (h, 1 H), and 4.68 (h, 1 H); mass spectrum parent peak *m/e* 212 (theory 212).

1,3-Diisopropyl-1,3-diazolidine-2,4-dione (IV). A 1.0-g portion of I was added to a mixture of 20 mL of 1 M KOH solution and 20 mL of ether with stirring. After 5 min, the ether layer was separated, dried over $CaCl_2$, and evaporated to give 0.75 g of dione (75%). This dione is a viscous liquid and was collected by VPC for analysis; IR 1700 cm^{-1}; NMR (CCl_4) δ 1.05 (d, 6 H), 1.50 (d, 6 H), 3.8 (m, 2 H), and 4.35 (s, 2 H); mass spectrum parent peak *m/e* 184 (theory 184).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.55; H, 8.92; N, 15.21.

Hydrolysis and Rearrangement of II. An 0.8-g (0.004-mol) portion of II was allowed to stand in air and after 2 weeks, VPC revealed the presence of two components, which were collected and analyzed.

4-Methyl-3-isopropyl-2,5-oxazolidinedione (V). A liquid: IR 1745 and 1820 cm^{-1}; NMR (CCl_4) δ 1.35 (d, 6 H), 1.46 (d, 3 H), 4.01 (h, 1 H), and 4.43 (q, 1 H).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.89; H, 7.47; N, 9.37.

5-Methyl-1,3-diisopropyl-1,3-diazolidine-2,4-dione (VI). A liquid: IR 1700 cm^{-1}; NMR (CCl_4) δ 1.05 (d, 6 H), 1.40 (d, 6 H), 1.45 (d, 3 H), 2.8 (m, 2 H), and 4.36 (q, 1 H).

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.28; H, 9.06; N, 13.95.

3-Isopropyl-2-isopropylimino-4-oxazolidinone (VII). To 0.01 mol of chloro-*N*-chloroacetyl-*N,N'*-diisopropylformamidine in 50 mL of hexane was added 1.4 mL (0.01 mol) of triethylamine at room temperature, followed immediately by the addition of excess water. After a few minutes the amine salt precipitated; the solution was filtered and the solvent evaporated to give 1.6 g (88%) of the 4-oxazolidinone; mp 46–48 °C; IR 1690 and 1750 cm^{-1}; NMR (CCl_4) δ 1.15 (d, 6 H), 1.35 (d, 6 H), 3.59 (s, 2 H), and 4.2 (m, 2 H); mass spectrum parent peak *m/e* 184 (theory 184).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.27; H, 8.48; N, 15.21.

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, 63059-02-9; II, 63059-03-0; III, 63059-04-1; IV, 63059-05-2; V, 63059-06-3; VI, 63509-07-4; VII, 57095-80-4; diisopropylcarbodiimide, 693-13-0; chloro-*N*-chloroacetyl-*N,N'*-diisopropylformamidine, 63059-08-5; chloro-*N*-(α-chloropropionyl)-*N,N'*-diisopropylformamidine, 63059-09-6; chloroacetyl chloride, 79-04-9; α-chloropropionyl chloride, 7623-09-8; *N*-chloroacetyl-*N,N'*-diisopropylurea, 63059-10-9; *N*-(α-chloropropionyl)-*N,N'*-diisopropylurea, 63059-11-0; *N*-(α-bromoisobutyryl)-*N,N'*-diisopropylurea, 63059-12-1; α-bromoisobutyryl chloride, 20469-89-0; chloro-*N*-(α-bromosiobutyryl)-*N,N'*-diisopropylformamidine, 63059-13-2.

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Substituent and Geometry Dependence of the Degenerate Ligand Exchange of Dialkoxysulfuranes with Hexafluoro-2-phenyl-2-propanol. Sulfuranes and Sulfilimines Derived from Thianthrene, Phenothiazine, and Phenoxathiin[1]

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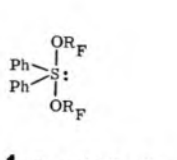
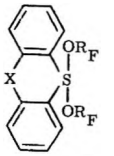
The oxidations of thianthrene, *N*-phenylphenothiazine, and phenoxathiin with bromine in the presence of the potassium salt of 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanol (R_FOH) lead to the formation of dialkoxysulfuranes. The characterization of sulfuranes is described. All three are very reactive in dehydrating *tert*-butyl alcohol at room temperature. The degenerate alkoxy ligand exchange with R_FOH is determined by NMR to be very fast, with the rates for sulfuranes derived from phenoxathiin, thianthrene, and *N*-phenylphenothiazine increasing in the order listed. The first two of these sulfuranes were shown to react with benzylamine to give the corresponding *N*-benzylsulfilimines.

Over the past few years several types of oxysulfuranes have been isolated and studied.[2] The chemistry of these species, notably that of dialkoxysulfurane **1**,[3] has been shown to derive from rapid ligand exchange reactions involving the weakly bound[2] apical alkoxy ligands. The mechanism for ligand exchange for **1** in solution has been found[4] to very probably be dissociative via the alkoxysulfonium ion. This paper reports the synthesis and some reactions, including a study of the rates of the degenerate ligand exchange with R_FOH, where R_F is $PhC(CF_3)_2$, of cyclic sulfuranes **2**, **3**, and **4**, in which an atom bridge is expected to allow a close approach to coplanarity of the two equatorial aryl ligands.



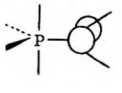
1, $R_F = C(CF_3)_2Ph$



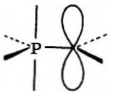
2, X = N-Ph
3, X = O
4, X = S

Results and Discussion

Experimental and theoretical bases exist[5] for the assertion that equatorial π-donor ligands in phosphoranes have a preferred orientation with the donor p orbital in the equatorial plane as in **5** rather than perpendicular to this plane as in **6**.[5k]



5



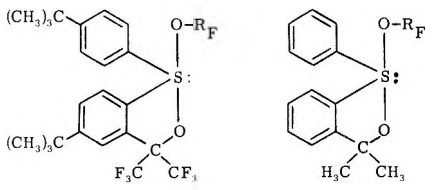
6

The situation is less clear cut in the case of sulfuranes, where calculations[6] suggest that the repulsive interaction of the π donor with the sulfur lone pair may predominate in a con-

formational equilibrium favoring the opposite orientation (**8** rather than **7**) for a π-donor equatorial ligand.

7 **8**

It would not be surprising to discover a dependence of sulfurane reactivity on the orientation of π-donor ligands in the equatorial plane. The orientation of the equatorial phenyl rings in **1** has been shown[7] to be skewed (32°22′ and 42°31′ from the plane defined by the sulfur atoms and the two carbon atoms bonded to sulfur) in the crystal, and a number of sulfuranes have been synthesized[8,9,10] in which π orbitals, at least for one of the aromatic equatorial aryl ligands, are expected[11] to be approximately perpendicular to the hypervalent S–O bonds, e.g., **9** and **10**. Sulfuranes **2, 3,** and **4,** having π orbitals

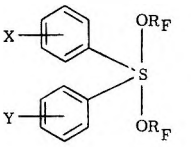


9 **10**

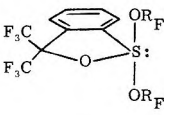
of the phenyl rings more nearly parallel[12] to the S–O apical bonds than any of the sulfuranes studied[2,4,8] thus far, might be expected to reflect in their patterns of reactivity the result of electronic interactions engendered by this steric constraint.

The syntheses of **2, 3,** and **4** were effected by the established procedure[13] in which a carbon tetrachloride solution or suspension of the sulfide is mixed with 2 equiv of KOR_F and 1 equiv of bromine. For sulfurane **2** it was necessary to add ~2 equiv of 1,4-endoxocyclohexane[8] as a cosolvent to dissolve the KOR_F. When the cosolvent was eliminated, no **2** was formed. However, when sulfurane **2** was prepared in ether at 4 °C, no cosolvent was necessary, since all materials were soluble. Attempts to form sulfuranes utilizing phenothiazine, 10-methylphenothiazine, 10-acetylphenothiazine, and thioxanthane by a procedure similar to method A in the Experimental Section did not succeed. Apparently oxidations involving other sites of the molecule predominated over sulfurane formation.

Although sulfuranes **3** and **4** are thermally stable compounds at ambient temperatures, sulfurane **2** is unstable under these conditions and is at least 68% destroyed in carbon tetrachloride solution after 2 days at room temperature to give unidentified products. Attempts to isolate **2** were unsuccessful, but sulfuranes **3** and **4** were easily isolated as crystalline solids (in 71 and 58% yields, respectively). Sulfuranes **3** and **4** show sizable molecular ions (1.5 and 3.5% of the base peak, respectively) in the 70-eV mass spectra and prominent ions at $M^+ \cdot - 244$ (loss of R_FOH) and $M^+ \cdot - 243$ (loss of OR_F). Although the assignments of the peaks in the 220 MHz proton NMR (CCl_4) for **2, 3,** and **4** were somewhat ambiguous, the chemical shifts of the protons ortho to sulfur are considerably upfield (at higher field than δ 7.6) from those observed for sulfurane **1**[3e] (δ 8.0 in $CDCl_3$) and related sulfuranes **11** (δ 7.8–7.9 $CDCL_3$).[4] The downfield shift seen for the ortho protons in these analogues, in which conformations having an equatorial aryl ligand ring coplanar with the apical substituents are either mandated (**9** or **10**) or allowed (**1, 11**), can be ascribed to the anisotropy of the apical S–O bond in the conformation which juxtaposes an ortho proton to this bond in a region of space parallel to it. Such a conformation is of course precluded for the sulfuranes (**2–4**) of this paper. The absence of this downfield shift for the ortho (to S) proton of **12** (δ 7.61,



11 a X = p-F; Y = H
b X = m-F; Y = H
c X = Y = p-t-Bu
d X = Y = p-OCH_3

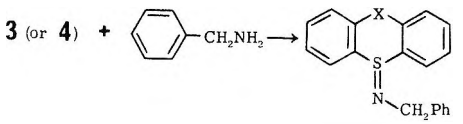


12

CCl_4) has been interpreted[14] as evidence for the novel conformation pictured with a diequatorially linked five-membered ring.

Sulfurane **1** is a powerful dehydration reagent[3f] and has been shown to dehydrate *tert*-butyl alcohol within seconds, even at temperatures as low as −80 °C, to give isobutylene, Ph_2SO, and R_FOH. Sulfuranes **2, 3,** and **4** also show comparable reactivity, giving isobutylene, R_FOH, and the corresponding sulfoxides.

Sulfurane **1** has been shown[15] to give sulfilimines upon reaction with primary amines. The reaction of sulfurane **3** or **4** with benzylamine gives the corresponding sulfilimine **13** or **14**. Examples of related sulfilimines have recently been reported.[16]



13 (X = O)
14 (X = S)

Exchange Studies. Solutions of sulfuranes **1–4** and R_FOH in diethyl ether were prepared such that the concentrations of sulfurane and R_FOH were 0.11–0.14 and 0.25–0.27 M, respectively. A series of low-temperature ^{19}F NMR spectra of these solutions, of an ether solution of **10** (0.13 M) with R_FOH (0.25 M), and of sulfurane **9** (0.56 M in dibenzyl ether solvent) with R_FOH (1.2 M) was obtained. In each case the lower temperatures showed widely separated (374–510 Hz at 94.1 MHz) ^{19}F peaks for R_FOH and for the ligand OR_F groups. As the temperature was raised these peaks coalesce toward a single peak (at the high temperature extreme). The approximate coalescence temperatures, the corresponding rates of exchange at the coalescence temperature, and the corresponding free energies of activation are summarized in Table I.

The concentration of R_FOH in a given solution remains constant, of course, since the exchange reaction being observed is a degenerate one, generating one free R_FOH molecule as another is bound to sulfurane sulfur as a ligand. The rate constants of Table I are therefore pseudo-first-order rate constants. The kinetic order in R_FOH is clearly greater than zero, from the observation that exchange rates decrease with decreasing R_FOH concentrations, but the order has not been determined rigorously. The concentration of R_FOH has the same value throughout the series, except for the larger concentration used for the least reactive sulfurane (**9**) of Table I. The coalescence temperatures are widely enough separated and the pseudo-first-order rate constants similar enough to provide an unambiguous ordering (at a constant temperature) of the rates for these degenerate exchange reactions as follows (fastest to slowest): **10** > **2** > **4** > **3** > **1** > **9**. The degenerate exchange rate can, of course, also be reduced by lowering the concentrations of sulfurane and R_FOH. Dilution of the above

Table I. Approximate Coalescence Temperatures for ^{19}F Peaks Reflecting the Rates of Degenerate Ligand Exchange of Dialkoxysulfuranes with R_FOH

Compd	Registry no.	[Sulfurane], M	[R_FOH], M	Coalescence temp, T_c (±3 °C)	Chemical shift difference, Hz[a]	k_1, s^{-1}	$\Delta G^{\ddagger}$, kcal/mol (at T_c)	[R_FOH], M, to produce coalescence[b]
10	63018-00-8	0.13	0.25	−45	374	830.8	10.2	≪0.031
2	63018-01-9	0.11	0.27	−30	412	915.2	10.8	≤0.034
4	63018-02-0	0.13	0.27	+10	455	1010.8	12.7	0.099
3	63018-03-1	0.11	0.26	+30	454	1008.5	13.6	0.26
1	32133-82-7	0.14	0.26	>30[c]	510	1132.9		
9[d]	52969-48-9	0.56	1.2	148[d]	120[e]	>266.6	>20.3	

[a] Between ^{19}F peaks for sulfurane OR_F ligands and for R_FOH at 94.1 MHz. [b] The concentration of R_FOH at which the coalescence of ^{19}F peaks was observed at 30 °C. [c] Peaks are just beginning to broaden as temperature is raised to 30 °C. [d] In diphenyl ether solvent. [e] Coalescence of ^{19}F quartets for the OR_F ligands only.

samples until the 30 °C spectra showed peak broadening approximating the coalesced spectra gave the same order of exchange rates as that which was deduced from the data reported in Table I.

A notable feature of this order is the placement of sulfuranes **9** and **10** at either extreme. These two molecules have similar geometries, since one aromatic ring is expected to be held[11] rigidly in place by the five-membered ring, essentially coplanar with the apical O–S–O axis. The predominant influence on exchange rates must here be a substituent effect (CH_3 vs. CF_3) in the apical alkoxy ligand trans to the leaving group. Although the base-catalyzed hydrolyses of chlorosulfuranes analogous to **9** and **10** have been shown[9] to proceed by an associative mechanism, the order of rates for the degenerate exchange with R_FOH clearly favor a dissociative mechanism for this reaction.

All of the sulfuranes except **10** have similar trans apical substituents, and α,α-bis(trifluoromethyl)-α-arylalkoxy group. The order **2** > **4** > **3** > **1** > **9** might therefore be reasonably expected to mirror the effects of geometry and of equatorial substitution.

Although **2**, **3**, and **4**, with their more nearly coplanar equatorial aryl ligands, are more reactive than sulfuranes **1** and **9** which have sterically enforced noncoplanarity of the equatorial aryl rings, the order seen is also approximately the order of electron density on the aryl rings. An earlier study[4] of meta- and para-substituted analogues of **1** led to the conclusion that the degenerate ligand exchange in that series of sulfuranes was accelerated by electron releasing substituents (an estimated Hammett ρ of −3). The qualitative order of rates in the present series of compounds is roughly in accord with the conclusion. Only the **4** > **3** order is reversed from that based on predictions from Hammett σ values[17] for model substituents for **2**, **4**, and **3** (σ_p for the $N(CH_3)_2$, the OCH_3, and the SCH_3 groups, respectively, −0.83, −0.27, and 0.00 lead to the predicted order **2** > **3** > **4**). While faster exchange reactions of **2**, **3**, and **4** may reflect an accelerating effect of the enforced geometry of the π-donor equatorial aryl ligands holding the aryl π-bond orbitals roughly parallel with the apical axis, it is not clear that such an effect is demanded.

Experimental Section

NMR spectra were obtained using tetramethylsilane or fluorotrichloromethane as internal standards for ^1H NMR and ^{19}F NMR, respectively. In cases where a dry solvent was necessary, these internal standards were dried over 4A molecular sieves (Linde). Melting points are not corrected. All manipulations of water-sensitive compounds were carried out in an inert atmosphere glove box.

Solvents and Reagents. 10-Phenylphenothiazine,[13] 1,4-endoxocyclohexane,[19] hexafluoro-2-phenyl-2-propanol (R_FOH),[20] and potassium hexafluoro-2-phenyl-2-propoxide (R_FOK)[13] were prepared according to published procedures. Ether was dried by several additions of sodium wire until the wire remained shiny. Carbon tetrachloride was dried by distillation from phosphorus pentoxide.

5-Bis[α,α-bis(trifluoromethyl)benzenemethanolato]-10-phenylphenothiazine (2) **(in solution). Method A.** A mixture of 0.133 g (0.49 mmol) of 10-phenylphenothiazine and 0.27 g (0.97 mmol) of R_FOK in 3.0 mL of dry CCl_4 was prepared in an inert atmosphere box in a 15-mL centrifuge tube, which was capped by a serum stopper. To this was added 0.100 mL (0.109 g, 1.11 mmol) of 1,4-endoxocyclohexane. The mixture was shaken until nearly all the solids were dissolved. Bromine (25 μL, 0.078 g, 0.49 mmol) was added by syringe and the tube was shaken for several minutes. The resulting mixture was centrifuged and the supernatant solution of **2** was used for NMR analysis and chemical reactions: ^1H NMR (220 MHz, CCl_4 with 1,4-endoxocyclohexane) δ 7.854 (d, 0.6, 4, 6 protons of 10-phenylphenothiazine 5-oxide impurity, J = 8 Hz), 7.632 (d, 2.0, J = 8 Hz), 7.545 (d with fine structure, 2.0, J = 7 Hz), 7.382 and 7.250 (multiplets, 6.3 and 8.0), 7.014 (t, 2.1, J = 7 Hz), 6.673 (m, 3.0); ^{19}F NMR (94.1 MHz, ether) 70.1 ppm upfield from $CFCl_3$.

Upon standing at room temperature for 48 h, 68% (by ^{19}F NMR) of the sulfurane is converted to unidentified ^{19}F-containing products with peaks at δ 70.4, 70.6, and 70.7 ppm upfield from $CFCl_3$.

Method B. A solution of 0.158 g (0.574 mmol) of 10-phenylphenothiazine and 0.32 g (1.15 mmol) of KOR_F in 3.0 mL of dry ether was treated in the above described manner with 29.4 μL of bromine (0.574 mmol). After centrifugation, the supernatant solution of **2** was used for subsequent reactions.

5-Bis[α,α-bis(trifluoromethyl)benzenemethanolato]phenoxathiin (3). Phenoxathiin (10.00 g, 0.05 mol) and KOR_F (28.2 g, 0.10 mol), suspended in 100 mL of dry CCl_4, was treated, as above, with 2.56 mL of bromine (0.05 mol). After 30 h of stirring the bromine color had nearly disappeared. Filtration of the mixture in a drybox, washing of the filter cake with CCl_4, and evaporation of the solvent in vacuo gave a cream-white solid which was recrystallized from ether–pentane to give 24.18 g (71%) of sulfurane **3**; mp (sealed tube) 105–107 °C (with decomposition); ^1H NMR (220 MHz, CCl_4) δ 7.545 (d with fine structure, 2.0, J = 8 Hz), 7.418 (m, 4.2), 7.090 (m, 12.4); ^{19}F NMR (94.1 MHz, ether) 70.1 ppm upfield from $CFCl_3$; mass spectrum (70 eV) m/e (rel intensity) 686 (1.5, $M^{+}\cdot$), 459 (1.0, $M^{+}\cdot - R_F$), 443 (21.8, $M^{+}\cdot - OR_F$), 442 (35.6, $M^{+}\cdot - HOR_F$), 244 (24.7, HOR_F^{+}), 227 (4.7, R_F^{+}), 216 (84.7), 215 (100.0), 200 (57.3), 187 (99.1), 175 (48.3), 168 (78.6), 139 (29.4),127 (25.9), 115 (27.2), 105 (78.0), 77 (45.8), 69 (34.2), 63 (27.9), 51 (38.8), 50 (20.5).

Anal.[21] Calcd for $C_{30}H_{18}F_{12}O_3S$: C, 52.49; H, 2.64; S, 4.67. Found: C, 50.87; H, 2.73; S, 4.66.

5-Bis[α,α-bis(trifluromethyl)benzenemethanolato]thianthrene (4). Thianthrene (1.005 g, 4.66 mmol) and KOR_F (2.625 g, 9.31 mmol) suspended in ca. 20 mL of dry CCl_4 were treated with 238.7 μL of bromine (4.66 mmol). After stirring overnight the bromine color was gone. The resulting mixture was filtered in the drybox, the salt cake was washed twice with CCl_4, and the solvent was removed in vacuo to leave an off-white solid. This was recrystallized from ether–pentane to give 1.89 g (58%) of **4** as transparent prisms: mp (sealed tube) 111–113 °C (with decomposition); ^1H NMR (220 MHz, CCl_4) δ 7.511 (d, 3.8, J = 9 Hz), 7.337 (t, 2.0, J = 7.5 Hz), 7.109 (m, 11.3); ^{19}F NMR (94.1 MHz, ether) 70.1 ppm upfield from $CFCl_3$; mass spectrum (70 eV) m/e (rel intensity) 702 (3.5, $M^{+}\cdot$), 475 (0.19, $M^{+}\cdot - R_F$), 458 (16.7, $M^{+}\cdot - HOR_F$), 459 (16.3, $M^{+}\cdot - OR_F$), 244 (27, HOR_F^{+}), 232 (27.3), 231 (28.8), 227 (5.49, R_F^{+}), 216 (81.3), 203 (35.2), 185 (15.8), 184 (100.0), 175 (46.2), 171 (40.9), 105 (70.3), 77 (32.7), 69 (35.3), 51 (16.9), 50 (12.3).

Anal.[21] Calcd for $C_{30}H_{18}F_{12}O_2S_2$: C, 51.29; H, 2.58; S, 9.13. Found: C, 49.47; H, 2.65; S, 9.14.

Reactions of 2, 3, and 4 with *tert*-Butyl Alcohol. To ca. 0.15 M

carbon tetrachloride solutions of each of sulfuranes **2**, **3**, and **4** was added 10 μL of *tert*-butyl alcohol at room temperature. Reaction was completed as soon as the NMR spectra could be run. The products isobutylene and R_FOH were detected by ^1H and ^{19}F NMR, respectively. The corresponding sulfoxides were isolated by extraction of the CCl_4 solution with 15% KOH, washing the organic phase with water, drying (Na_2SO_4), and evaporation of the solvent to give the corresponding sulfoxides by comparison with authentic samples (NMR and melting point).

5-(Benzylimino)phenoxathiin (13). To 0.1568 g (0.229 mmol) of **3** in 0.6 mL of dry $CHCl_3$ was added 25 μL (0.229 mmol) of benzylamine and the solution was shaken. The solution was extracted twice with 1–2 mL of 15% KOH solution, twice with water, and dried (Na_2SO_4). After removal of solvent on the rotary evaporator, 49.3 mg (70.6%) of a white solid remained. This was recrystallized from ether–pentane to give 26.0 mg (37.2%); mp 120–122 °C (some crystal changes noted), 130–145 °C (all melted); ^1H NMR (60 MHz, $CDCl_3$) δ 7.88 (d of d, 2.1, 4, 6 protons of sulfilimine, J_{AB} = 7.5, J_{BC} = 2.0 Hz), 7.36 (m, 11.0, remaining aromatic protons), 3.51 (s, 2.0, $-CH_2C_6H_5$); IR ($CHCl_3$) 3075 (w), 3083 (w), 3018 (m), 2928 (m), 1594 (s), 1497 (m), 1479 (m), 1465 (s), 1438 (s), 1322 (m), 1271 (s), 1130 (m), 1093 (m), 1070 (m), 1030 (m), 888 (m), 858 (m), 791 (m,br), 701 (m), 674 (w), 665 (w) cm^{-1}.

Anal. Calcd for $C_{19}H_{15}NOS$: C, 74.72; H, 4.95; N, 4.58; S, 10.50. Found: C, 74.54; H. 5.06; N, 4.46; S. 10.64.

5-(Benzylimino)thianthrene (14). The above procedure was used in the preparation of sulfilimine **14**. From 0.5462 g (0.778 mmol) of sulfurane **4** was obtained a mixture of 53% of sulfilimine **14** detected by NMR (benzylic protons, δ 4.20 in $CDCl_3$) and 47% of thianthrene *S*-oxide resulting from hydrolysis either of the original sulfurane or of the sulfilimine in the workup. Separation of the materials by recrystallization proved impossible. Hydrolysis of sulfilimine **14** to the sulfoxide was observed when the above mixture dissolved in ca. 5 mL of CCl_4 was treated with gaseous HCl followed by a 15% aqueous KOH extraction. After drying (Na_2SO_4) and evaporation of solvent the NMR ($CDCl_3$) indicated 35% of sulfilimine **14** remaining and new benzylamine peaks at δ 3.82 ($-CH_2-$) and 1.98 (br, $-NH_2$).

Exchange Rate Studies. Solutions of sulfuranes **1**–**4** and **10** in dry ether were prepared (0.11–0.14 M). Some hydrolysis occurred due to traces of moisture present in the ether. Sufficient R_FOH was added until the molarity of the R_FOH was roughly twice that of the sulfurane (0.25–0.27 M). The temperature dependence of ^{19}F NMR spectra was studied at 94.1 MHz. The results are listed in Table I. Also a number of sulfuranes (**2**, **3**, **4**, and **10**) were studied at 30 °C. In these studies dilutions of one-half, one-fourth, and one-eighth of original concentrations were used and the NMR behavior recorded. In only two sulfuranes (**3** and **4**) was it possible to slow exchange sufficiently to see two peaks by this dilution procedure (see Table I). For sulfurane **2**, the coalescence point was being approached at one-eighth of original concentration; however, for sulfurane **10** the original sulfurane–R_FOH singlet was only broadening at one-eighth of its original concentration. The exchange rates are calculated in the usual way,[22] and the Eyring equation was used to calculate the activation energies.

For sulfurane **9**, the compound was dissolved in dibenzyl ether and due to the presence of moisture was partially hydrolyzed. The concentrations of **9** and R_FOH were calculated from the ^{19}F NMR integral and the sample was studied over the temperature interval 28–148 °C. A dilute sample in ether (ca. 0.02 M) with a large excess (ca. 0.2 M) of R_FOH showed no exchange nor any broadening at 28 °C.

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Registry No.—**13**, 61558-76-7; **14**, 61558-80-3; 10-phenylphenothiazine, 7152-42-3; R_FOH, 37818-31-8; phenoxathiin, 262-20-4; thianthrene, 92-85-3; benzylamine, 100-46-9.

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Synthesis and Rearrangement of Thioxanthene *N*-*p*-Toluenesulfonylsulfilimine[1]

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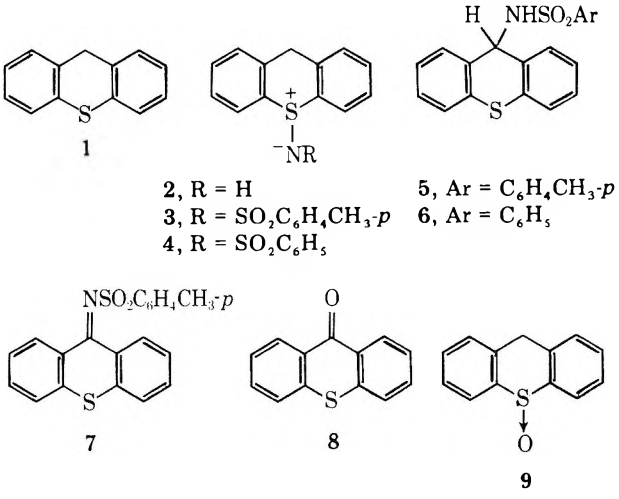
The reaction of thioxanthene with chloramine-T in methanol–methylene chloride in the presence of small amounts of acetic acid gave thioxanthene *N*-*p*-toluenesulfonylsulfilimine (**3**) and 9-(*N*-*p*-toluenesulfonamido)-thioxanthene (**5**). The sulfilimine **3** underwent acid- or base-catalyzed rearrangement to **5**. Mechanisms for the formation of **3** and **5** and for the rearrangement of **3** to **5** are discussed.

Despite current interest in the chemistry of thioxanthene 10-oxides[2] and 10-alkyl or aryl salts,[3] little information is available about the nitrogen analogue, thioxanthenesulfilimines. Recently we have noticed the unusual behavior of a 10-aminothioxanthenium salt which, upon treatment with base, produces a dimeric compound presumably via the nonisolable free sulfilimine **2**.[4,5] This result prompted us to examine the behavior of the corresponding *N*-*p*-toluenesulfonylsulfilimine **3**. In this paper we describe details of the preparation of **3** and its rearrangement to 9-(*N*-*p*-toluenesulfonamido)thioxanthene (**5**).[7]



Results and Discussion

Syntheses. The reaction of sulfides with chloramine-T provides a general synthetic route to *N*-*p*-toluenesulfonylsulfilimines.[8] However, as previously noted,[7] treatment of thioxanthene (**1**) with chloramine-T gives many compounds, including thioxanthene *N*-*p*-toluenesulfonylsulfilimine (**3**)[9] and 9-(*N*-*p*-toluenesulfonamido)thioxanthene (**5**), depending upon the reaction conditions.

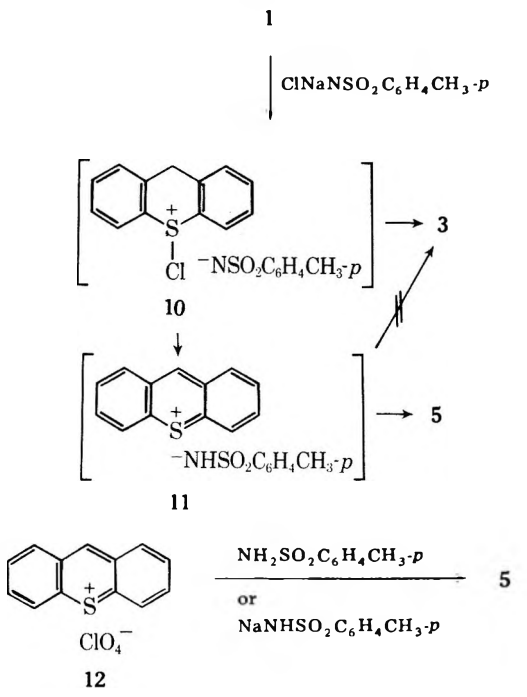
For the preparation of the sulfilimine **3**, the following procedure gave the most satisfactory and reproducible result. A solution of equimolar quantities of **1** and chloramine-T trihydrate in methanol–methylene chloride (2:1) in the presence of small amounts of acetic acid was stirred for 60 min at room temperature. After evaporation of the solvent under reduced pressure the crude material was chromatographed on silica gel and eluted with benzene–ethyl acetate to give **3** and **5** in 38 and 26% yields, respectively. That the reaction is catalyzed by acetic acid became evident by the fact that when **1** was treated with chloramine-T in the absence of acetic acid, the reaction proceeded very slowly and, in addition to unreacted **1**, as many as five products were formed: **3**, **5**, 9-(*N*-*p*-toluenesulfonimido)thioxanthene (**7**), thioxanthone (**8**), and thioxanthene 10-oxide (**9**).

The structures of these products were easily confirmed by their spectral evidence and chemical interconversions. The sulfilimine **3** showed the molecular ion peak at *m/e* 367 and two strong fragment ion peaks at *m/e* 211 ($M^+ - p$-$CH_3C_6H_4SO_2$-H) and 197 (thioxanthylium ion) in its mass spectrum. Its IR spectrum showed strong absorption at 1300, 1150, and 1095 cm^{-1}, typical of an SO_2 group, and at 970 cm^{-1}, a characteristic band for an S^+–N^- bond.[10-13] In the NMR spectrum two benzylic protons appeared as an AB quartet at δ_A 4.32 and δ_B 3.88 with J_{AB} = 17 Hz. Compound **3** smoothly rearranged to **5** by refluxing in benzene containing small amounts of concentrated HCl or by treating with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) in benzene at room temperature. The IR spectrum of **5** showed an NH absorption band at 3367 cm^{-1} and the NMR spectrum revealed an AB quartet at δ_A 5.59 (a benzylic proton) and δ_B 5.27 (NH) with J_{AB} = 8 Hz. Treatment of **5** with an equimolar quantity of chloramine-T in methanol–acetic acid (20:1) at room temperature gave **7** in 72% yield. Confirmation of structure **7** was given by acid hydrolysis to thioxanthone (**8**) and *p*-toluenesulfonamide.

Under the similar conditions used for the preparation of **3**, the reaction of thioxanthene (**1**) with chloramine-B dihydrate gave thioxanthene *N*-benzenesulfonylsulfilimine (**4**) and 9-(*N*-benzenesulfonamido)thioxanthene (**6**) in 55 and 40% yields, whose structures were confirmed by comparison of their spectral data with those of **3** and **5**, respectively.

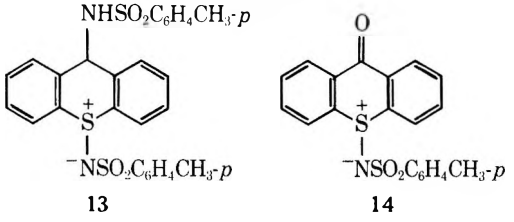
Because the sulfilimine **3** was shown to undergo acid- or base-promoted rearrangement to **5**, it was initially believed that **5** was derived from **3** under the reaction conditions. However, since **3** proved to be totally stable to the reaction conditions used,[14] it was concluded that both **3** and **5** must arise directly from **1**. A mechanistic rationalization of the formation of **3** and **5** involves an assumption that **1** is first converted to chlorosulfonium salt **10** (Scheme I). Such a process is in accord with the generally accepted mechanism[15] for the formation of *N*-*p*-toluenesulfonylsulfilimines from sulfides and chloramine-T. A direct attack of *p*-toluenesulfonamide anion on the sulfur atom of **10** may lead to **3**, and a competitive ejection of hydrogen chloride from **10** followed by an attack of *p*-toluenesulfonamide anion at the **9** position of the resulting thioxanthylium ion **11** may account for the formation of **5**. An intriguing alternative route to **3** would involve the same thioxanthylium ion **11**, which could be attacked by *p*-toluenesulfonamide anion on the sulfur atom. This type

Scheme I



of reaction has in fact been observed in the reaction of thioxanthylium perchlorate (**12**) with phenyllithium.[3c] However, this possibility was eliminated by the fact that no deuterium was incorporated into **3** when the reaction of **1** with chloramine-T was carried out in methanol-*d*–methylene chloride. Furthermore, **12** treated with either *p*-toluenesulfonamide or sodium *p*-toluenesulfonamide in acetonitrile gave exclusively **5**.

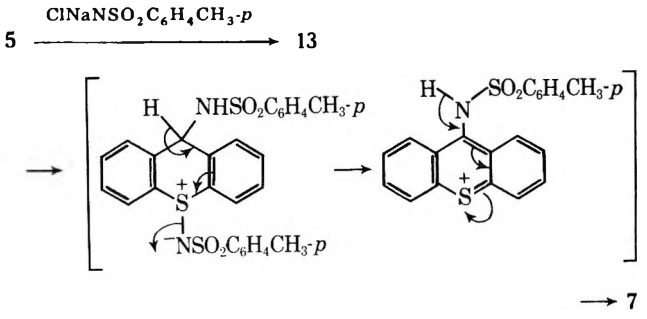
To obtain mechanistic information on the formation of secondary product **7** the reaction of **5** with chloramine-T was further investigated. Treatment of **5** with an equimolar quantity of chloramine-T trihydrate in methanol–methylene chloride (2:1) containing small amounts of acetic acid resulted in the formation of two new sulfilimines **13** and **14**, in addition



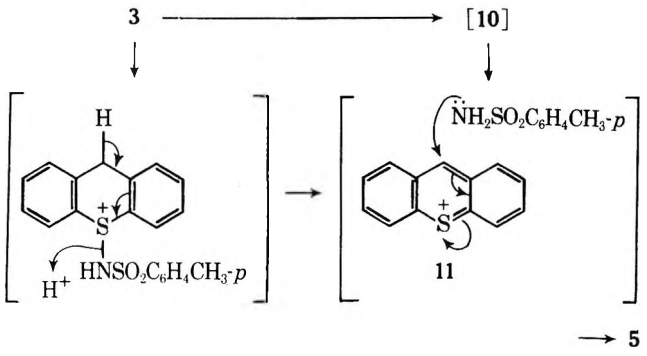
to **7** and unreacted **5**. Evidence for the structures of **13** and **14** was derived from elemental analyses and spectra of these substances (see Experimental Section). The isolation of **13**, together with the fact that **13** was converted into **7** simply by refluxing in ethanol for 5 h, suggests a mechanism for the formation of **7**, which involves initial formation of the sulfilimine **13** followed by a series of elimination reactions as shown in Scheme II. The possibility of a direct oxidation of **5** by chloramine-T may be a less likely alternative, since treatment of **5** with chloramine-T in methanol in the absence of acetic acid recovered starting material even after stirring for 2 days at room temperature.

Acid-Promoted Rearrangement. We next investigated in some detail the acid-promoted rearrangement of **3**. As described before, sulfilimine **3** undergoes rearrangement to **5** by refluxing in benzene containing small amounts of concentrated HCl. When a benzene solution of equimolar quantities of **4** and *p*-toluenesulfonamide (or **3** and benzenesulfonamide) was refluxed in the presence of small amounts of concentrated HCl, a mixture of **5** and **6** was obtained in a ratio of 2:1 (by

Scheme II



Scheme III

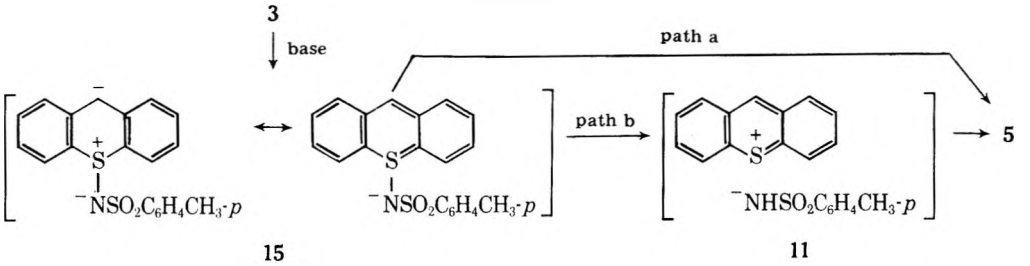


NMR spectroscopy). This observation indicates that the rearrangement is intermolecular. A reasonable mechanism for this rearrangement involves protonation at the imino nitrogen of **3** followed by sulfur–nitrogen bond cleavage with synchronous elimination of proton at the 9 position to lead to thioxanthylium ion **11**, which is then attacked by *p*-toluenesulfonamide to give **5** (Scheme III). There is an analogy for this type of reaction found in the rearrangement of thioxanthene 10-oxide to 9-hydroxythioxanthene in concentrated sulfuric acid.[2] An alternative pathway to **11** could involve displacement by chloride ion on the sulfur atom to give **10**, followed by elimination of hydrogen chloride. Strong support for the intervention of **11** was derived from the fact that treatment of thioxanthylium perchlorate (**12**) with a mixture of equimolar amounts of *p*-toluenesulfonamide and benzenesulfonamide in acetonitrile gave the same ratio (2:1) of a mixture of **5** and **6**. The difference in the ratio may be attributed to the difference in nucleophilicity of two sulfonamides, which is most likely a reflection of the electron-donating effect of the methyl group. In comparison, the reaction of **12** with equimolar amounts of sodium *p*-toluenesulfonamide and sodium benzenesulfonamide in acetonitrile or dimethylformamide gave a 1:1 mixture of **5** and **6**, in which the intrinsic strong nucleophilicity of the anions appears to over-shadow the small effect of the methyl group.

Base-Promoted Rearrangement. At room temperature in the presence of small quantities of base such as DBU or triethylamine, sulfilimine **3** underwent almost quantitative conversion to **5**.

In principle, two mechanisms for this rearrangement could be considered as shown in Scheme IV: (a) a concerted intramolecular 1,4-sigmatropic rearrangement via a thianthracene anion (**15**); or (b) an intermolecular, dissociation–recombination process involving thioxanthylium ion **11**. Path a is permitted by orbital symmetry considerations and parallels the mechanism proposed for the base-catalyzed rearrangement of 10-arylthioxanthenium salts to 9-arylthioxanthenes.[3a,c] Path b also involves the initial formation of **15**, but this anion could then undergo sulfur–nitrogen bond cleavage to give thioxanthylium ion **11**. This step is then followed by attack of *p*-toluenesulfonamide anion at the 9 position of **11**

Scheme IV



to give **5**. A similar process to [**3** → **11**] has been proposed in the base-catalyzed Pummerer-type reaction of some sulfilimines.[16] The fact that a red color developed at the beginning of the reaction when dimethylformamide was used as solvent supports the involvement of **15** or **11** as intermediate.

In order to obtain further mechanistic information on this rearrangement, crossover experiments were carried out. Thus, when a solution of equimolar amounts of benzenesulfonylsulfilimine **4** and sodium *p*-toluenesulfonamide[17] in dimethylformamide[18] was stirred at room temperature for 2.5 h, a ca. 1:3 mixture of **5** and **6** was obtained. With *p*-toluenesulfonylsulfilimine **3** and sodium benzenesulfonamide, a ca. 3:1 mixture of **5** and **6** was obtained. Incorporation of the sulfonamide added was relatively low in both cases and the product ratios [**5**/**6**] observed were not consistent with that (**5**/**6** = ca. 1:1) obtained from the reaction of thioxanthylium perchlorate (**12**) with sodium benzenesulfonamide and sodium *p*-toluenesulfonamide in dimethylformamide. These observations would suggest that the migrating sulfonamide anion of **11** is not completely disrupted from the thioxanthylium system, or that the process [**11** → **5**] in path b is so fast that two sulfonamide anions cannot be mixed up completely prior to going to the final product. An alternative possibility that part of **5** is produced via an intramolecular concerted process (path a) is less likely, although it was not possible to rule it out completely.

Experimental Section

Melting points are uncorrected. NMR spectra were determined with a Varian HR-60 spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded with a Hitachi EPI-G3 spectrophotometer and UV spectra with a Hitachi 124 spectrophotometer. Mass spectra were obtained with a Hitachi RMU-6MG instrument with a direct inlet system operating at 70 eV.

Reaction of 1 with Chloramine-T. Thioxanthene (**1**) (990 mg) and chloramine-T·3H_2O (1.4 g) were added all at once to a stirred solution of methanol (25 mL) and CH_2Cl_2 (12.5 mL) containing acetic acid (0.05 mL) at room temperature. The solution immediately turned to yellow and soon after a white powder precipitated. After 60 min, $CHCl_3$ (50 mL) was added to the reaction mixture and the solution was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. The residual solid was chromatographed on silica gel. Elution with benzene–AcOEt (1:5) gave 9-(*N*-*p*-toluenesulfonamido)thioxanthene (**5**) (460 mg, 26%) as white crystals: mp 172–173 °C (from benzene–*n*-hexane); IR ($CHCl_3$) 3367, 1330, 1160, 1098 cm^{-1}; UV_{max} (CH_3OH) 223 sh (log ε 4.50), 263 nm (4.19); NMR ($CDCl_3$) δ 7.0–7.7 (m, 12, aromatic protons), 5.59, 5.27 (ABq, 1 each, J = 8 Hz, benzylic proton and NH, respectively), 2.33 (s, 3, CH_3); mass spectrum *m/e* (rel intensity) 367 (3.4, M^+), 211 (66), 197 (100).

Anal. Calcd for $C_{20}H_{17}NO_2S_2$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.49; H, 4.79; N, 3.69.

Further elution with the same solvent gave thioxanthene *N*-*p*-toluenesulfonylsulfilimine (**3**) (675 mg, 38%) as white crystals: mp 138–139 °C (from benzene–methanol); IR ($CHCl_3$) 1300, 1150, 1095, 970 (S^+–N^-) cm^{-1}; UV_{max} (CH_3OH) 227 (log ε 4.50), 264 nm (3.58); NMR ($CDCl_3$) δ 7.25–8.2 (m, 12, aromatic protons), 4.32, 3.88 (ABq, 1 each, J = 17 Hz, benzylic protons), 2.37 (s, 3, CH_3); mass spectrum *m/e* (rel intensity) 367 (2.7, M^+), 211 (56), 197 (100).

Anal. Calcd for $C_{20}H_{17}NO_2S_2$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.44; H, 4.91; N, 3.75.

Reaction of 1 with Chloramine-B. By using the similar procedure as described above, thioxanthene *N*-benzenesulfonylsulfilimine (**4**) (194 mg, 55%) and 9-(*N*-benzenesulfonamido)thioxanthene (**6**) (143 mg, 40%) were obtained from **1** (198 mg) and chloramine-B·2H_2O (250 mg).

Compound **4** had: mp 183–185 °C (from benzene–methanol); IR ($CHCl_3$) 1300, 1150, 1085, 965 (S^+–N^-) cm^{-1}; UV_{max} (CH_3OH) 223 sh (log ε 4.36), 265 (3.53), 272 nm (3.51); NMR ($CDCl_3$) δ 7.3–8.1 (m, 13, aromatic protons), 4.32, 3.92 (ABq, 1 each, J = 17 Hz, benzylic protons); mass spectrum *m/e* (rel intensity) 353 (5.6, M^+), 211 (65), 197 (100).

Anal. Calcd for $C_{19}H_{15}NO_2S_2$: C, 64.58; H, 4.28; N, 3.96. Found: C, 64.50; H, 4.25; N, 4.13.

Compound **6** had: mp 158–161 °C (from benzene–*n*-hxane); ir ($CHCl_3$) 3360, 1330, 1158, 1093 cm^{-1}; UV_{max} (CH_3OH) 213 sh (log ε 4.54), 263 nm (4.19); NMR ($CDCl_3$) δ 7.05–7.75 (m, 13, aromatic protons), 5.65, 5.25 (1 each, ABq, J = 7.5 Hz, benzylic proton and NH, respectively); mass spectrum *m/e* (rel intensity) 353 (6.2, M^+), 211 (73), 197 (100).

Anal. Calcd for $C_{19}H_{15}NO_2S_2$: C, 64.58; H, 4.28; N, 3.96. Found: C, 64.69; H, 4.28; N, 4.10.

Reaction of 1 with Chloramine-T without Acetic Acid. To a solution of **1** (2.0 g) in CH_2Cl_2 (10 mL) was added a solution of chloramine-T·3H_2O (3.13 g) in methanol (80 mL). The mixture was refluxed for 3 min, then stirred at room temperature for 2 h, and concentrated. The residue was extracted with $CHCl_3$ and the extract was washed with 10% NaOH solution and water, dried ($MgSO_4$), and concentrated. The yellow residual solid was submitted to column chromatography on silica gel. Successive elution with benzene, benzene–AcOEt, and AcOEt gave unreacted **1** (1.35 g, 67%), thioxanthone (**8**) (30 mg, 1.4%), 9-(*N*-*p*-toluenesulfonimido)thioxanthene (**7**) (24 mg, 0.7%), **5** (391 mg, 11%), thioxanthene 10-oxide (**9**) (272 mg, 11%), and **3** (191 mg, 5.2%) in this order.

Compounds **8** and **9** were identified by direct comparisons with authentic samples.

Compound **7** had: mp 212 °C (from ether); IR ($CHCl_3$) 1540, 1310, 1160, 1090 cm^{-1}; UV_{max} (CH_3OH) 224 (log ε 4.35), 269 nm (4.47); NMR ($CDCl_3$) δ 8.5–8.8 (m, 2, aromatic protons), 7.2–8.05 (m, 10, aromatic protons), 2.40 (s, 3, CH_3); mass spectrum *m/e* (rel intensity) 365 (82, M^+), 301 (72), 300 (80), 211 (30), 210 (100), 209 (68), 184 (19), 183 (31), 155 (15), 139 (33).

Anal. Calcd for $C_{20}H_{15}NO_2S_2$: C, 65.73; H, 4.14; N, 3.83. Found: C, 65.95; H, 3.99; N, 3.77.

Reaction of 3 with Chloramine-T. A solution of **3** (184 mg) and chloramine-T·3H_2O (464 mg) in methanol (10 mL) was refluxed for 4.5 h. After the solvent was removed, the residue was dissolved in $CHCl_3$ and the solution was washed with 10% NaOH solution and water, dried ($MgSO_4$), and concentrated. The residue was submitted to preparative TLC on silica gel and benzene–AcOEt (2:1) as solvent to give **7** (111 mg, 61%) as a major product.

Reaction of 5 with Chloramine-T. A. To a solution of **5** (1.0 g) and chloramine-T·3H_2O (0.78 g) in methanol (20 mL) was added dropwise acetic acid (1 mL) with stirring. After 20 h, the precipitated crystals were collected and recrystallized from methanol–benzene to give **7** (720 mg, 72%).

B. To a solution of **5** (1.34 g) in CH_2Cl_2–methanol (1:4) (50 mL) was added a solution of chloramine-T·3H_2O (1.13 g) in methanol (25 mL) and 1 drop of acetic acid at room temperature. After stirring for 30 min, the reaction mixture was concentrated and extracted with $CHCl_3$. The extract was washed with 5% NaOH solution and water, dried ($MgSO_4$), and concentrated. The residue was submitted to dry column chromatography using silica gel and benzene–AcOEt as solvent to give **7** (419 mg, 32%), **5** (225 mg, 17%), 9-(*N*-*p*-toluenesulfonamido)thioxanthone *p*-toluenesulfonylsulfilimine (**13**) (343 mg, 18%), and thioxanthene *p*-toluenesulfonylsulfilimine (**14**) (256 mg, 18%).

Compound **13** had: mp 174–176 °C (after washing with ether); IR (KBr) 3400, 1290, 1160, 1140, 1090, 965 (S^+–N^-) cm^{-1}; the NMR spectrum could not be measured because of low solubility in most

organic solvents for NMR; its mass spectrum showed the same fragmentation pattern as that of **7**, due to prior decomposition of **13**.

Anal. Calcd for $C_{27}H_{24}N_2O_4S_3$: C, 60.42; H, 4.51; N, 5.22. Found: C, 60.41; H, 4.59; N, 5.29.

Compound **14** had: mp 203–204 °C (from CH_2Cl_2–*n*-hexane); IR (KBr) 1680, 1335, 1140, 1090, 940 (S^+–N^-) cm^{-1}; NMR ($CDCl_3$) δ 8.25–8.50 (m, 2, aromatic protons), 7.20–7.95 (m, 10, aromatic protons), 2.43 (s, 3, CH_3); mass spectrum *m/e* (rel intensity) 381 (1, M^+), 226 (100, $M^+ - p$-$CH_3C_6H_4SO_2$-H), 212 (67, thioxanthene ion radical).

Anal. Calcd for $C_{20}H_{15}NO_3S_2$: C, 62.97; H, 3.96; N, 3.67. Found: C, 62.78; H, 3.88; N, 3.93.

Conversion of 13 to 7. A mixture of **13** (40 mg) in ethanol (5 mL) was refluxed for 5 h and concentrated. The residue was chromatographed on silica gel with benzene as solvent to give **7** (10 mg, 37%), mp 212 °C (from ether).

Hydrolysis of 7. A solution of **7** (365 mg) in methanol (15 mL) and concentrated HCl (0.5 mL) was refluxed for 2.5 h. The mixture was concentrated and $CHCl_3$ was added to the residual solid. The insoluble solid was collected and recrystallized from H_2O to give *p*-toluenesulfonamide (131 mg, 81%). Concentration of the $CHCl_3$ layer followed by recrystallization of the residual solid from benzene–methanol gave **8** (157 mg, 74%).

Rearrangement of 3 to 5. A. With Acid Catalysis. A solution of **3** (357 mg) in benzene (20 mL) containing concentrated HCl (0.2 mL) was refluxed for 5 h (the reaction was followed by TLC). The solution was washed with 5% NaOH solution and water, dried ($MgSO_4$), and concentrated. The residue was recrystallized from benzene–*n*-hexane to give **5** (279 mg, 76%).

Use of acetic acid–water (1:1) in place of concentrated HCl gave a similar result.

B. With Base Catalysis. To a stirred suspension of **3** (80 mg) in benzene (5 mL) was added DBU (20 mg) at room temperature. After 4 h (the reaction was followed by TLC), benzene (20 mL) was added to the mixture and the benzene solution was washed with 5% HCl and water, dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC on silica gel with $CHCl_3$ as solvent to give **5** (64 mg, 84%).

Crossover Experiments. A. With Acid Catalysis. A solution of **4** (80 mg) and *p*-toluenesulfonamide (39 mg) in benzene (5 mL) containing concentrated HCl (0.04 mL) was refluxed for 7 h. The reaction mixture was cooled and concentrated. The residue was purified by preparative TLC on silica gel with $CHCl_3$ as solvent to give a mixture of **5** and **6** (37 mg) in a ratio of 2:1 (by NMR spectroscopy). Similar treatment of **3** and benzenesulfonamide gave a similar result.

B. With Base Catalysis. (i) To a solution of sodium benzenesulfonamide (49 mg) in dimethylformamide (15 mL) was added all at once **3** (100 mg). At the beginning of the reaction the solution turned to red, but soon after was decolorized. The reaction mixture was stirred at room temperature for 2.5 h. Workup gave a mixture of **5** and **6** (50 mg) in a ratio of 3:1 (by NMR spectroscopy). With **4** (100 mg) and sodium *p*-toluenesulfonamide (49 mg), a 1:3 mixture of **5** and **6** (50 mg) was obtained.

(ii) A mixture of **4** (80 mg) and *p*-toluenesulfonamide (40 mg) was stirred in benzene (5 mL) in the presence of DBU (40 mg) at room temperature. Workup gave a crude material (65 mg) whose NMR spectrum indicated that it consisted of only **6**.

The use of other solvents such as dimethylformamide, *tert*-butyl alcohol, acetone, or dioxane gave the same results, but, when the same mixture was treated in methanol, a ca. 1:1 mixture of **5** and **6** was obtained in total yield of 33%.

Reaction of 12 with Sodium *p*-Toluenesulfonamide. Thioxanthylium perchlorate (**12**)[19] (150 mg) and sodium *p*-toluenesulfonamide (97 mg) were added to acetonitrile (30 mL) with stirring at room temperature. The red solution was gradually decolorized. After 10 min, the mixture was poured into water and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and concentrated. The residue was submitted to preparative TLC on silica gel with $CHCl_3$ as solvent to give **5** (108 mg, 61%) and **1** (12 mg).

Reaction of 12 with Sodium *p*-Toluenesulfonamide and Sodium Benzenesulfonamide. Using the procedure as described above, a 1:1 mixture of **5** and **6** (76 mg) was obtained from the reaction of **12** (150 mg) with equimolar amounts of sodium *p*-toluenesulfonamide (97 mg) and sodium benzenesulfonamide (90 mg). The use of dimethylfomamide as solvent gave the same result.

Reaction of 12 with *p*-Toluenesulfonamide. Thioxanthylium perchlorate (**12**) (150 mg) and *p*-toluenesulfonamide (86 mg) were added to acetonitrile (30 mL). The red solution was not decolorized even after stirring for 2 days. Workup gave **5** (30 mg, 17%).

Reaction of 12 with *p*-Toluenesulfonamide and Benzenesulfonamide. Using the procedure as described above, a 2:1 mixture of **5** and **6** (28 mg) was obtained from the reaction of **12** (150 mg) with equimolar amounts of p-toluenesulfonamide (86 mg) and benzenesulfonamide (79 mg).

Registry No.—**1**, 261-31-4; **3**, 58508-92-2; **4**, 58508-89-5; **5**, 60914-90-1; **6**, 63076-58-4; **7**, 60914-91-2; **12**, 2567-20-6; **13**, 63076-59-5; **14**, 58508-91-1; chloramine-T, 127-65-1; chloramine-B, 127,52-6; *p*-toluenesulfonamide, 70-55-3; sodium *p*-toluenesulfonamide, 18522-92-4; sodium benzenesulfonamide, 18522-93-5; benzenesulfonamide, 98-10-2.

References and Notes

(1) Part 5 in the series of Organic Sulfur Compounds. For Part 4 see: M. Kise, M. Murase, M. Kitano, and H. Murai, *Tetrahedron Lett.*, 4355 (1976).
(2) H. J. Shine and L. Hughes, *J. Org. Chem.*, **31**, 3142 (1966); D. W. Chasar, A. L. Ternay, Jr., L. Hughes, H. J. Shine, and S. A. Evans, *ibid.*, **40**, 1737 (1975).
(3) (a) G. H. Senkler, Jr., J. Stackhouse, B. E. Maryanoff, and K. Mislow, *J. Am. Chem. Soc.*, **96**, 5648 (1974); (b) F. Ogura, W. D. Hounshell, C. A. Maryanoff, W. J. Richter, and K. Mislow, *ibid.*, **98**, 3615 (1976), and references cited therein; (c) H. Pirelahi, Y. Abdoh, and A. Afzali, *Tetrahedron Lett.*, 4609 (1976).
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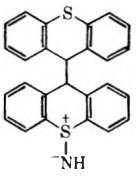
(5) The structure of the dimer reported in ref 4 should be revised to **16**, because the deaminated product obtained from the dimer by nitrous acid treatment or thermolysis was identified as dithioxanthyl by direct comparison with an authentic sample prepared by irradiation of an ethanolic solution of **1** in the presence of oxygen.[6] The stereochemistry of **16** is unknown.



16

(6) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 657 (1945).
(7) Y. Tamura, K. Sumoto, M. Ikeda, M. Murase, and M. Kise, *J. Chem. Soc., Chem. Commun.*, 507 (1976).
(8) F. G. Mann and W. J. Pope, *J. Chem. Soc.*, **121**, 1052 (1922).
(9) Although Shah[10] has recently claimed the syntheses of **3**, **4**, and **14**, their melting points, and UV and IR spectral data are incompatible with ours.
(10) J. J. Shah, *Can. J. Chem.*, **53**, 2381 (1976).
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(12) A. Kucsman, I. Kapovits, and F. Ruff, *Tetrahedron*, **22**, 1575 (1966).
(13) K. Tsujihara, N. Furukawa, and S. Oae, *Bull. Chem. Soc. Jpn.*, **43**, 2153 (1970).
(14) It should be emphasized here that sulfilimine **3** undergoes the rearrangement to **5** when refluxed in benzene in the presence of small amounts of acetic acid and water (1:1) (but no rearrangement took place without water). In addition we have found that **3** is converted to **7** by refluxing in methanol with an excess of chloramine-T trihydrate for 4.5 h. Thus, the previous observation[7] that treatment of thioxanthene (**1**) with chloramine-T trihydrate in methanol–acetic acid (20:1) at 60–70 °C produces only trace amounts of **3** and instead **5** and **7** as the major products may be rationalized by assuming that once formed **3** rearranged to **5** under the reaction conditions (as described later, **7** is a secondary product from **5**).
(15) F. Ruff, K.Komoto, N. Furukawa, and S. Oae, *Tetrahedron*, **32**, 2763 (1976), and references cited therein.
(16) For a recent review, see J. G. Tillett, *Chem. Rev.*, **76**, 747 (1976).
(17) It should be noted that, when *p*-toluenesulfonamide and DBU as base were used instead of sodium *p*-toluenesulfonamide in the crossover experiments, no incorporation of the sulfonamide was observed in various solvents such as benzene, dimethylformamide, *tert*-butyl alcohol, acetone, or dioxane. However, an equimolar mixture of **4** and *p*-toluenesulfonamide in methanol was treated in the presence of DBU to give a ca. 1:1 mixture of **5** and **6**. Although the total yield of the rearranged products was low (33%), it is possible that the rearrangement in methanol involves a species **11** in which the migrating sulfonamide anion is completely dissociated from the cation.
(18) Owing to low solubility of sodium benzenesulfonamide and sodium *p*-toluenesulfonamide in nonpolar solvents dimethylformamide was used.
(19) W. Bonthrone and D. H. Reid, *Chem. Ind. (London)*, 1192 (1960).

Reaction of Ethyl β-Aminocrotonate with Trichloromethanesulfenyl Chloride

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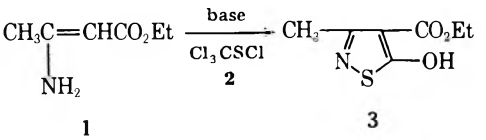
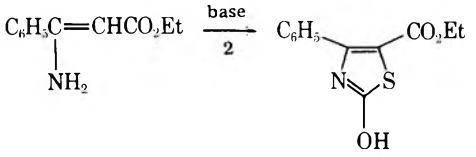
Reaction of ethyl β-aminocrotonate (**1**) with trichloromethanesulfenyl chloride (**2**) in ether or THF produced ethyl β-amino-α-(trichloromethylthio)crotonate (**6**) as the major product (70–79% yield). Hydrolysis of **6** in aqueous base resulted in a complex mixture in which ethyl 2-chloro-4-methyl-5-thiazolecarboxylate (**8**, 33% yield) and ethyl 2-hydroxy-4-methyl-5-thiazolecarboxylate (**9**, 27%) were the major products.

Synthesis of ethyl 5-hydroxy-3-methyl-4-isothiazolecarboxylate (**3**) in 30–40% yield from reaction of ethyl β-aminocrotonate (**1**) with trichloromethanesulfenyl chloride (**2**) in the presence of base was reported recently.[1] However, no physical properties were given for the product. Reaction of ethyl β-aminocinnamate with **2** in the presence of base produced ethyl 2-hydroxy-4-phenyl-5-carboxylate (**4**), identical



1 **3**



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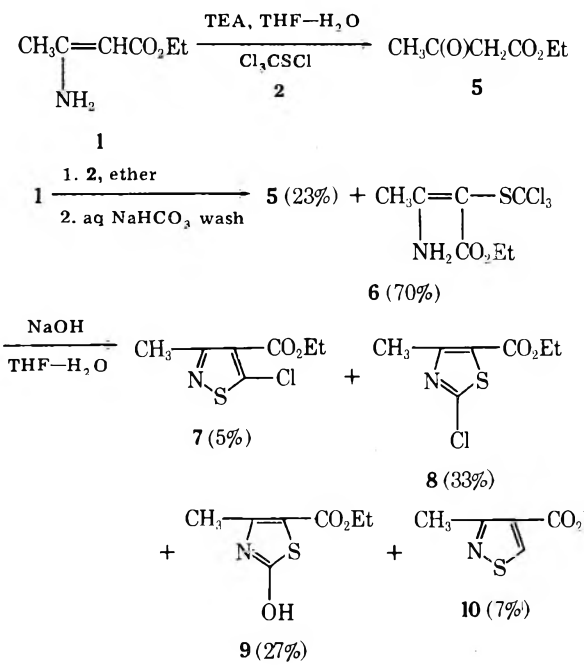
with authentic material prepared by another route.[2] Because of the apparent conflict in these results and because of our interest in isothiazoles,[3] we reinvestigated the first reaction.

Addition of **2** to ethyl β-aminocrotonate and 4 equiv of triethylamine in aqueous THF at 0–5 °C led predominantly to ethyl acetoacetate (**5**) (Scheme I). Addition of **2** to **1** in ether

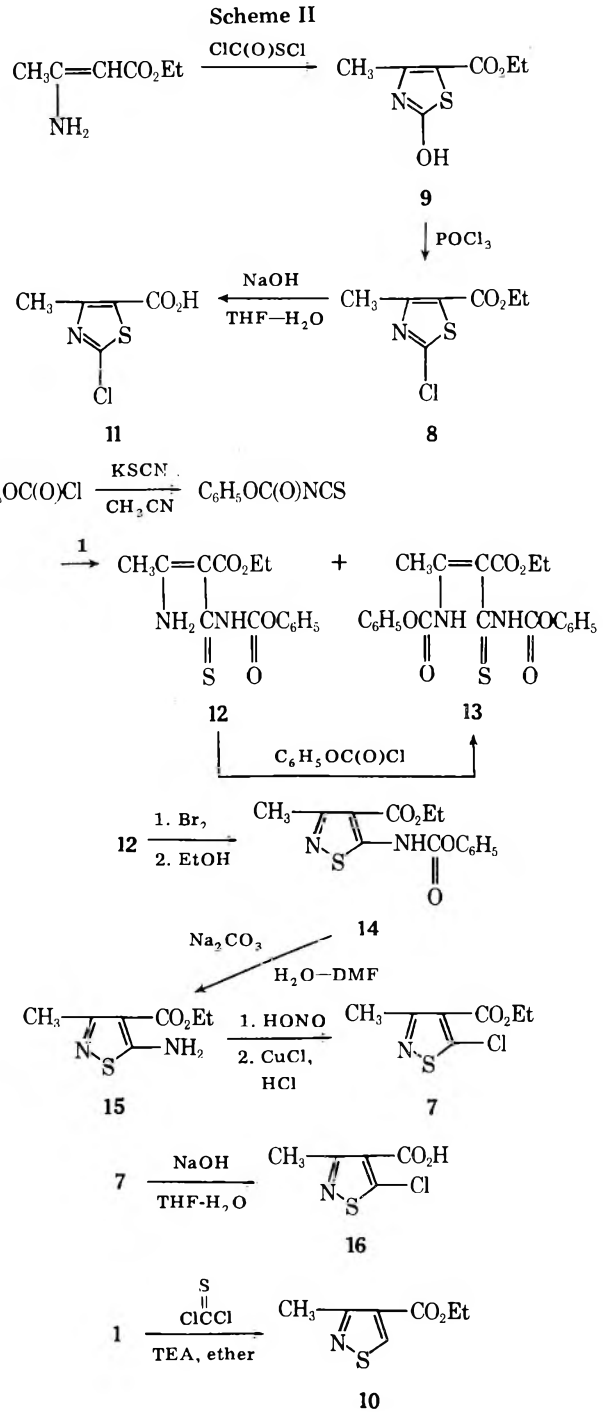
Scheme I



7 (5%) **8** (33%) **9** (27%) **10** (7%)

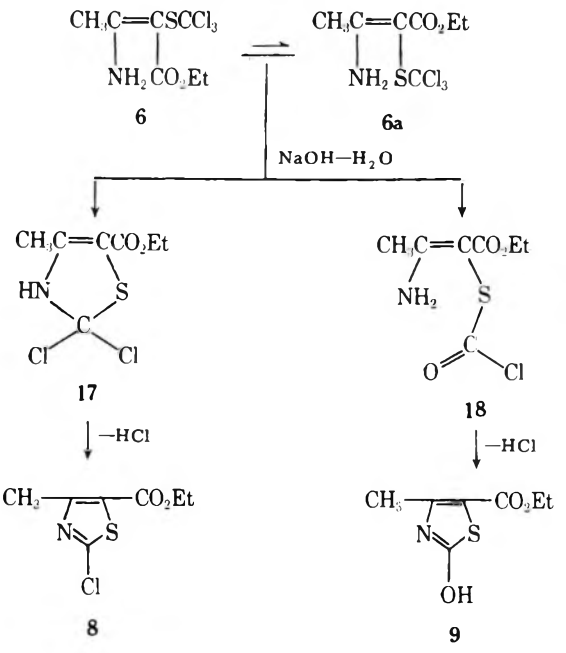
followed by an aqueous sodium bicarbonate wash gave **5** (23%) and ethyl β-amino-α-(trichloromethylthio)crotonate (**6**, 70%) with traces (ca. 1% each) of several other materials (NMR

Scheme II



9 **11** **8** **12** **13** **14** **15** **7** **16** **10**

Scheme III



analysis). Pure **6**, an unstable solid, was isolated in 24% yield and was completely characterized by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectra (see Experimental Section).

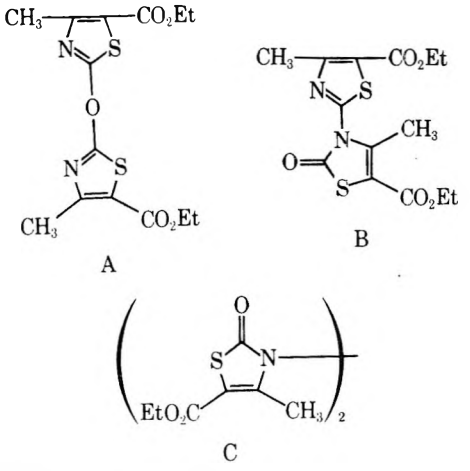
Hydrolysis of pure **6** in NaOH–H_2O–THF gave an ester mixture (Scheme I) that contained 5% of ethyl 5-chloro-3-methyl-4-isothiazolecarboxylate (**7**), 33% of ethyl 2-chloro-4-methyl-5-thiazolecarboxylate (**8**), 27% of ethyl 2-hydroxy-4-methyl-5-thiazolecarboxylate (**9**), 7% of ethyl 3-methyl-4-isothiazolecarboxylate (**10**), and at least three high-boiling materials with molecular weights of 356, 372, and 372, respectively. Pure **9** was isolated from the reaction mixture in 10% yield. Several hydrolysis experiments gave the same products, but their ratios varied, probably due largely to whether or not the THF and water layers were miscible (layer separation occurred in the 20–30 °C range) and to the particular concentrations employed.

Reaction of **2** with **1** in THF gave, after an aqueous sodium bicarbonate wash, mainly **6** (79%), with traces of other products that included **5** (4%) and **7** (6%). Hydrolysis with aqueous sodium hydroxide of the reaction mixture from treatment of **1** with **2** in THF led to a product mixture similar to that obtained from hydrolysis of pure **6**.

Product assays were performed by NMR, IR, GC–MS, and TLC analyses. Authentic samples of **7**,[4] **8**,[5] **9**,[6] and **10**[7] were prepared by literature procedures (Scheme II) to calibrate the GC–MS, NMR, TLC, and IR analyses. The procedure of Goerdeler and Horn[8] for preparation of **12** led to a mixture of **12** and **13** that had the properties reported[8] for **12**. In a separate experiment, pure **12** was converted to **13** with phenyl chloroformate. Mild hydrolysis of **8** and **7** gave **11**[9] and **16**,[4] respectively.

Quite evidently, the reaction of **6** with aqueous base is complex. The pathways for formation of **7** and **10** from **6** are unknown.[10] Certain major features are apparent, however. The predominant reaction of **1** with **2** occurs via attack of the sulfenyl chloride **2** on the α carbon of **1**, in accord with other studies[5,11] of reactions of sulfenyl chlorides with **1**. Based on the IR spectrum of **6**, which exhibits a hydrogen-bonded, conjugated carbonyl absorption at 6.07 μm, compound **6** exists mainly in the form with amino and carbethoxy groups cis to each other because of the stabilization due to intramolecular hydrogen bonding. Rotation about the double bond to give **6a** should be a facile process, however, and should occur at room temperature based on analogy with the reported[12,13] low barriers of rotation about the double bond for similar compounds. A competition exists between cyclization of **6** to **17** and partial hydrolysis to **18** (Scheme III). Compound **17** produces **8**, and **18** produces **9**. The hydrolysis of **8** to **11** (Scheme II) reveals that **8** is not a precursor of **9**. No evidence for formation of ethyl 5-hydroxy-3-methyl-4-isothiazolecarboxylate (**3**) was found.[14]

In regard to the high-boiling materials formed in the hydrolysis of **6**, the material with mol wt 356 had mass spectrum *m/e* (relative intensity; fragment) 356 (56.7, M^+), 357 (6.9 M^+ + 1), 358 (4.4, M^+ + 2), 311 (16.5, M^+ − OEt), 310 (41.8, M^+ − HOEt), 282 (100, M^+ − HOEt − CO), indicative of a structure containing an even number of nitrogen atoms, two sulfur atoms, and no chlorine atoms; this material might be either A or B, arising from reaction of the sodium salt of **9** with **8**. The materials with mol wt 372 remain unidentified, although in the mass spectrum of one of them the M^+ = 372 peak (rel intensity 35.3) and the M^+ + 2 = 374 peak (rel intensity 3.2) suggest a structure containing a even number of nitrogen atoms, two sulfur atoms, and no chlorine atoms, corresponding in gross features to a structure such as C. Formation of C conceivably could occur by N-chlorination of **9** and reaction of the *N*-chloro compound with the anion of **9**.



The source of chlorine or hypochlorite anion required in this process could arise from an intermediate that ultimately produces **10**.[10]

Experimental Section

Ethyl β-Amino-α-(trichloromethylthio)crotonate. To a solution of 12.9 g (0.10 mol) of ethyl β-aminocrotonate in 100 mL of ether was added dropwise, during 60 min with stirring at −5 to 0 °C, 18.6 g (0.10 mol) of trichloromethanesulfenyl chloride in 25 mL of ether under dry N_2. A white precipitate formed. The mixture was stirred at 0–15 °C for 2.5 h and then was extracted with 0.20 mol of $NaHCO_3$ in 150 mL of cold water. The ether layer was dried ($CaSO_4$) and concentrated under aspirator vacuum (<30 °C) to give 23.4 g of oil that contained 70% of product **6** and 23% of ethyl acetoacetate, with traces (ca. 1% each) of at least three other materials (NMR analysis). The oil was triturated with 450 mL of hexane; the supernatant was decanted from a little insoluble black oil, treated with a little charcoal, filtered, and seeded to give 5.15 g of beige solid, mp 83–84.5 °C dec. The filtrate was cooled to −30 °C for a second crop of 3.2 g of solid, mp 78–80 °C; two rapid recrystallizations of this solid from hexane gave 1.5 g of solid, mp 83–84.5 °C. The combined yield was 23.9%.

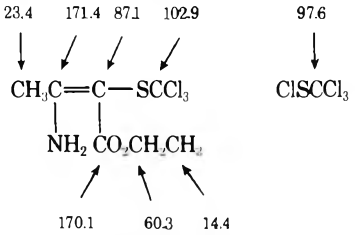
Recrystallization of 1.0 g of the beige product from hexane (charcoal) gave 0.75 g of white solid: mp 83–84.5 °C dec; IR (mineral oil mull) 2.85, 3.02 (NH_2), 6.07 (conjugated H-bonded C=O), 6.23 μm (C=C); ^{1}H NMR ($CDCl_3$) δ 9.60 (br s, 1, NH), 5.63 (br s, 1, NH), 4.20 (q, 2, OCH_2), 2.43 (s, 3, CH_3), 1.27 (t, 3, CH_3). The ^{13}C NMR spectrum of **6** in $CDCl_3$ was determined with a JEOL FX-100 spectrometer, using 8K data points plus 8K data point zero fill over a spectral width of 6024 Hz, a pulse width of 2 μs (18°), and a pulse repetition time of 0.8 s. Completely decoupled, off-resonance, and fully coupled spectra were obtained; the following spectral data are for the fully coupled

Table I. Methyl Resonances in $CDCl_3$[a]

Compd	Registry no.	CH_3, δ, ppm
1	7318-00-5	1.88
5	141-97-9	2.25[b]
6	63089-24-7	2.43
7	22131-53-9	2.63
8	7238-62-2	2.67
9	40235-78-7	2.47
10	15901-51-6	2.72

[a] EM-360 spectrometer. [b] CH_2 at δ 3.47.

spectrum of **6**: δ 171.4 (q, J_{CCH} = 5.4 Hz), 170.1 (t, J_{COCH} = 2.9 Hz), 102.9 (s), 87.1 (q, $J_{CCH} \simeq$ 3 Hz), 60.3, (t, J_{CH} = 147.1 Hz, of small quartets, J_{CCH} = 4.4 Hz), 23.4 (q, J_{CH} = 129.4 Hz), 14.4 (q, J = 127.2 Hz, of small triplets, J_{CCH} = 2.2 Hz).



Anal. Calcd for $C_7H_{10}Cl_3NO_2S$: C, 30.18; H, 3.62; Cl, 38.18; N, 5.03; S, 11.51. Found: C, 30.21; H, 3.61; Cl, 37.93; N, 4.96; S, 11.48.

Reaction of 1 and 2 in THF. To a solution of 12.9 g (0.10 mol) of ethyl β-aminocrotonate in 100 mL of THF was added dropwise, with stirring at 0–5 °C, 18.6 g (11.0 mL, 0.10 mol) of trichloromethanesulfenyl chloride during 20 min. The cloudy mixture was stirred at 0–10 °C for 3 h. An aliquot withdrawn after this time, diluted with CH_2Cl_2, washed with ice cold $NaHCO_3$ solution, dried ($CaSO_4$), and concentrated under vacuum gave a mixture that NMR analysis indicated to contain 79% of **6**, 6% of **7**, 4% of **5**, and <1% of **8**, with other minor components below the 4% level; GC–MS data obtained on the solution confirmed the presence of **7**.

Hydrolysis of 6. To a solution of 5.1 g (0.0183 mol) of ethyl β-amino-α-(trichloromethylthio)crotonate (**6**) in 50 mL of THF was added dropwise a solution of 2.2 g (0.0549 mol, 3 equiv) of NaOH in 50 mL of water with stirring at 10–20 °C during 30 min. The mixture was stirred at 20–30 °C for 24 h (pH at 7 after this time), acidified with a few milliliters of concentrated HCl, and extracted with two 50-mL portions of $CHCl_3$. The chloroform layers were combined, dried ($CaSO_4$), and concentrated under vacuum to 50 °C at 11 Torr to give 3.8 g of semisolid. NMR analysis of this material indicated it to contain 33% of **8**, 5% of **7**, 27% of **9**, and 7% of **10**. GC–MS data confirmed the presence of these components, and in addition showed the presence of at least three high-boiling, minor components with molecular weights of 356, 372, and 372. Trituration of the semisolid with 20 mL of ether gave 0.4 g of solid, mp 160–170 °C. Recrystallization of the solid gave 0.34 g (10%) of solid **9**, mp 175.5–177.5 °C (lit.[5] mp 177–178 °C), identical with authentic **9** based on mixture melting point and IR and NMR spectral data.

Ethyl 2-Hydroxy-4-methyl-5-thiazolecarboxylate (9). Use of the procedure of Grohe and Heitzer[5] led to product, mp 167–172 °C, in 60% yield. Recrystallization of the product from benzene gave pure product, mp 176–178 °C (lit.[5] mp 177–178 °C), in 40% yield. This material was identical in all respects with an authentic sample prepared from reaction of ethyl 2-chloroacetoacetate and ammonium thiolcarbamate.[6]

Ethyl 2-Chloro-4-methyl-5-thiazolecarboxylate (8). Use of the procedure of Ganapathi and Venkataraman[6] led to the desired product, mp 46–47.5 °C (lit.[6] mp 48–51 °C) in 91% yield. Recrystallization of a 2.0-g sample from cold ethanol gave 1.0 g of white solid, mp 47–48 °C.

Ethyl β-Amino-α-[*N*-(phenoxycarbonyl)thiocarbamoyl]-crotonate (12) and Ethyl β-(Phenoxycarbonylamino)-α-[*N*-(phenoxycarbonyl)thiocarbamoyl]crotonate (13). The procedure of Goerdeler and Horn[8] was employed. A mixture of 43 g (0.275 mol) of phenyl chloroformate and 25.8 g (0.26 mol) of potassium thiocyanate in 75 mL of CH_3CN was stirred at 10–15 °C for 25 min. Then, a solution of 32.75 g (0.25 mol) of ethyl β-aminocrotonate in 50 mL of CH_3CN was added during 15 min with vigorous stirring at 10 °C. The mixture was then stirred for 30 min without cooling and was poured into 1.5 L of water. The resultant mixture was stirred for 1.5 h, and the supernatant was decanted from a viscous oil. The oil was dissolved in 500 mL of benzene, and the solution was filtered through benzene-prewet filter paper and concentrated under vacuum to a semisolid. Trituration of the semisolid with 150 mL of ethyl acetate at 5 °C gave 10.9 g of yellow solid, mp 132–133 °C dec (lit.[8] mp 130 °C dec for **12**), which was found to be a mixture of 92% of **13** and 8% of **12** by NMR analysis. Recrystallization of this solid from ethyl acetate (minimum heating time) gave 4.5 g of yellow solid, mp 146.5–147.5 °C, that was pure **13** (NMR analysis): IR (mineral oil mull) 3.1, 5.66, 5.76, 5.98, 6.16 μm; NMR ($CDCl_3$) δ 11.70 (br s, 1, NH), 9.60 (br s, 1, NH), 7.33 (m, 10, ArH), 4.30 (q, 2, OCH_2) 2.53 (s, 1, CH_3), 1.28 (t, 3, CH_3).

Anal. Calcd for $C_{21}H_{20}N_2O_6S$: C, 58.86; H, 4.70; N, 6.53; S, 7.48. Found: C, 58.68; H, 4.65; N, 6.36; S, 7.10.

Concentration of the first ethyl acetate filtrate and crystallization of the residue from 50 mL of benzene gave 16.2 g of yellow solid, mp 112–114 °C, that was pure **12** (NMR analysis): IR (mineral oil mull) 2.97, 3.01, 5.70, 6.00, 6.07, 6.20 μm; NMR ($CDCl_3$) δ 10.0 (br s, 1, NH), 9.8–6.3 (v br, 2, NH_2), 7.30 (m, 5, ArH), 4.23 (t, 2, OCH_2), 2.32 (s, 1, CH_3), 1.20 (t, 3, CH_3).

A modification of the procedure of Goerdeler and Horn[8] was employed in another experiment. A mixture of 78.3 g (0.50 mol) of phenyl chloroformate and 48.6 g (0.50 mol) of powdered potassium thiocyanate in 150 mL of acetonitrile was stirred under N_2 at 10–15 °C for 30 min. Then, a solution of 65.0 g (0.502 mol) of ethyl β-aminocrotonate in 100 mL of acetonitrile was added with stirring during 1 min at −7 to 6 °C (ice–methanol bath). After another minute, the mixture was stirred for 1 h without cooling and then was poured into 1.5 L of water. The mixture was allowed to stand 1 h, and the aqueous supernatant was decanted from a thick oil. The oil was triturated well with two 300-mL portions of water to give a semisolid. This material was dissolved in $CHCl_3$, and the solution was dried ($CaSO_4$) and concentrated under vacuum (<40 °C). The residue, 153.2 g of red-orange oil, consisted of an 84:16 mixture of **12** and **13**, with traces of ethyl β-aminocrotonate and ethyl acetoacetate. Dilution of the residue with 300 mL of benzene and seeding with **12** resulted in crystallization of 27.6 g of pure **12**, mp 105–108 °C. Addition of 100 mL of hexane to the filtrate resulted in 15.8 g of 96% pure **12**, mp 98–104 °C. Addition of 200 mL of hexane to the last filtrate gave an oil. Trituration of the oil with 100 mL of ethyl acetate gave 6.0 g of solid, mp 129–131 °C dec, that consisted of 87% of **13** and 13% of **12**. Concentration of the last hexane filtrate and trituration of the residue with 100 mL of ethyl acetate gave 5.8 g of solid, mp 109–112 °C, that was 93% pure **12**. A total of 52.2 g of fairly pure **12** was obtained (34% yield).

Preparation of 13 from 12. To 1.50 g (5.0 mmol) of pure **12** in 25 mL of acetonitrile was added 0.78 g (5.0 mmol) of phenyl chloroformate. After 18 h, a solid had formed. The mixture was diluted with 100 mL of water and filtered to give 1.7 g (81% yield) of yellow solid **13**, mp 137–139 °C dec, that contained no residual **12**. The IR and NMR spectra of this material were identical with those of the by-product **13** isolated in the proceeding experiment. Crystallization of the 1.7 g of solid from 20 mL of benzene gave 0.95 g of solid, mp 148–149 °C dec.

Ethyl 3-Methyl-5-(phenoxycarbonylamino)-4-isothiazolecarboxylate (14). The procedure of Goerdeler and Horn[8] was employed. Pure product, mp 79–80 °C (lit.[8] mp 81 °C), was obtained in 76% yield.

Ethyl 5-Amino-3-methyl-4-isothiazolecarboxylate (15). The procedure of Goerdeler and Horn[8] was employed. The work-up procedure was modified, however. The crude solid isolated according to Goerdeler and Horn was extracted alternatively with $CHCl_3$ and water until almost all of it dissolved. The aqueous extracts were combined and extracted with $CHCl_3$. All the $CHCl_3$ layers were combined, dried ($CaSO_4$), and concentrated under vacuum to 12.1 g (85% yield) of solid, mp 114–115 °C (lit.[8] mp 113.5 °C).

Ethyl 5-Chloro-3-methyl-4-isothiazolecarboxylate (7). The procedure of Machón[4] was employed. The crude product before distillation was obtained in 55% yield and was found by GC analysis to consist of 90% of **7** and 10% of ethyl 3-methyl-4-isothiazolecarboxylate (**10**). Distillation of the 7.3 g of crude product gave three fractions: (1) 2.35 g of liquid, bp 99–101 °C (5 Torr), 84% of **7** and 16% of **10**; (2) 2.00 g of liquid, bp 101–103 °C (5 Torr), mp 22–25 °C, 93% of **7** and 7% of **10**; (3) 0.75 g of liquid , bp 103 °C (5 Torr), mp 20–23 °C, 90% pure **7** [lit.[4] bp 77 °C (3 Torr)].

2-Chloro-4-methyl-5-thiazolecarboxylic Acid (11). Solutions of 1.0 g (0.00488 mol) of ethyl 2-chloro-4-methyl-5-thiazolecarboxylate in 10 mL of THF and 0.2 g (0.005 mol) of NaOH in 20 mL of water were stirred together for 30 h. The solution was acidified with dilute HCl and was extracted twice with $CHCl_3$. The $CHCl_3$ extracts were

combined, dried ($CaSO_4$), and concentrated under vacuum to 0.80 g of white solid, mp 150–155 °C dec, which was shown by IR and NMR analysis to be **11**. Recrystallization of the solid from benzene gave 0.50 g of white solid, mp 154–155 °C (lit.[9] mp 144–148 °C dec).

5-Chloro-3-methyl-4-isothiazolecarboxylic Acid (16). Solutions of 1.0 g (0.00486 mol) of 93% pure ethyl 5-chloro-3-methyl-4-isothiazolecarboxylate (containing 7% of ethyl 3-methyl-4-isothiazolecarboxylate) in 50 mL of THF and 1.1 g (0.0225 mol) of NaOH in 50 mL of water were stirred together for 24 h. The solution was acidified strongly with dilute HCl and extracted with three 75-mL portions of ether. The ether layers were combined, dried ($CaSO_4$), and concentrated under vacuum to 0.85 g of white solid, mp 199–205 °C, that consisted of 94% of **16** and 6% of 3-methyl-4-isothiazolecarboxylic acid (NMR analysis in basic D_2O). Crystallization of the solid from 1,2-dichloroethane gave 0.60 g of solid, mp 205–206.5 °C (lit.[4] mp 205–207 °C).

Ethyl 3-Methyl-4-isothiazolecarboxylate (10). Treatment of ethyl β-aminocrotonate with triethylamine and thiophosgene according to a literature procedure,[7a] followed by redistillation of the product thus obtained, gave pure **10**, bp 71–72 °C (1.5 Torr) [lit.[7c] bp 102–103 °C (8 Torr)].

Registry No.—**2**, 2757-23-5; **12**, 63089-25-8; **13**, 63089-26-9; **16**, 22131-56-2; phenyl chloroformate, 1885-14-9; potassium thiocyanate, 333-20-0; 3-methyl-4-isothiazolecarboxylic acid, 15903-66-9.

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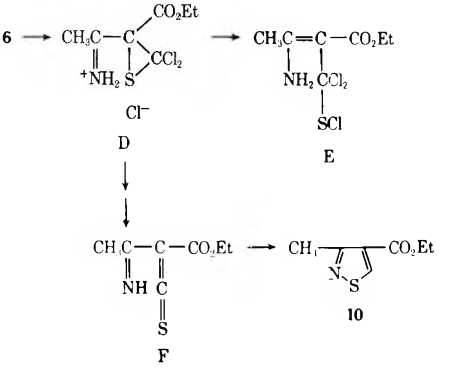
(7) (a) U.S. Patent 3 403 209 (1968); (b) R. B. Wocdward, *Harvey Lect.*, **59**, 34–37 (1965); (c) D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.*, 2032 (1963).
(8) J. Goerdeler and H. Horn, *Chem. Ber.*, **96**, 1551 (1963).
(9) *Beilstein*, **27**, 316.
(10) Several mechanistic possibilities can be postulated starting, for example, with D and E, but the mechanisms are so highly speculative that we prefer not to dignify them with enumeration. Along these speculative lines, dechlorination and dehydrochlorination of D or an intermediate (other than E) formed from D could lead to F and thus **10**. Species F is probably an intermediate in the reaction[7] of thiophosgene with **1** to produce **10**.



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(12) A. Mannschreck and U. Koelle, *Tetrahedron Lett.*, 863 (1967).
(13) Y. Shvo, E. C. Taylor, and J. Bartulin, *Tetrahedron Lett.*, 3259 (1967).
(14) Dr. Waite has acknowledged in a most cordial fashion that their structure assignment[1] for **3** rested strongly on analogies[1] and that, in light of the present work, the material that they isolated must have been **9**, the product that we obtained [J. A. Waite, private communication].

Reductive Sulfenylation. A General Method for the α-Sulfenylation of Cyclic Ketones

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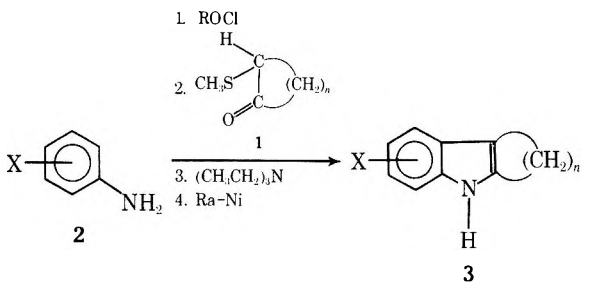
A general method has been developed for the reductive sulfenylation of cyclic α,β-unsaturated ketones. Sulfenylation with dimethyl disulfide has been shown to occur by preferential pseudoaxial attack on the intermediate enolate anions. The regiospecificity and preferential pseudoaxial attack were established by a combination of NMR and circular dichroism studies.

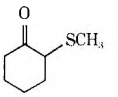
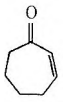
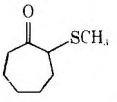
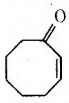
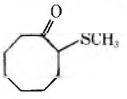
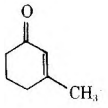
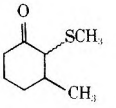
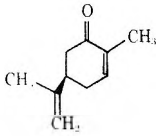
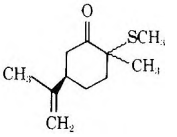
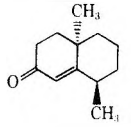
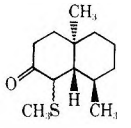
As part of our general program of exploring the scope and utility of our versatile indole synthesis,[2] and in anticipation of our utilization of this process in the preparation of polycyclic natural product intermediates, we found ourselves in need of highly specific methods for the addition of an α-methylthio function to a variety of cyclic ketones. The availability of cyclic ketones of general formula **1** would permit the conversion of anilines of general formula **2** into indoles of general formula **3** according to the procedure outlined. Thus,



we had a particular interest in regiospecifically methylsulfenylating cyclic ketones. While a variety of methods have appeared in the literature for the sulfenylation of ketones,[2-5] most of these methods can be traced back to the initial functionalization of a mixture of the thermodynamically most stable enolate anion[2,3] or enol form of the ketonic precursor[4,5] and the thermodynamically less stable enolate or enol form. This provides little control over regiospecificity. In view of the regiospecificity attained in the reductive alkylation of α,β-unsaturated ketones,[6] we investigated the sulfenylation of lithium enolates generated from the lithium in liquid ammonia reduction of α,β-unsaturated ketones. We now wish to report that the reductive sulfenylation of α,β-unsaturated ketones is a useful method for the regiospecific introduction of the thiomethoxyl moiety.

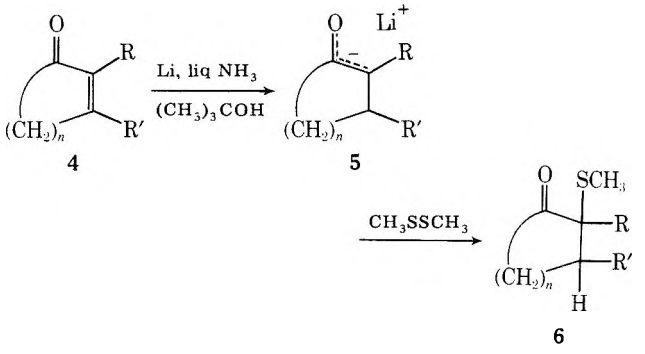
In a general procedure, a solution of 1 equiv of α,β-unsaturated ketone and 1 equiv of *tert*-butyl alcohol in ether was added to a solution of 2.2 equiv of lithium in liquid ammonia. After 1 h, 1 equiv of dimethyl disulfide was added and allowed to react, and the product was isolated. In this way, **4** could be

Table I. Yields Obtained in the Reductive Methylsulfenylation of Cyclic α,β-Unsaturated Ketones

Starting ketone	Registry no.	Product	Registry no.	% yield
	930-68-7		52190-35-9	43
	1121-66-0		52190-36-0	62
	1728-25-2		52190-37-1	38
	1193-18-6		Cis, 63017-47-0 Trans, 63017-48-1	48[a]
	6485-40-1		Cis, 63017-49-2 Trans, 63017-50-5	47[b]
	17990-00-0		Epimer I, 63017-51-6 Epimer II, 63087-56-9	65[c]

[a] A 55:45 mixture of epimers was obtained. [b] An 83:17 mixture of epimers was obtained. [c] A mixture of epimers at C-1 was obtained.

cleanly converted into **5**, which on sulfenylation gave **6**. As has been well established in the literature,[6,7] exchange reactions of **5** are relatively slow. Thus, excellent regiospecificity was obtained in the sulfenylation to give **6**. Table I lists the ketones studied and the yields obtained by this procedure. In general, the yields were sufficiently high to make this a synthetically useful procedure.

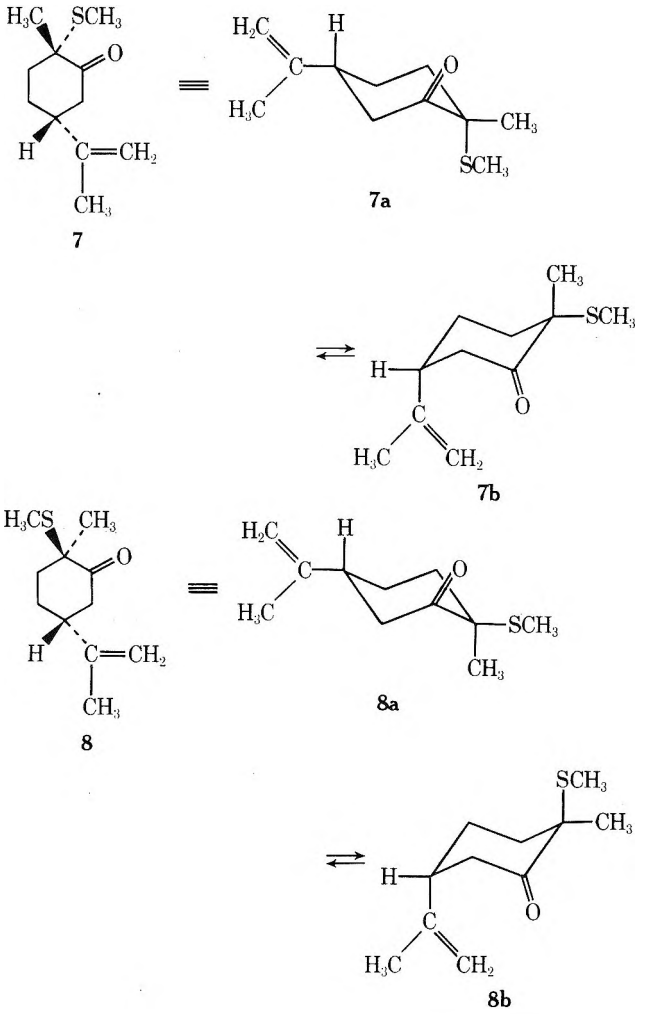


4 5 6

Some aspects of the general procedure merit comment. While good results were obtained with most cyclic ketones, cyclopentenone failed to yield monosulfenylated material under our conditions. Instead, a very low yield of disulfenylated material (4%) was obtained in addition to oligomeric material. In terms of the stereochemistry of the methylsulfenylation reaction, a mixture of epimers was obtained in all cases where mixed stereochemistry was possible.[8]

An intriguing aspect of these sulfenylations was associated with the direction from which the dimethyl disulfide approaches the enolate anion. In principle, the choices are either pseudoaxial or pseudoequitorial attack. Comparison with alkylation of enolate anions indicates that the balance between these two modes of reaction may be delicate, with some slight preference for the axial approach.[9] On the basis of NMR analysis, it has been suggested that sulfenylation also gives preferential pseudoaxial attack.[3d] Our findings would tend to substantiate this claim. In the case of the reductive sulfenylation of 3-methyl-2-cyclohexenone, NMR evidence suggested that the cis/trans ratio was 55:45.[10] More convincing evidence was available from the reductive sulfenylation of *l*-carvone (*p*-mentha-6,8-dien-2-one). Separation of the 83:17 mixture gave pure samples of **7** and **8**, respectively. Since the α-methylthio group interacts strongly with the carbonyl, a very enhanced carbonyl absorption occurred in the UV between 300 and 315 nm (ε 250–300).[12] More importantly, the fact that **7** and **8** were optically active permitted the analysis of their circular dichroism spectra.[13] The major isomer, which was tentatively assigned structure **7**, was expected to have a strong positive Cotton effect on the basis of the octant rule.[14] It was observed that the major isomer showed a [θ] of +30 100 at 312 nm. This is consistent with the presence of an axial α-methylthio group in a positive quadrant. These results imply that the major conformer present in solution is **7a** and that there is relatively little contribution from conformer **7b**.

In the case of the minor isomer, which was tentatively assigned structure **8a**, a small positive Cotton effect would be expected if **8a** were the major conformer. Instead, we found that the minor isomer exhibited a negative Cotton effect with a [θ] of −11 000 at 313 nm. The negative curve implies a major contribution from conformer **8b**. As Trost has shown,[3d] an α-methylthio group interacts with a carbonyl in such a way that the axial stereochemistry is preferred by 0.4 kcal/mol. This is in contrast to the methylthio group as a normal cyclohexane substituent, which prefers to be equitorial by 1.0 kcal/mol (at −90 °C).[15] If we estimate the $\Delta G°$ for an isopropenyl group to be ca. 1.65 kcal/mol,[16] we can make a rough estimate of the equilibrium between **7a** and **7b** and, more importantly, of the equilibrium between **8a** and **8b**. For **7**, estimates based on $\Delta G°$ values predict that the **7a–7b** ratio would be greater than 99:1 at room temperature. For **8**, the same approach predicts an **8a–8b** ratio of ca. 3:7. Surprisingly **8b**, which has an axial isopropenyl group, should be the preferred conformer. This is entirely consistent with the observed



circular dichroism spectrum of 8 and with the NMR spectrum of the minor product, which shows a splitting of the vinylic protons. In conformer **8b**, the magnetic environment of the two vinylic protons would be quite different.

In summary, we have shown that reductive sulfenylation is a viable method for the regiospecific introduction of a methylthio group α to a carbonyl group. Furthermore, sulfenylation appears to parallel alkylation of enolate anions in terms of preferred pseudoaxial attack. This is in line with the generally stated premise[18] "if a cyclohexanone derivative already has one alkyl substituent at the α position, the proportion of the second alkyl group introduced at this α position from an axial direction is enhanced."

Experimental Section[19]

General Procedure for the Reductive Sulfenylation of Cyclic α,β-Unsaturated Ketones. To a solution of 2 equiv of lithium wire dissolved in liquid ammonia (3 mL of ammonia/mmol of lithium) at −78 °C under nitrogen was added dropwise a solution of 1 equiv each of α,β-unsaturated ketone and *tert*-butyl alcohol in anhydrous ether (1 mL of ether/mmol of ketone). After stirring for 30 min at −78 °C, the cooling bath was removed and the reaction mixture was allowed to reflux (dry ice condenser) for an additional 30 min. Ether (1 mL/mmol of ketone) was added, the reaction mixture was cooled to −78 °C, and 1 equiv of dimethyl disulfide in ether (1 mL/mmol of disulfide) was added quickly, followed by an additional equal volume of ether. After stirring for 1 h at −78 °C, the cooling bath was removed, the dry ice condenser was replaced by a water-cooled condenser, and the ammonia was allowed to evaporate (12 h). The reaction mixture was carefully acidified with 3 N hydrochloric acid and the layers were separated. The aqueous layer was extracted with ether and the combined ether extracts were washed with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The ether layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated in vacuo. Unless otherwise noted, the residue was purified by fractional distillation.

2-(Methylthio)cyclohexanone. According to the general procedure outlined above, 2-cyclohexenone (4.36 g, 45 mmol) was sulfenylated with dimethyl disulfide (4.30 mL, 45 mmol) to yield 2.85 g (43%) of 2-(methylthio)cyclohexanone: bp 56–57 °C (0.28 mm); n^{25}_D 1.5086; IR (neat) 2930, 2860, 1705, 1450, 1425, 1230, 1120, 915, 825 cm^{-1}; UV (hexane) λ_{max} (ε) 215 (1089), 250 (330), 307 (242), 314 nm (242); NMR (CCl_4) δ 3.32–2.58 (2 H, br m), 2.47–1.65 (7 H, br m), 1.98 (3 H, s, SCH_3) [lit.[2] bp 45.5–48.0 °C (0.2 mm); n^{24}_D 1.5088].

2-(Methylthio)cycloheptanone. According to the general procedure outlined above 5.00 g (45 mmol) of 2-cycloheptenone was sulfenylated with 4.3 mL (45 mmol) of dimethyl disulfide to give 4.4 g (28 mmol, 62%) of 2-(methylthio)cycloheptanone: bp 53–54 °C (0.5 mm); n^{26}_D 1.5094; IR (neat) 2920, 2850, 1695, 1455, 1320, 1245, 1165, 935 cm^{-1}; UV (hexane) λ_{max} (ε) 216 (1780), 248 (538), 305 nm (270); NMR (CCl_4) δ 3.18–2.50 (2 H, br m), 2.50–1.05 (11 H, br m), 2.00 (3 H, s, SCH_3) [lit.[20] bp 66–67 °C (0.5 mm); n^{21}_D 1.511]. A 2,4-dinitrophenylhydrazone derivative was prepared, mp 129–130 °C [lit.[20] mp 128 °C].

2-(Methylthio)cyclooctanone. The general procedure was employed using 4.0 g (32 mmol) of 2-cyclooctenone with 3.1 mL (32 mmol) of dimethyl disulfide to yield 2.1 g (12 mmol, 38%) of 2-(methylthio)cyclooctanone: bp 58–62 °C (0.55 mm); n^{25}_D 1.5138; IR (neat) 2905, 2850, 1690, 1470, 1450, 1330, 1225, 1160, 1125, 1060, 848 cm^{-1}; UV (hexane) λ_{max} (ε) 215 (1928), 248 (710), 306 nm (291); NMR (CCl_4) δ 3.20–2.46 (2 H, br m), 2.45–0.71 (11 H, br m), 1.91 (3 H, s, SCH_3) [lit.[21] bp 59–61 °C (0.5 mm); n^{20}_D 1.5130].

3-Methyl-2-(methylthio)cyclohexanone. Reductive sulfenylation of 10.0 g (91 mmol) of 3-methyl-2-cyclohexenone with 24.5 mL (273 mmol) of dimethyl disulfide according to the general procedure described above gave 6.92 g (44 mmol, 48%) of 3-methyl-2-(methylthio)cyclohexanone as a 55:45 mixture of epimers, bp 94–95 °C (7.0 mm). The mixture of epimers could not be separated in our laboratory by vapor-phase chromatography. Thus, the ratio of epimers was determined by NMR analysis. All physical properties were those of this mixture: n^{25}_D 1.5020; IR (neat) 2940, 2870, 1670, 1430, 1381, 1350, 1328, 1253, 1197, 1050, 1040, 962, 885, 755 cm^{-1}; NMR (CCl_4) δ 3.17–2.62 (2 H, m), 2.54–1.00 (6 H, m), 2.00 and 1.97 (3 H, 2s, 2 SCH_3), 1.14 and 1.12 (3 H, 2d, J = 6.5 Hz, 2 $CHCH_3$).

Anal. Calcd for $C_8H_{14}OS$: C, 60.72; H, 8.92; S, 20.25. Found: C, 60.72; H, 8.89; S, 20.54.

$\Delta^{8(9)}$-1-(Methylthio)-2-*p*-menthenone. The general procedure was employed using 6.81 g (45 mmol) of *l*-carvone and 4.3 mL (45 mmol) of dimethyl disulfide to yield 4.2 g (21 mmol, 47%) of a 17:83 mixture of epimers of $\Delta^{8(9)}$-1-(methylthio)-2-*p*-menthenone: bp 61–63 °C (0.15 mm); n^{25}_D 1.5091.

Anal. Calcd for $C_{11}H_{18}OS$: C, 66.62; H, 9.14; S, 16.17. Found: C, 66.91; H, 9.16; S, 15.90.

The epimers were preparatively separated by VPC on a 10 ft × ¼ in. 10% SE-30 on 60/80 Chromosorb W column at 160 °C. The major isomer eluted first and had the following physical properties: IR (neat) 3380, 3075, 2920, 2850, 1695, 1655, 1440, 1375, 1270, 1190, 1075, 890 cm^{-1}; UV (hexane) λ_{max} (ε) 249 (430), 304 nm (264); NMR (CCl_4) δ 4.75 (2 H, s, $=CH_2$), 3.22–1.43 (7 H, br m), 1.85 (3 H, s, SCH_3), 1.76 (3 H, s, allylic CH_3), 1.30 (3 H, s, α-CH_3); *m/e* calcd for $C_{11}H_{18}OS$ 198.108, found 198.107.

Minor isomer: IR (neat) 3375, 3075, 2915, 2845, 1695, 1440, 1380, 1270, 1190, 1075, 890 cm^{-1}; UV (hexane) λ_{max} (ε) 248 (358), 307 nm (242); NMR (CCl_4) δ 4.89 and 4.65 (2 H, 2s, $=CH_2$), 3.45–1.46 (7 H, br m), 1.82 (3 H, s, SCH_3), 1.70 (3 H, s, allylic CH_3), 1.23 (3 H, s, α-CH_3); *m/e* calcd for $C_{11}H_{18}OS$ 198.108, found 198.109.

8,10-Dimethyl-1-(methylthio)-2-decalone. In a slight modification of the general procedure, 0.52 g (75 mmol) of lithium in 200 mL of liquid ammonia was allowed to react with 6.10 g (34 mmol) of *trans*-8,10-dimethyl-1(9)-octal-2-one,[22] 2.70 g (34 mmol) of *tert*-butyl alcohol, and 9.2 mL (102 mmol) of dimethyl disulfide to yield 7.59 g of crude product, which was chromatographed on silica gel with benzene–petroleum ether as eluent to give 4.97 g (22 mmol, 65%) of 8,10-dimethyl-1-(methylthio)-2-decalone as a yellow oil: n^{25}_D 1.5262; IR (neat) 2882, 1695, 1458, 1385, 1232 cm^{-1}; NMR ($CDCl_3$) major peaks δ 3.03 (1 H, d, J = 5.9 Hz, SCH), 2.03 (3 H, s, SCH_3), 1.15 (3 H, s, 10-CH_3), 0.88 (3 H, d, J = 6.3 Hz, $CHCH_3$).

Anal. Calcd for $C_{13}H_{22}OS$: C, 68.97; H, 9.80; S, 14.16. Found: C, 68.95; H, 9.97; S, 14.17.

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spectra. We also wish to thank Professor A. Moscowitz for helpful discussions.

Registry No.—Dimethyl disulfide, 624-92-0.

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(19) Boiling points are uncorrected. Spectral data were obtained through the use of the following instruments: Varian A-60-D nuclear magnetic resonance spectrometer; Perkin-Elmer R-24-B nuclear magnetic resonance spectrometer; Perkin-Elmer Model 137 Infracord; AEI MS-30 mass spectrometer. Microanalyses were performed by the Scandinavian Microanalytical Laboratories, Herlev, Denmark. We wish to acknowledge financial assistance from the General Electric Foundation in the purchase of the Perkin-Elmer R-24-B NMR spectrometer.
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Sulfenylation of Amides

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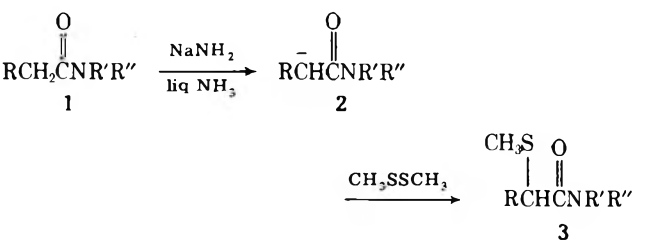
A variety of amides and lactams have been sulfenylated. It was found that, in general, lithium diisopropylamide in tetrahydrofuran was a useful base–solvent system for the α-monosulfenylation of N,N-disubstituted amides. In contrast, sodium amide in liquid ammonia was a superior base–solvent system for polysulfenylation of such amides.

Recently, we have described in detail the [2,3] sigmatropic rearrangement of ylides derived from azasulfonium salts as part of our general synthesis of indoles[1] and oxindoles.[2] Crucial to the preparation of the requisite azasulfonium salt precursors was the availability of a variety of sulfides. In connection with the synthesis of oxindoles, we were particularly concerned with the preparation of α-methylthioamides.[2] Of the various methods available for the introduction of an α-methylthio moiety, we were attracted to the possibility of directly sulfenylating anions of the appropriate amide or lactam with dimethyl disulfide. The recent comprehensive report on the sulfenylation of ketones and esters,[3,4] and of more direct relationship, the phenyl sulfenylation of 1-methyl-2-pyrrolidone and 1-methyl-2-piperidone recently described by Zoretic and Soja,[5] prompted us to report herein our results on the methyl sulfenylation of amides. Of particular interest in this regard are the major differences between the findings of Zoretic and Soja and those from our laboratory, especially those associated with the effect of different solvents on the nature of the reaction.

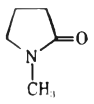
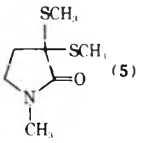
Previously, we[6] and others[7] had demonstrated the suitability of sodium amide as a base for the α-alkylation of amides. Thus, it seemed reasonable that treatment of **1** with sodium amide in liquid ammonia would produce **2**, which on reaction with dimethyl disulfide would yield **3**. In practice, this



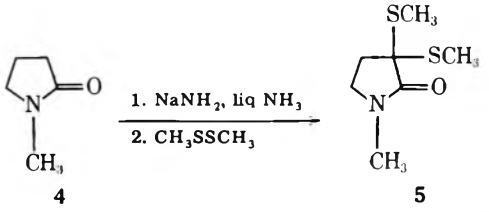
1 2 3

reaction was not suitable for monosulfenylation of amides. When 1 equiv of *N*-methylpyrrolidone (**4**) was treated with 1 equiv of sodium amide in liquid ammonia, followed by the addition of 1 equiv of dimethyl disulfide, only the disubstituted lactam **5** and unreacted **4** were obtained. When 2 equiv

Table I. Polysulfenylation of Amides with Sodium Amide–Dimethyl Disulfide in Liquid Ammonia[a]

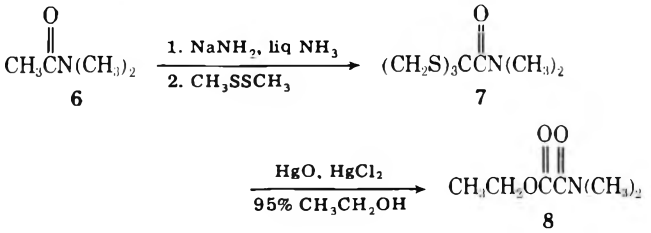
Starting amide	Registry no.	Product(s)	Registry no.	% yield(s)
	872-50-4	 (5)	63017-89-0	45
$CH_3\overset{O}{\overset{\|}{C}}N(CH_3)_2$	127-19-5	$(CH_3S)_3C\overset{O}{\overset{\|}{C}}N(CH_3)_2$ (7)	63017-90-3	45
$CH_3CH_2\overset{O}{\overset{\|}{C}}-N(CH_3)C_6H_5$	5827-78-1	$(CH_3S)_2C(CH_3)\overset{O}{\overset{\|}{C}}-N(CH_3)C_6H_5$	63017-91-4	60
$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}-N(CH_3)C_6H_5$	42883-79-4	$(CH_3S)_2C(C_2H_5)\overset{O}{\overset{\|}{C}}-N(CH_3)C_6H_5$ +	63017-92-5	43
		$C_2H_5CH(SCH_3)\overset{O}{\overset{\|}{C}}-N(CH_3)C_6H_5$	63017-93-6	40
$C_6H_5CH_2\overset{O}{\overset{\|}{C}}-N(CH_3)C_6H_5$	40669-47-4	$(CH_3S)_2C(C_6H_5)\overset{O}{\overset{\|}{C}}-N(CH_3)C_6H_5$ +	63017-94-7	40[b]
		$C_6H_5CH(SCH_3)\overset{O}{\overset{\|}{C}}-N(CH_3)C_6H_5$	63017-95-8	60[b]

[a] All yields listed resulted from the reaction of 1 equiv of amide or lactam with 2 equiv each of base and dimethyl disulfide. [b] Yields were determined by NMR spectroscopy.



4 5

of base and 2 equiv of disulfide were used, disubstitution was observed again. As shown in Table I, the problem of polysulfenylation was general under the reaction conditions described above. Of particular interest in this regard was *N,N*-dimethylacetamide (6), which gave a 45% yield of the trisulfenylated product 7. In addition to establishing the structure of 7 by spectroscopic and elemental analysis, the oxidation state was further proven via hydrolysis to ethyl *N,N*-dimethyloxamate (8). As indicated by the results outlined in Table I, with sodium amide in liquid ammonia as the solvent–base system, a propensity for polysulfenylation existed. This tendency toward polysulfenylation appeared to be sensitive to the steric effect of the environment. Whereas *N*-methylpyrrolidone, *N,N*-dimethylacetamide, and *N*-methyl-*N*-phenylpropionamide gave only polysulfenylation, those amides with more hindered methylenes adjacent to the carbonyl, namely *N*-methyl-*N*-phenylbutyramide and α,*N*-diphenyl-*N*-methylacetamide, gave mixtures of monosubstitution and disubstitution. From the data in hand, it cannot be determined whether the shift from selective polysulfenylation to partial monosulfenylation was due solely to the increased steric hindrance at the reaction site or whether this change was due to a combination of steric and electronic effects. These results correlate quite well with those of Zoretic and Soja in THF–HMPA using an amide–base–disulfide ratio of 1:2:2.[5]

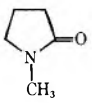
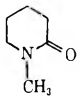
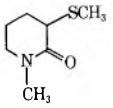
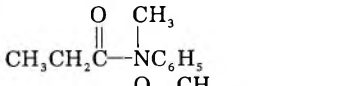
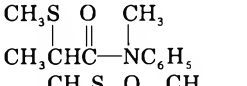
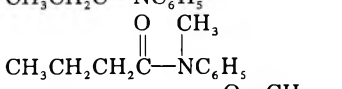
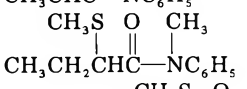
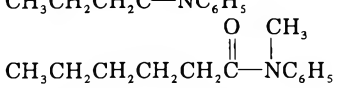
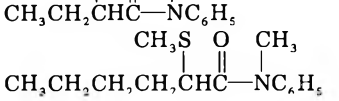


6 7 8

In view of the problems associated with polysulfenylation when sodium amide in liquid ammonia was used as the base–solvent system, we decided to explore other base–solvent systems. Since lithium dialkylamides have been used previously to promote sulfenylations,[3-5] we investigated the reaction of amines with lithium diisopropylamide (LDA) in tetrahydrofuran, while maintaining the 1 equiv excess of both base and sulfenylating agent in order to observe any tendency to produce polysulfenylation. As shown in Table II, our results with excess LDA and excess sulfenylating agent both differ from and parallel those of Zoretic and Soja. Whereas Zoretic and Soja found that a 1:2:2 ratio of amide–base–diphenyl disulfide afforded bissulfenylation, we found that this ratio gave monosulfenylation in most of the cases which we have studied in THF. However, it should be stressed that Zoretic and Soja were using a different solvent system and a different sulfenylating agent. We found good to excellent yields of monosulfenylation products in most cases (only with *N*-methylpyrrolidone was polysulfenylation observed). The reason for the dichotomy between our two base–solvent systems was not intuitively obvious. The possibility that the contrasting behavior was due to the difference in gegenion was ruled out when it was demonstrated that lithium amide in liquid ammonia gave essentially the same results as sodium amide in liquid ammonia.

It would appear that the differences discussed above were associated primarily with the use of tetrahydrofuran as sol-

Table II. Sulfenylation of Amides with Lithium Diisopropylamide in Tetrahydrofuran[a]

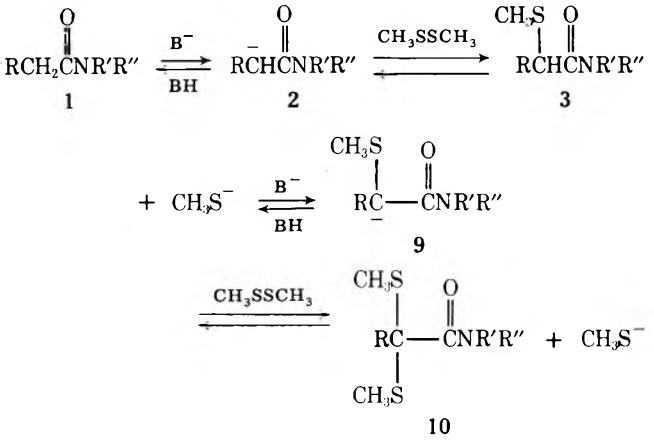
Starting amide	Registry no.	Product	Registry no.	% yield
		5		87
	931-20-4		63017-97-0	69
			63017-98-1	87
				80
	63017-96-9		63017-99-2	65

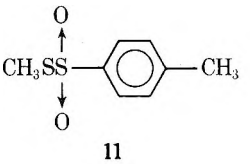
[a] All yields listed resulted from the reaction of 1 equiv of amide with 2 equiv of base and 2 equiv of dimethyl disulfide.

vent. As noted by other workers:[3] "In THF solutions, bissulfenylation of ketone enolates with diphenyl disulfide or of ester enolates with dimethyl disulfide were not observed regardless of the amount of excess base or disulfide. In THF–HMPA mixtures, bissulfenylation of ketone enolates can occur." The overall mechanistic picture can best be discussed in terms of Scheme I. There is little doubt that both base–solvent systems result in the conversion of **1** into **2** and that this is probably reversible. Dimethyl disulfide undoubtedly reacts with **2** to yield **3** and thiomethoxide. Since the α proton on **3** should be more readily removed by base than that on **1**, it would be anticipated that **3** would be rapidly converted into **9**, especially in the presence of excess base. Apparently when the base–solvent system was sodium amide–liquid ammonia, **9** was readily formed and subsequently reacted with the excess dimethyl disulfide to form **10** and thiomethoxide. In contrast, with LDA in tetrahydrofuran, **10** was not formed. The possibility of **10** being formed reversibly was ruled out by the experimental demonstration that the reaction of **10** with thiomethoxide to give **9** was a very slow reaction in tetrahydrofuran, giving only 20% conversion of **10** into **9** during the normal reaction time. Furthermore, when methylthio tosylate (**11**) was used as the sulfenylating agent in tetrahydrofuran, only monosulfenylation was observed. Similar results were observed when *N*-methylthiosuccinimide (**12**) was used as the sulfenylating agent. Thus, it would appear that the lack of disulfenylation in tetrahydrofuran was due primarily to the relative stability of the lithium salt of **9** in tetrahydrofuran.

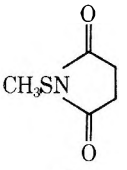
An interesting side aspect of this study was the curious difference in behavior noted for *N*-methylpyrrolidone vs. *N*-methylpiperidone. Whereas *N*-methylpyrrolidone gave disulfenylated products in both base–solvent systems, *N*-methylpiperidone afforded the monosulfenylated product (69%) in tetrahydrofuran. This demonstrated a sharp contrast in reactivity between the five- and six-membered lactams under identical conditions. Presumably, this was a consequence of the different geometries of the two rings in question.

Scheme I





11



12

In summary, it appears that lithium diisopropylamide in tetrahydrofuran is a useful base–solvent system for the α-monosulfenylation of N,N-disubstituted amides. In contrast, sodium amide in liquid ammonia is a superior base–solvent system for polysulfenylation of such amides.

Experimental Section[8]

General Procedure for Sulfenylation Utilizing Sodium Amide in Liquid Ammonia with Dimethyl Disulfide. Sodium amide was formed through the portionwise addition of 4.6 g (0.20 mol) of sodium into 100 mL of dry liquid ammonia containing a catalytic amount of ferric chloride. When the formation of sodium amide was complete, 10.0 g (0.10 mol) of *N*-methyl-2-pyrrolidone was added dropwise. The resulting green suspension was stirred for 20 min, then 19.0 g (0.20 mol) of dimethyl disulfide was added dropwise. After stirring for 2 h, the ammonia was allowed to evaporate, water was added carefully, and the solution was acidified with concentrated hydrochloric acid. The solution was extracted with four 50-mL portions of chloroform, dried over anhydrous magnesium sulfate, and filtered, and the filtrate was concentrated by rotatory evaporation. The residue was fractionally distilled to yield 2.1 g of starting lactam, bp 35–40 °C (0.4 mm), and 8.5 g (45%) of *N*-methyl-3,3-di(methylthio)-2-pyrrolidone, bp 115 °C (0.4 mm), which crystallized on standing, mp 33–35 °C, after recrystallization from *n*-hexane: NMR (CCl_4) δ 3.35 (2 H, t, J = 7 Hz), 2.82 (3 H, s), 2.28 (2 H, t, J = 7 Hz), 2.12 (6 H, s); *m/e* calcd for $C_7H_{13}NOS_2$ 191.044, found 191.045.

Anal. Calcd for $C_7H_{13}NOS_2$: C, 43.98; H, 6.81; N, 7.32. Found: C, 43.87; H, 6.83; N, 7.23.

***N,N*-Dimethyl-2,2,2-tri(methylthio)acetamide (7).** The general procedure outlined above was used with 8.7 g (0.10 mol) of *N,N*-dimethylacetamide to give 6.8 g (45%) of *N,N*-dimethyl-2,2,2-tri(methylthio)acetamide (**7**) after recrystallization from *n*-hexane, mp 84–86 °C: IR (KBr) 6.20 μm; NMR (CCl_4) δ 3.23 (6 H, s), 2.03 (9 H, s); *m/e* calcd for $C_7H_{15}NOS_3$ 225.032, found 225.037.

Anal. Calcd for $C_7H_{15}NOS_3$: C, 37.33; H, 6.67; N, 6.22. Found: C, 37.49; H, 6.78; N, 6.13.

***N*-Methyl-*N*-phenyl-2,2-di(methylthio)propionamide.** The general procedure described above was used with 8.0 g (0.05 mol) of *N*-methyl-*N*-phenylpropionamide. Utilization of 2 equiv of sodium amide and 2 equiv of dimethyl disulfide gave 10 g of crude product, which on distillation gave 7.5 g (60%) of *N*-methyl-*N*-phenyl-2,2-di(methylthio)propionamide: bp 105–110 °C (0.13 mm); IR (neat) 6.10 μm; NMR (CCl_4) δ 7.30 (5 H, s), 3.39 (3 H, s), 2.05 (6 H, s), 1.44 (3 H, s); *m/e* calcd for $C_{12}H_{17}NOS_2$ 255.075, found 255.073.

Anal. Calcd for $C_{12}H_{17}NOS_2$: C, 56.47; H, 6.66; N, 5.49. Found: C, 56.75; H, 6.76; N, 5.69.

***N*-Methyl-*N*-phenyl-2,2-di(methylthio)butyramide and *N*-Methyl-*N*-phenyl-2-methylthiobutyramide.** The general procedure described above was used with 9.0 g (0.05 mol) of *N*-methyl-*N*-phenylbutyramide. The crude product was distilled to yield 4.45 g (40%) of *N*-methyl-*N*-phenyl-2-methylthiobutyramide, bp 105–135 °C (0.3 mm), and 5.75 g (43%) of *N*-methyl-*N*-phenyl-2,2-di(methylthio)butyramide as a crystalline pot residue, mp 65–70 °C. Recrystallization from *n*-hexane gave an analytical sample: mp 72–73 °C; IR (KBr) 6.14 μm; NMR ($CDCl_3$) δ 7.31 (5 H, s), 3.37 (3 H, s), 1.94 (6 H, s), 1.47 (2 H, q, J = 7.2 Hz), 1.00 (3 H, t, J = 7.2 Hz); *m/e* calcd for $C_{13}H_{19}NOS_2$ 269.091, found 269.090.

Anal. Calcd for $C_{13}H_{19}NOS_2$: C, 57.99, H, 7.06; N, 5.24. Found: C, 57.97; H, 7.14; N, 5.19.

***N*-Methyl-2,*N*-diphenyl-2,2-di(methylthio)acetamide and *N*-Methyl-2,*N*-diphenyl-2-methylthioacetamide.** The general procedure described above was used with 11.3 g (0.05 mol) of *N*-methyl-2,*N*-diphenylacetamide to give a quantitative yield of a mixture of mono- and disulfenylated product. The mixture was not readily separated by standard techniques on a preparative scale. Analysis by NMR spectroscopy indicated 60% monosulfenylation and 40% disulfenylation. The two products were separated by thin layer chromatography on silica gel. The separated products were then molecularly distilled.

N-Methyl-2,*N*-diphenyl-2,2-di(methylthio)acetamide was distilled at 150 °C (1.5×10^{-4} mm): IR (neat) 6.10 μm; NMR ($CDCl_3$) δ 7.5–6.7 (10 H, br m), 3.10 (3 H, s), 1.95 (6 H, s); *m/e* calcd for $C_{17}H_{19}NOS_2$ 317.091, found 317.092.

Anal. Calcd for $C_{17}H_{19}NOS_2$: C, 64.35; H, 5.99; N, 4.42. Found: C, 64.40; H, 6.16; N, 4.42.

N-Methyl-2,*N*-diphenyl-2-methylthioacetamide was distilled at 110 °C (0.15 mm): IR (neat) 6.05 μm; NMR (CCl_4) δ 7.5–7.0 (10 H, br m), 4.25 (1 H, s), 3.22 (3 H, s), 1.82 (3 H, s); *m/e* calcd for $C_{16}H_{17}NOS$ 271.103, found 271.104.

Anal. Calcd for $C_{16}H_{17}NOS$: C, 70.85; H, 6.27; N, 5.17. Found: C, 70.59; H, 6.44; N, 5.02.

Ethyl *N,N*-Dimethyloxamate (8). To a solution of 450 mg (2 mmol) of *N,N*-dimethyl-2,2,2-tri(methylthio)acetamide in 55 mL of 95% ethanol was added 2.28 g of mercuric chloride and 706 mg of mercuric oxide. The resulting suspension was refluxed for 5.5 h under an atmosphere of nitrogen. After cooling, the reaction mixture was filtered and the separated solids were washed with methylene chloride. The filtrate was diluted with water, ammonium chloride solution was added, and the methylene chloride solution was separated, dried over Drierite, and filtered, and the filtrate was evaporated to yield 257 mg (88%) of ethyl *N,N*-dimethyloxamate (8), which showed no impurities by NMR analysis.

General Procedure for Sulfenylation Utilizing Lithium Diisopropylamide in Tetrahydrofuran. *N*-Methyl-*N*-phenyl-2-methylthiopropionamide. A tetrahydrofuran solution of lithium diisopropylamide (LDA) was prepared by the slow addition of 9 mL of 2.2 M methyllithium to 2.0 g (0.02 mol) of dry diisopropylamine in 50 mL of tetrahydrofuran (THF) at −78 °C under nitrogen. To this solution was added dropwise 1.63 g (0.01 mol) of *N*-methyl-*N*-phenylpropionamide in 10 mL of THF at −78 °C. The solution was stirred at −78 °C for 30 min, after which 2.0 g (~0.02 mol) of dimethyl disulfide was added. After stirring for 2 h at −78 °C, the solution was allowed to warm to room temperature and quenched by the addition of 50 mL of water. The reaction mixture was extracted with four 50-mL portions of chloroform. The organic extracts were combined, washed with dilute hydrochloric acid and saturated sodium chloride, and dried over Drierite. After filtration, the solvent was removed and the crystalline residue was recrystallized from *n*-hexane to give 1.83 g (87%) of *N*-methyl-*N*-phenyl-2-methylthiopropionamide, mp 71.5–73.0 °C: IR (KBr) 6.08 μm; NMR (CCl_4) δ 7.28 (5 H, s), 3.22 (3 H, s), 3.12 (1 H, q, J = 7 Hz), 2.03 (3 H, s), 1.32 (3 H, d, J = 7 Hz); *m/e* calcd for $C_{11}H_{15}NOS$ 209.087, found 209.086.

Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.16; H, 7.18; N, 6.70. Found: C, 63.24; H, 7.29; N, 6.68.

***N*-Methyl-*N*-phenyl-2-methylthiobutyramide.** According to the general procedure described above, 1.7 g (0.01 mol) of *N*-methyl-*N*-phenylbutyramide was treated with 2 equiv of LDA and dimethyl disulfide. Workup afforded 2.35 g, which was purified by molecular distillation (60 °C pot temperature, 0.12 mm) to give 1.73 g (80%) of *N*-methyl-*N*-phenyl-2-methylthiobutyramide as a light yellow oil: IR (neat) 6.05 μm; NMR (CCl_4) δ 7.40 (5 H, s), 3.27 (3 H, s), 2.87 (1 H, d of d, J = 9 and 7 Hz), 2.25–1.25 (2 H, complex m), 2.02 (3 H, s), 0.88 (3 H, t, J = 7 Hz); *m/e* calcd for $C_{12}H_{17}NOS$ 223.103, found 223.102.

Anal. Calcd for $C_{12}H_{17}NOS$: C, 64.57; H, 7.62; N, 6.28. Found: C, 64.27; H, 7.75; N, 6.14.

***N*-Methyl-*N*-phenyl-2-methylthiohexanamide.** According to the general procedure outlined above, 2.0 g (0.1 mol) of *N*-methyl-*N*-phenylhexanamide was treated with 2 equiv each of LDA and dimethyl disulfide. Workup gave an oil which crystallized on cooling in *n*-hexane to yield 1.6 g (65%) of *N*-methyl-*N*-phenyl-2-methylthiohexanamide as yellow prisms, mp 46–48 °C: IR (KBr) 6.11 μm; NMR (CCl_4) δ 7.31 (5 H, s), 3.21 (3 H, s), 2.85 (1 H, d of d, J = 9 and 6 Hz), 2.20–0.50 (9 H, complex m), 2.01 (3 H, s); *m/e* calcd for $C_{14}H_{21}NOS$ 251.134, found 251.134.

Anal. Calcd for $C_{14}H_{21}NOS$: C, 66.93; H, 8.37; N, 5.58. Found: C, 66.85; H, 8.39; N, 5.59.

***N*-Methyl-3-methylthiopiperidone.** As described above, 1.13 g (0.01 mol) of *N*-methylpiperidone was treated with 2 equiv each of LDA and dimethyl disulfide. The crude product was purified by chromatography on silica gel (ether eluent) to give 1.10 g (69%) of *N*-methyl-3-methylthiopiperidone. Molecular distillation (60 °C pot temperature, 0.15 mm) gave an analytical sample: IR (neat) 6.15 μm; NMR (CCl_4) δ 3.40–3.00 (3 H, m), 2.82 (3 H, s), 2.22 (3 H, s), 2.22–1.50 (4 H, complex m); *m/e* calcd for $C_7H_{13}NOS$ 159.072, found 159.073.

Anal. Calcd for $C_7H_{13}NOS$: C, 52.83; H, 8.18; N, 8.81. Found: C, 52.83; H, 8.30; N, 8.71.

***N*-Methyl-3,3-di(methylthio)-2-pyrrolidone (5).** Utilizing the procedure outlined above, 1.0 g (0.01 mol) of *N*-methylpyrrolidone was treated with 2 equiv each of LDA and dimethyl disulfide. Workup gave 1.70 g of an oil, which crystallized on standing. This material was identical in all respects with the *N*-methyl-3,3-di(methylthio)-2-pyrrolidone described above.

Desulfenylation of *N*-Methyl-*N*-phenyl-2,2-di(methylthio)-propionamide with Lithium Thiomethoxide. Methanethiol (500 mg, 0.01 mol) was added to 1 equiv of LDA in 50 mL of THF and the solution was stirred for 30 min at −78 °C under nitrogen. *N*-Methyl-*N*-phenyl-2,2-di(methylthio)propionamide (1.2 g, 5 mmol) was added to the solution and the reaction mixture was stirred for 2 h at −78 °C and then allowed to warm to room temperature. Water (50 mL) was added, the layers were separated, and the aqueous layer was extracted with four 50-mL portions of chloroform. The organic extracts were combined, washed with dilute hydrochloric acid and saturated brine solution, and dried over Drierite. Filtration followed by evaporation of the solvent gave 80% of starting material and 20% of *N*-methyl-*N*-phenyl-2-methylthiopropionamide as determined by NMR analysis.

***N*-Methyl-*N*-phenyl-2-methylthiopropionamide Utilizing Methanethiol *p*-Toluenesulfonate.** According to the general procedure, 0.8 g (5 mmol) of *N*-methyl-*N*-phenylpropionamide was treated with 2 equiv each of LDA and methanethiol *p*-toluenesulfonate. Workup gave a crude product which on analysis by NMR spectroscopy showed only monosulfenylation of the starting amide.

A similar experiment utilizing *N*-methylthiosuccinimide gave 85% monosulfenylation and 15% disulfenylation as determined by NMR spectroscopic analysis.

Acknowledgement. We are indebted to the National Cancer Institute of the Public Health Service for Grant CA-16967, to the National Institute for General Medical Sciences for Grant GM-22346, and to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this investigation.

Registry No.—Dimethyl disulfide, 624-92-0; methanethiol *p*-toluenesulfonate, 4973-66-4; *N*-methylthiosuccinimide, 2043-24-5.

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(8) Melting points and boiling points are uncorrected. Spectral data were obtained through the use of the following instruments: Varian CFT-20 or HFT-80 magnetic resonance spectrometer; Perkin-Elmer R-24-B nuclear magnetic resonance spectrometer; Perkin-Elmer 137 infrared spectrometer; AEI MS-30 mass spectrometer. Microanalyses were performed by the Scandinavian Microanalytical Laboratories, Herlev, Denmark.

Use of [2,3] Sigmatropic Rearrangements for the Specific Ortho-Substitution of Polycyclic Aromatic Amines. The Methylation of Naphthylamines and the Synthesis of 1*H*-Benz[*g*]indoles and 3*H*-Benz[*e*]indoles

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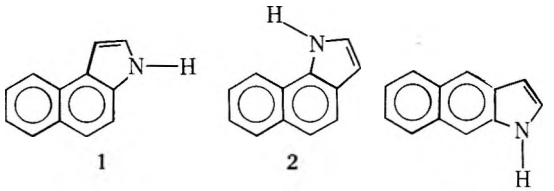
Procedures have been developed for the specific ortho-alkylation of polycyclic aromatic amines. Both α- and β-naphthylamine have been ortho-methylated by a procedure involving sequential treatment of the amine with (a) *tert*-butyl hypochlorite, (b) dimethyl sulfide, (c) sodium methoxide, and (d) Raney nickel. This procedure, which uses a [2,3] sigmatropic rearrangement of an ylide in the key ring functionalization step, gave only ortho-substitution. Replacement of the dimethyl sulfide by sulfides having a carbonyl group in the β position permitted the synthesis of 1*H*-benz[*g*]indoles and 3*H*-benz[e]indoles from the appropriate naphthylamine precursors.

Recently, the need for general methods for the specific ortho-substitution of polycyclic aromatic amines has been discussed in connection with oncological studies of related nonsubstituted aromatic amines.[1] Being fully aware of the need for such selective procedures for ortho-alkylation and also of the lack of good general methods for the synthesis of 1*H*-benz[*g*]indoles and 3*H*-benz[e]indoles, we decided to attempt to apply our general procedures for ortho-alkylation[2-6] and for the synthesis of indoles[6-9] to the polycyclic aromatic amines. We now wish to report in detail the specific ortho-substitution of α- and β-naphthylamine.

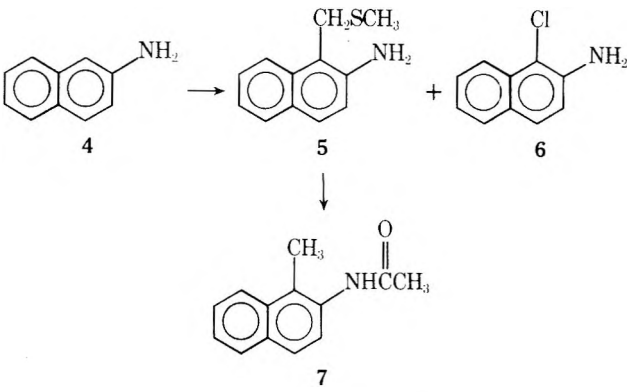
Benzindoles, although first reported in the literature in the late 19th century,[10,11] have not been extensively studied. 3*H*-Benz[*e*]indole (**1**) was first described in 1886,[10] while 1*H*-benz[*g*]indole (**2**) was reported the following year.[11] Both were prepared through application of the Fischer indole synthesis.[12] Subsequently, a variety of methods appeared in the literature for the preparation of **1** and **2** and for derivatives of these two systems.[13] It is interesting to note at this point that sound chemical evidence for the structure of **1** has never been provided. Instead, the structure of **1** was postulated on the basis of its nonidentity with 1*H*-benz[*f*]indole (**3**). As part



1 **2** **3**

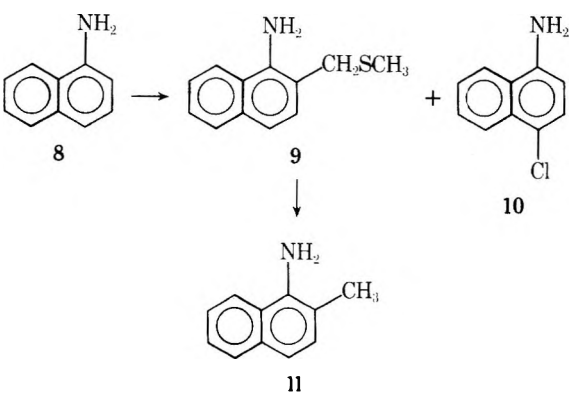
of the present study, we have provided what we believe to be a definitive structure proof of the 3*H*-benz[*e*]indole nucleus.

We first examined the simple ortho-alkylation of 2-aminonaphthalene (**4**) according to our standard process. In a sequential series of reactions, 1 equiv of *tert*-butyl hypochlorite, 1 equiv of dimethyl sulfide, and 1.5 equiv of sodium methoxide were added to 1 equiv of **4** at −78 °C. Workup gave a 95% yield of a 3:1 mixture of **5** and **6**. Separation of the mixture followed by Raney nickel desulfurization of **5** and



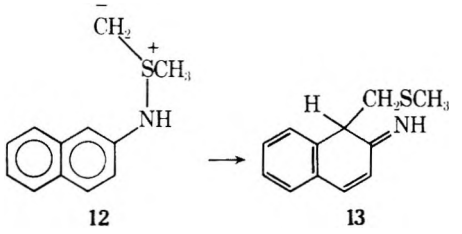
4 **5** **6** **7**

acetylation with acetyl chloride gave a 70% overall yield of the recrystallized acetamide **7**. A similar study was carried out with α-naphthylamine (**8**) as the starting material. Under our standard reaction conditions **8** gave 40% yields of **9** and **10**. Raney nickel desulfurization of **9** gave a 90% yield of **11**. Overall, the preparation of **7** and **11** illustrate the utility of our general process for ortho-alkylation of polycyclic aromatic

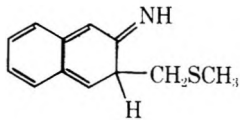


8 **9** **10** **11**

amines. Since the crucial step in the process involves the [2,3] sigmatropic rearrangement of ylides derived from azasulfonium salts such as **12**, only ortho-substitution via dienone imines such as **13** was possible. Hydrogen transfer accompanied by rearomatization then produces products such as **5**. The sigmatropic nature of the aromatic substitution step results in little, if any, charge buildup on the aromatic nucleus. Thus, polar substituents on the ring should have little effect on such substitution reactions. It is interesting to note that the rearrangement of **12** was highly specific in that only the 1 position was attacked. This was probably due to the loss of aromaticity which would result from attack at the 3 position, since initial substitution at that point would produce **14**, in which the aromatic resonance energy of both rings would be temporarily lost.

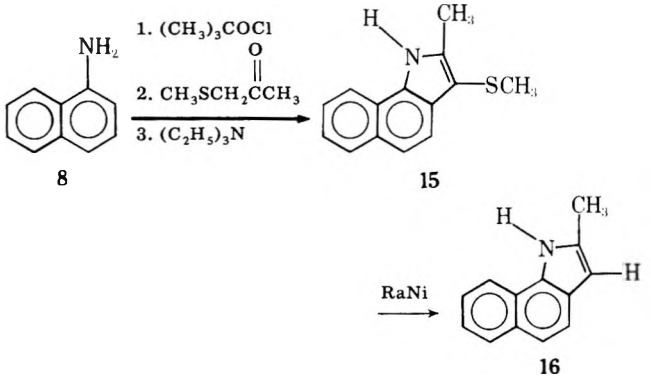


12 **13**



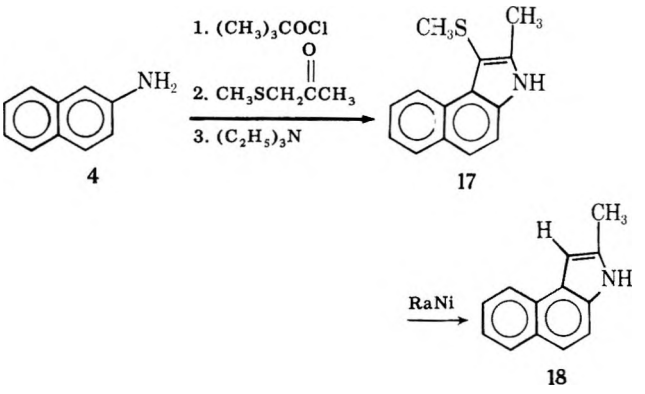
14

In order to explore the utility of our indole synthesis with polycyclic aromatic amines, the preparation of 1*H*-benz[*g*]-indoles and 3*H*-benz[*e*]indoles was attempted via replacement of the dimethyl sulfide from the procedure described above with an appropriate β-keto sulfide. Treatment of **8** with 1 equiv of *tert*-butyl hypochlorite followed by 1 equiv of methylthio-2-propanone and then by triethylamine gave a 65% yield of **15**. Raney nickel desulfurization of **15** gave a 90% yield of **16**. In a similar fashion, β-naphthylamine was converted into 1-methylthio-2-methyl-3*H*-benz[*e*]indole (**17**) in 73% yield. Raney nickel desulfurization of **17** gave **18** in 88% yield.

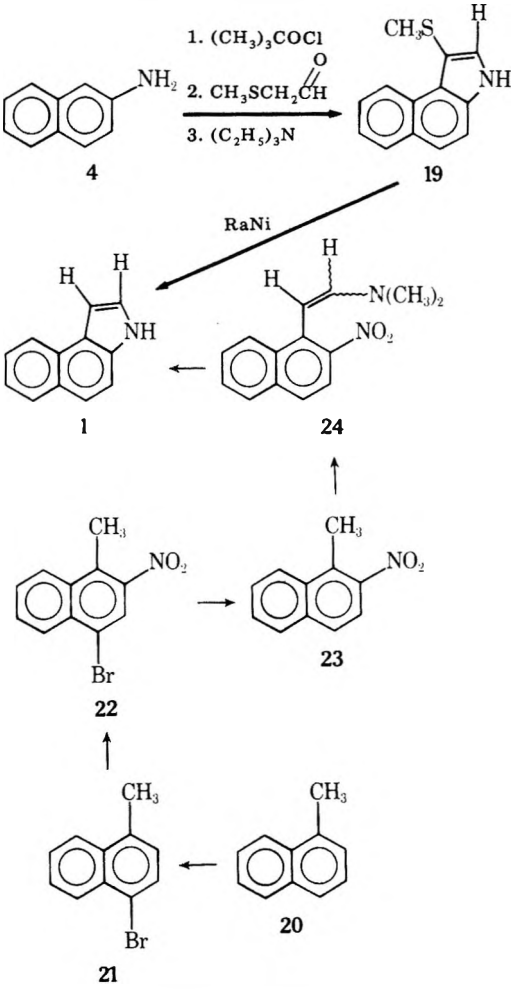


8 **15** **16**

While spectroscopic data indicated that **4** gave exclusively the 3*H*-benz[*e*]indole system, it was felt that a sound chemical proof of structure was merited. Toward this end, **4** was converted into **19** and, subsequently, into **1** by our general procedure. An authentic sample of **1** was prepared by an alternate and what we believe is an unequivocal route. As shown below, the alternate synthesis is based on the elegant Leimgrüber indole synthesis.[13j] Thus, 1-methylnaphthalene (**20**) was brominated to give a 95% yield of **21**. Nitration of **21** with nitric acid–sulfuric acid mixture gave 77% of **22**. Cuprous oxide reduction of **22** gave a 57% yield of **23**. Reaction of **23** with dimethylformamide diethyl acetal gave **24**, which was converted into **1** on reduction over palladium on carbon. The yield of **1** from **23** was 24% and the overall yield based on **20** was 10%.



4 **17** **18**



4 **19** **1** **24** **23** **22** **20** **21**

The samples of **1** prepared by the two different routes were identical in all respects.

In summary, we have demonstrated that our general processes for the ortho-alkylation of aromatic amines and for the preparation of indole derivatives can be readily extrapolated to polycyclic aromatic amines.

Experimental Section[14]

Caution! The aminonaphthalenes, 4 and 8, are known carcinogens. As such, they should only be handled under proper working conditions and by experienced personnel.

1-Methylthiomethyl-2-aminonaphthalene (5). To a stirred solution of 2.86 g (0.02 mol) of **4** in 75 mL of tetrahydrofuran, which was cooled to ca. −70 °C, was added dropwise 2.20 g (0.02 mol) of *tert*-butyl hypochlorite with vigorous stirring under a nitrogen atmosphere. The reaction mixture was stirred for 5 min, 1.5 mL (0.02 mol) of di-

methyl sulfide was added, and the reaction mixture was stirred for an additional 2 h at −70 °C. A solution of sodium methoxide (1.60 g, 0.03 mol) in 10 mL of methanol was then added dropwise and the reaction mixture was stirred until it reached room temperature. The inorganic salts were removed by filtration and the tetrahydrofuran was removed under reduced pressure. The residue was dissolved in 50 mL of ether and this solution was washed with three 30-mL portions of water. The ether layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give a dark red oil in essentially quantitative yield. Analysis of this oil by high-pressure liquid chromatography showed it to contain 5% of **4**, 24% of 1-chloro-2-aminonaphthalene (**6**), and 71% of 1-methylthiomethyl-2-aminonaphthalene (**5**). These components were separated by preparative HPLC using a ¼ in. × 2 ft μ-poracil column with chloroform–petroleum ether as eluent. The 1-chloro-2-aminonaphthalene (**6**) had spectral and physical properties identical with those reported in the literature for this compound, mp 59.5–60.5 °C (lit.[15] mp 58–59 °C).

The 1-methylthiomethyl-2-aminonaphthalene (**5**) which was separated crystallized on standing: mp 41–42 °C; IR (neat) 2.91, 2.98, 6.14, 6.60, 6.96, 12.3, 12.5 μm; NMR ($CDCl_3$) δ 2.00 (3 H, s), 4.02 (4 H, br s), 6.80 (1 H, d), 8.0–7.0 (5 H, m).

Anal. Calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.44; N, 6.89. Found: C, 70.78; H, 6.37; N, 6.86.

1-Methyl-2-aminonaphthaleneacetamide (7). To a stirred solution of 0.47 g of **5** in 50 mL of methanol was added ~9 g of freshly prepared W-2 Raney nickel. The reaction mixture was stirred for 1 h at room temperature and the organic solution was decanted. The Raney nickel residue was washed with two 50-mL portions of methanol. The methanolic solutions were combined and filtered through Celite, and the filtrate was concentrated at reduced pressure. The residue was dissolved in chloroform, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered. Concentration of the filtrate under reduced pressure gave a red oil, which was chromatographed on silica gel (hexane–ether eluent) to yield the desired 1-methyl-2-aminonaphthalene: IR (neat) 2.89, 2.96, 6.16, 6.64, 7.22, 12.44, 13.5 μm; NMR ($CDCl_3$) δ 2.30 (3 H, s), 3.65 (2 H, br s), 6.85 (1 H, d), 8.0–7.0 (5 H, m). This material was allowed to react with acetyl chloride in pyridine to yield 0.32 g (70%) of **7** after recrystallization from ethanol, mp 188–189 °C (lit.[16] mp 189 °C).

2-Methylthiomethyl-1-aminonaphthalene (9). The procedure used in the synthesis of **9** was identical with that described above for the preparation of **5**. A mixture, which contained a 40% yield of 1-chloro-4-aminonaphthalene (**10**) and a 40% yield of 2-methylthiomethyl-1-aminonaphthalene (**9**), was obtained. The structure of **10** was established through the identity of its spectral properties and physical constants with those in the literature, mp 93–95 °C (lit.[17] mp 95–97 °C). The 2-methylthiomethyl-1-aminonaphthalene (**9**) had the following properties: mp 40–42 °C; IR (neat) 2.88, 2.95, 6.16, 6.62, 6.92, 7.20 μm; NMR ($CDCl_3$) δ 1.95 (3 H, s), 3.80 (2 H, s), 4.41 (2 H, s), 7.9–7.1 (6 H, m).

Anal. Calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.44; N, 6.89. Found: C, 70.78; H, 6.55; N, 6.70.

1-Amino-2-methylnaphthalene (11). To a stirred solution of 0.20 g of **9** in 50 mL of methanol was added ~6 g of W-2 Raney nickel and the reaction mixture was stirred at room temperature for 2 h. The methanol solution was decanted and the Raney nickel residue was washed twice with 50-mL portions of methanol. The combined methanol solution was filtered through Celite, and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with three 30-mL portions of water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give 0.14 g (90%) of 1-amino-2-methylnaphthalene (**11**), which was shown to be pure by HPLC analysis: IR (neat) 2.88, 2.95, 6.16, 6,60, 7.12, 7.23, 12.60, 12.99, 13.52 μm; NMR ($CDCl_3$) δ 2.17 (3 H, s), 3.80 (2 H, br s), 7.9–7.0 (6 H, m). A hydrochloride was prepared, mp 227–230 °C (lit.[18] mp 228–231 °C).

1-Methylthio-2-methyl-3*H*-benz[*e*]indole (17). To a stirred solution of 3.75 g (26 mmol) of 2-aminonaphthalene (**4**) in 75 mL of tetrahydrofuran at ca. −70 °C was added dropwise 2.83 g (26 mmol) of *tert*-butyl hypochlorite under a nitrogen atmosphere. The reaction mixture was stirred at −70 °C for 5 min and 2.73 g (26 mmol) of methylthio-2-propanone[7,9] in 10 mL of tetrahydrofuran was added dropwise. A voluminous white precipitate formed shortly after this addition. The reaction mixture was stirred for 2 h at ca. −70 °C, followed by the dropwise addition of 5 mL of triethylamine. The cooling bath was removed and the reaction mixture was stirred until it reached room temperature. Distilled water (10 mL) was added and the organic layer was separated and concentrated under reduced pressure. The residue was dissolved in 50 mL of ether and the ethereal solution was washed with three 30-mL portions of 1 N hydrochloric acid and one 30-mL portion of distilled water. The ether layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give crude **17**. Chromatography on silica gel (benzene eluent) gave 4.5 g (76%) of 1-methylthio-2-methyl-3*H*-benz[*e*]indole (**17**), mp 112–113 °C. Recrystallization from hexane gave an analytical sample: mp 112.0–112.5 °C; IR (KBr) 2.90, 7.29, 7.52, 8.30, 10.35, 12.35, 13.36, 14.42 μm; NMR ($CDCl_3$) δ 2.25 (3 H, s), 2.37 (3 H, s), 7.0–8.0 (6 H, m), 9.60 (1 H, d).

Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16. Found: C, 73.96; H, 5.78; N, 6.21.

2-Methyl-3*H*-benz[*e*]indole (18). To a vigorously stirred solution of 2.0 g (8.8 mmol) of **17** in 100 mL of ethanol was added ~20 g of W-2 Raney nickel. The slurry was stirred for 1 h and the ethanolic solution was decanted. The Raney nickel residue was washed with two 100-mL portions of ethanol and the solutions were combined and filtered through Celite. The solvent was removed under reduced pressure, the residue was dissolved in 50 mL of dichloromethane and washed with distilled water, and the organic solution was dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel (benzene eluent) to give 1.20 g of a light yellow oil. Molecular distillation of the material gave 1.10 g (88%) of pure 2-methyl-3*H*-benz[*e*]indole: IR (neat) 2.93, 3.28, 6.50, 7.35, 12.50, 13.10, 13.45 μm; NMR ($CDCl_3$) δ 2.40 (3 H, s), 6.75 (1 H, m), 8.3–7.1 (6 H, m).

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 85.90; H, 6.08; N, 7.66.

3-Methylthio-2-methyl-1*H*-benz[*g*]indole (15). A procedure identical with that described above for the preparation of **17** was used to convert **8** into **15** (65% yield): mp 117–118 °C; IR (KBr) 2.93, 7.23, 12.85, 13.85, 18.40 μm; NMR ($CDCl_3$) δ 2.28 (3 H, s), 2.55 (3 H, s), 8.05–7.15 (6 H, m), 8.55 (1 H, br s).

Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16. Found: C, 73.78; H, 5.78; N, 6.21.

2-Methyl-1*H*-benz[*g*]indole (16). The procedure used for the preparation of **16** was identical with that described above for the synthesis of **18**. In this manner **16** was prepared in 90% yield: mp 134–135 °C (lit.[11,13e] mp 132 °C, 132.5–136.0 °C); IR (KBr) 2.94, 6.49, 7.22, 12.49, 13.43, 14.67, 19.20, 20.10 μm; NMR ($CDCl_3$) δ 2.52 (3 H, s), 6.38 (1 H, br s), 8.15–7.20 (6 H, m), 8.6 (1 H, br s).

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 85.92; H, 6.14; N, 7.76.

1-Methylthio-3*H*-benz[*e*]indole (19) and 3*H*-Benz[*e*]indole (1). To a stirred solution of 2.86 g (20 mmol) of 4 in 75 mL of tetrahydrofuran at ca. −70 °C was added dropwise 2.20 g (20 mmol) of *tert*-butyl hypochlorite under nitrogen. After stirring for 5 min, a solution of 1.80 g (20 mmol) of methylthioacetaldehyde[7,9] in 10 mL of tetrahydrofuran was added dropwise and the reaction mixture was stirred for 4 h at ca. −70 °C. Triethylamine (5 mL) was added and the reaction mixture was stirred and allowed to warm to room temperature. When the reaction mixture reached room temperature it was filtered and the filtrate was concentrated under reduced pressure to yield a dark oil, which was dissolved in 100 mL of ether, washed with three 30-mL portions of water, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the residue was shown to contain a 2:1 mixture of 1-chloro-2-aminonaphthalene and 1-methylthio-3*H*-benz[*e*]indole (**19**) along with several minor components by HPLC analysis. Purification by chromatography on silica gel (ether–hexane eluent) gave 0.37 g of **19** as a red oil: NMR ($CDCl_3$) δ 2.44 (3 H, s), 7.92–7.20 (6 H, m), 8.58 (1 H, br s), 9.23 (1 H, d).

This material was dissolved in 50 mL of methanol and stirred with ~9 g of W-2 Raney nickel for 3 h at room temperature. The methanol solution was decanted and the Raney nickel residue was washed with two 50-mL portions of methanol. The combined methanolic solution was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 50 mL of methylene chloride and the solution was washed with three 30-mL portions of water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to yield 0.24 g (8% based on **4**) of 3*H*-benz[*e*]indole (**1**) as a yellow oil: IR (neat) 2.93, 7.37, 12.60, 13.50, and 13.90 μm; NMR ($CDCl_3$) δ 8.5–6.9 (9 H, m).

4-Bromo-1-methylnaphthalene (21). This material was prepared from 1-methylnaphthalene (**20**) according to the procedure of Topsom and Vaughan[19] in 95% yield: bp 170–171 °C (20 mm); n^{25}_D 1.6500 [lit.[19] bp 170–171 °C (20 mm)].

4-Bromo-1-methyl-2-nitronaphthalene (22). The procedure of Veselý and co-workers[20] was used to convert **21** into **22** in 77% yield: mp 119.5–120.5 °C (lit.[19,20] mp 122 °C).

1-Methyl-2-nitronaphthalene (23). This compound was prepared by reduction of **22** according to the literature procedure[19] to give 57% of **23**: mp 59–60 °C (lit.[19] mp 56 °C); IR (KBr) 6.59, 7.40, 12.30, 12.56, 13.30 μm; NMR ($CDCl_3$) δ 3.77 (3 H, s), 8.4–7.5 (6 H, m).

1-(*N,N*-Dimethylamino)-2-(2-nitro-1-naphthyl)ethene (24) and 3*H*-Benz[*e*]indole (1). A solution of 2.60 g (17.7 mmol) of dimethylformamide diethyl acetal and 3.30 g (17.6 mmol) of **23** in 10 mL of dry dimethylformamide was heated to 155 °C for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure to yield crude **24** as a dark red oil: IR (neat) 6.14, 6.60, 7.30, 9.14, 12.50, 13.25 μm; NMR ($CDCl_3$) δ 2.80 (6 H, s), 5.66 (1 H, d, J = 13.7 Hz), 6.40 (1 H, d, J = 13.7 Hz). This material was used in the following step without additional purification.

The material obtained above was dissolved in 50 mL of benzene in a Parr hydrogenation vessel and 0.25 g of 5% palladium on carbon was added. This material was hydrogenated at 40 psi hydrogen pressure until the solution turned to a clear yellow. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (ether–hexane eluent) to yield 0.70 g (24% based on 1-methyl-2-nitronaphthalene) of 3*H*-benz[e]indole (1). This material was identical in all respects with that described above.

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Registry No.—**1**, 232-84-8; **4**, 91-59-8; **5**, 63017-82-3; **8**, 134-32-7; **9**, 34774-85-1; **11**, 2246-44-8; **15**, 63017-83-4; **16**, 18505-87-8; **17**, 63017-84-5; **18**, 57582-31-7; **19**, 63017-85-6; **20**, 90-12-0; **21**, 6627-78-7; **22**, 63017-86-7; **23**, 63017-87-8; **24**, 63017-88-9; 1-methyl-2-aminonaphthalene, 771-13-1; methylthio-2-propanone, 14109-72-9; methylthioacetaldehyde, 23328-62-3; dimethylformamide diethyl acetal, 1188-33-6.

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Hydroboration of Alkenes and Alkynes by 1,3,2-Dithiaborolane

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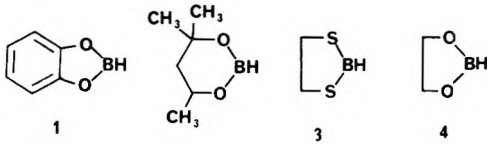
Treatment with diethyl ether–trifluoroborane or trichloroborane liberates 1,3,2-dithiaborolane (3) from its complex with trimethylamine. At 50 °C in benzene, hydroboration by 1,3,2-dithiaborolane efficiently converts a representative group of alkenes and alkynes into alkyl- and alkenyl-1,3,2-dithiaborolanes. Hydrolysis of these products yields the corresponding boronic acids.

From studies of boronic acids and their derivatives have come several important developments. Meriting special attention is the observation that certain derivatives of benzeneboronic acid accumulate in tumors of the brain.[1] Since ^{10}B has an unusually large cross section for the capture of thermal neutrons and since subsequent nuclear fission of $^{11}_{5}B$ releases locally lethal amounts of energy, neutron irradiation can be used to destroy the cells of tumors selectively.[2] The powerful, reversible inhibition of α-chymotrypsin and subtilisin by 2-phenylethaneboronic acid and benzeneboronic acid has given boronic acids a role to play in the study of specific inhibitors of enzymes.[3] Finally, boronic acids are useful intermediates in syntheses: for example, terminal alkynes can be converted into *trans*-vinyl iodides and *cis*-vinyl bromides;[4a] oxidation of boronic acids $RB(OH)_2$ with ammoniacal silver oxide gives simple coupled products R–R;[4b] a cross-coupling reaction mediated by boronate complexes derived from boronic esters and vinyllithium reagents can be used to prepare substituted olefins;[4c] and the reactions of carbonyl compounds with lithium bis(ethylenedioxyboryl)methide and then with hydrogen peroxide yield the homologous aldehydes.[4d]

An old, general method for preparing boronic acids and esters employs the reaction of appropriate organometallic compounds with esters of boric acid.[5] Redistribution reactions of trialkylboranes[6] or tetraalkylstannanes[7] with trichloroborane and redistribution reactions of trialkylboranes with esters of boric acid[8] produce derivatives of boronic acids, but frequently more efficient is the direct hydroboration of alk-

enes and alkynes by one of the following reagents: 1,3,2-benzodioxaborole (1),[9] 4,4,6-trimethyl-1,3,2-dioxaborinane (2),[10]

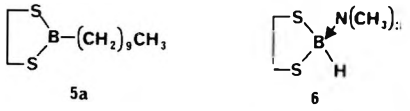


chloroborane,[11] and dichloroborane.[12] Now, 1,3,2-dithiaborolane (3) can be added to this list.

1,3,2-Dithiaborolane, first prepared by the reaction of diborane with 1,2-ethanedithiol in diethyl ether and characterized by Egan et al.,[13] is a colorless, crystalline solid which is only slightly soluble in tetrahydrofuran. The pure solid does not undergo disproportionation below 90 °C.[13] Measurement of the molecular weight in the gas phase and examination of the infrared spectra of the vapor and the solid showed that 1,3,2-dithiaborolane is monomeric in the gas phase and suggested that quaternization of boron occurs in the solid through intermolecular coordinate bonds between boron and sulfur.[13] 1,3,2-Dithiaborolane is a stronger Lewis acid than its close relative 1,3,2-dioxaborolane (4), since trimethylamine–1,3,2-dithiaborolane shows no tendency to dissociate at 25 °C, but trimethylamine–1,3,2-dioxaborolane is dissociated completely in the gas phase at 25 °C.[13]

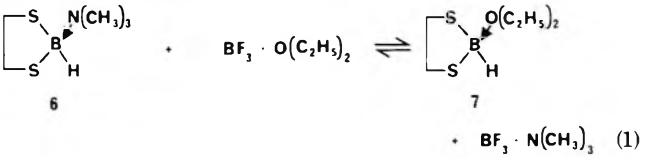
Results and Discussion

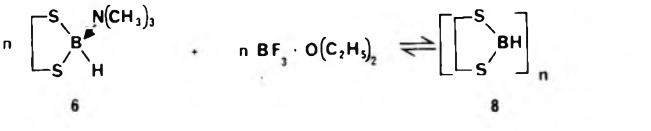
Because of the simplicity of its synthesis, its stability, and the strength of its Lewis acidity, 1,3,2-dithiaborolane promised to be a superior reagent for the preparation of boronic acids. To learn whether or not a solution of 1,3,2-dithiaborolane in fact could be prepared and used to effect the hydroboration of alkenes and alkynes, we performed the following experiment. When a solution of tetrahydrofuran–borane in tetrahydrofuran was treated at 0 °C with an equimolar amount of ethanedithiol and warmed to 25 °C, 2 molar equiv of hydrogen were liberated rapidly. Reaction of the homogeneous mixture with 1-decene at 25 °C for 15 h led, after oxidation of the products, to a 74% yield of 1-decanol. But only part of this 1-decanol could have been derived from the expected intermediate, 2-decyl-1,3,2-dithiaborolane (**5a**), since



analysis of the reaction mixture showed that a significant amount of tridecylborane was present before oxidation. Reversing the order in which borane and ethanedithiol were combined and changing the temperatures of various steps in this sequence did not reveal conditions for a more efficient synthesis of compound **5a**. Disproportionation of thioboranes produced by the initial reaction of borane with ethanedithiol may regenerate borane and account for the formation of tridecylborane, since borane should compete successfully with 1,3,2-dithiaborolane for 1-decene.[11b]

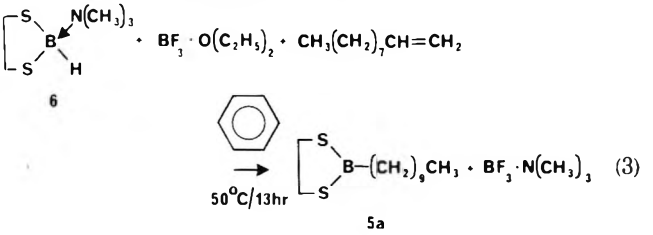
Entirely satisfactory results, however, were obtained when 1,3,2-dithiaborolane was generated in a less direct manner. Its trimethylamine complex **6**, reported by Egan et al.,[13] can be prepared conveniently as a crystalline solid by the sequential treatment of tetrahydrofuran–borane in tetrahydrofuran with ethanedithiol and trimethylamine. Since trimethylamine–1,3,2-dithiaborolane (**6**) is thermally stable below 100 °C even under high vacuum, we were not surprised to find that it failed to react with 1-decene in boiling benzene, and we attempted to prepare a more active reagent by removing trimethylamine from the complex. Treatment of a solution of trimethylamine–1,3,2-dithiaborolane (**6**) in chloroform-d_1 at 25 °C with an equimolar amount of diethyl ether–trifluoroborane yielded a mixture which initially was homogeneous. Immediate examination by ^{1}H NMR spectroscopy revealed the presence of trimethylamine–trifluoroborane (broad singlet at δ 2.67), which could be isolated and characterized, and showed that less than 5% of the original amounts of diethyl ether–trifluoroborane and trimethylamine–1,3,2-dithiaborolane (**6**) remained. The other signals, a triplet at δ 1.20, a broad singlet at δ 3.30, and a quartet at δ 3.52, could be attributed to a weak complex **7** of diethyl ether and 1,3,2-dithiaborolane (reaction 1) or to a mixture of diethyl ether and an oligomer **8** of 1,3,2-dithiaborolane (reaction 2). Formation of oligomer **8** seems more likely, however, since the





chemical shifts of the triplet and quartet are very nearly the same as those of diethyl ether itself in chloroform-d_1.

Oligomer **8** proved to be significantly more reactive than trimethylamine–1,3,2-dithiaborolane (**6**), and the addition of an equimolar amount of diethyl ether–trifluoroborane to mixtures of trimethylamine–1,3,2-dithiaborolane (**6**) and 1-decene had a dramatic and beneficial effect: after 13 h at 50 °C, 1-decene had been consumed completely, and the product was simply a mixture of 2-decyl-1,3,2-dithiaborolane (**5a**) and trimethylamine–trifluoroborane (reaction 3). When complex **6** was treated with 1-decene and diethyl ether–trifluoroborane in benzene or chloroform and kept at 25 °C for 24 h, the major product, 2-decyl-1,3,2-dithiaborolane (**5a**), was contaminated with tridecylborane. Since an appropriate control experiment demonstrated that compound **5a** is stable, the tridecylborane probably is derived from diborane generated by disproportionation of oligomer **8** or complex **7**. A similarly impure product was isolated when a solution of trimethylamine–



1,3,2-dithiaborolane (**6**) and 1-decene in chloroform at 25 °C was treated with trichloroborane; a minor advantage of this procedure was the immediate and quantitative precipitation of trimethylamine–trichloroborane.

Application of the satisfactory conditions of reaction 3 to a representative series of alkenes and alkynes gave the results summarized in Figure 1. The physical properties and chemical behavior of compounds **5a–f** were those of derivatives of 1,3,2-dithiaborolane substituted at boron, a few examples of which already had been prepared by the reaction of boranes with ethanedithiol and by the reaction of 2-halo-1,3,2-dithiaborolanes with organometallic reagents.[14] Hydrolysis of compounds **5a** and **5b** in aqueous tetrahydrofuran very rapidly and efficiently yielded boronic acids, and hydrolysis followed by oxidation with aqueous hydrogen peroxide and base converted compounds **5a** and **5c** into the corresponding alcohols. In addition, the ^{1}H NMR spectra of these dithiaborolanes in chloroform-d_1 exhibited in all cases a sharp singlet at δ 3.2

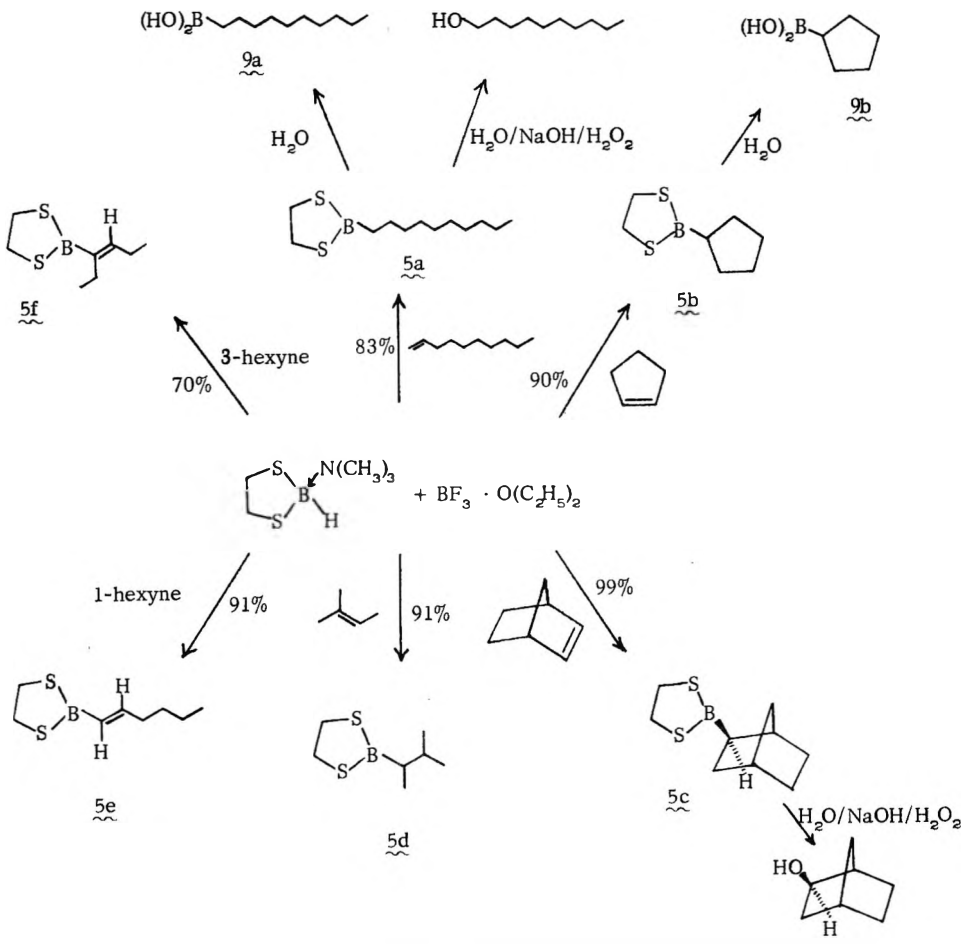


Figure 1. Products from the reaction of trimethylamine–1,3,2-dithiaborolane (6) with diethyl ether–trifluoroborane and a representative series of alkenes and alkynes in benzene at 50 °C.

attributed previously to the hydrogens of the dithiaborolane ring.[14c,d] Finally, the structures assigned to compounds **5a–d** were consistent with their mass spectra, which revealed prominent ions arising from the loss of the elements of 1,3,2-dithiaborolane by dehydroboration.

Simple derivatives of boronic acids have been prepared directly by the reactions of alkenes and alkynes with 1,3,2-benzodioxaborole (**1**),[9] 4,4,6-trimethyl-1,3,2-dioxaborinane (**2**),[10] chloroborane,[11] and dichloroborane.[12] Unfortunately, compounds **1** and **2** react sluggishly with alkenes; only at temperatures above about 100 °C do these hydroborations occur at satisfactory rates. The disadvantages of the chloroboranes, which are more reactive alternatives, are their instability and the intricacy of their preparation. We believe that the reactivity of 1,3,2-dithiaborolane, the stability of its trimethylamine complex, and the simplicity of its synthesis make trimethylamine–1,3,2-dithiaborolane a particularly effective reagent for the synthesis of boronic acids by hydroboration.

Experimental Section

General Procedures. All infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Varian A-60, T-60, HA-100, and XL-100 spectrometers were used to obtain ^1H nuclear magnetic resonance (NMR) spectra. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ). An AEI MS-9 double-focusing spectrometer was used to obtain mass spectra (MS) at 70 eV. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points (mp) were measured on a Thomas-Hoover capillary apparatus and are uncorrected. Vapor-phase chromatographic analyses were performed on columns of 2% Apiezon L (5 ft × 0.25 in.), 10% SE-30 (6 ft × 0.25 in.), and 10% Carbowax-20M (5 ft × 0.25 in.) on Chromosorb W in a Varian Aerograph Model 1420 instrument equipped with a thermal-conductivity detector. All glassware was dried at 120 °C and cooled under dry N_2 immediately before use. Benzene and hexane were dried over sodium wire, and tetrahydrofuran was distilled from the sodium ketyl of benzophenone. A solution of tetrahydrofuran–borane in tetrahydrofuran was obtained from the Ventron Corporation. All other reagents were commercial products of the highest purity obtainable.

Preparation of Trimethylamine–1,3,2-Dithiaborolane (6). Under dry N_2, a stirred solution of tetrahydrofuran–borane in tetrahydrofuran (56 mL, 1.0 M, 56 mmol) at 0 °C was treated dropwise during 30 min with freshly distilled 1,2-ethanedithiol (5.3 g, 56 mmol). The mixture, from which gas issued vigorously, was stirred at 0 °C for 2 h. Then after an excess of trimethylamine had been introduced by the slow distillation of a liquid sample (6 mL at 0 °C) into the reaction vessel, the mixture was kept at 0 °C for an additional 2 h. Removal of solvent by evaporation at 25 °C in vacuo left complex **6** as a mass of colorless crystals, and sublimation of this material at 50 °C and 0.004 Torr efficiently provided an analytically pure sample of trimethylamine–1,3,2-dithiaborolane in the form of glassy prisms (7.0 g, 43 mmol, 77%): mp 100–101 °C dec; IR (solution in CH_2Cl_2) 2405 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.65 (s, 9 H), 2.93 (s, 4 H); MS *m/e* (rel intensity) 104 (36), 103 (12), 76 (16), 61 (12), 60 (52), 59 (44), 58 (100). Anal. Calcd for $C_5H_{14}BNS_2$: C, 36.82; H, 8.65; B, 6.63; N, 8.59; S, 39.31. Found: C, 36.99; H, 8.70. Trimethylamine–1,3,2-dithiaborolane (**6**) dissolved readily in organic solvents like benzene, chloroform, and tetrahydrofuran at 25 °C, and solutions with concentrations greater than 0.80 M could be prepared.

Preparation of 2-Decyl-1,3,2-dithiaborolane (5a). Under dry N_2, a solution of trimethylamine–1,3,2-dithiaborolane (**6**; 246 mg, 1.50 mmol) and freshly distilled 1-decene (213 mg, 1.52 mmol) in benzene (5.0 mL) was stirred at 50 °C, treated dropwise during 2 min with freshly distilled diethyl ether–trifluoroborane (190 μL, 1.50 mmol), and then heated at 50 °C for 13 h. After the mixture had been cooled to 25 °C, solvent was removed by evaporation in vacuo and the residue was treated with hexane (5.0 mL). A colorless solid which failed to dissolve was separated by filtration under dry N_2; the IR spectrum and MP of this material could not be distinguished from those of a sample of trimethylamine–trifluoroborane prepared by the method of Amster and Taylor.[15] Evaporation of hexane from the filtrate at 25 °C in vacuo left a colorless liquid residue of 2-decyl-1,3,2-dithia-

borolane (**5a**; 306 mg, 1.25 mmol, 83%) in which no contaminants could be detected spectroscopically. Molecular distillation of this material at 85 °C and 0.2 Torr provided a sample which was analytically pure: IR (liquid film) 2940, 2850, 1280, 900, 840 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.9 (m, 3 H), 1.3 (m, 18 H), 3.23 (s, 4 H); MS *m/e* (rel intensity) 244 (7), 140 (7), 96 (29), 76 (20), 61 (93), 60 (100), 59 (71), 58 (36). Anal. Calcd for $C_{12}H_{25}BS_2$: C, 59.00; H, 10.32; B, 4.43; S, 26.25. Found: C, 58.76; H, 10.14.

Reactions of 2-Decyl-1,3,2-dithiaborolane (5a). a. Under dry N_2, 2-decyl-1,3,2-dithiaborolane (**5a**; 212 mg, 0.868 mmol) was treated with tetrahydrofuran (2.0 mL) and water (2.0 mL), and the mixture was stirred at 25 °C for 2 h. Removal of the volatile components by evaporation in vacuo at 25 °C left a colorless solid residue of decyldihydroxyborane (**9a**; 146 mg, 0.785 mmol, 90%). A sample of this material which had been recrystallized twice from a 1:1 mixture of nitromethane and ethyl acetate melted at 76–77 °C (lit.[16] 76–78 °C).

b. Under dry N_2, a mixture of 2-decyl-1,3,2-dithiaborolane (**5a**; 114 mg, 0.467 mmol), tetrahydrofuran (1.5 mL), and water (1.5 mL) was stirred at 25 °C for 75 min. After the volatile components of this mixture had been removed by evaporation in vacuo, the residue was treated with tetrahydrofuran (3.0 mL), aqueous NaOH (3 N, 500 μL), and aqueous H_2O_2 (30%, 500 μL) and heated at 50 °C for 30 min. After the mixture had been cooled and partitioned between diethyl ether and water, the ethereal phase was washed with water and saturated aqueous NaCl and then was dried over K_2CO_3. Evaporation of the solvent under reduced pressure left a residue of 1-decanol (58 mg, 0.37 mmol, 78%) containing no impurities which could be detected by spectroscopy or vapor-phase chromatography.

Preparation of 2-Cyclopentyl-1,3,2-dithiaborolane (5b). To a solution of trimethylamine–1,3,2-dithiaborolane (**6**; 1.59 g, 9.74 mmol) and cyclopentene (681 mg, 10.0 mmol) in benzene (15.0 mL), stirred under dry N_2 at 50 °C, freshly distilled diethyl ether–trifluoroborane (1.20 mL, 9.77 mmol) was added dropwise. After the mixture had been heated at 50 °C for 13 h and cooled to 25 °C, volatile components were removed by evaporation in vacuo and the residue was extracted with hexane (10.0 mL). Removal of hexane from the filtered extracts by evaporation in vacuo left a colorless liquid residue of 2-cyclopentyl-1,3,2-dithiaborolane (**5b**; 1.51 g, 8.77 mmol, 90%). Molecular distillation of this material at 55 °C and 0.7 Torr yielded a sample which was analytically pure: IR (liquid film) 2940, 2860, 1280, 880, 840 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.6 (m, 9 H). 3.25 (s, 4 H); MS *m/e* (rel intensity) 172 (93), 144 (47), 116 (25), 104 (93), 103 (29), 76 (25), 68 (100), 67 (28), 61 (60), 60 (57), 59 (27). Anal. Calcd for $C_7H_{13}BS_2$: C, 48.85; H, 7.61; B, 6.28; S, 37.26. Found: C, 48.76; H, 7.57.

Preparation of Cyclopentyldihydroxyborane (9b). A mixture of 2-cyclopentyl-1,3,2-dithiaborolane (**5b**; 334 mg, 1.94 mmol), tetrahydrofuran (2.0 mL), and water (2.0 mL) was stirred under N_2 at 25 °C for 2 h. Removal of the volatile components by evaporation in vacuo at 25 °C left a colorless solid residue of cyclopentyldihydroxyborane (**9b**; 212 mg, 1.86 mmol, 96%). A sample of this material which had been recrystallized twice from water and dried over anhydrous sulfuric acid was analytically pure: mp 90–92 °C; IR (KBr) 3300, 2950, 2860, 1370 cm^{-1}; ^1H NMR (60 MHz, Me_2SO-d_6) δ 1.6 (m, 9 H). Anal. Calcd for $C_5H_{11}BO_2$: C, 52.70; H, 9.73; B, 9.49; O, 28.08. Found: C, 52.89; H, 9.77.

Preparation of 2-(*exo*-2-Bicyclo[2.2.1]heptyl)-1,3,2-dithiaborolane (5c). To a solution of trimethylamine–1,3,2-dithiaborolane (**6**; 1.45 g, 8.88 mmol) and bicyclo[2.2.1]hept-2-ene (0.840 g, 8.92 mmol) in benzene (15.0 mL), stirred under dry N_2 at 50 °C, freshly distilled diethyl ether–trifluoroborane (1.10 mL, 9.11 mmol) was added dropwise. After the mixture had been heated at 50 °C for 13 h and cooled to 25 °C, volatile components were removed by evaporation in vacuo and the residue was extracted with hexane (10.0 mL). Removal of hexane from the filtered extracts by evaporation in vacuo left a colorless liquid residue of 2-(exo-2-bicyclo[2.2.1]heptyl)-1,3,2-dithiborolane (**5c**; 1.75 g, 8.83 mmol, 99%). Molecular distillation of this material at 75 °C and 0.7 Torr provided a sample which was analytically pure: IR (liquid film) 2950, 2860, 1280, 900, 840, 825 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.3, 1.5 (m, 9 H), 2.3 (m, 2 H), 3.20 (s, 4 H); MS *m/e* (rel intensity) 198 (72), 170 (77), 169 (59), 130 (44), 95 (26), 94 (100), 81 (33), 76 (28), 67 (38), 66 (31), 61 (67), 60 (100), 59 (44). Anal. Calcd for $C_9H_{15}BS_2$: C, 54.55; H, 7.63; B, 5.45; S, 32.36. Found; C, 54.62; H, 7.57.

A mixture of 2-(exo-2-bicyclo[2.2.1]heptyl)-1,3,2-dithiaborolane (**5c**; 536 mg, 2.70 mmol), tetrahydrofuran (4.0 mL), and water (4.0 mL) was stirred under N_2 for 2 h at 25 °C. After volatile components of this mixture had been removed by evaporation in vacuo, the residue was treated with tetrahydrofuran (4.0 mL), aqueous NaOH (3 N, 1.0 mL), and aqueous H_2O_2 (30%, 1.0 mL) and heated at 50 °C for 90 min. After the mixture had been cooled and partitioned between diethyl ether and water, the ethereal phase was washed with water and saturated aqueous NaCl and then was dried over K_2CO_3. Evaporation of the solvent under reduced pressure left a residue of *exo*-2-bicyclo[2.2.1]-heptanol (189 mg, 1.68 mmol, 62%) containing no impurities which could be detected by IR or NMR spectroscopy; analysis by gas chromatography revealed that less than 3% of the endo isomer was present.

Preparation of 2-(1,2-Dimethylpropyl)-1,3,2-dithiaborolane (5d). Freshly distilled diethyl ether–trifluoroborane (420 μL, 3.38 mmol) was added dropwise to a solution of trimethylamine–1,3,2-dithiaborolane (**6**; 554 mg, 3.40 mmol) and 2-methyl-2-butene (250 mg, 3.56 mmol) in benzene (5.0 mL), stirred under N_2 at 50 °C. After the mixture had been heated at 50 °C for 20 h, a crude sample of 2-(1,2-dimethylpropyl)-1,3,2-dithiaborolane (**5d**; 542 mg, 3.11 mmol, 91%) was isolated in the usual manner. Molecular distillation of this material at 35 °C and 0.45 Torr provided a sample which was analytically pure: IR (liquid film) 2950, 2860, 1280, 880, 840 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.95 (d, 6 H, J = 6 Hz), δ 1.05 (d, 3 H, J = 6 Hz), δ 1.5 (m, 2 H), δ 3.23 (s, 4 H); MS *m/e* (rel intensity) 174 (96), 173 (33), 159 (46), 146 (35), 145 (40), 132 (99), 131 (78), 104 (77), 103 (45), 76 (29), 71 (63), 70 (100), 61 (94), 60 (88), 59 (33), 55 (67). Anal. Calcd for $C_7H_{15}BS_2$: C, 48.28; H, 8.68; B, 6.21; S, 36.83. Found: C, 48.46; H, 8.73.

Preparation of 2-[(*E*)-1-Hexenyl]-1,3,2-dithiaborolane (5e). Freshly distilled diethyl ether–trifluoroborane (240 μL, 1.95 mmol) was added dropwise to a solution of trimethylamine–1,3,2-dithiaborolane (**6**; 313 mg, 1.92 mmol) and 1-hexyne (159 mg, 1.94 mmol) in benzene (5.0 mL), stirred under N_2 at 50 °C. After the mixture had been heated at 50 °C for 12 h, 2-[(*E*)-1-hexenyl]-1,3,2-dithiaborolane (**5e**; 325 mg, 1.75 mmol, 91%) was isolated in the usual manner. Molecular distillation of this material at 55 °C and 0.45 Torr yielded a sample which was analytically pure: IR (liquid film) 2950, 2860, 1280, 990, 900, 840 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.9 (m, 3 H), 1.2 (m, 4 H), 2.2 (m, 2 H), 3.27 (s, 4 H), 6.11 (d, 1 H, J = 17 Hz), 6.69 (d of t, 1 H, J = 6, 17); MS *m/e* (rel intensity) 186 (100), 185 (25), 176 (33), 158 (34), 157 (33), 144 (90), 143 (29), 130 (90), 129 (34), 116 (42), 105 (30), 61 (92), 60 (96), 59 (55). Anal. Calcd for $C_8H_{15}BS_2$: C, 51.62; H, 8.12; B, 5.81; S, 34.45. Found: C, 51.79; H, 8.19.

Preparation of 2-(1-Ethyl-(*Z*)-1-butenyl)-1,3,2-dithiaborolane (5f). Freshly distilled diethyl ether–trifluoroborane (0.960 mL, 7.81 mmol) was added dropwise to a solution of trimethylamine–1,3,2-dithiaborolane (**6**; 1.20 g, 7.36 mmol) and 3-hexyne (0.634 g, 7.72 mmol) in benzene (10.0 mL), stirred under N_2 at 50 °C. After the mixture had been heated at its boiling point for 13 h, a colorless liquid (1.24 g) was isolated in the usual manner and shown to consist of a mixture of 2-(1-ethyl-(*Z*)-1-butenyl)-1,3,2-dithiaborolane (**5f**; 83%) and tris(1-ethyl-(*Z*)-1-butenyl)borane (**10**; 17%). Various changes in the conditions of reaction did not alter the composition significantly, and neither molecular distillation at 80 °C and 0.4 Torr nor preparative vapor-phase chromatography on Apiezon L cleanly separated the components. A sample of compound **10** was prepared independently by the reaction of a solution of tetrahydrofuran–borane in tetrahydrofuran (4.0 mL, 0.25 M, 1.0 mmol) with 3-hexyne (259 mg, 3.15 mmol) at 25 °C under dry N_2 for 24 h. Removal of volatile materials by evaporation in vacuo left a colorless, liquid residue of tris(1-ethyl-(*Z*)-1-butenyl)borane (**10**; 208 mg, 0.80 mmol, 80%): IR (liquid film) 2940, 2850, 1590 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.00 (t, 18 H, J = 7 Hz), 2.2 (m, 12 H), 5.70 (t, 3 H, J = 7 Hz); MS *m/e* 260.[17] The chromatographic behavior and spectroscopic properties of this sample could not be distinguished from those of the minor component of the mixture and were similar to those of the major product **5f**: IR (liquid film) 2940, 2850, 1605, 895, 840; ^1H NMR (60 MHz, $CDCl_3$) δ 1.00 (t, 6 H, J = 7 Hz), 2.2 (m, 4 H), 3.27 (s, 4 H), 6.37 (t, 1 H, J = 7 Hz); MS *m/e* 186 (95), 158 (45), 157 (51), 144 (97), 143 (39), 129 (32), 116 (44), 84 (31), 81 (36), 76 (31), 69 (47), 67 (40), 61 (100), 60 (100), 59 (84), 58 (38), 55 (94). The *Z* configuration has been assigned to compound **5f** since addition of 1,3,2-dithiaborolane to 1-hexyne is stereospecifically cis.

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Registry No.—**3**, 6675-41-4; **5a**, 63076-46-0; **5b**, 63076-47-1; **5c**, 63076-48-2; **5d**, 63076-49-3; **5e**, 63076-50-6; **5f**, 63104-21-2; **6**, 13291-21-9; **9b**, 63076-51,7; **10**, 63076-52-8; trimethylamine, 75-50-3; 1-decene, 872-05-9; cyclopentene, 142-29-0; bicyclo[2.2.1]hept-2-ene, 498-66-8; 2-methyl-2-butene, 513-35-9; 3-hexyne, 928-49-4; 1-hexyne, 693-02-7.

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Coupling Reactions of Diorganophosphides with Organic Halides. Evidence for a One-Electron Path

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The reactions of diorganophosphides with organic halides have been examined by ^{31}P CIDNP and product analysis. These reactions are shown to proceed in part by a radical mechanism and in part by a competing nonradical path. The preference for one mechanism or the other is highly dependent on the nature of the organic group, halide, and substituents bound to phosphorus. Thus, alkyl, allyl, and benzyl iodides and bromides react, to some degree, by a radical mechanism; alkyl chlorides follow an apparent S_N2 path. There is no evidence for radical participation in the reactions of dialkylphosphides with aryl halides or of diarylphosphides with alkyl halides. For those examples proceeding by a radical mechanism, the CIDNP data are consistent with an electron-transfer step, followed by coupling of the dialkylphosphinyl and organic radicals.

Diorganophosphide anions are useful precursors for the synthesis of *tertiary*[1] and polydentate phosphines.[1a,b,d,2] Their utility arises, in part, from their ready availability and because coupling reactions with organic halides generally proceed in high yields and tolerate substantial variation of phosphide or substrate.[1,2] To the inorganic chemist the primary asset of procedures employing these reagents is the ability to design ligands with specific electronic and steric properties or containing a functionality as a probe for ligand–metal interactions. Organophosphide ions are generally regarded as potent nucleophiles[1-4] and coupling reactions have long been assumed to proceed by an S_N2 mechanism with metal–halogen exchange as a competing or, in some cases, dominant factor.[1a,b,d,5]

In the course of preparing cyclopropylmethyldimethylphosphine from bromomethylcyclopropane and potassium dimethylphosphide, we noted the anticipated product was formed together with a comparable amount of 3-butenyldimethylphosphine. Inasmuch as this result suggested a predominant radical path, we were prompted to undertake a mechanistic study to determine whether one-electron steps were involved in these couplings and, if so, whether conditions could be found to enhance the S_N2 component. We report herein CIDNP and product distribution evidence that alkyl, allylic, and benzylic halides do, in fact, react with diorganophosphides via a mechanism involving substantial radical participation, the degree of which is highly sensitive to the nature of the phosphide, substrate, and halide employed.

Experimental Section

All manipulations and reactions were performed in an atmosphere of nitrogen. Solvents were distilled from sodium benzophenone ketyl before use. Benzene-d_6 and 1,2-dimethoxyethane-d_{10} were dried over calcium hydride and distilled in vacuo prior to use in NMR experiments.

1-Bromo-5-hexene was obtained from Tridom-Fluka and 1-chloro-5-hexene from ICN. Bromomethylcyclopropane was prepared by the literature method.[6] All other halides were readily obtainable from a number of common sources. Potassium diphenylphosphide,[7] lithium dimethylphosphide,[8] and sodium dimethylphosphide[8] were prepared by the literature procedures. ^{31}P and ^{1}H NMR experiments were performed on a Varian XL-100 spectrometer. Analysis of organophosphide/organic halide reactions was performed utilizing a Data General Nova 2 computer hardwired to an AEI MS 1073 dual-beam mass spectrometer/gas chromatograph. Mass spectra of isolated phosphines were obtained on an AEI MS-9 spectrometer. Product distribution analyses for the bromomethylcyclopropane and 1-halo-5-hexene reactions were performed on an F & M 720 gas chromatograph with a 1/4 in. × 8 ft, 3.8% SE-52 column. Response factors were determined for each of the products using *n*-decane or *n*-undecane as internal standards. Analyses were performed by adding a stoichiometric amount of organic halide to a 2-mL volumetric flask capped with a septum and containing a known amount of organophosphide in THF. GLC measurements were initiated immediately after adding the internal standard and diluting to the mark. Representative preparative scale reactions are given below.

Potassium Dimethylphosphide. Following a modification of the preparation of sodium dimethylphosphide,[8] 5.7 g of tetramethylbiphosphine[2i] (47 mmol) and 6.6 g of potassium (0.17 g-atom) in 150 mL of THF were stirred for 10 h under reflux to produce a deep red solution. After cooling and filtration through Celite, the volume was

reduced in vacuo to 50 mL and 70 mL of dioxane was added, precipitating the product. Two washings with ethyl ether afforded a light yellow, pyrophoric solid (4.4 g, 36%). Variable amounts of dioxane were retained, although after prolonged drying under high vacuum, the ^{1}H NMR spectrum showed no appreciable dioxane of solvation. An analytical sample was recrystallized from hot dioxane: ^{1}H NMR (THF-d_8) δ 1.22 (d, J_{PH} = 3 Hz); ^{31}P-{^{1}H} NMR (DME/benzene) 117.5 ppm (s).

Anal. Calcd for C_2H_6KP: C, 23.99; H, 6.04. Found: C, 23.42; H, 6.40.

Potassium Diisopropylphosphide. Diisopropylphosphine[9] (12.15 g, 0.103 mol) and potassium hydride (4.0 g, 0.10 mol) were heated in 125 mL of refluxing THF for 20 h. Filtration through Celite and evaporation of the THF gave an amorphous solid, which was washed with hexane and treated with 5 mL of dioxane. Drying in vacuo gave a yellow solid (4.0 g, 25%). An analytical sample was prepared by recrystallization from a small amount of dioxane: ^{1}H NMR (THF-d_8) δ 1.1 (m, 12 H), 2.33 (m, 2 H); ^{31}P-{^{1}H} NMR (DME/benzene) −23.2 ppm (s).

Anal. Calcd for $C_6H_{14}KP$: C, 46.12; H, 9.03. Found: C, 44.65; H, 8.59.

Cyclopropylmethyldimethylphosphine. A solution of potassium dimethylphosphide was prepared by refluxing 15.9 g of tetramethylbiphosphine[2i] (0.130 mol) with 11.9 g of freshly cut potassium in 120 mL of THF for 16 h. The orange solution was decanted from excess potassium and cooled to −78 °C. Dropwise addition of 29.1 g of bromomethylcyclopropane in 100 mL of THF over a 3-h period gave a thick, white slurry. After warming to 25 °C, the reaction mixture was hydrolyzed by cautious addition of 40 mL of water and treated with 30 mL of ether. After separation of the organic phase, the aqueous solution was extracted with an additional 20 mL of ether. The pooled extracts were washed with 20 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and fractionally distilled. The fraction boiling at 105–132 °C was collected (17.0 g, 68%) and shown to be a mixture of cyclopropylmethyldimethylphosphine and 3-butenyldimethylphosphine (54/46) by GLC analysis. Separation was effected by spinning band distillation. Cyclopropylmethyldimethylphosphine: bp 119–120 °C; mass spectrum *m/e* 116.0748 (calcd for $C_6H_{13}P$, 116.0755); ^{1}H NMR (DME-d_{10}) δ 0.37 (m, 4 H), 0.89 (d, 6 H, J_{PCH} = 2.8 Hz), 1.20 (m, 2 H), the unique ring proton is obscured by the P-methyl groups; ^{31}P-{^{1}H} NMR (DME/benzene) 53.4 ppm (s). 3-Butenyldimethylphosphine: bp 114–116 °C; mass spectrum *m/e* 116.0741 (calcd for $C_6H_{13}P$, 116.0755); ^{1}H NMR (DME-d_{10}) δ 0.90 (d, 6 H, J_{PCH} = 2.4 Hz), 1.30 (m, 2 H), 2.05 (m, 2 H), 4.89 (m, 2 H), and 5.73 (m, 1 H); ^{31}P-{^{1}H} NMR (DME/benzene) 53.4 ppm (s).

5-Hexenyldimethylphosphine. To a solution of sodium dimethylphosphide (84.0 mmol) in 60 mL of $NH_{3(l)}$[2i] was added 9.84 g of 1-chloro-5-hexene (83.0 mmol) dropwise over a 20-min period. The ammonia was allowed to evaporate overnight and the product distilled directly from the residue (95%): bp 170–172 °C; mass spectrum *m/e* 144.1067 (calcd for $C_8H_{17}P$, 144.1068); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 2 H, J_{PCH} = 2.0 Hz), 1.4 (m, 6 H), 1.9 (m, 2 H), 4.9 (m, 2 H), and 5.6 (m, 1 H); ^{31}P-{^{1}H} NMR (DME/benzene) 54.2 ppm (s).

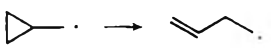
Other phosphines were prepared analogously to cyclopropylmethyl- or 5-hexenlydimethylphosphine: butyldimethylphosphine[1d] [^{31}P-{H} NMR (DME/benzene) 52.3 ppm (s)]; cyclohexyldimethylphosphine;[10] ethyldimethylphosphine;[1d] allyldimethylphosphine[11] (from allyl *chloride*) [^{31}P-{^{1}H} (DME/benzene) 54.2 ppm (s)]; cyclopentylmethyldimethylphosphine [mass spectrum *m/e* 144.1068 (calcd for $C_8H_{17}P$ 144.1068); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6 H J_{PCH} = 2.5 Hz), 1.13 (m, 2 H), 1.47 (br m, 9 H); ^{31}P-{^{1}H} NMR (DME/benzene) 54.2 ppm (s)]; *tert*-butyldimethylphosphine;[12] diphenylbutylphosphine;[1d] diisopropylbutylphosphine [mass spectrum *m/e* 174.1542 (calcd for $C_{10}H_{23}P$, 174.1537); ^{31}P-{^{1}H} NMR (DME/benzene) −2.5 ppm (s)]; benzyldimethylphosphine[13] (from benzyl *chloride*) [^{31}P-{^{1}H} NMR (DME/benzene) 46.9 ppm (s)]; cyclopropylmethyldiphenylphosphine [mass spectrum *m/e* 240.1059 (calcd for $C_{16}H_{17}P$, 240.1069); ^{31}P-{^{1}H} NMR (DME/benzene) 16.9 ppm (s)].

CIDNP Spectra. ^{1}H CIDNP spectra were obtained for the reaction of bromomethylcyclopropane with potassium dimethyl phosphide[14] in dimethoxyethane-d_{10} by mixing the halide with the phosphide solution in a 5-mm tube directly in the probe of the spectrometer. As soon as the halide was deposited and spinning resumed, a kinetics program was initiated which collected individual transients at the rate of ten per minute.

Mixing problems encountered in ^{31}P NMR experiments due to density differences were overcome by fitting each tube with a capillary pipet cut to a length such that the capillary end extended one-third of the way below the surface of the solution. This was held in place by a tight-fitting septum which also served to seal the ^{31}P NMR tube from the atmosphere. It was possible to deposit an appropriate amount of organic halide in the pipet portion of this apparatus and avoid mixing with the phosphide solution while the field was locked and an initial spectrum acquired. A small volume of nitrogen injected into the pipet with the assembly still in the probe effected mixing and the spectra were collected in the normal manner.

Results and Discussion

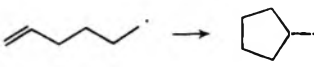
Inasmuch as the cyclopropylcarbinyl radical is known to undergo rapid ring opening[15,16] (eq 1), the formation of substantial amounts of 3-butenyldimethylphosphine from the reaction of bromomethylcyclopropane and potassium dimethylphosphide (Table I, reaction 1) suggested radical



(1)

participation in these coupling reactions. Subsequently, we observed CIDNP[17] when the reaction was monitored by ^{1}H NMR, confirming radical involvement. The spectra were, however, too complex and unresolved to be of any mechanistic use.

Because of the complexity of the spectra and the short duration of polarization,[18] detection and interpretation of CIDNP in the ^{1}H NMR spectra of the coupling reactions of diorganophosphides with organic halides was, in general, difficult. Since ^{31}P longitudinal relaxation times are typically longer than those of protons,[19,20] we utilized ^{31}P NMR as a more leisurely probe for CIDNP. Additionally, a technique was employed which allowed accumulation of data during mixing of the reagents. Moreover, the simplicity of the spectra facilitate interpretation of the CIDNP phenomenon (vide infra). For these reasons, we employed ^{31}P NMR as a rapid technique for assessing radical participation with a wide variety of substrates.[22] While it is clear that CIDNP implies radical combination as a product-forming step,[17] we will assume that, for these systems, a lack of CIDNP implies a nonradical path. This assumption is supported by product studies. For instance, in those cases amenable to use of 1-halo-5-hexene as a substrate ^{31}P CIDNP, when observed, was accompanied by cyclization; lack of CIDNP correlated with negligible cyclization. Since the 1-hexenyl radical is known to cyclize[23] (eq 2), this behavior is consistent with the assumption.

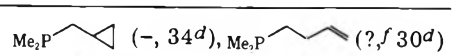
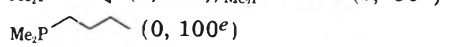
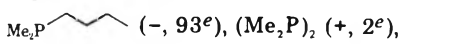
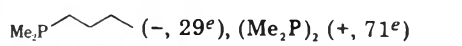
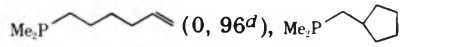
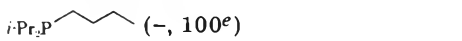
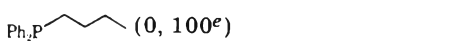
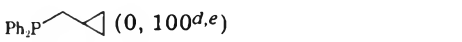
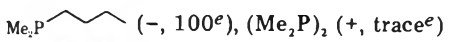
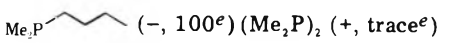
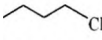
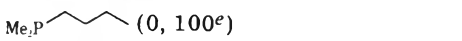
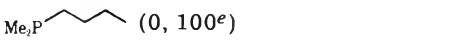
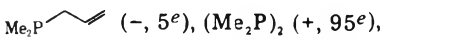
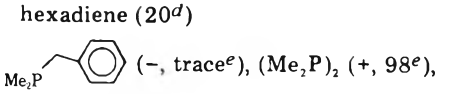
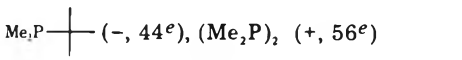
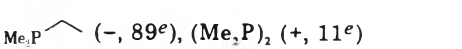
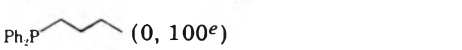


(2)

Further, the observation of CIDNP was generally accompanied by formation of side products (predominant, in some cases) attributable to radical couplings. These products were generally absent in reactions which exhibited no CIDNP.

In order to assess the effect of the halide on the course of the reaction of a constant alkali metal dialkylphosphide with alkyl halides, we investigated a series of reactions of potassium dimethylphosphide with *n*-butyl chloride, bromide, and iodide. Inspection of Table I (reactions 2, 3, and 4) shows that in all cases, the predominant product was *n*-butyldimethylphosphine. However, CIDNP was observed only for reactions 3 and 4; see Figure 1. Further, small amounts of tetramethylbiphosphine (with enhanced emission) and octane were formed with the bromide and iodide, but not for *n*-butyl chloride. The reaction of potassium dimethylphosphide with 1-chloro-5-hexene and the bromo analogue gave the cyclization product (i.e., cyclopentylmethyldimethylphosphine) only with the organic bromide (Table I, reactions 5 and 6). This result establishes that the course of these coupling reactions is highly dependent on the nature of the halide in the organic substrate; *i.e., significant radical participation occurs only for organic bromides and iodides.* Alkyl chlorides presumably react by an S_N2 mechanism. We note that this observation is of synthetic significance. For this method, alkyl chlorides are

Table I. Reactions of Diorganophosphides with Organic Halides

Reaction	Organic halide	Registry no.	Alkali metal phosphide	Registry no.	Products (0,[a] −,[b] −,[c] %[d,e])
1		7051-34-5	$KPMe_2$	4336-59-8	 (−, 34[d]), (?,[f] 30[d])
2		109-69-3	$KPMe_2$		 (0, 100[e])
3		109-65-9	$KPMe_2$		 (−, 93[e]), $(Me_2P)_2$ (+, 2[e]), octane (trace[d])
4		542-69-8	$KPMe_2$		 (−, 29[e]), $(Me_2P)_2$ (+, 71[e])
5		928-89-2	$KPMe_2$		 (0, 96[d]), (0, trace[d])
6		2695-47-8	$KPMe_2$		 (−, 65[d]), (?,[f] 14[d]), $(Me_2P)_2$ (+, trace[e])
7			$KP\text{-}i\text{-}Pr_2$	63088-98-2	 (−, 100[e])
8			$KPPh_2$	15475-27-1	 (0, 100[e])
9			$KPPh_2$		 (0, 100[d,e])
10			$LiPMe_2$	21743-25-9	 (−, 100[e]), $(Me_2P)_2$ (+, trace[e])
11			$NaPMe_2$	27393-70-0	 (−, 100[e]) $(Me_2P)_2$ (+, trace[e])
12			$LiPMe_2$		 (0, 100[e])
13			$NaPMe_2$		 (0, 100[e])
14		106-95-6	$KPMe_2$		 (−, 5[e]), $(Me_2P)_2$ (+, 95[e]), hexadiene (20[d])
15		100-39-0	$KPMe_2$		 (−, trace[e]), $(Me_2P)_2$ (+, 98[e]), bibenzyl (31[d])
16		507-19-7	$KPMe_2$		 (−, 44[e]), $(Me_2P)_2$ (+, 56[e])
17	PhBr	108-86-1	$KPMe_2$		Me_2PPh (0, 70[e]), $(Me_2P)_2$ (0, 30[e])
18		74-96-4	$KPMe_2$		 (−, 89[e]), $(Me_2P)_2$ (+, 11[e])
19			$KPPh_2$		 (0, 100[e])

[a] 0 = no CIDNP observed. [b] + = enhanced absorption. [c] − = enhanced emission. [d] Yields determined by GLC and based on MPR_2. [e] Yields determined by ^{31}P NMR and based on MPR_2. [f] Obscured by other products, see text.

the preferred substrate for the preparation of tertiary phosphines incorporating groups prone to radical rearrangements.

While rates for S_N2 and radical mechanisms generally have the same halide dependence,[24] it appears that, in these instances, the rate for S_N2 processes is less affected than that for the radical process by progressing to the lighter congeners.

The effects of varying the organic substituent of the diorganophosphide are illustrated by the reactions of *n*-butyl bromide with potassium dimethyl-, diisopropyl-, and diphenylphosphides (Table I, reactions 3, 7, and 8). CIDNP is observed with the potassium dialkylphosphides, but not with potassium diphenylphosphide. Moreover, ring opening does not occur when bromomethylcyclopropane is used as the substrate (reaction 9), in contrast to reaction 1. Hence, the degree of radical participation is affected by the electronegativity of the organic substituent bound to the phosphide. Inasmuch as the oxidation potential of the diorganophosphide is anticipated to be strongly dependent on group electronegativities, this is consistent with an electron-transfer mechanism operating for dialkylphosphides and absent with diarylphosphides, in keeping with the CIDNP observations.

CIDNP was observed in the reactions of *n*-butyl bromide with lithium, sodium, and potassium dimethylphosphides (Table I, reactions 10, 11, and 3). Additionally, CIDNP is not observed in the reactions of *n*-butyl chloride with the same series (reactions 12, 13, and 2). Thus, no measurable effect is attributed to the metal; i.e., any changes in degree of aggregation or ion pairing due to variation of alkali metal do not strongly affect choice of mechanism.[25]

The results above clearly establish a one-electron component in the reactions of alkyl bromides and iodides with dialkylphosphides, apparently in competition with an S_N2 path (predominant for alkyl chlorides). The one-electron path is characterized by observation of CIDNP in the ^{31}P NMR resonance of the coupling product and by the presence of side products indicative of radical recombinations (e.g., tetramethylbiphosphine, which itself exhibits CIDNP). For allyl and benzyl bromides, these side products are dominant (Table I, reactions 14 and 15). In both cases, only traces of the tertiary phosphines are received; the major products are tetrameth-

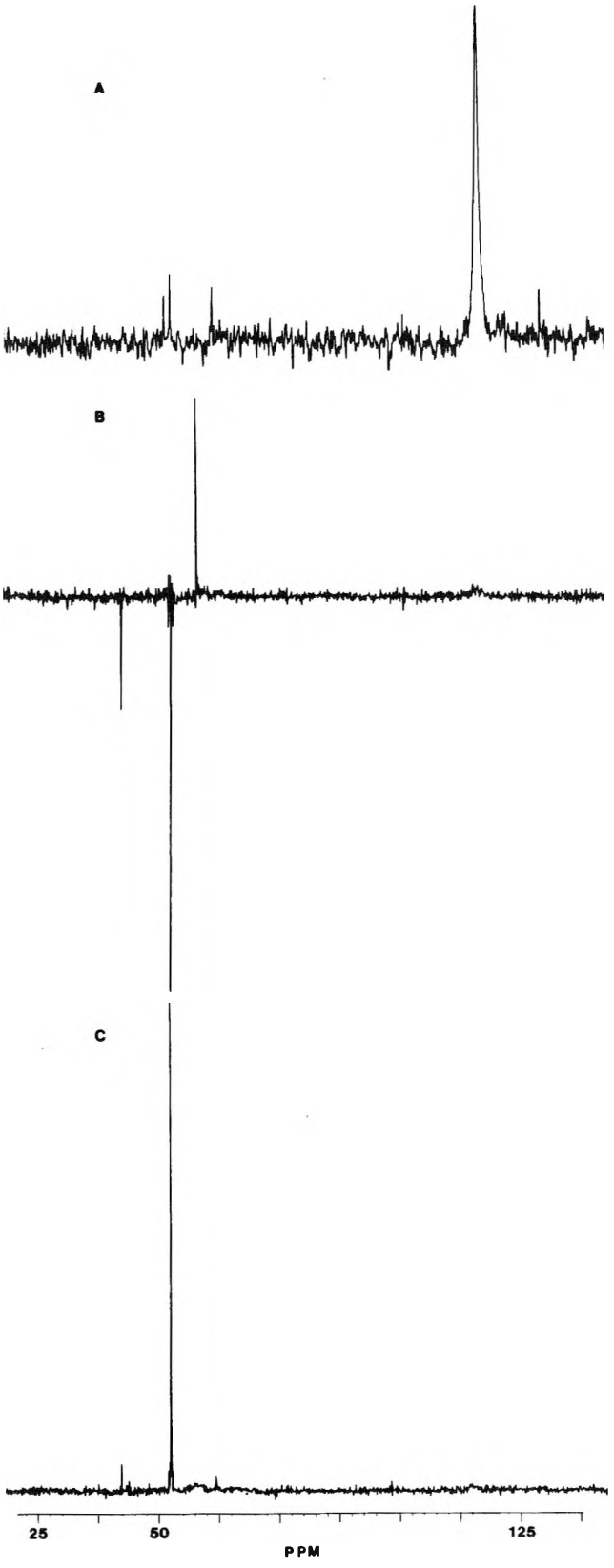
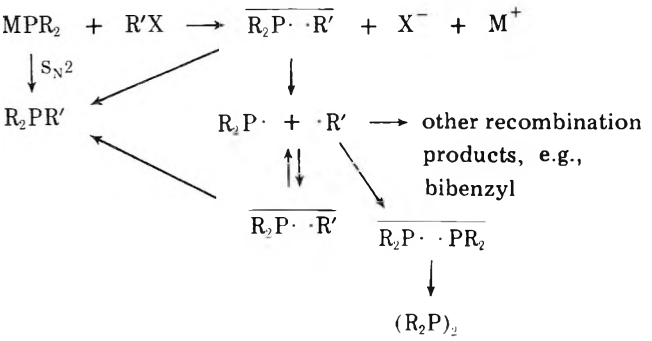


Figure 1. The 40.5-MHz $^{31}P-\{^1H\}$ FT NMR spectrum of: $K[PMe_2]$ in benzene-d_6/1,2-dimethoxyethane: (a) before reaction; (b) after addition of *n*-butyl bromide (one transient 15 s after addition); (c) after relaxation. The resonance at 52.3 ppm is *n*-butyldimethylphosphine; the signal at 59.6 ppm is tetramethylbiphosphine.

ylbiphosphine and hexadiene or bibenzyl. *tert*-Butyl bromide gives a poor yield of *tert*-butyldimethylphosphine (reaction 16). The favored product is, again, tetramethylbiphosphine. Thus, the yield of the tertiary phosphine depends directly on the established order of radical stability.[24]

Phenyldimethylphosphine is formed from aryl halides in good yields without CIDNP. Tetramethylbiphosphine is a detectable side product, but also fails to exhibit CIDNP when formed (Table I, reaction 17).

These results constitute strong evidence that a product-forming step involving radical pair combination, presumably preceded by electron transfer, is in competition with an S_N2 process. Further, the choice of mechanism depends in a systematic way on the nature of the halide and the properties of the organic groups. The scheme below, in which the coupling

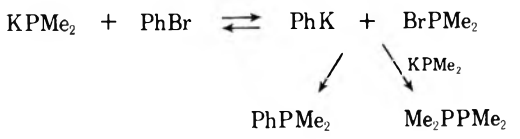


product arises from either a radical pair with initial singlet spin correlation or via a nonradical path, is consistent with the data. The *g* values for dialkylphosphinyl radicals do not appear to have been reported. However, that for $(C_6H_5)_2P\cdot$ is 2.009.[26] Since hydrocarbon radicals have *g* values close to that of the free electron in the absence of strongly electron-withdrawing groups,[27] $\Delta g > 0$. Further, the hyperfine interaction, $A_{^{31}P}$, is anticipated to be greater than zero.[22] Therefore, the ^{31}P resonance of products derived by recombination of the initial singlet correlated geminate pair should exhibit enhanced emission,[17] as observed. The net emission should be reduced, to some degree, by the recombination of secondary pairs with uncorrelated spins and opposite polarization. Tetramethylbiphosphine must result from collapse of a symmetric radical pair with $\Delta g = 0$; any polarization observed must arise in the primary pair with recombination of the escaped, free dimethylphosphinyl radicals occurring before nuclear relaxation is complete.[28] Hence, any polarization observed in the biphosphine must occur with sign opposite that of the primary product, i.e., enhanced absorption, as is found. The apparent exception to this scheme is cyclopentylmethyldimethylphosphine. Since the rate of ring closure of the hexenyl radical (ca. 10^5 s^{-1})[23] is substantially slower than that of geminate recombination (ca. 10^{10} s^{-1}),[17,29] the ring-closed species must be an excape product derived from a radical pair with initially uncorrelated spins and should appear with polarization opposite that of 5-hexenyldimethylphosphine, i.e., enhanced absorption. However, cyclopentylmethyldimethylphosphine and 5-hexenyldimethylphosphine are not resolved in their 40.5-MHz ^{31}P NMR spectra. Even under high-resolution conditions, mixtures appear as a single resonance.[31] Presumably, the *A* polarization of the ring-closed product is outweighed by the *E* polarization of ring-opened product. ^{13}C NMR spectra, in which the products are distinct, would be capable of resolving this point. However, CIDNP proved too weak to observe within the required solubility limits. ^1H NMR were complex and overlapping and of little value.[32]

The dialkylphosphinyl radical, $R_2P\cdot$, invoked in this scheme, has been implicated in the photoinitiated addition of secondary phosphines and biphosphines to alkenes[34] and in the photolytic oxidation of tetraphenylbiphosphine with ethanol.[35]

Metal–halogen exchange of the type established for alkyl lithium–benzyl halide reactions[36] has been proposed as being

responsible for the formation of coupling products in the reaction of dialkylphosphides with chlorophenylacetylene,[37] 1-bromo-2-diethylaminoethane,[38] 1,2-dibromoethane,[16] and aryl halides.[16] The principal evidence is the formation of tetraalkylbiphosphines and organic coupling products.[16] Our results clearly establish that observation of these products is insufficient evidence to propose metal–halogen exchange. In most cases (vide supra) these products are radical derived. However, that the steady formation of tetramethylbiphosphine and phenyldimethylphosphine occurs without CIDNP in the reaction of potassium dimethylphosphide with phenyl bromide (reaction 16) suggests that exchange *may* occur in



this and other instances. In this regard, we examined the reaction of PhLi with $ClPMe_2$ via ^{31}P NMR. Phenyldimethylphosphine is formed without CIDNP as would be required. The intimate mechanism of addition of alkyl- and arylphosphides to aryl[4,16] and vinylic substrates[2e,39] is not clarified by our results, although they do allow the possibility of metal–halogen exchange.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (CHE-75-19177) for support of this research.

Registry No.—Tetramethylbiphosphine, 3676-91-3; potassium, 7440-09-7; diisopropylphosphine, 20491-53-6; potassium hydride, 7693-26-7; cyclopropylmethyldimethylphosphine, 63059-20-1; 3-butenyldimethylphosphine, 55831-90-8; 5-hexenyldimethylphosphine, 63059-21-2; butyldimethylphosphine, 55842-34-3; allyldimethylphosphine, 26681-86-7; allyl chloride, 107-05-1; cyclopentylmethyldimethylphosphine, 63058-99-1; diisopropylbutylphosphine, 63059-00-7; benzyldimethylphosphine, 13954-37-5; benzyl chloride, 100-44-7; cyclopropylmethyldiphenylphosphine, 63059-01-8.

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$$R'\cdot + PR_2^- \rightarrow R'PR_2^-\cdot$$

$$R'PR_2^-\cdot + R'X \rightarrow R'PR_2 + R'X^-\cdot$$

$$R'X^-\cdot \rightarrow R'\cdot + X^-$$

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Organoboranes. 22. Light-Induced Reaction of Bromine with Alkylboronate Esters. A Convenient Synthesis of α-Bromoalkylboronate Esters

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In the presence of light, bromine reacts rapidly with trimethylene esters of alkylboronic acids possessing a tertiary or benzylic hydrogen α to boron to give high yields of the corresponding α-bromoalkylboronate esters. This procedure permits a facile entry into the highly versatile but relatively inaccessible class of α-substituted organoboron derivatives.

Some of the most promising synthetic routes based on organoboranes are postulated to proceed through α-haloorganoboranes.[2] A notable example is the alkoxide-induced alkylation and arylation of α-halo esters, ketones, and nitriles with organoboranes (eq 1).

$$BrCH_2CO_2Et \xrightarrow{KOC(CH_3)_3} \bar{B}rCHCO_2Et \xrightarrow{R_3B} R_3\bar{B}CHBrCO_2Et$$

$$\longrightarrow R_2BCHRCO_2Et \xrightarrow{HOC(CH_3)_3} RCH_2CO_2Et + R_2BOC(CH_3)_3 \quad (1)$$

However, characterization and chemical exploration of this important class of compounds has been sparse, due in part to their high reactivity and lack of convenient routes for their synthesis.[3] To our knowledge, only three α-haloalkyldialkylboranes have been isolated and characterized.[4-6] These compounds exhibit extraordinary reactivity, undergoing very fast rearrangement with mild heat, various electrophiles, and nucleophiles as weak as tetrahydrofuran or water (eq 2).[4-7]

$$\underset{\text{Br}}{\overset{|}{CH_3CHB(CH_2CH_3)_2}} \xrightarrow[<1\text{ min}]{H_2O,\ 0°C} \underset{\text{OH}}{\overset{CH_3CH_2}{\overset{|}{CH_3CHBCH_2CH_3}}} + HBr \quad (2)$$

On the other hand, α-haloalkylboronate esters are much less reactive.[3,8,9] These compounds may be distilled at moderate temperatures (~120 °C) without rearrangement. They may be formed in tetrahydrofuran. It has even proved possible to hydrolyze the ester linkages while leaving the α-halogen intact. Nevertheless, the α-haloalkylboronate esters exhibit fascinating potentiality for mechanistic studies and useful synthetic transformations.[3,10,11] Unfortunately, the available synthetic routes for their preparation are relatively few and limited in scope.[3,9]

Through the pioneering efforts of Matteson, α-haloalkylboronate esters may be formed by additions of polyhalomethanes (eq 3) or hydrogen halides (eq 4) across the double bond of alkenylboronate esters.[3,9]

$$CH_2{=}CHB(OC_4H_9)_2 + Cl_3CBr \xrightarrow[\text{initiator}]{\text{radical}} Cl_3CCH_2CH(Br)B(OC_4H_9)_2 \quad (3)$$

$$CH_2{=}C(CH_3)B(OC_4H_9)_2 + HBr\ (\text{liquid}) \xrightarrow{-60\,°C} (CH_3)_2C(Br)B(OC_4H_9)_2 \quad (4)$$

However, the starting alkenylboronate esters are somewhat troublesome to make and the direction of the addition of hydrogen halide across the double bond is highly sensitive to structural features of the alkenylboronate esters and reaction conditions. Radical additions of polyhalomethanes result in the presence of an extraneous feature normally not desired—a fully halogenated γ carbon.

The base-induced reaction of hindered borinic esters with α,α-dichloromethyl methyl ether constitutes a valuable procedure for the synthesis of α-chloroalkylboronate esters (eq 5).[8]

$$R_2BOR' + CHCl_2OCH_3 + LiOCEt_3 \xrightarrow{THF}$$

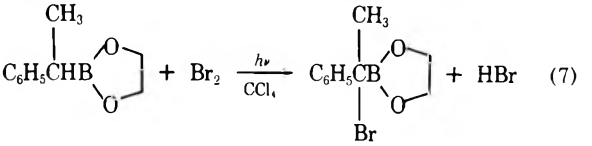
$$R_2C(Cl)B(OCH_3)OR' + LiCl + HOCEt_3 \quad (5)$$

Unfortunately, this synthetic method precludes the formation of simpler α-haloalkylboronate esters, such as α-halobenzyl-, -cyclopentyl-, or -norbornylboronate esters, $RCHClB(OR')_2$. Esters of dichloromethylboronic acid are available in 52–60% yield by the reaction of dichloromethyllithium with trimethyl borate (eq 6).[12]

$$Cl_2CHLi + B(OCH_3)_3 \xrightarrow[-110\,°C]{THF} Cl_2CHB(OCH_3)_2 \xrightarrow[ROH]{HCl} Cl_2CHB(OR)_2 \quad (6)$$

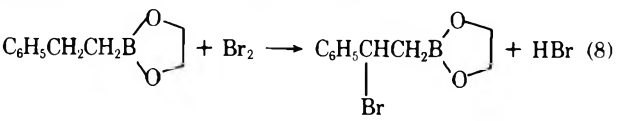
Treatment of these with organometallics provides a route to such α-chloroalkylboronic esters.[12]

Based on our needs for certain α-bromoalkylboronate esters not available by the previously discussed methods, we decided to explore the possibility of forming these compounds by the direct halogenation of alkylboronate esters. Preliminary studies along these lines indicate mixed results. Chlorination of di-*tert*-butyl methylboronate gives impractically small amounts of $ClCH_2B(OR)_2$.[3,9] Pasto reports that bromination of ethylene 1-phenylethyl- or 1-methylpentylboronate provides high yields of the α-bromoalkylboronates (eq 7).[13,14]



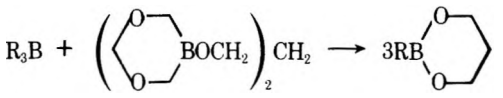
(7)

However, he reports that hexylboronate esters are inert to bromine, while ethylene 2-phenylethylboronate gives β-bromination predominantly (eq 8).[13,14]



(8)

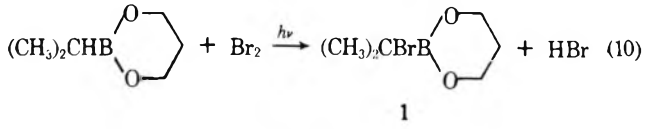
We decided to explore the generality of this bromination procedure in hopes of developing a practical procedure which would permit applying the α-bromoalkylboronate esters as convenient synthetic intermediates. Since the 2-alkyl-1,3,2-dioxaborinanes (trimethylene alkylboronate esters) are stable to disproportionation and readily available from the



clean, quantitative, and general redistribution of trialkylboranes with trimethylene borate (eq 9),[15] we decided to explore the reaction of bromine with these compounds.

Results and Discussion

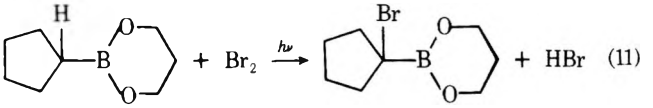
In the presence of light, bromine reacts readily and cleanly with alicyclic derivatives such as trimethylene, 1-methylpropyl or 1-methylethyl boronate to give trimethylene α-bromoalkylboronate esters. Although the reaction in methylene chloride or pentane proceeds at a moderate rate under normal laboratory lighting, a 275-W sunlamp greatly accelerates the reaction. Complete decolorization of the bromine takes place in 1–10 min and simple distillation gives the trimethylene



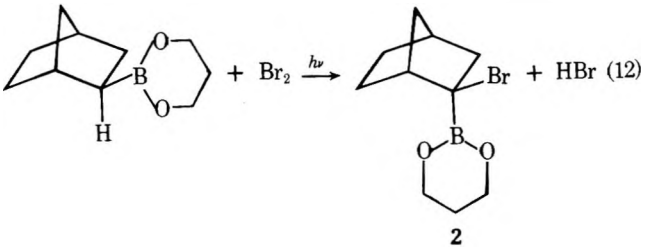
1

α-bromoalkylboronate esters in high yield and purity (eq 10).

The reaction is also applicable to trimethylene cyclohexyl- and cyclopentylboronate esters. This permits the first synthesis of cyclic α-bromoalkylboronate esters (eq 11).



Previous attempts to prepare isolable α-halonorbornylorganoboranes via hydroboration of 2-halonorbornenes have failed.[16,17] Yet trimethylene 2-bromonorbornylboronate is readily obtained by the current procedure (eq 12). Although

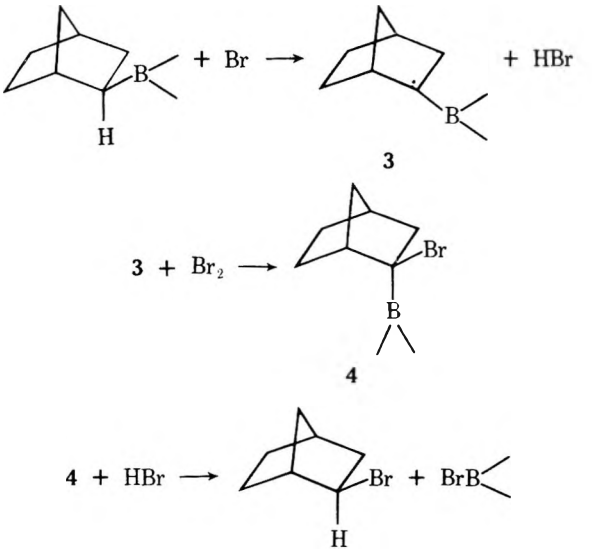


2

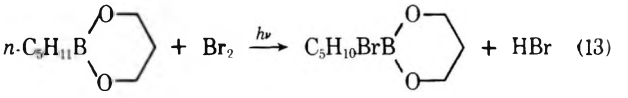
we have not yet established the stereochemistry of the α-bromonorbornylboronate ester (2), the bromine is presumably in the exo configuration. This would be consistent with the previously reported results that the free radical bromination of tri-*exo*-norbornylborane and *B*-*exo*-norbornyl-9-borabicyclo[3.3.1]nonane followed by hydrogen bromide cleavage of the boron–carbon bond produces >99% *exo*-2-bromonorbornane.[18,19] This has been interpreted[20] as indicating that bromine attacks the α-boranorbornyl free radical (3) from the least sterically hindered exo side to give α-bromo-*endo*-norbornylborane intermediates (4). The subsequent hydrogen bromide cleavage then proceeds with clean retention of configuration to produce stereochemically pure *exo*-2-bromonorbornane (Scheme I).

The alkylboronate esters, such as trimethylene or dimethyl butyl- or pentylboronate esters, are not inert to bromine, as

Scheme I



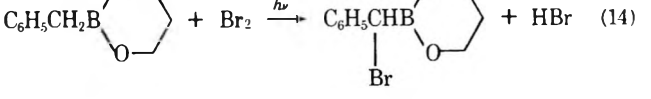
previously reported.[13,14] In carbon tetrachloride, methylene chloride, or pentane, they react somewhat sluggishly with bromine. However, although an equivalent of bromine is decolorized in 30–50 min in the presence of a sunlamp, some 60–80% of starting material is unreacted. For example, treatment of trimethylene pentylboronate with 1 equiv of bromine in carbon tetrachloride in the presence of a sunlamp results in decolorization of the bromine in 30 min. ^{1}H NMR analysis of the reaction mixture shows two overlapping triplets for the trimethylene protons α to oxygen at δ 3.93 and 4.03 and overlapping quintets for the trimethylene protons β to oxygen at δ 1.90 and 1.97. The remainder of the spectrum is complex, showing multiplets at δ 4.3–4.6, 3.1–3.5, and 0.8–2.6. The area ratio of the trimethylene protons to the rest of the protons is approximately 6:10, which stoichiometrically corresponds to incorporation of one bromine into the *n*-pentyl moiety (eq 13).



However, GLC analysis shows a complicated reaction mixture containing 70–80% of unreacted trimethylene pentylboronate. Distillation gives 67% of recovered starting material. Only a 16% yield of trimethylene 1-bromopentylboronate could be isolated from the complex mixture.

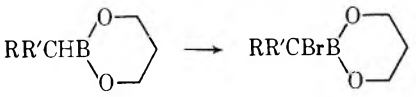
The results indicate that bromine does not attack the trimethylene ester group, but instead polybrominates the *n*-alkyl moieties. This interesting observation was beyond the scope of our research objectives and we did not pursue it further.[21]

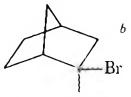
Apparently, when the alkylboronate esters possess a tertiary hydrogen α to boron, reaction with bromine results in clean substitution of the α-hydrogen by bromine (eq 10–12). With alkylboronate esters possessing secondary α-hydrogens, such as butyl- and pentylboronate esters, the reaction does not proceed as desired. Free radical halogenation of methylboronate esters also fails to provide useful amounts of α-halomethylboronate esters.[3,9] However, we found activation by a phenyl group permits the bromination to be carried out



successfully (eq 14). The results of this study are summarized in Table I.

Table I. Preparation of Trimethylene α-Bromoalkylboronate Esters by the Light-Induced Bromination of Trimethylene Alkylboronate Esters



RR'CH–	Registry no.	RR'CHBr–	Registry no.	Isolated yield,[a] %	Bp, °C (mm)
Isopropyl	62930-27-2	$(CH_3)_2CBr$–	62930-29-4	96	51 (0.9)
sec-Butyl	30169-72-3	$CH_3CH_2C(CH_3)Br$–	62930-30-7	84	62 (0.1)
Cyclopentyl	30169-74-5		62930-31-8	88	75–76 (0.1)
Cyclohexyl	30169-75-6		62930-32-9	89	85–87 (0.05)
exo-Norbornyl	30154-25-7		62930-33-0	85	81–82 (0.1)
n-Butyl	30169-71-2	$CH_3(CH_2)_2CHBr$–	62930-34-1	20[c]	60–62 (0.1)
Benzyl	62930-28-3	C_6H_5CHBr–	62930-35-2	73	130–140 (0.3)

[a] All compounds gave satisfactory ^1H NMR spectra and correct elemental analysis for C, H, B, Br. [b] Stereochemistry was not established. [c] 60–80% of starting material recovered.

Summary

It is evident that the facile light-induced reaction of bromine with alkylboronate esters provides an important synthetic procedure for the preparation of a wide variety of α-bromoalkylboronate esters. Some of these compounds are difficult to obtain by previously reported procedures.

The α-halogen of such compounds is easily substituted by a number of nucleophiles.[3,9] This suggests that the α-haloalkylboronate esters are promising intermediates for synthetic applications. We are actively pursuing such possibilities.

Experimental Section

General Comments. General procedures for solvent purification and laboratory manipulation of air-sensitive compounds have been presented.[2] Bromine, ACS Reagent, was used as received from the Fisher Scientific Co. The pure trimethylene alkylboronate esters were prepared by the procedure of Brown and Gupta[15] except for trimethylene 1-methylethyl- and benzylboronate esters, which were prepared by esterification of the respective boronic acids with propane-1,3-diol.[22] ^1H NMR spectra were recorded on a Varian T-60 (60 MHz) in $CDCl_3$ and chemical shifts are relative to tetramethylsilane (δ0). Products gave ^1H NMR in agreement with the indicated structures. Microanalyses were performed by the Purdue Microanalytical Laboratories and the results were within the accepted limits (±0.2%). Boiling points were uncorrected.

Preparation of Trimethylene 2-Bromo-2-methylethylboronate [α-Bromoisopropyl Boronate (1)]. The following procedure for the preparation of trimethylene α-bromoisopropylboronate is representative. A dry 500-mL flask, equipped with a septum inlet, magnetic stirrer, and reflux condenser topped with a connecting tube was flushed with nitrogen and maintained under a static pressure of the gas. By means of a hypodermic syringe, 200 mmol (25.6 g) of trimethylene 2-methylethylboronate was added to the flask followed by 200 mL of dry, olefin-free pentane (or methylene chloride). Then, 200 mmol (10.4 mL) of bromine was introduced all at once with an all-glass syringe with a Teflon needle and a Sears 275-W sunlamp was directed about 1 in. from the reaction flask. An exothermic reaction ensued with reflux of the reaction mixture and evolution of hydrogen bromide gas, which should be vented to a trap containing aqueous sodium hydroxide. Within 3 min, the bromine color disappeared and the solvent was removed immediately by aspirator vacuum. The residual liquid was transferred to a dry, nitrogen flushed distillation apparatus by a double-ended needle. Simple distillation gave 39.8 g (a 96% yield) of the trimethylene α-bromoisopropylboronate, bp 51 °C (0.9 mm). The ^1H NMR showed signals at δ 1.72 (s, 6 H, *gem*-dimethyl), 1.97 (quintet, J = 6 Hz, 2 H, trimethylene β-methylene), and 4.07 (t, J = 6 Hz, 4 H, trimethylene α-methylenes). The ^{11}B NMR (32.1 MHz, $CDCl_3$, BF_3·OEt_2 = δ 0) showed a singlet at δ −27.8.

Anal. Calcd for $C_6H_{12}BBrO_2$: C, 34.83; H, 5.85; B, 5.22; Br, 38.63. Found: C, 35.04; H, 5.98; B, 5.09; Br, 38.78.

The trimethylene α-bromoalkylboronate esters undergo no apparent change in several months and were stored in a cold room and protected from light, air, and moisture.

Registry No.—Bromine, 24959-67-9.

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Catalytic Hydrogenation of Organic Compounds in Liquid Hydrogen Fluoride

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The noble metal catalyzed hydrogenation of certain aliphatic ketones, acids, esters, and anhydrides and various aromatic compounds in liquid HF is described. For example, 4-methyl-2-pentanone is reduced at 16 psi H_2 pressure over PtO_2 to 2- and 3-methylpentane, and dodecanoic acid is reduced at 5000 psi H_2 pressure to dodecane, dodecyl ether, and dodecyl dodecanoate. Skeletal rearrangements, suggesting the presence of carbonium ion intermediates, are observed in many cases.

The noble metal catalyzed hydrogenation of many organic functional groups is known to be effected by the use of acidic solvents.[1] Anhydrous hydrogen fluoride is a strong acid, inert to reduction, and a good solvent for many organic compounds.[2] Furthermore, the low boiling point of anhydrous HF should facilitate product recovery and recycle of the solvent. Despite these advantages, relatively little has been reported on hydrogenations in HF. The reduction of nitrobenzenes to *p*-fluoroanilines in HF has been described.[3] More recently, several reports on hydrogenations in HF–super acid systems have appeared.[4-7] In this paper, the noble metal catalyzed hydrogenation of several organic functional groups in anhydrous HF is described. Most noteworthy are the observations that certain aliphatic carboxylic acids are reduced over PtO_2 in HF and that aliphatic ketones are reduced to hydrocarbons in HF under extremely mild conditions. Rearrangements typical of carbonium ion intermediates are observed in many systems.

Results

Aliphatic Ketones (Table I). The catalytic hydrogenation of ketones is well known.[1] Expect for aryl ketones, where reduction to methylene is observed, the normal reduction product is the corresponding alcohol. In anhydrous HF, however, reduction of a representative aliphatic ketone, 4-methyl-2-pentanone, took a different course. Stirring a mixture of the ketone and a catalytic amount of PtO_2 under 16 psi of H_2 at room temperature resulted in a rapid uptake of hydrogen. Workup as described in the Experimental Section

$$\underset{\displaystyle\overset{\displaystyle O}{\|}}{CH_3CCH_2CH(CH_3)_2} \xrightarrow[HF]{H_2/PtO_2} \underset{71\%}{CH_3CH_2CH_2CH(CH_3)_2} + \underset{29\%}{CH_3CH_2CH(CH_3)CH_2CH_3} \quad (1)$$

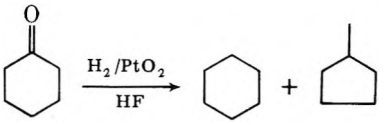
gave an essentially quantitative yield of two hydrocarbons, identified as 2- and 3-methylpentane. As indicated in Table I, this novel reduction was explored under a variety of conditions. In addition to PtO_2, RuO_2 was found to be an active catalyst for the hydrogenation. In this case, however, 2- and 3-methylpentane comprised only ca. 73% of the product, the remainder being a mixture of at least six other C_5 to C_7 hydrocarbons. Other catalysts (Pd/C, Pt/C, Rh/Al_2O_3, PdO_2, nickelocene, Re_2O_7, $Co_2(CO)_8$, and $PtCl_2$) were not effective. Using PtO_2, variation of the hydrogen pressure from 16 to 5000 psi had little effect on the ratio of rearranged to unrearranged products. An attempted reduction in the presence of carbon monoxide gave only unreacted starting material.

The corresponding alcohol, 4-methyl-2-pentanol, was not detected in any of the reductions using pure HF as the solvent. In a mixed solvent of ethyl ether/HF (5/1 v/v), however, hydrogenation of the ketone over PtO_2 gave the alcohol in 94%

$$\underset{\displaystyle\overset{\displaystyle O}{\|}}{CH_3CCH_2CH(CH_3)_2} \xrightarrow[HF/ether]{H_2/PtO_2} \underset{94\%}{\underset{\displaystyle OH}{\underset{|}{CH_3CHCH_2CH(CH_3)_2}}} + \underset{6\%}{CH_3CH_2CH_2CH(CH_3)_2} \xrightarrow[H_2/PtO_2]{HF} CH_3CH_2CH_2CH(CH_3)_2 + CH_3CH_2CH(CH_3)CH_2CH_3 \quad (2)$$

yield together with 6% of 2-methylpentane. No hydrogenation occurred in pure ether under these conditions. Treatment of the alcohol in pure HF with PtO_2 and hydrogen under the above conditions resulted in little H_2 uptake. The product was an undistillable oil showing only saturated hydrocarbon absorption in its infrared and NMR spectra.

A representative alicyclic ketone was also briefly studied. Hydrogenation of cyclohexanone in HF at 16 psi H_2 pressure



(3)

over PtO_2 gave a mixture of cyclohexane (62%) and methylcyclopentane (38%) as the only detectable products.

The hydrogenation is not entirely general however. Attempted reduction of the electronegatively substituted ketone, ethyl acetoacetate, under the above conditions gave only unreacted starting material.

Aliphatic Carboxylic Acids and Derivatives. Carboxylic acids are generally considered among the most difficult functional groups to hydrogenate.[1] They normally require high temperatures and high pressures using ruthenium, rhenium, or copper–barium–chromium catalysts which only give reduction to the alcohol. The facile reduction of ketones over PtO_2 in HF suggested the possibility that carboxylic acids could be reduced under these conditions. Using dodecanoic

$$CH_3(CH_2)_{10}COOH \xrightarrow[\substack{5000\ psi\\ HF\\ 20\ h}]{H_2/PtO_2} \underset{21\%}{CH_3(CH_2)_{10}CH_3} + \underset{42\%}{[CH_3(CH_2)_{10}CH_2]_2O} + \underset{6\%}{CH_3(CH_2)_{10}\overset{\displaystyle O}{\overset{\|}{C}}OCH_2(CH_2)_{10}CH_3} \quad (4)$$

Table I. Hydrogenation of Ketones in HF[b]

Substrate (g)	Catalyst (g)	Conditions	% conversion	Products (%)[a]
4-Methyl-2-pentanone (6.0)	PtO_2 (0.5)	25 °C, 5 h, 16 psi H_2	100	2-Methylpentane (71) 3-Methylpentane (29)
4-Methyl-2-pentanone (6.0) 4-Methyl-2-pentanone (0.6)	PtO_2 (0.04)	25 °C, 2 h, 1000 psi H_2	100	2-Methylpentane (73) 3-Methylpentane (27)
4-Methyl-2-pentanone (0.6) 4-Methyl-2-pentanone (0.6)	PtO_2 (0.05)	25 °C, 3 h, 5000 psi H_2	100	2-Methylpentane (71) 3-Methylpentane (29)
4-Methyl-2-pentanone (5.0)	PtO_2 (0.5)	50 °C, 4 h, 5000 psi 1:1 H_2/CO	0	
4-Methyl-2-pentanone (3.0)	10% Pd/C (0.3)	25 °C, 19 h, 16 psi H_2	0	
4-Methyl-2-pentanone (3.0)	10% Pt/C (0.3)	25 °C, 5 h, 16 psi H_2	0	
4-Methyl-2-pentanone (3.0)	5% Rh/Al_2O_3 (0.3)	25 °C, 4 h, 16 psi H_2	0	
4-Methyl-2-pentanone (3.0)	RuO_2 (0.3)	25 °C, 4 h, 16 psi H_2	87	2-Methylpentane (52) 3-Methylpentane (21) + 6 other hydrocarbons
4-Methyl-2-pentanone (3.0)	PdO_2 (0.3)	25 °C, 5 h, 16 psi H_2	0	
4-Methyl-2-pentanone (3.0)	Nickelocene (0.3)	25 °C, 5 h, 16 psi H_2	0	
4-Methyl-2-pentanone (3.0)	Re_2O_7 (0.3)	25 °C, 6 h, 16 psi H_2	0	
4-Methyl-2-pentanone (3.0)	$Co_2(CO)_8$ (0.3)	25 °C, 5 h, 16 psi H_2	0	
4-Methyl-2-pentanone (3.0)	$PtCl_2$ (0.3)	25 °C, 5 h, 16 psi H_2	0	
4-Methyl-2-pentanone (3)	PtO_2 (0.3)	25 °C, 1 h, 16 psi H_2 5 mL HF, 25 mL ether	100	2-Methylpentane (6) 4-Methyl-2-pentanol (94)
Cyclohexanone (6)	PtO_2 (0.5)	25 °C, 4 h, 16 psi H_2	100	Cyclohexane (62) Methylcyclopentane (38)
Ethyl acetoacetate (6)	PtO_2 (0.5)	25 °C, 4 h, 16 psi H_2	0	

[a] Percentages by GLC analysis of the distilled product. [b] Registry no.: HF, 7664-39-3; 4-methyl-2-pentanone, 108-10-1; cyclohexanone, 108-94-1; ethyl acetoacetate, 141-97-9.

acid as a representative aliphatic carboxylic acid, no reduction was observed over PtO_2 in HF at 16 psi. Under higher pressures (5000 psi H_2), however, a slow but smooth uptake of H_2 occurred at room temperature. Workup as described in the Experimental Section gave three products, identified as dodecane, dodecyl ether, and dodecyl dodecanoate. Under the same conditions, both dodecyl anhydride and dodecyl dodecanoate were reduced only to dodecyl ether in 77 and 78%

$$CH_3(CH_2)_{10}\overset{O}{\overset{\|}{C}}OCH_2(CH_2)_{10}CH_3 \xrightarrow[\text{HF}\\\text{5000 psi}\\\text{20 h}]{H_2/PtO_2} [CH_3(CH_2)_{10}CH_2]_2O \quad 77\% \qquad (5)$$

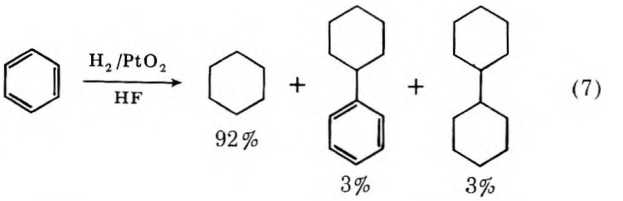
isolated yield, respectively. Thus, the anhydride formed by HF-catalyzed condensation of two acid molecules is the likely precursor to the ester and ether in the hydrogenation of the carboxylic acid. The corresponding alcohol, dodecanol, was not detected in the reduction of the acid, ester, or anhydride. Treatment of dodecanol under the hydrogenation conditions gave only high molecular weight oils. The hydrogenation of

$$[CH_3(CH_2)_{10}\overset{O}{\overset{\|}{C}}]_2O \xrightarrow[\text{HF}\\\text{5000 psi}\\\text{20 h}]{H_2/PtO_2} [CH_3(CH_2)_{10}CH_2]_2O \quad 78\% \qquad (6)$$

acetic anhydride (0.6 g) over 0.1 g of PtO_2 in 5 g of HF at room temperature and 5000 psi H_2 pressure gave a mixture of ethyl acetate (40%) and diethyl ether (5%) plus unreacted anhydride. Under similar conditions, the mixed anhydride of acetic and propionic acids gave a mixture of all three possible ether products (ethylpropyl, diethyl, and dipropyl) plus propyl acetate and ethyl acetate.

The reduction of acids or anhydrides in HF appears to suffer from three major limitations as a preparative process. First, rather large amounts of catalyst were required to achieve acceptable reaction rates. With dodecanoic acid in HF at room temperature and 5000 psi H_2 pressure, the conversions after 20 h using 10 and 17% (w/w) of PtO_2 relative to substrate were 41 and 69%, respectively. Second, the reduction of α-branched acids or anhydrides resulted in the isolation of extremely complex product mixtures. Thus, the hydrogenation of either cyclohexane carboxylic acid anhydride or trimethylacetic acid gave 30+ products as analyzed by GLC. Finally, as in the case of the ketone hydrogenations, substitution of the molecule by a second electronegative function appears to inhibit the reduction process. The reduction of maleic anhydride proceeded smoothly to succinic anhydride, but no further reduction was detected. Oxalic acid was inert.

Aromatic Compounds (Table II). Benzene was reduced in HF over PtO_2 at 16 psi H_2 pressure to cyclohexane plus small amounts of cyclohexylbenzene and bicyclohexyl. Chlorobenzene was reduced to cyclohexane; toluene was reduced to methylcyclohexane. Both *m*- and *p*-xylene under-



(7)

went rearrangements during hydrogenation in HF. Six dimethyl cyclohexanes were detected by GLC with *cis*-1,3- and

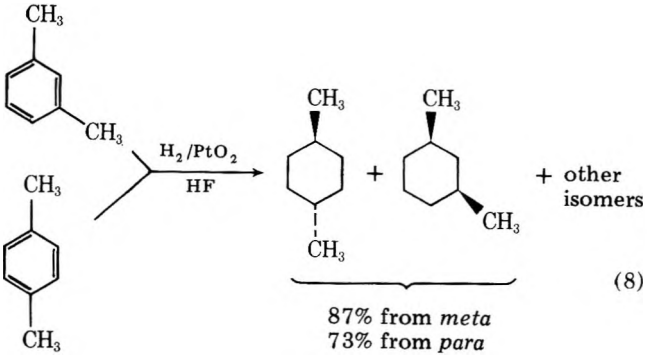


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Table II. Hydrogenation of Aromatic Compounds in Liquid HF

Substrate (g)	Registry no.	Catalyst (g)	Conditions	% conversion	Products (%)[a]
Benzene (2.6)	71-43-2	PtO_2 (0.3)	25 °C, 5 h, 16 psi H_2	67	Cyclohexane (92) Cyclohexylbenzene (4) Bicyclohexyl (4)
Benzene (5.2)		PtO_2 (5.2)	25 °C, 2 h, 16 psi H_2	60	Cyclohexane (89) Cyclohexylbenzene (11)
Toluene (3)	108-88-3	PtO_2 (0.3)	25 °C, 2 h, 16 psi H_2	43	Methylcyclohexane (100)
p-Xylene (3)	106-42-3	PtO_2 (0.3)	25 °C, 3 h, 16 psi H_2	95	*cis*-1,3-Dimethylcyclohexane, *trans*-1,4-Dimethylcyclohexane (73) *cis*-1,2-Dimethylcyclohexane, *trans*-1,2-Dimethylcyclohexane (8) *trans*-1,3-Dimethylcyclohexane (6) *cis*-1,4-Dimethylcyclohexane (5)
m-Xylene (3)	108-38-3	PtO_2 (0.3)	25 °C, 3 h, 16 psi H_2	100	*cis*-1,3-Dimethylcyclohexane, *trans*-1,4-Dimethylcyclohexane (87) + 4 other Dimethylcyclohexanes (13)
Chlorobenzene (3)	108-90-7	PtO_2 (0.3)	25 °C, 5 h, 16 psi H_2	29	Cyclohexane (100)
Phenol (3)	108-95-2	PtO_2 (0.3)	25 °C, 5 h, 16 psi H_2	88	Cyclohexane (70) Cyclohexanone (30)
Phenol (3)		PtO_2 (0.3)	25 °C, 17 h, 16 psi H_2	100	Cyclohexane (85) Methylcyclopentane (15)
Acetophenone (4)	98-86-2	PtO_2 (0.2)	25 °C, 1.5 h, 16 psi H_2	30	Ethylcyclohexane (87) *cis*-1,3-Dimethylcyclohexane, *trans*-1,4-Dimethylcyclohexane (13)
Nitrobenzene (6.2)	98-95-3	PtO_2 (0.05)	25 °C, 5 h, 16 psi H_2	100	Aniline (36), 4-Fluoroaniline (19) [b]
4-Chloronitrobenzene (4)	100-00-5	PtO_2 (0.2)	25 °C, 7 h, 16 psi H_2	92	4-Fluoroaniline (28), 4-Chloroaniline (57) [b]
Quinoline (3)	91-22-5	PtO_2 (0.3)	25 °C, 1.5 h, 16 psi H_2	83	4,5,6,7-Tetrahydroquinoline (90) 1,2,3,4-Tetrahydroquinoline (10)
Quinoline (3)		PtO_2 (0.3)	25 °C, 17 h, 16 psi H_2	100	4,5,6,7-Tetrahydroquinoline (50) Decahydroquinoline (50)
Isoquinoline (12.9)	119-65-3	PtO_2 (0.6)	25 °C, 18 h, 5000 psi H_2	66	4,5,6,7-Tetrahydroisoquinoline
Benzonitrile (3.0)	100-47-0	PtO_2 (0.3)	25 °C, 5 h, 16 psi H_2	100	Benzaldehyde (76) Benzamide (3) $PhCH{=}NCH_2Ph$ (14) $PhCH{=}NCH_2C_6H_{11}$ (6)
p-Xylene (3.0)		PtO_2 (0.3)	25 °C, 2 h, 16 psi H_2 5 mL HF, 25 mL ether	100	*cis*-1,4-Dimethylcyclohexane (67) *trans*-1,4-Dimethylcyclohexane (33)
Benzene (2.6) Pyridine (14)	110-86-1	PtO_2 (0.3)	25 °C, 5 h, 16 psi H_2	47 (benzene) 0 (pyridine)	Cyclohexane

[a] GLC analysis of distilled product unless otherwise indicated. [b] Percent yield.

trans-1,4-dimethylcyclohexane predominating from both xylenes. These isomers could not be separated by GLC, but were detected by careful infrared examination of the major GLC product peak. In a mixture of HF and ether (1/5, v/v) *p*-xylene was reduced over PtO_2 at 16 psi H_2 pressure to a mixture of 67% *cis*-1,4- and 33% *trans*-1,4-dimethylcyclohexane. In pure ether, no reduction was observed under these conditions.

The reduction of acetophenone in pure HF at 16 psi H_2 pressure occurred with extensive rearrangement. Hydrogenation of the compound to 30% conversion over PtO_2 gave the expected ethylcyclohexane (87%) plus a mixture (13%) of *cis*-1,3- and *trans*-1,4-dimethylcyclohexane.

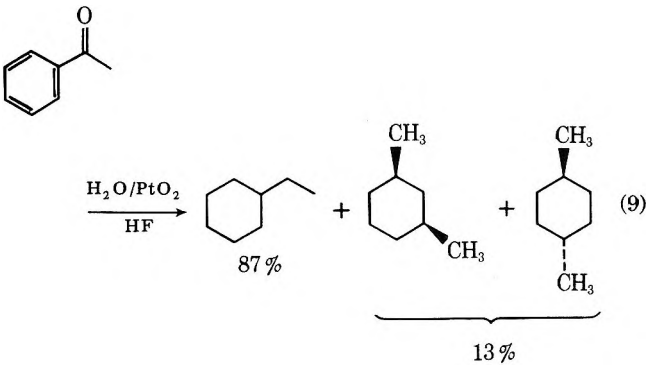
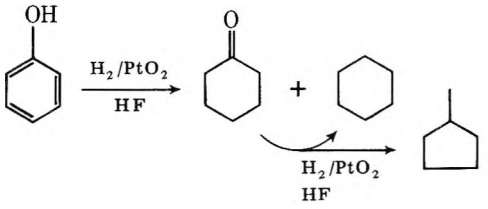


Table III. Reduction of Quinoline over PtO_2 in Strong Acids

Acid	Wt % catalyst	Pressure H_2, psi	Reaction time, h	% yield[c]
Concentrated HCl[a]	12	50	30	70
12 N H_2SO_4[a]	12	50	4.5	74
Trifluoroacetic acid[a]	12	50	0.45	84
Trifluoroacetic acid[a]	12	16	8.5	80
HF[b]	10	16	1.5	75

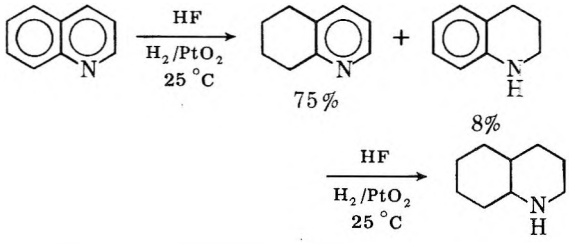
[a] Reference 8. [b] This study. [c] Yield of 4,5,6,7-tetrahydroquinoline by GLC.

The hydrogenation of phenol to 88% conversion gave a product mixture containing 70% cyclohexane and 30% cyclohexanone. If the reaction was allowed to continue until H_2 uptake ceased, the product mixture consisted of cyclohexane (85%) and methylcyclopentane (15%).



(10)

The regiospecific reduction of unsubstituted quinoline or isoquinoline to the 1,2,3,4-tetrahydro isomers over PtO_2 under mildly acidic conditions is well known.[1] By contrast, in anhydrous HF, at 16 psi H_2 pressure, quinoline was selectively hydrogenated over PtO_2 to 4,5,6,7-tetrahydroquinoline with only 10% of the 1,2,3,4-tetrahydro isomer produced. Further hydrogenation gave decahydroquinoline. With isoquinoline,



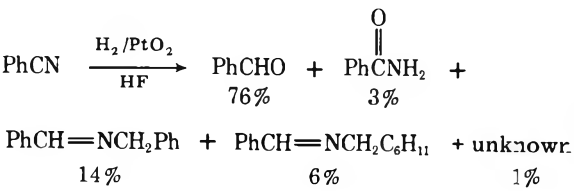
(11)

hydrogenation in HF gave only 4,5,6,7-tetrahydroisoquinoline; none of the 1,2,3,4-tetrahydro isomer was detected.

Recently, Vierhapper and Eliel[8] reported similar results using concentrated HCl, H_2SO_4, or trifluoroacetic acid. A comparison of the various strong acids used in the hydrogenation of quinoline is contained in Table III. The reduction in HF appears faster than in H_2SO_4, HCl, or trifluoroacetic acid with comparable selectivities.

In line with these results, hydrogenation of a mixture of 3 mL of benzene and 15 mL of pyridine in HF over PtO_2 resulted only in the reduction of the benzene to cyclohexane; no piperidine or other products from the reduction of pyridine could be detected.

Reduction of benzonitrile over PtO_2 in HF at 16 psi H_2 pressure followed by treatment of the crude mixture with dilute aqueous base gave five products (12) which were identified by GLC and GC/MS. The major product, obtained in 76% yield, was benzaldehyde, presumably formed by hydrolysis of an intermediate imine.[9]



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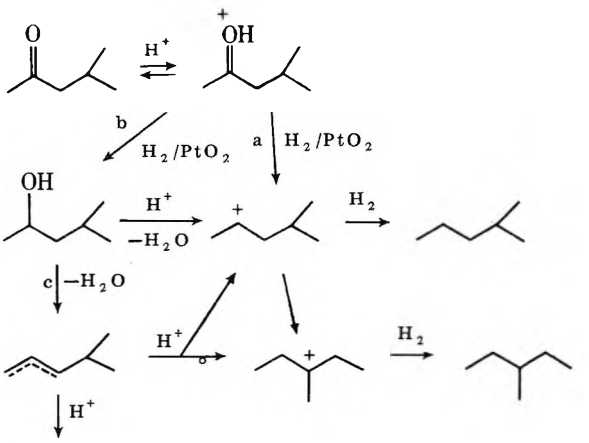
Scheme I



Nonvolatile hydrocarbon

Discussion

Any mechanistic proposal on catalytic hydrogenations in HF must account for the following observations: (1) HF has a catalytic effect, i.e., many of the reported reductions are faster in HF than in less acidic media. (2) A carbonyl is reduced to methylene, while the corresponding alcohol gives polymeric products. (3) Extensive skeletal rearrangements, characteristic of carbonium ion intermediates, are observed in many cases. (4) Reduction of a group is inhibited by the presence of an electronegative function elsewhere in the molecule.

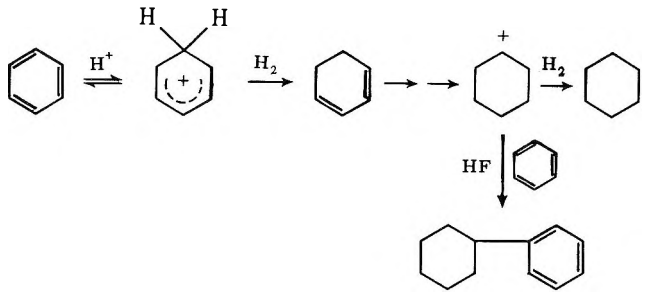
A potential mechanistic scheme for carbonyl reduction in HF using 4-methyl-2-pentanone as a model is shown in Scheme I. Ketones are known to protonate in HF, usually without further reaction.[2] The catalytic effect of the strong acid suggests that the protonated carbonyl is more easily reduced than the neutral molecule. Several pathways are available for reduction of the protonated carbonyl. Direct reduction (pathway a), in effect a hydrogenolysis, would generate water and the 4-methyl-2-pentyl cation. Partition of this species between reduction and rearrangement followed by reduction would give the observed products. The reduction of carbonium ions by hydrogen in acidic media is well known.[4-7]

Alternatively, the protonated carbonyl might be reduced to the alcohol (pathway b) as a discrete intermediate followed by protonation and loss of water to give the same carbonium ions. Loss of water from the alcohol to give olefin(s) (pathway c) followed by protonation would also form the carbonium ions.

At first glance, pathways b and c are ruled out by the observation that reaction of the alcohol under hydrogenation conditions gives only nonvolatile hydrocarbon with little or no methylpentane formation. However, a simple concentration factor might account for this discrepancy. If in the reduction of the carbonyl, step b is the slow step, the concentration of polymerizable intermediate(s) is kept small, favoring the formation of monomeric products. With the preformed alcohol, a large concentration of polymerizable intermediate(s) might be produced, resulting in formation of the nonvolatile hydrocarbon residue. Olefins polymerize readily in HF. A similar scheme can be proposed for the reduction of carboxylic acids and their derivatives in HF.

The failure of ethyl acetoacetate, oxalic acid, and succinic anhydride to undergo reduction may be due to the decreased

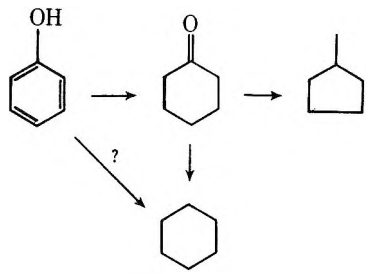
Scheme II



basicity of these compounds from the presence of two electronegative functions in the molecule.[11]

The reduction of the aromatic systems is also catalyzed by HF, probably again by protonation of the substrate, followed by a metal-catalyzed hydride donation. Although the concentration of protonated benzene in pure HF is not detectable by physical methods,[12] a kinetically significant amount could still be present in solution (Scheme II). The intervention of carbonium ion intermediates is further suggested by the formation of cyclohexylbenzene in the reduction of benzene and by the formation of the methyl shift products in the xylene and acetophenone hydrogenations.

The complete hydrogenation of both phenol and cyclohexanone gives cyclohexane and methylcyclopentane. The ratio of unrearranged products is larger, however, from phenol than from cyclohexanone. Furthermore, partial conversion of phenol gives cyclohexanone and cyclohexane (no methylcyclopentane). Thus, at least two pathways are indicated in the reduction of phenol, one preceding through cyclohexanone to give cyclohexane and methylcyclopentane and a second which gives only cyclohexane. Details of this latter process remain obscure.



The results obtained in the reduction of quinoline and the benzene/pyridine mixture in HF can be explained if N protonation of the nitrogen lone pair on the heteroatom ring inhibits formation of a more easily reduced π-protonated species. Thus, a weak acid catalyzes reduction of the pyridine ring in quinoline, whereas a strong acid catalyzes reduction of the benzene ring because of a change in mechanism for the reduction step.

In summary, the evidence suggests that the reduction of many functional groups in HF proceeds at least in part by a sequence of proton addition–hydride donations rather than by a concerted addition of molecular hydrogen.

Finally, some comment should be made concerning the practicality of running catalytic hydrogenations in HF.

A major disadvantage of HF is the inability to use common laboratory glassware, but widespread availability of laboratory apparatus constructed from HF-resistant polymers largely overcomes this problem. Most of the reactions reported here are run at moderate temperatures and pressures where this equipment is very satisfactory. On the other hand, HF lacks some of the problems encountered with other strong acids. Workup is facilitated by its low boiling point. A simple distillation can often be used in place of messy and hazardous dilution and extraction procedures. The reactions reported here were in most cases remarkably clean with little or no by-product formation. Side reactions common with other strong acids such as sulfuric acid (sulfonation and/or oxidation of the substrate or products) are generally absent.

Experimental Section

Caution! Hydrogen fluoride is extremely corrosive to human tissue, contact resulting in painful, slow healing burns. Laboratory work with HF should be conducted only in an efficient hood with the operator wearing full face shield and protective clothing.

General. Anhydrous hydrogen fluoride (Air Products) and other reagents were used as received. Gas chromatographic analyses (GC) were preformed on a Hewlett-Packard 5700 instrument equipped with a thermal conductivity detector. Peak areas were measured by the cut and weigh technique and unless otherwise indicated are not corrected for relative detector response. Gas chromatographic/mass spectroscopic measurements (GC/MS) were performed on a Du Pont 21490 instrument equipped with a VG2040 data system.

Procedure. Reactions at pressures above 16 psi or temperatures above room temperature were run in 80 or 200 mL Hastelloy C shaker tubes. Other reactions were run in Kel-F vessels attached to a vacuum line constructed from Kel-F and Teflon fluorocarbon resin. In general, the organic reagent and catalyst were loaded to the reaction vessel, which was cooled in dry ice/acetone or liquid N_2, evacuated, and charged with HF (10–30 times the volume of organic reagent) by vacuum transfer from the commercial cylinder. The reaction vessel was pressured with H_2 and heated to the required reaction temperature. After suitable reaction time, the excess H_2 pressure was vented and the product was worked up by one of three techniques. If the desired product was relatively nonvolatile, the HF was pumped out of the reaction vessel using an aspirator. The residue was dissolved in an organic solvent and washed with water or dilute base or was treated with sodium fluoride powder, as appropriate, to remove traces of HF. If a volatile product was expected, the reaction vessel was attached in series to a copper trap containing NaF pellets, a glass trap cooled in dry ice/acetone or liquid N_2, and a source of vacuum. The NaF pellets quantitatively scrubbed the HF from the gas stream and the organic product was isolated from the glass trap. Rarely (because of the potential hazards involved) a well-chilled reaction mixture was slowly poured over ice, the aqueous solution neutralized with 20% aqueous KOH and the product extracted with an organic solvent.

After appropriate processing, usually distillation, the reaction products were analyzed and identified by GLC comparison with authentic samples, GC/MS, and/or NMR spectroscopy. The results are contained in Tables I and II and in the Results section. Three representative experiments are reported in detail below.

Hydrogenation of Dodecanoic Acid. An 80-mL Hastelloy shaker tube was charged with 6.0 g (0.03 mol) of dodecanoic acid and 1.0 g of PtO_2. The vessel was cooled in dry ice/acetone, evacuated, and charged with 40 g of HF. The vessel was pressured to 5000 psi with H_2 and agitated at 30 °C for 17 h. The H_2 pressure was released and the HF was evaporated using an aspirator. The residue was taken up in 150 mL of ether, filtered, washed with several portions of water, dried ($MgSO_4$), and concentrated on a rotary evaporator to 4.8 g of clear oil. GLC analysis (6 ft × ⅛ in. 10% UCW-982 column, temperature programmed from 100 to 250 °C at 16°/min) showed four peaks: A (retention time = 4.5 min, 21%); B (retention time = 7.5 min, 31%, identified as dodecanoic acid by comparison with authentic sample); C (retention time = 21 min, 42%); and D (retention time = 25 min, 6%).

A 4.0-g sample of the product was chromatographed over 100 g of silica gel. Elution of the column with petroleum ether gave pure dodecane (0.70 g), followed by 1.5 g of pure dodecyl ether: NMR (δ, CCl_4) 0.89 (t, 6 H), 1.28 (brs, 40 H), 3.30 (4 H, t); IR (CCl_4) 1110 cm^{-1} (s). Anal. Calcd for $C_{24}H_{50}O$: C, 81.28; H, 14.21; O, 4.52. Found: C, 81.18; H, 14.13; O, 4.14. Elution of the column with 10% ether in petroleum ether gave 1.8 g of oily solid, a mixture by GLC of dodecanoic acid and component D. D was isolated by preparative GLC and identified as dodecycl dodecanoate by NMR, IR, and GLC comparison with an authentic sample.

Hydrogenation of 4-Methyl-2-pentanone. A 200-mL Kel-F vessel attached to a vacuum line constructed from Kel-F and Teflon fluorocarbon resin was charged with 6.0 g of 4-methyl-2-pentanone and 0.5 g of PtO_2. The vessel was cooled in liquid N_2, evacuated on a vacuum pump, and charged with 50 mL of HF by vacuum transfer from a commercial cylinder. The vessel was pressured to 6 psi with H_2 and the reaction mixture was allowed to warm to room temperature. The H_2 pressure was adjusted to 16 psi. Magnetic stirring of the HF mixture initiated uptake of hydrogen. When the system pressure

fell to 8 psi, the vessel was repressurized to 16 psi from the hydrogen cylinder. After 11 such repressurizations, H_2 uptake ceased (~5 h). The reaction vessel was connected in series to a copper trap containing ~300 g of NaF pellets, a calibrated glass trap cooled in liquid N_2, and a vacuum pump. The contents of the reaction vessel were slowly (~2 h) pumped through the trap system. When the reaction vessel had pumped dry, the vacuum was disconnected and the glass trap was warmed to room temperature. It contained 6.5 mL of colorless liquid. GLC analysis (6 ft × 1/8 in. 10% UCW-982 column, oven temperature = 25 °C, He carrier gas at 40 mL/min) showed two components in a 71:29 ratio. They were identified by comparison of their GLC retention time and mass spectroscopic cracking pattern (GC/MS) as 2-methylpentane and 3-methylpentane, respectively.

Hydrogenation of Quinoline. Following the preocedure employed for 4-methyl-2-pentanane, 3.0 g (0.023 mol) of quinoline was reduced over 0.3 g of PtO_2 for 1.5 h at 8–16 psi hydrogen pressure. After removing the HF by aspirator, the residue was dissolved in 50 mL of H_2O, made alkaline by the addition of 20% aqueous KOH, and extracted with three 100-mL portions of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated on a rotary evaporator. Bulb-to-bulb distillation of the residue (0.1 mm) gave 2.7 g of oil. GLC analysis (10 ft × 1/4 in. 10% SE-30 column at 200 °C) showed three well-resolved peaks: A (retention time = 6 min, 75%), B (retention time = 9 min, 17%), C (retention time = 13 min, 8%). Peaks B and C were identified as quinoline and 1,2,3,4-tetrahydroquinoline, respectively, by co-injection with authentic samples. Peak A was collected by preparative GLC and identified as 5,6,7,8-tetrahydroquinoline: mass spectrum *m/e* 133.0895, calcd for $C_9H_{11}N$ 133.0891; NMR δ 8.32 (d, 1 H), 6.8–7.3 (m, 2 H), 1.1–1.6, and 2.0–2.5 (m, 8 H).

Registry No.—Dodecanoic acid, 143-07-7; dodecyl ether, 4542-57-8; 5,6,7,8-tetrahydroquinoline, 10500-57-9.

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Difunctional Derivatives of *syn*-Dimethanoperhydro-*s*-hydrindacene

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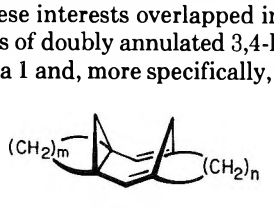
Prompted by a desire to prepare a bisannulated homotropilidene whose localized *cis*-divinylcyclopropane structure might be sufficiently destabilized to force adoption of neutral homoaromatic character, a study of the reducibility of difunctional *syn*-dimethanoperhydro-*s*-hydrindacenes was undertaken. Thus, 4-acetyl-*s*-hydrindacene was converted to the quinone **5** by two different series of reactions. The first consisted of a sequence involving Baeyer–Villiger oxidation, hydride reduction, and Fremy salt oxidation of the resulting phenol. The second involved Beckmann rearrangement, hydrolysis, and dichromate oxidation of the aniline. The quinone adds 2 mol of diazomethane exclusively from the same surface but in opposite senses to give bispyrazoline **8**, photolysis of which provides the desired bishomoquinone **10**. The structure and stereochemistry of **8** and **10** follow unequivocally from their subsequent conversion to **11**, **12**, and **13** and the ^{13}C NMR spectra of the entire series of compounds. All attempts to force these difunctional derivatives to undergo either reductive 1,4-elimination or cleavage have proven uniformly unsuccessful.

Each of our groups has had an interest in molecules capable of rapid degenerate valence isomerization and, in particular, in the question of possible removal of the barrier to Cope rearrangement to arrive at a neutral homoaromatic ground state species. These interests overlapped in work on the attempted synthesis of doubly annulated 3,4-homotropilidenes of general formula **1** and, more specifically, the hydrocarbon



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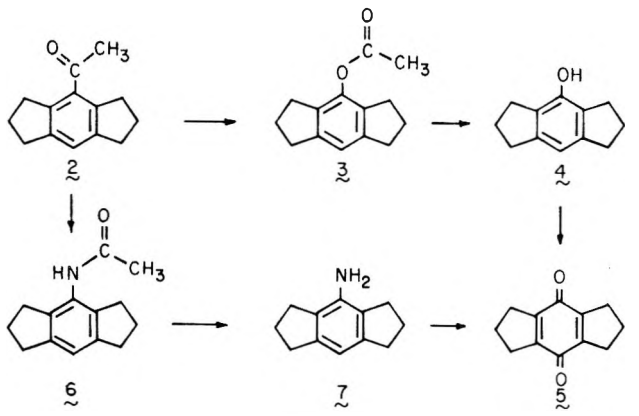
with $m = n = 3$. This paper describes the results of those experiments which have provided access to several disubstituted *syn*-dimethanoperhydro-*s*-hydrindacene precursors to **1** and outlines the difficulties encountered in our attempts to subsequently introduce the divinylcyclopropane part structure.

4-Acetyl-*s*-hydrindacene (**2**) has previously been synthesized in connection with Arnold and Rondestvedt's study of Mills–Nixon effects.[2] Although Baeyer–Villiger oxidation of **2** proved to be typically sluggish, prolonged refluxing with *m*-chloroperbenzoic acid in dichloromethane afforded acetate **3** in 84% yield based upon recovered ketone. More vigorous conditions appeared to cause competing decomposition of the ester formed. Treatment of the derived phenol (**4**) with Fremy's salt[4] led in 87% yield to the bright yellow *p*-quinone **5**, access to which could also be gained by sequential Beckmann rearrangement of 2-oxime, hydrolysis of **6**, and sodium dichromate oxidation of aniline **7**.

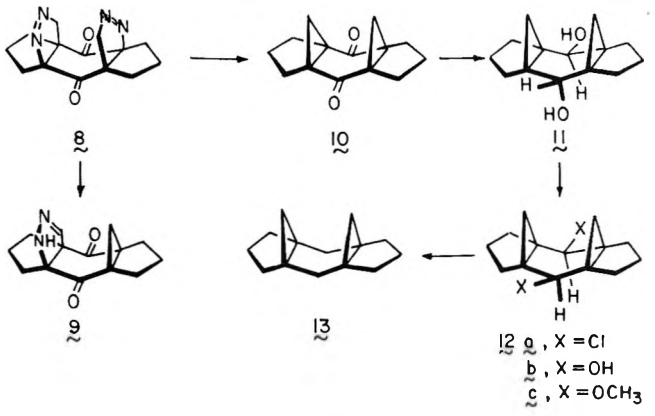
As in the case of duroquinone,[5] **5** enters into dipolar cycloaddition with diazomethane to form a single bispyrazoline in >80% isolated yield. Analysis of the symmetry required by



the ^{13}C NMR spectrum of this adduct (seven lines) as well as those of its further transformation products (to be discussed subsequently) established unequivocally that addition had occurred in opposite directions to the same face of the quinone as in **8**.

When treated with small amounts of perchloric acid in acetic acid at room temperature, **8** was converted to a viscous oil from which a crystalline substance could be isolated by column chromatography in 47% yield. The elemental analysis denoted that one molecule of nitrogen had been liberated. The ^1H NMR spectrum clearly revealed the presence of an >NH proton at δ 5.6 and an olefinic proton at 6.3. The infrared spectrum showed bands at 3240 and 1635 cm^{-1}. These data identify the product as **9** where it seems reasonable that the residual heterocyclic ring experienced prototropic shift during cyclopropane formation.

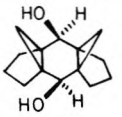
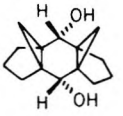
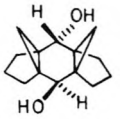
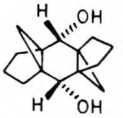
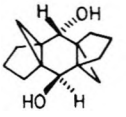
When irradiated in acetone solution with a 450-W Hanovia lamp through Pyrex, **8** was transformed in high yield to **10**.



This diketone exhibits an AB pattern (J = 3.5 Hz) for the cyclopropyl hydrogens and a relatively narrow multiplet for the overlapping signals of the methylene protons attached to the five-membered rings. In this system, δ_{AB} amounts to 1.08 ppm due chiefly to the carbonyl anisotropy, well in the range observed with other bishomoquinones.[5-7] The symmetry of **10** follows also from the ^{13}C NMR spectrum (5 lines), although the composite data remain inadequate for the purpose of relative configurational assignment to the two cyclopropane rings.

Lithium aluminum hydride reduction of **10** in tetrahydrofuran permitted ultimate establishment of the stereochemistry in this series. The major component (mp 183–185 °C) of the mixture of isomeric diols formed under these conditions was isolated by repeated recrystallization from chloroform or by preparative thin layer chromatography and exhibits *eight* peaks in its ^{13}C NMR spectrum. From among all configurational possibilities for diols of this general formula (Table I), it can be seen that this spectrum conforms uniquely to the trans diol having C_s symmetry, given by structure **11**. This finding requires cis orientation of the cyclopropane rings in **11** (C_{2v} rather than C_i symmetry in **10**) and also reduces the possible structural assignments to **8** to the one depicted (C_2 rather than C_i symmetry). The ^{13}C NMR of this heterocycle had already limited the possibilities to the structure shown and the one in which addition had occurred in opposite senses on opposite faces.

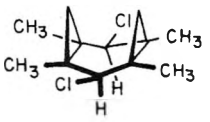
Table I. Symmetry Considerations for the Various Possible Dimethanodihydro-*s*-hydrindacene Diols

Isomer	Point group	Anticipated number of ^{13}C peaks
	C_{2v}	5
	C_{2v}	5
	C_s	8
	C_s	9
	C_i	7

With sodium borohydride, **10** was converted to a different mixture of diols in which one of the cis isomers of C_{2v} symmetry (mp 210–212 °C) predominated. The substance is believed to be **12b** for steric reasons and because the chemical shifts of its two different cyclopropyl protons are similar to those in **12a** and **12c** (see Experimental Section). Treatment of either set of diols with dry hydrogen chloride in benzene–chloroform solution at 0 °C led to formation of a single dichloride in essentially quantitative yield. As anticipated,[8,9] rapid conversion of the biscyclopropylcarbinol moieties to their respective cations was accompanied by stereospecific capture of chloride ion from the direction syn to the three-membered rings. In accord with this analysis, the ^1H NMR spectrum of **12a** consists inter alia of a singlet of area 2 at δ 4.52 for the >C*H*Cl protons and an AB quartet (J = 7 Hz) with δ_A = 0.63 and δ_B = 1.04 for the methylene hydrogens bonded to the cyclopropane rings. Since the ^{13}C NMR spectrum shows but *five* lines, the dichloride must possess C_{2v} symmetry (see Table I). To be quite sure that no structural bond reorganization had occurred, **12a** was reduced with sodium borohydride in aqueous diglyme at room temperature, advantage being taken of the high solvolytic reactivity of this substance and the known ability of $NaBH_4$ to capture transient carbocations by hydride transfer.[10] The resultant mixture was dominated by the previously characterized[8] cis hydrocarbon **13** (90%). Although the minor constituent remains unidentified, it is decidedly not *anti*-dimethanoperhydro-*s*-hydrindacene.[8] Upon dissolution in methanol containing sodium carbonate, **12a** was converted to ether **12c** without difficulty.

The difunctional derivatives **10–12** were viewed as suitable precursors to the desired bisannulated homotropilidene. This hypothesis required, of course, that 1,4 reductive elimination or cleavage be possible under conditions where the hydro-

carbon product would suffer no further reaction. In the case of **12a**, support for this condition was garnered from the earlier finding that **14** undergoes essentially quantitative conversion



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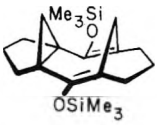

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to 1,3,5,7-tetramethylhomotropilidene.[9] However, **12a** was unreactive to these conditions (lithium amalgam, ether, 25 °C), the dichloride being totally recovered after 24 h. Since the amalgam in refluxing dioxane (2 h) proved adequate to destroy **12a** without giving rise to a volatile product, this reaction was reexamined at 45 °C (18 h), but the consequences of this moderate temperature were similarly disastrous. What organic product had been generated had evidently polymerized and precipitated with the lithium chloride.

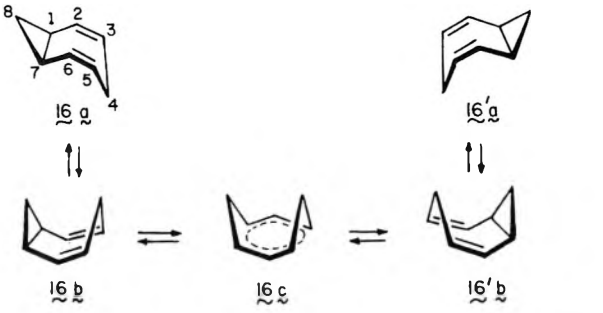
At this point, recourse was made to sodium–potassium alloy (1:5) because of the known greater potential of this couple. Upon admixture with **12a** in tetrahydrofuran-d_8 solution at −45 °C there was observed the rather rapid disappearance of the δ 4.74 singlet and cyclopropane AB quartet which characterize the dichloride, and appearance of a δ 5.00 singlet. Attempts to isolate a product from such reactions yielded only polymer. At longer reaction times (still at −45 °C), there was obtained in low yield a dihydro olefin (*m/e* 188) whose structure has remained elusive. Ether **12c** was inert to this reagent.

This development suggested the possibility that the desired hydrocarbon might be more easily reduced than its dichloride precursor. The reduction of **12a** under polarographic conditions was therefore briefly investigated. In anhydrous tetrahydrofuran 0.1 M in tetra-*n*-butylammonium perchlorate, **12a** did not undergo reduction until −3.46 V (vs. Ag/0.1 M $AgClO_4$ in THF), just prior to solvent breakdown (−3.69 V). Cyclic voltammetry revealed the process to be irreversible as expected. In anhydrous hexamethylphosphoramide solution, reduction occurred at −2.82 V again just on the fringe of solvent breakdown (−3.10 eV). For comparison purposes, the same technique applied to (1-chloroethyl)cyclopropane led to reduction at −2.03 V in HMPA,[11] thereby providing some indication of the striking difficulty of electron transfer to **12a**. By analysis of the polarographic wave heights, it could be established that the reduction of **12a** involves somewhat more than one electron per molecule (1.2–2 ϵ). However, we cannot be certain of the species that is being further reduced.

When a solution of **12a** in tetrahydrofuran-d_8 cooled to −45 °C was treated with *tert*-butyllithium and allowed to warm slowly, solvent dedeuteration was observed prior to consumption of dichloride. Addition of sodium iodide to a solution of **12a** in dry acetone[12] at room temperature caused gradual decomposition without providing evidence for a transient product. These findings, as well as our inability to reduce **10** directly[13] to the bistrimethylsiloxy diene **15**, led us to seek a method wherein the diene would be immediately trapped as a metal complex upon generation. As an extension of Collman's interesting work,[14] **12a** was treated directly with disodium tetracarbonylferrate in tetrahydrofuran and benzene solution at various temperatures. However, it again did not prove possible to deter the onset of dark coloration and decomposition at temperatures above 25 °C (where no reaction occurred).

Discussion

The study of symmetrical molecules capable of completely reversible Cope rearrangement has played a central role in the development of our understanding of fluxional behavior. Discovery by Doering and Roth in 1963[15] of the rapid degenerate valence isomerism in bicyclo[5.1.0]octa-2,5-diene (3,4-homotropilidene, **16**) set the stage for the subsequent elaboration of more highly bridged divinylcyclopropane systems such as bullvalene, barbaralane, semibullvalene, and many of their derivatives. That the measured barrier to Cope rearrangement in **16** (E_a = 12.6–13.0 kcal/mol, $\Delta H^{\ddagger}$ = 11.8–12.3 kcal/mol)[16,17] is somewhat higher than those of its congeners ($\Delta H^{\ddagger}$ = 4.8–13.3 kcal/mol)[18] is due to the greater thermodynamic preference for transoid conformers **16a** and

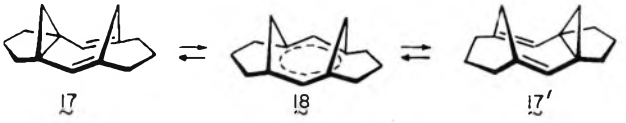


16a **16'a**

16b **16c** **16'b**

16'a (by ca. 4 kcal/mol),[9] and the electronic requirement that isomerization occur via cisoid transition state **16c**. Consequently, the experimentally determined activation parameters necessarily encompass the free energy difference between **16a** and **16b** (**16'a** and **16'b**) as well as the energy demands for 6-electron reorganization. Although 2,6-disubstitution of **16** does cause a decrease in rearrangement rate, perhaps because of steric destabilization of the cisoid conformation,[19] the influence of methyl groups at the 1,3,5, and 7 positions appears to be minimal.[9,17,20]

One structural modification which serves to constrain the homotropilidene ring system to a cisoid conformation is given in generalized form by **1**. Among the many possible members of this series, **17** was considered particularly interesting because of its unique combination of ring strain and strongly canted orbitals. Although the extent to which the trimethylene bridges would destabilize **17** and **17'** relative to **18** was not



17 **18** **17'**

known, the possibility of altering the relative stabilities of the localized and delocalized forms of this homotropilidene sufficiently to make **18** the ground state was intriguing. One consequence of the removal of the barrier to Cope rearrangement would be evolution of **18** as a neutral homoaromatic ground state species.

The effect of bracketing the 1 and 6 positions of cycloheptatriene with a trimethylene bridge, studied by Vogel,[21] is to shift the equilibrium heavily in favor of the norcaradiene form. In contrast, Paquette has shown that comparable bridging across C_2 and C_8 of semibullvalene does not lead to development of a gross equilibrium imbalance in favor of one valence isomer.[22] Rather, this highly fluxional nucleus uniquely accommodates the additional ring in a manner which generates approximately equal amounts of the two tautomers at room temperature. No bishomobenzene character is observed, but unsymmetrical substitution is not expected to be conducive to reduction of the Cope transition state energy to a negative value. The most obvious characteristic of **17** is the inherently symmetrical arrangement of the two trimethylene bridges, the resulting effect of which on valence isomerization has not heretofore been examined. The possibility that such a structural modification might merge the two valleys of tautomerism into a single valley of resonance was of especial interest.

The predescribed experimental observations clearly reveal

that dichloride **12a** does not share with its lower homologue **14** the same propensity for 1,4 reductive elimination. The difficulties accompanying introduction of the divinylcyclopropane part structure could be the result of substantially increased ground state strain in the bisannulated homotropilidene,[23] an unusual electronic structure for this hydrocarbon which renders the molecule particularly susceptible to further rapid reaction, a combination of these factors, or yet other considerations. A final resolution of these questions must await an alternate viable synthesis of **17** (**18**), or at least some further appreciation of the effect of bisannulation upon the energetics of [3,3]sigmatropic rearrangements, particularly in degenerate Cope systems.

Experimental Section

Proton magnetic resonance spectra were recorded with Varian A-60A and HA-100 instruments, while carbon magnetic resonance spectra were obtained with a Bruker 90 spectrometer. Apparent splittings are given in all cases. Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrometer, whereas mass spectra were obtained with an AEI-MS9 instrument at an ionizing potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

4-Acetyl-*s*-hydrindacene (2). Freshly distilled acetic anhydride (37.7 g, 0.37 mol) was added during 45 min to a vigorously stirred slurry of *s*-hydrindacene (28.57 g, 0.176 mol)[24] and anhydrous aluminum chloride (114.3 g, 0.857 mol) in 600 mL of 1,1,2,2-tetrachloroethane cooled to −35 °C. After 2 h the mixture was poured onto 1200 g of ice and 480 mL of concentrated hydrochloric acid. The organic phase was separated and the aqueous phase extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and brine prior to drying and solvent evaporation. Recrystallization of the residue from methanol afforded 34.8 g (97%) of **2** as colorless crystals, mp 75–78 °C (lit.[11] mp 80–81 °C).

4-Acetoxy-*s*-hydrindacene (3). A solution of *m*-chloroperbenzoic acid (35 g, 0.20 mol) in dichloromethane (450 mL, freshly distilled from $CaCl_2$) was added during 1 h to a solution of **2** (12 g, 0.06 mol) in 200 mL of the same solvent cooled to −35 °C. The mixture was allowed to warm slowly to room temperature overnight and then refluxed for 64 h. After cooling, the excess peracid was removed by washing with cold 10% sodium hydroxide solution (2 × 100 mL), water, and brine. Drying and evaporation left an oil which was chromatographed on activity I silica gel (elution with benzene). There was obtained 8.69 g (67.1%) of **3** and 2.4 g (20%) of recovered **2**. Recrystallization of **3** from ethanol and ether–pentane afforded colorless crystals: mp 75–76 °C; ν_{max} 1760 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 7.05 (s, 1), 3.06–2.73 (m, 8), 2.45 (s, 3), and 2.40–2.06 (m, 4).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.57; H, 7.45.

4-Hydroxy-*s*-hydrindacene (4). To a stirred suspension of lithium aluminum hydride (7.0 g, 0.184 mol) in anhydrous ether (150 mL) was added dropwise a solution of **3** (6.96 g, 0.032 mol) in 30 mL of ether. The mixture was heated at reflux for 6 h, cooled in ice, and treated slowly with 20% hydrochloric acid until clear. The organic phase was washed with water and brine, dried, and evaporated. The residue was sublimed (100 °C, 0.05 mm), taken up in hot 10% sodium hydroxide solution, filtered, neutralized with concentrated hydrochloric acid, and cooled to precipitate the phenol. Recrystallization from ethanol gave 4.71 g (84.5%) of **4**: mp 166–166.5 °C; δ_{Me_4Si} ($CDCl_3$) 6.76 (s, 1), 4.42 (br s, 1), 3.04–2.70 (m, 8), and 2.28–1.94 (m, 4).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.57; H, 8.00.

4-Acetamido-*s*-hydrindacene (6). A 4-g sample of **2** was treated with 10 g of hydroxylamine in 80 mL of 7% aqueous sodium hydroxide solution. The mixture was heated with stirring and enough ethanol was added to keep the compound in solution. After being heated at the reflux temperature for 2 h and cooled, the reaction mixture was diluted with water and filtered. There was isolated 3.7 g (92%) of oxime, mp 165–167 °C (lit.[25] mp 162–163 °C).

The oxime (4 g) was dissolved in a mixture of glacial acetic acid and acetic anhydride (60 mL, 1:1). While cooled in ice water, the solution was saturated with dry hydrogen chloride, left overnight (20 h) at room temperature, and diluted with water. The resulting precipitate was separated by filtration, washed with water, and recrystallized from ethanol–benzene. There was obtained 3.8 g (95%) of **6**, mp 249–250 °C (lit.[25] mp 248–250 °C).

4-Amino-*s*-hydrindacene (7). A suspension of **6** (450 mg) in 25% sulfuric acid (40 mL) was treated with sufficient ethanol (ca. 30 mL) to give an almost clear solution. This mixture was heated at reflux for 24 h, treated if necessary with charcoal, filtered while hot, cooled,[26] and neutralized with 20% sodium hydroxide solution. The precipitated amine (285 mg, 80%) was filtered and recrystallized from methanol, mp 85–86 °C.

Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73. Found: C, 83.14; H, 8.57.

4,8-Hydrindacenequinone (5). A. Fremy's Salt Oxidation of Phenol 4. A mixture of **4** (730 mg, 4.2 mmol), ether (60 mL), water (100 mL), disodium hydrogen phosphate (3.7 g), and sodium hydroxide (1.8 g) was combined at 0 °C and 2.25 g of moist nitroso disodium sulfonate[27] was added. The flask was tightly stoppered and shaken for 5 h at room temperature. Second and third 2.25-g portions of oxidant were introduced after 5 and 16 h of elapsed time, and after 19 h the mixture was separated, washed with water and brine, dried, and evaporated without heat. Elution of the residue through Florisil with toluene returned 80 mg of **4** and furnished 610 mg (86.9% based on recovered **4**) of quinone **5**. Sublimation gave bright yellow crystals: mp 148–150 °C; ν_{max}^{KBr} 1649 cm^{-1}; δ_{Me_4Si} ($(CD_3)_2CO$) 2.69 (t, J = 3.7 Hz, 8) and 2.00 (quintet, J = 3.7 Hz, 4).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.14; H, 6.53.

B. Dichromate Oxidation of Aniline 7. A solution of **7** (1.6 g, 9.2 mmol) in 400 mL of 25% sulfuric acid (heating necessary) was cooled while adding ether (100 mL) and a saturated aqueous solution of sodium dichromate (0.9 g) during 15 min. After 6–7 h at room temperature, the ether layer was separated and replaced with 100 mL of fresh solvent. After the addition of an equal amount of oxidant, the mixture was stirred overnight. The ether layer was again separated, a third portion of oxidant was added, and the mixture was immediately extracted with ether (300 mL). The combined ether layers were washed with sodium bicarbonate solution, dried, and evaporated. The dark yellow residue was treated with pentane, filtered through neutral alumina (activity 2.5), and freed of solvent. There was isolated 0.90 g of **5**, mp 148–150 °C.

Diazomethane Addition to 5. Freshly sublimed quinone (1.36 g, 7.23 mmol) was dissolved in ether (50 mL), cooled to −78 °C, treated with 45 mL of 0.49 M ethereal diazomethane, and maintained for 5 days in a sealed vessel at −3 °C. The remaining solvent was pipetted away from the crystals which had deposited and these were recrystallized from chloroform–ether to give 1.63 g (81.7%) of **8** as a fine white powder, mp 153–154 °C dec; ν_{max}^{KBr} 1715 and 1553 cm^{-1}; δ_{Me_4Si} (CD_3CN) 4.91 and 4.65 (ABq, J_{AB} = 20 Hz, 4) and 2.27–1.72 (m, 12); ^{13}C NMR (CD_3CN) 200.68, 115.46, 91.72, 60.35, 37.90, 35.26, and 21.39 ppm.

Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.65; H, 6.03; N, 20.73.

Acid Catalyzed Decomposition of Bispyrazoline 8. A solution of **8** (340 mg, 1.25 mmol) in 40 mL of glacial acetic acid was treated at room temperature with 10 drops of 70% perchloric acid. Nitrogen evolution commenced immediately. The clear yellow solution was kept at room temperature for 2 h, neutralized with sodium carbonate, and extracted with ether. The concentrated extract was chromatographed on neutral alumina (activity 2.5), elution with pentane–ether (10:1) affording 140 mg (47%) of **9** as a crystalline solid, mp 222 °C dec; ν_{max}^{KBr} 3240 and 1635 cm^{-1}; the ^{1}H NMR spectrum clearly revealed the N–*H* proton at δ 5.6 and the olefinic proton at 6.3.

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.73; H, 6.60. Found: C, 68.75; H, 6.54.

Photochemical Decomposition of 8. Bishomoquinone 10. A solution of bispyrazoline **8** (56 mg, 0.206 mmol) in dry distilled acetone (400 mL) was irradiated through Pyrex with a 450-W Hanovia lamp for 8 h. The concentrated residue was chromatographed on alumina (activity 2.5; elution with ether–hexane (1:1)) to give 42 mg (94.2%) of **10**: mp 149–150 °C; ν_{max}^{KBr} 1678 and 1662 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 2.31 and 1.23 (ABq, J_{AB} = 3.5 Hz, 4) and 2.12–1.93 (m, 12); ^{13}C NMR ($CDCl_3$) 203.88, 46.88, 28.50, 23.83, and 19.48 ppm.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.63; H, 7.83.

Lithium Aluminum Hydride Reduction of 10. A solution of **10** (50 mg, 0.23 mmol) in anhydrous tetrahydrofuran (3 mL) was added to lithium aluminum hydride in 5 mL of the same solvent under nitrogen. The mixture was heated at reflux for 100 min, cooled, and treated with 0.4 mL of water and 0.4 mL of 15% sodium hydroxide solution, and filtered. Solvent removal afforded a residue which was recrystallized from chloroform–pentane (2:1) to give 49 mg (96.4%) of diol mixture. Repeated recrystallization from chloroform (or preparative TLC isolation) afforded pure trans diol **11**: mp 183–185 °C; ν_{max}^{KBr} 3360 and 3320 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 4.33 (m, 2), 2.22–2.01 (m,

4), 1.82–1.13 (m, 10), 0.58 (d, J = 6.2 Hz, 2), and 0.33 (d, J = 6.2 Hz, 2); ^{13}C NMR ($CDCl_3$) 73.67, 66.09, 37.63, 35.53, 34.53, 29.14, 20.58, and 13.65 ppm.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.86; H, 9.09.

Conversion of 11 to *cis*-Dichloride 12a. A 101 mg (0.46 mmol) sample of diol **11** was dissolved with heating in 150 mL of benzene and 10 mL of chloroform under nitrogen. A mixture of nitrogen and dry hydrogen chloride was bubbled through this solution at 0 °C for 2 h. Evaporation of solvent and sublimation of the residue at 68–70 °C and 5×10^{-3} Torr afforded 117 mg (99.2%) of **12a** as a white solid: mp 123–125 °C dec; δ_{Me_4Si} (CCl_4) 4.52 (s, 2), 2.28–2.04 (m, 4), 1.74–1.42 (m, 8), 1.04 (d, J = 7 Hz, 2), and 0.63 (d, J = 7 Hz, 2); ^{13}C NMR ($CDCl_3$) 69.01, 44.24, 35.39, 20.61, and 17.48 ppm.

Anal. Calcd for $C_{14}H_{18}Cl_2$: C, 65.38; H, 7.05. Found: C, 65.28; H, 6.99.

***syn*-Dimethanoperhydro-*s*-hydrindacene (13).** A solution of **12a** (62 mg, 0.33 mmol) in 1 mL of dry diglyme was introduced into a vigorously stirred solution of sodium borohydride (750 mg, 19.7 mmol) in 65% aqueous diglyme (5 mL) during 15 min at room temperature. Stirring was continued for another 30 min prior to pouring into water (20 mL) and extraction with pentane (5 × 20 mL). The combined organic phases were washed with water (3 × 5 mL), dried, and carefully evaporated. Analysis of the product by VPC (2 m 6.5% Se-30, 90 °C) revealed the presence of two components in a 9:1 ratio. The main component was isolated by preparative VPC (25 mg, 60%) and shown to be the cis hydrocarbon **13** by spectral comparison. The minor constituent was not identified, although it was established that it is not the trans hydrocarbon.

Solvolysis of 12a in Methanol. A solution of **12a** (84 mg, 0.33 mmol) in methanol (5 mL) was treated with a small amount of sodium carbonate and stirred at room temperature under a dry argon atmosphere for 3 h. The mixture was filtered and evaporated. Molecular distillation of the residue (75 °C, 0.005 mm) gave 36 mg (44.3%) of **12c**: δ_{Me_4Si} (THF-d_8) 3.82 (s, 2), 3.35 (s, 6), 2.39–0.72 (m, 12), 0.54 (d, J = 6 Hz, 2), and 0.37 (d, J = 6 Hz, 2); m/e 248.1781 (calcd 248.1776).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 76.69; H, 9.70.

Sodium Borohydride Reduction of 10. A solution of **10** (806 mg, 3.73 mmol) and sodium borohydride (5 g) in 300 mL of 2-propanol was heated at reflux for 18 h, evaporated, and partitioned between water and dichloromethane. The organic phase was dried and evaporated to leave a residue which was recrystallized twice from chloroform. There was obtained 350 mg (42.7%) of cis diol **12b**: mp 210–212 °C; ν_{max}^{KBr} 3380 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 3.19 (s, 2), 2.07–0.96 (br m, 14), 0.92 (d, J = 5.7, Hz, 2), and 0.27 (d, J = 5.7 Hz, 2).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.86; H, 9.09.

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Registry No.—**2,** 63089-52-1; **3,** 63089-53-2; **4,** 63089-54-3; **5,** 63089-55-4; **6,** 63122-46-3; **7,** 63089-56-5; **8,** 63089-57-6; **9,** 63089-58-7; **10,** 63089-59-8; **11,** 63089-60-1; **12a,** 63089-61-2; **12b,** 63121-83-5; **12c,** 63089-62-3; diazomethane, 334-88-3.

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The Anomalous Course of the Reduction of Diphenyl-2,2′-disulfonyl Chloride. An Old Mystery Reexamined and Explained

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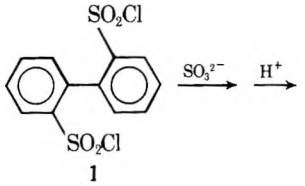
It has been known for many years that the reduction of diphenyl-2,2′-disulfonyl chloride (1) with sodium sulfite, followed by acidification of the reaction solution, gives not the expected diphenyl-2,2′-disulfinic acid (2), but rather the cyclic thiolsulfonate 3; the reasons for this anomalous behavior have, however, remained a mystery. We have now shown unambigously that the sequence of events involved in the conversion of 1 to 3 is as follows: (1) reduction of 1 with excess sulfite leads, as expected, to disodium diphenyl-2,2′-disulfinate (2-Na); (2) acidification of the aqueous reaction mixture containing 2-Na leads to the initial separation of disulfinic acid 2 as a second phase; (3) in this second phase the equilibrium constant for the formation of the cyclic sulfinyl sulfone 11 from 2 is large enough so that at equilibrium a considerable fraction of the disulfinic acid is present as 11; (4) once formed, the cyclic sulfinyl sulfone 11 is reduced to 3 by the excess sulfite (now present as H_2SO_3 and $NaHSO_3$) left over from the original reduction of 1. A similar sequence of reactions is thought also to be involved in those reductions of other disulfonyl chlorides by sulfite that have been reported (ref 2) to lead to cyclic thiolsulfonates rather than disulfinic acids. One also predicts that formation of a cyclic thiolsulfonate, rather than a disulfinic acid, will be the end result of the sulfite reduction of any other disulfonyl chlorides where the equilibrium constant for formation of the cyclic sulfinyl sulfone from the disulfinic acid is sufficiently favorable.

One of the standard synthetic routes for the preparation of aromatic sulfinic acids is the reduction of the corresponding sulfonyl chloride with excess sodium sulfite in a weakly alkaline solution, followed by acidification of the resulting solution to convert the aromatic sulfinate to the sulfinic acid; the sulfinic acid normally precipitates from the final solution.

$$ArSO_2Cl \xrightarrow{\text{excess } SO_3^{2-}} ArSO_2^- \xrightarrow{H^+} ArSO_2H \qquad (1)$$

In 1928 Barber and Smiles[1] reported that when diphenyl-2,2′-disulfonyl chloride (1) was reduced with sulfite and the solution subsequently acidified, what was isolated was not the expected diphenyl-2,2′-disulfinic acid (2), but rather the cyclic thiolsulfonate 3, dibenzo [c,e]-1,2-dithiin 1,1-dioxide (eq 2).



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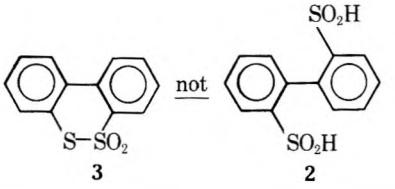
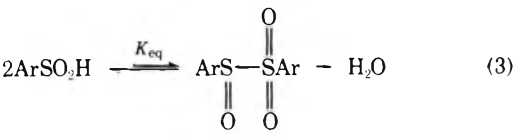


3 2 (2)

A similar result was obtained in 1956 by Armarego and Turner[2a] upon reduction of the closely related compound 4,4′,6,6′-tetramethyldiphenyl-2,2′-disulfonyl chloride with sulfite, and a year later the same workers[2b] also reported another instance where reduction of an aromatic disulfonyl chloride with sulfite led eventually to a cyclic thiolsulfonate. Although the anomalous behavior of 1 and related disulfonyl chlorides upon reduction with sulfite has thus been known for many years, the reasons for it have remained unknown.

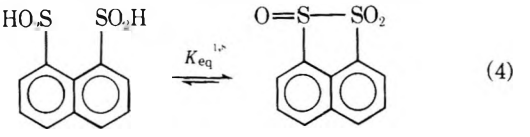
Recent work by Kice and Margolis[3] has revealed that, while the equilibrium constant for formation of the corresponding sulfinyl sulfone 4 from ordinary aromatic sulfinic acids (eq 3) in 60% aqueous dioxane is so small that the concentration of sulfinyl sulfone present at equilibrium is undetectable (<0.01%), the equilibrium constant for formation of the cyclic



(3)

4

sulfinyl sulfone 6, naphthol[1,8-*cd*]-1,2-dithiole 1,1,2-trioxide, from naphthalene-1,8-disulfinic acid (eq 4), is many orders



(4)

5 6

of magnitude larger, and at equilibrium in 60% dioxane almost 75% of the material is present as the sulfinyl sulfone.

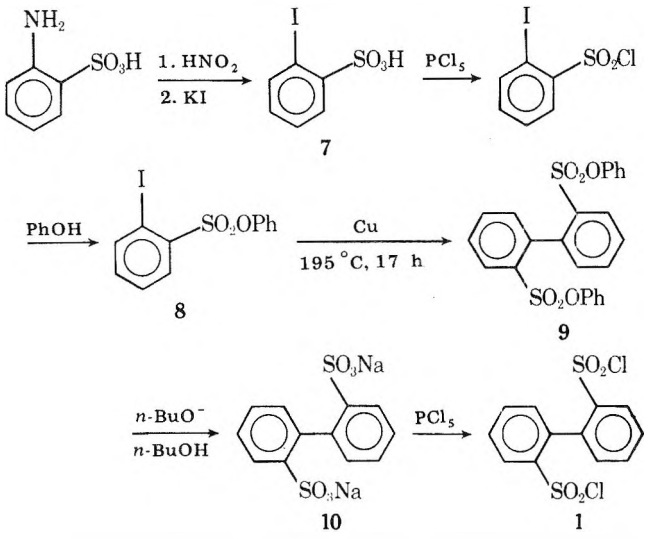
This demonstration that with appropriately structured disulfinic acids the cyclic sulfinyl sulfone can be strongly favored over the disulfinic acid, even in highly aqueous media, led us to wonder about whether a similar situation might exist for disulfinic acid 2, and whether this might not in some way lie at the root of the peculiar behavior observed upon reduction of disulfonyl chloride 1 with sulfite and subsequent acidification of the solution.

We therefore decided to carry out a careful reinvestigation of the system originally studied by Barber and Smiles[1] in order to find out exactly how cyclic thiolsulfonate 3 arose. The present paper describes the results of that study and outlines the solution to the almost 50-year-old mystery of the origin of 3. The nature of the explanation is such as to suggest that it is also in general applicable to the disulfonlyl chlorides studied by Armarego and Turner.[2] It also suggests that similar anomalous behavior upon sulfite reduction is likely to be encountered with many other appropriately structured disulfonyl chlorides.

Results and Discussion

Synthesis of Diphenyl-2,2′-disulfonyl Chloride. The synthesis of disulfonyl chloride 1 is outlined in Scheme I. Despite numerous attempts we were unable to repeat the reported[1] coupling of iodosulfonic acid 7 directly to 10. We therefore resorted to the type of route for coupling used by Armarego and Turner,[2] converting 7 to its phenyl ester 8 and

Scheme I. Synthesis of Diphenyl-2,2′-disulfonyl Chloride



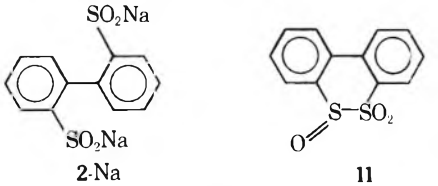
then coupling this to give **9** in good yield (77%), using copper powder at an elevated temperature. Treatment of **9** with excess sodium *n*-butoxide in *n*-butyl alcohol gave **10**; this was converted to the desired disulfonyl chloride **1** using phosphorus pentachloride.

The melting point of the **1** which we obtained (144–145 °C) was somewhat higher than that reported by Barber and Smiles[1] (138 °C). However, the various spectral and analytical data for our material left no doubt that it was in fact **1**; the compound prepared by Barber and Smiles[1] was therefore apparently somewhat impure.

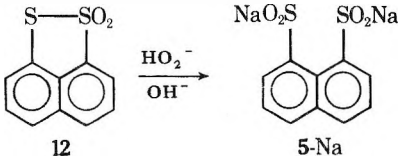
Reduction of Diphenyl-2,2′-disulfonyl Chloride with Sodium Sulfite. Upon heating a suspension of disulfonyl chloride **1** in a weakly alkaline aqueous solution containing a 25-fold excess of sodium sulfite, the disulfonyl chloride gradually dissolves and a colorless, clear solution results. Acidification of this solution with sulfuric acid to a pH of <1 causes the solution quickly to become cloudy as a second phase separates. If the mixture is warmed briefly, the cloudy suspension coagulates to a well-defined precipitate which, when filtered off, proves to be pure **3**, and is obtained in 93% yield. It is thus clear that **1** yields **3** quantitatively. No significant amount of any other organic product is formed.

The cyclic thiolsulfonate **3** has a relatively sharp, long-wavelength absorption maximum, λ_{max} 296 nm (ϵ 8.7 × 10^3), which is useful in distinguishing it from the other compounds to be encountered in this study.

Preparation of Disodium Diphenyl-2,2′-disulfinate and the Cyclic Sulfinyl Sulfone Derived from Diphenyl-2,2′-disulfinic Acid. To investigate the details of the conversion of **1** to **3** we had to have pure samples of both disodium diphenyl-2,2′-disulfinate (**2**-Na) and the cyclic sulfinyl sulfone (**11**) derived from diphenyl-2,2′-disulfinic acid.

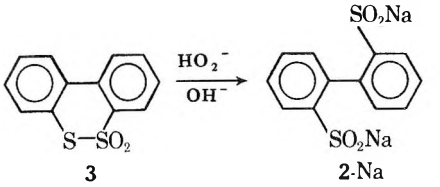


Previous work by Kice and Margolis[3] has shown that disodium naphthalene-1,8-disulfinate (**5**-Na) can be prepared in quantitative yield by reaction of the cyclic thiolsulfonate **12** with hydrogen peroxide anion (eq 5). Treatment of cyclic



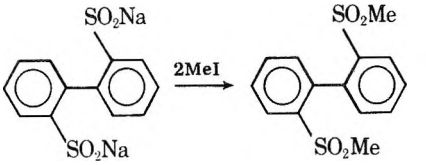
(5)

thiolsulfonate **3** with 1 mol each of HO_2^- and OH^- in aqueous dioxane at room temperature led to the formation of **2**-Na in quantitative yield (eq 6). The identity of **2**-Na was proven both



(6)

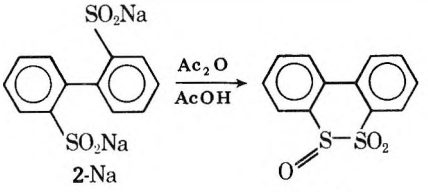
by its spectral properties and by its alkylation with methyl iodide to give the dimethyl sulfone **13** (eq 7). It was also further



(7)

substantiated by the conversion of **2**-Na to sulfinyl sulfone **11** discussed below.

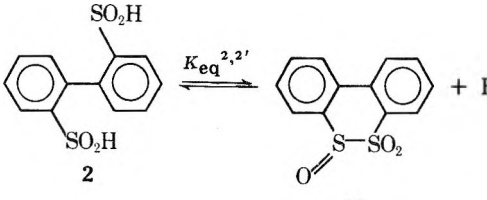
Disodium diphenyl-2,2′-disulfinate (**2**-Na) was treated with a mixture of equal volumes of glacial acetic acid and acetic anhydride. After removal of the excess acetic acid and anhydride the residue was extracted with chloroform to separate the sulfinyl sulfone from the sodium acetate that had also been formed. Workup of the chloroform extract yielded the cyclic sulfinyl sulfone **11**, dibenzo[c,*e*]-1,2-dithiin 1,1,2-trioxide, in 65% yield (eq 8). All spectral and analytical data were in accord



(8)

with those expected for **11**. The cyclic sulfinyl sulfone has a long-wavelength absorption maximum at 310 nm (ϵ 5400) that can be used very conveniently to detect its presence in dilute solutions and also to distinguish it easily from cyclic thiolsulfonate **3**.

The Diphenyl-2,2′-disulfinic Acid–11 Equilibrium. As noted earlier, Kice and Margolis[3] found that acidification of a dilute (10^{-4} M) 60% dioxane solution of **5**-Na resulted in a mixture of **5** and **6** (eq 4) in which 75% of the material was present as the sulfinyl sulfone **6**. In contrast, acidification of a 10^{-4} M solution of disodium diphenyl-2,2′-disulfinate (**2**-Na) in 60% dioxane led to a situation where no significant fraction of the material was present as sulfinyl sulfone **11**. Clearly, then, the equilibrium constant for the equilibrium between **2** and **11** (eq 9) is much smaller than K_{eq}[1,8] for the equilibrium between **5** and **6**.



(9)

$$K_{eq}^{2,2'} = [11]/[2]$$

One should also note that we found *no* evidence that **2** alone upon standing in acidic aqueous dioxane forms any significant amount of cyclic thiolsulfonate **3**.

Although K_{eq} for the **2**–**11** equilibrium (eq 9) is much smaller than that for the **5**–**6** equilibrium (eq 4), experiments in acetic acid–water solvent demonstrate that it is at the same

time *much larger* than K_{eq} for the equilibrium between an ordinary aromatic monosulfinic acid and its sulfinyl sulfone shown in eq 3.

When **2**-Na (10^{-4} M) was dissolved in acetic acid–5% water–0.10 M H_2SO_4 the absorbance of the solution at 310 nm increased from an initial value of 0.03 and finally leveled off at an equilibrium value of 0.33, owing to the conversion of **2** to an equilibrium mixture of **2** and **11** where the ratio [**11**]/[**2**] = 1.4 ± 0.2. The same value for $([11]/[2])_{equil}$ was also obtained by dissolving a sample of **11** (10^{-4} M) in the same solvent and observing the decrease in absorbance at 310 nm until it leveled off at a final constant value.

From earlier studies[4] one can estimate[5] that for the equilibrium in eq 3 (Ar = Ph), $K_{eq} = [PhS(O)SO_2Ph]/[PhSO_2H]^2 = 0.0023$ in acetic acid–5% water–0.10 M H_2SO_4. This means that K_{eq} for the **2**–**11** equilibrium (1.4 ± 0.2) is about 600 times larger than the equilibrium constant for sulfinyl sulfone formation from benzenesulfinic acid. A single experiment in acetic acid–1% water–0.10 M H_2SO_4 which indicated $([11]/[2])_{equil} \cong 8$ in that medium, as compared with $[PhS(O)SO_2Ph]/[PhSO_2H]^2 = 0.0133$ previously measured[4b] for $PhSO_2H$ under the same conditions, suggests that generally K_{eq} for the **2**–**11** equilibrium is about 600 times larger than that for the $PhSO_2H$–$PhS(O)SO_2Ph$ equilibrium.

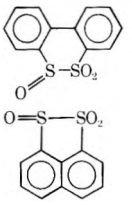
Rate of Spontaneous Hydrolysis of Sulfinyl Sulfone 11. The rate of spontaneous hydrolysis of **11** in 60% dioxane can be conveniently monitored by observing the decrease in absorbance at 310 nm and follows excellent first-order kinetics. The results are shown in Table I together with data on the rates of spontaneous hydrolysis of phenyl benzenesulfinyl sulfone and cyclic sulfinyl sulfone **6** in the same solvent.[3,6] One sees that the rates of hydrolysis of the three sulfinyl sulfones differ by only a factor of 20, the open-chain compound hydrolyzing about ten times faster than **11**, while the latter hydrolyses about twice as fast as the 1,8-naphthalene derivative **6**.

These results show that the large differences in K_{eq} for sulfinyl sulfone formation among the different compounds are only in modest measure due to differences in the rates of hydrolysis of the different sulfinyl sulfones. The major factor is, as seems quite reasonable, differences in the rates of formation of the sulfinyl sulfone from the corresponding sulfinic acids.

Behavior of Disodium Diphenyl-2,2′-disulfinate upon Acidification in the Presence of Sulfite. A 60% dioxane solution of disodium diphenyl-2,2′-disulfinate (**2**-Na 10^{-4} M) and a 20-fold excess of sodium sulfite was allowed to stand for several hours at room temperature. There was no change in the UV spectrum of the solution, indicating that **2**-Na and sulfite do not react. The solution was then acidified with aqueous sulfuric acid until $[H^+] = 0.1$ M. A strong peak, previously shown by experiments involving sulfite alone to be due to H_2SO_3, appeared in the spectrum. To determine if any **3** or **11** had been formed, the H_2SO_3 was purged from the solution. Examination of the ultraviolet spectrum after the H_2SO_3 had been removed showed that no detectable amount of either **3** or **11** had been formed. The spectrum was the same as that observed previously when a dilute aqueous dioxane solution of **2**-Na alone was acidified. This shows conclusively that diphenyl-2,2′-disulfinic acid (**2**) itself does *not* react with either H_2SO_3 or HSO_3^- to give cyclic thiolsulfonate **3**.

At this point we began to wonder whether or not **2**-Na was in fact the product formed from disulfonyl chloride **1** upon sulfite reduction, since, at least in experiments in homogeneous solution, **2**-Na showed no tendency to go over upon acidification to thiolsulfonate **3**, either in the presence or absence of sulfite. Proof that **2**-Na is indeed the product of the reduction of **1** by sulfite was provided by the experiment described in the following paragraph.

Table I. Rates of Spontaneous Hydrolysis of Selected Sulfinyl Sulfones in 60% Aqueous Dioxane[a]

Compd	$k_{hyd} \times 10^3$, s^{-1}
$PhS(O)SO_2Ph$	16
	1.6
	0.7

[a] Data are for 25 °C.

Proof That Disodium Diphenyl-2,2′-disulfinate Is the Product of the Reduction of Diphenyl-2,2′-disulfonyl Chloride by Sulfite. A sample of disulfonyl chloride **1** was reduced with excess sulfite in the usual manner and a small portion of the final clear reaction solution was added to 100 times its volume of anhydrous dioxane to make a solution 10^{-4} M in the reduction product of **1**. The excess sulfite could then be removed by filtration because sodium sulfite is quite insoluble in anhydrous dioxane. That the reduction product was the disulfinate **2**-Na was then demonstrated by treating the dilute solution of the reduction product in anhydrous dioxane with some acetic anhydride. This led to the immediate rapid development of the 310-nm peak in the ultraviolet spectrum of the solution associated with the formation of the cyclic sulfinyl sulfone **11**. The final intensity of the peak was approximately that expected if reduction of **1** by sulfite leads entirely to **2**-Na.

We had previously shown in a separate experiment that addition of the same amount of acetic anhydride to a dilute (1×10^{-4} M) solution of an authentic sample of disulfinate **2**-Na in anhydrous dioxane did in fact lead to the formation of the 310-nm peak associated with **11**.

Thus, we can state with confidence that the reduction of disulfonyl chloride **1** by sulfite in weakly alkaline solution results in the formation of disulfinate **2**-Na. The problem now is to explain why acidification of the final reaction mixture from this reduction (a concentrated aqueous solution of **2**-Na plus excess sodium sulfite) leads to **3**, when acidification of **2**-Na in a dilute aqueous dioxane solution, either in the presence or absence of sulfite, does not.

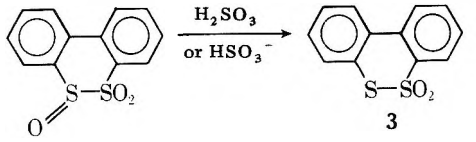
Acidification of a Concentrated Aqueous Solution of Disodium Diphenyl-2,2′-disulfinate. Acidification of a relatively concentrated (0.1 M) *aqueous* solution of disulfinate **2**-Na led to the immediate separation of a second phase, presumably *initially* disulfinic acid **2**. This second phase was extracted using chloroform, and the extract dried. Addition of hexane to the chloroform solution led to the separation in 60% yield of material shown by spectral examination to consist of a mixture of disulfinic acid **2** and sulfinyl sulfone **11**, in which the latter predominated. Equally important, a TLC on the chloroform extract prior to the addition of hexane showed that it contained *no detectable amount* of cyclic thiolsulfonate **3**.

Thus, in marked contrast to the situation in aqueous dioxane, in the second, "sulfinic acid" phase which separates on acidification of a *purely* aqueous solution of **2**-Na there is present at equilibrium along with disulfinic acid **2** a significant amount of the cyclic sulfinyl sulfone **11**. The [**11**]/[**2**] ratio at equilibrium in this phase is thus akin to the type of situation found in acetic acid–5% water, and very different from that in media of much higher water content such as aqueous dioxane.

However, the lack of formation of any cyclic thiolsulfonate **3** under these conditions, even though a substantial fraction

of the disulfinic acid is present as **11**, shows that one other ingredient is necessary before **3** can be formed at a significant rate. As the experiments in the next section show, that ingredient is the excess sulfite present at the end of the reduction of **1** by Na_2SO_3.

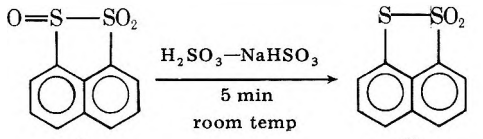
Reduction of Cyclic Sulfinyl Sulfones 11 and 6 by Sulfite in Acid Solution. An aqueous solution of disulfinate **2**-Na (0.12 M) and sodium sulfite (1.2 M) was acidified with aqueous sulfuric acid. A second phase separated immediately. The mixture was stirred for about 30 min at room temperature. The second phase was then removed and examined. Upon recrystallization cyclic thiolsulfonate **3** was obtained in 88% yield. Since the only difference between this experiment and the one described in the preceding section is the presence of sulfite, and since we have already shown that the disulfinic acid **2** is itself not affected by either H_2SO_3 or $NaHSO_3$, the obvious conclusion is that sulfite (as either H_2SO_3 or HSO_3^-) is capable of reducing sulfinyl sulfone **11** to thiolsulfonate **3** (eq 10), and that it is this reduction which



11 3 (10)

is the final key step in the formation of **3** upon the reduction of **1** with excess sulfite and subsequent acidification of the reaction solution.

The relatively rapid spontaneous hydrolysis of **11** to **2** in aqueous dioxane makes it inconvenient to explore the proposed reaction shown in eq 10 in homogeneous aqueous dioxane medium. However, with cyclic sulfinyl sulfone **6** hydrolysis of the sulfinyl sulfone in acidic aqueous dioxane is not a problem, since, as noted earlier, **6** is strongly favored at



6 12 81% (11)

equilibrium over its hydrolysis product, disulfinic acid **5**. Using **6** as the substrate one can therefore easily explore in a homogeneous solution whether a sulfinyl sulfone can in fact be readily reduced to the corresponding thiolsulfonate by an acidified solution of sodium sulfite in aqueous dioxane.

Treatment of a solution of sulfinyl sulfone **6** (0.020 M) in acidic ([H^+] = 0.1 M) 60% dioxane with a solution of H_2SO_3 and $NaHSO_3$ ([total sulfite] = 0.5 M) in the same solvent, after 5 min at room temperature, gave upon workup an 81% yield of the corresponding cyclic thiolsulfonate **12** (eq 11). This experiment demonstrates unambiguously that a sulfinyl sulfone can be reduced easily to the corresponding thiolsulfonate by an acid solution containing sulfite. The existence of the reaction involving **11** and H_2SO_3 or $NaHSO_3$ shown in eq 10 would therefore seem to be proven beyond any reasonable doubt.

We do not as yet know anything definite about the mechanism of this reduction of sulfinyl sulfones by H_2SO_3 or $NaHSO_3$. Some speculative possibilities are discussed briefly in a footnote.[7]

Conclusions

The 50-year-old mystery[1] of the origin of the cyclic thiolsulfonate **3** formed upon reduction of diphenyl-2,2′-disulfonyl chloride (**1**) with sodium sulfite followed by acidification of the reaction solution has now been solved. The initial reduction of **1** by sulfite does indeed give disodium diphenyl-2,2′-disulfinate (**2**-Na), the expected, "normal" product of reduction of the disulfonyl chloride by sulfite. If acidification of the reaction mixture containing the disulfinate and excess sodium sulfite is carried out under conditions where both the disulfinic acid **2** formed on protonation of **2**-Na does not separate as a second phase, and also in a medium where the water concentration is high, then no **3** is formed, because the disulfinic acid **2** itself does not give **3**, either in the presence or absence of sulfite. On the other hand, the usual procedure of acidification of a concentrated aqueous solution of **2**-Na leads to the separation of disulfinic acid **2** as a second, separate phase, and in this second phase conditions are such that at equilibrium a substantial fraction of the disulfinic acid goes over to the cyclic sulfinyl sulfone **11** (eq 9). The excess sulfite left over from the original reduction of the disulfonyl chloride, and now present as a mixture of H_2SO_3 and $NaHSO_3$, then readily reduces sulfinyl sulfone **11** to thiolsulfonate **3** (eq 10).

Although unambigously established only for the transformation of disulfonyl chloride **1** to thiolsulfonate **3**, a similar sequence of events would seem almost certain to be involved in those other cases[2] in which sulfite reduction of an aromatic disulfonyl chloride has been reported to lead to a cyclic thiolsulfonate. Furthermore, one might well expect that analogous behavior, i.e., formation of cyclic thiolsulfonates, will be observed upon sulfite reduction of any disulfonyl chloride where the equilibrium constant for sulfinyl sulfone formation from the resulting disulfinic acid is large enough so that there will be a significant amount of the sulfinyl sulfone present at equilibrium. This sulfinyl sulfone will then undergo reduction by H_2SO_3 or HSO_3^- to the corresponding thiolsulfonate.

Experimental Section

General. *p*-Dioxane was purified according to the procedure of Hess and Frahm;[9] the freshly distilled dioxane was frozen and stored at −20 °C to prevent the formation of peroxides prior to use. Acetic acid was purified by a procedure described by Wiberg:[10] refluxing with acetic anhydride for 24 h followed by careful fractional distillation, only the middle third of the distillate, bp 115–116 °C, being retained. All water used in kinetic studies was doubly distilled from glass. The purity of the concentrated sulfuric acid used was determined by titration.

2-Iodobenzenesulfonic Acid (7). Commercial aniline-2-sulfonic acid (48 g, 0.25 mol) was dissolved in 300 mL of water and anhydrous sodium carbonate (14 g, 0.132 mol) was added with stirring until a homogeneous solution was obtained. Sodium nitrite (20 g, 0.28 mol) was then added to this solution and dissolved. After cooling to 0 °C the solution was added to 50 mL of concentrated hydrochloric acid plus 250 g of crushed ice. Immediate precipitation of the diazonium salt was observed. A solution of potassium iodide (50 g, 0.30 mol) in 50 mL of water was then added slowly with stirring. The mixture was allowed to warm slowly to room temperature and then heated to boiling to remove all nitrogen. Upon concentration of the solution crystalline **7** was obtained in 78% yield (55 g, 0.195 mol): mp 344–345 °C; IR (KBr) 3497 (m) and 1210 cm^{-1} (s).

2-Iodobenzenesulfonyl Chloride. Sulfonic acid **7** was neutralized by titration with sodium hydroxide solution in order to obtain sodium 2-iodobenzenesulfonate. This salt was dried in vacuo (0.1 Torr) at 150 °C for 3 h. Treatment of the sodium salt (10 g, 32.7 mmol) with phosphorus pentachloride (10 g, 48 mmol) at room temperature gave, after a few minutes, a liquid mixture with the generation of heat. After distilling off the phosphorus oxychloride that had been formed at reduced pressure, the sulfonyl chloride was collected by distillation at 135 °C (1 Torr). It was recrystallized from chloroform and hexane to give 8.0 g (80%) of 2-iodobenzenesulfonyl chloride: mp 51.5–52.5 °C; IR (KBr) >SO_2 group absorptions at 1362 (s) and 1178 cm^{-1} (s); mass spectral peaks at 60 °C and 20 eV (intensity), *m/e* 304 (M^+, 18.2), 302 (M^+, 53.5), 267 (M^+ − Cl, 44.1), 203 (M^+ − SO_2Cl, 100), 127 (I, 17.9), 113 (10.7), 111 (31.9), and 76 (C_6H_4, 96.4).

Phenyl 2-Iodobenzenesulfonate (8). 2-Iodobenzenesulfonyl chloride (4.4 g, 14.5 mmol) was mixed with phenol (2.8 g, 29.8 mmol) and anhydrous sodium carbonate (2.4 g, 22.6 mmol) at room temperature. After heating to 120 °C for 1.5 h, the excess phenol was distilled off at reduced pressure, and the residue was crystallized from chloroform and hexane. Compound **8** was obtained in 96% yield (5.0

g, 13.9 mmol): mp 91.5–92.5 °C; IR (KBr) >SO_2 group absorptions at 1371 and 1198 cm^{-1}; mass spectral peaks at 60 °C and 20 eV (intensity), *m/e* 360 (M^+, 34.2), 267 ($M^+ - OC_6H_5$, 38.1), 203 ($M^+ - SO_2OC_6H_5$, 64.1), and 76 (C_6H_4, 35.0).

Diphenyl Diphenyl-2,2′-disulfonate (9). Compound 8 (25 g, 69.4 mmol) was mixed with 25 g of copper dust, and the mixture was heated to 195 °C for 17 h with occasional stirring. After cooling back to room temperature, the mixture was extracted with chloroform for 10 h in a Soxhlet extractor. Crystalline **9** was obtained from the chloroform extract upon addition of hexane in 78% yield (12.7 g, 54.1 mmol): mp 127–128 °C; IR (KBr) >SO_2 group absorptions at 1376 (s) and 1158 cm^{-1} (s). The mass spectrum of the compound (140 °C and 70 eV) does not show a molecular ion peak, the highest *m/e* peak observed being at 373 ($M^+ - OC_6H_5$). However, the conversion of **9** to disulfonyl chloride **10** and the analytical data on the disulfonyl chloride leave no doubt that **9** has the structure assigned to it.

Diphenyl-2,2′-disulfonyl Chloride (1). Compound **9** (29 g, 62.2 mmol) was suspended in 100 mL of *n*-butyl alcohol, and a solution of sodium *n*-butoxide, prepared by dissolving 5 g (0.22 g-atom) of sodium metal in 250 mL of *n*-butyl alcohol, was added. The mixture was heated under reflux for 14 h. At the end of this time 300 mL of *n*-butyl alcohol was distilled off and the residue was added to 250 mL of water. After filtering, the solution was acidified with concentrated hydrochloric acid to pH 1. It was then extracted three times with 100-mL portions of ether in order to remove phenol. The acidic aqueous solution was then neutralized with 10% sodium hydroxide to pH 7 and evaporated to dryness. Without further purification the crude disodium diphenyl-2,2′-disulfonate was dried in vacuo (0.1 Torr) at 150 °C for 8 h. The crude powdered salt was then treated with 26 g (0.125 mol) of phosphorus pentachloride. This resulted in the generation of heat and the formation of a thick slurry. After distilling off the phosphorus oxychloride that had been formed under water pump vacuum, the solid residue was dissolved by treating it with a mixture of chloroform and 10% aqueous sodium carbonate. The chloroform layer was removed, filtered, and the filtrate dried over magnesium sulfate. Crystalline **1** was obtained from the chloroform solution upon addition of hexane in 78% yield (17.0 g): mp 144–145 °C; IR (KBr) SO_2 group absorptions at 1371 (s) and 1179 cm^{-1} (s). Anal. Calcd for $C_{12}H_8S_2O_4Cl_2$: C, 41.04; H, 2.30; Cl, 20.19. Found: C, 40.98; H. 2.19; Cl, 20.08. Compound **1**, like diester **9**, does not show a molecular ion peak in its mass spectrum (150 °C, 20 eV). The highest *m/e* peak observed is at *m/e* 315 (M^+ − Cl) and the strongest peak is at *m/e* 251 ($M^+ - SO_2Cl$). However, the elemental analysis data above leave no doubt that the compound is in fact the disulfonyl chloride **1**, even though its melting point is a few degrees higher than that previously reported for **1** by Barber and Smiles.[1]

Dibenzo[*c,e*]-1,2-dithiin 1,1-Dioxide (3). Disulfonyl chloride **1** (11.4 g, 32.6 mmol) was suspended in 400 mL of 30% sodium sulfite solution (25-fold excess), and 45 mL of 10% NaOH was added. After heating under reflux for 1 h a clear, colorless solution was obtained. This was filtered and then acidified slowly by addition of concentrated sulfuric acid in the cold until the pH of the solution was <1.0. The resulting white cloudy mixture was heated slowly with stirring until the supernatant liquid was clear again. The white precipitate which had separated was collected and recrystallized from chloroform–hexane to afford 7.4 g (93%) of cyclic thiolsulfonate **3**: mp 132–133 °C; IR (KBr) SO_2 absorptions at 1310 (s), 1161 (m), and 1123 cm^{-1} (s); UV (60% dioxane) λ_{max} 296 (ε 8660) and 262 nm (ε 9330); mass spectral peaks at 75 °C and 70 eV (intensity), *m/e* 248 (M^+, 42.3), 184 ($M^+ - SO_2$, 100), 152 ($M^+ - S_2O_2$, 16.1), and 139 (42.9). Anal. Calcd for $C_{12}H_8S_2O_2$: C, 58.04; H, 3.25; S 25.82. Found: C, 57.95; H, 3.16; S, 25.91.

Disodium Diphenyl-2,2′-disulfinate (2-Na). Cyclic thiolsulfonate **3** (2.5 g, 10 mmol) was dissolved in 30 mL of pure dioxane, and a mixture of 1.14 mL of 30% hydrogen peroxide and 20 mL of 1 N NaOH solution was added to the dioxane solution of **3** with stirring. Reaction appeared to be immediate. The solvents were removed by evaporation under reduced pressure, with the final traces of solvent being removed by heating the sample at 50 °C for 12 h under 0.05-Torr pressure. The salt was obtained in quantitative yield: mp 145–146 °C dec; IR (KBr) 1016 (s) and 958 cm^{-1} (s). Positive identification of the structure of **2**-Na was provided by its conversion to (a) dimethyl diphenyl-2,2′-disulfone and (b) dibenzo[c,e]-1,2-dithiin 1,1,2-trioxide in the experiments described in the next two paragraphs.

Dimethyl Diphenyl-2,2′-disulfone (13). Treatment of disulfinate 2-Na (1.3 g, 4.0 mmol) in 25 mL of pure methanol with methyl iodide (2 mL, 32.1 mmol) under reflux for 5 h gave a brownish solution. After removing all the solvent, the brownish residue was dissolved in 25 mL of chloroform and the chloroform solution extracted once with 10% sodium sulfite to remove traces of iodine. The chloroform layer was concentrated and then chromatographed through a column of silica gel (150 g) using benzene as eluent. The fractions containing disulfone **13** were combined and evaporated to dryness. An NMR spectrum and integral of the crude oily residue (1.3 g) showed that the disulfone was about 90% pure. After standing at room temperature for 2 days the disulfone finally began to crystallize. The first crop of crystals was recrystallized from chloroform–ethanol to give analytically pure **13** (0.3 g, 24%): mp 161–162 °C; IR (KBr) SO_2 absorptions at 1304 (s) and 1142 cm^{-1} (s); NMR ($CDCl_3$) δ 2.97 (s, 3, CH_3), 7.35–7.84 (m, 3), and 8.12–8.35 (m, 1). Anal. Calcd for $C_{14}H_{14}S_2O_4$: C, 54.42; H, 4.55; S, 20.62. Found: C, 54.29; H, 4.40; S, 20.78.

Dibenzo[*c,e*]-1,2-dithiin 1,1,2-Trioxide (11). A sample of disulfinate **2**-Na (0.76 g, 2.33 mmol) was treated with 5 mL of hot glacial acetic acid and 3 mL of acetic anhydride for 15 min. A clear solution resulted. After removing all the solvent in vacuo, the residue was extracted three times with 10-mL portions of hot chloroform. Crystalline sulfinyl sulfone **11** was obtained upon addition of hexane to the concentrated chloroform extracts in 65% yield (0.40 g, 1.51 mmol): mp 146–147 °C (dec); IR (KBr) 1320 (s), 1149 (s), and 1066 cm^{-1} (ms); UV (acetic acid) λ_{max} 310 nm (ε 5400). Anal. Calcd for $C_{12}H_8S_2O_3$: C, 54.55; H, 3.05; S, 24.22. Found: C, 54.66; H, 3.10; S, 24.02.

Disodium Naphthalene-1,8-disulfinate (5-Na). Cyclic thiolsulfonate **12** (1.11 g, 5 mmol), prepared by the method of Zweig and Hoffman,[11] was dissolved in 30 mL of anhydrous dioxane, and a solution of 0.67 mL of 30% hydrogen peroxide (5 mmol) and sodium hydroxide (0.40 g, 10 mmol) in 20 mL of water was added all at once with stirring. The resulting solution was evaporated to dryness and disulfinate **5**-Na was obtained in quantitative yield: IR (KBr) 1033 (s), 980 (s), and 910 cm^{-1} (s); UV (dioxane) λ_{max} 295 nm (ε 7100). This procedure used for the preparation of **5**-Na is a modification of the one originally used by Margolis[12] for the preparation of **5**-Na. It appears to be somewhat superior and to give a somewhat purer product.

Naphtho[1,8-*cd*]-1,2-dithiole 1,1,2-Trioxide (6). A solution of 0.80 g (2.66 mmol) of disulfinate 5-Na in 10 mL of water was acidified with sulfuric acid to pH <1. The brownish precipitate of crude **6** was filtered off. Recrystallization of the crude material from chloroform–hexane gave pure cyclic sulfinyl sulfone **6** in 71% yield (0.45 g, 1.89 mmol): mp 168–169 °C; IR (KBr) 1330 (s), 1166 (s), 1136 (s), and 1081 cm^{-1} (s). Compound **6** was previously prepared by Margolis[3,12] by acidification of **5**-Na in somewhat poorer yield and with a slightly lower melting point (160–162 °C). The infrared spectra of the two samples are identical, however.

Study of the Equilibrium between Diphenyl-2,2′-disulfinic Acid (2) and Cyclic Sulfinyl Sulfone 11. A stock solution of disodium diphenyl-2,2′-disulfinate (2-Na, 1.14×10^{-2} M) was prepared by dissolving 3.70 mg of **2**-Na in 1.0 mL of water. The ultraviolet spectrum of **2**-Na was recorded by transferring 32 μL of the stock solution through a microsyringe to a quartz, 1-cm UV cell containing 3.6 mL of 60% dioxane. The resulting concentration of **2**-Na in the final solution was 1×10^{-4} M. After recording the spectrum of **2**-Na, the solution in the cell was acidified by the addition of 60 μL of 12 N H_2SO_4; this makes the concentration of H^+ in the final solution 0.10 M. This acidification of the solution did not result in any significant change in the spectrum of the solution. In particular, even after allowing the solution to stand for 3 h, there was no significant increase in the absorbance of the solution at either 310 or 296 nm, such as would have been the case if significant amounts of either sulfinyl sulfone **11** or thiolsulfonate **3**, respectively, were being formed from disulfinic acid **2** under these conditions.

In contrast, addition of 32 μL of the stock solution of the disulfinate **2**-Na to 3.6 mL of acetic acid–5% water–0.10 M H_2SO_4 (prepared by the procedure outlined by Kice and Bowers[13]) led to an increase in the absorbance of the solution in the UV cell at 310 nm from an initial value of 0.03 to a final equilibrium value of 0.33, due to the formation from **2** of a significant amount of **11** at equilibrium. That the same value for the equilibrium ratio of [11]/[2] was obtained when the equilibrium was approached from the reverse direction was shown by an experiment in which 36 μL of a stock solution of sulfinyl sulfone **11** in acetic acid (prepared by dissolving 2.64 mg of **11** in 1.0 mL of acetic acid) was added to 3.6 mL of acetic acid–5% water–0.10 N H_2SO_4 and the absorbance of the solution at 310 nm was shown to decrease from an initial value of 0.53 to a final equilibrium value of 0.31. In another experiment 36 μL of the acetic acid stock solution of **11** was added to 3.6 mL of acetic acid–1% water–0.10 N H_2SO_4;[13] in this case the absorbance at 310 nm decreased from an initial value of 0.53 to a final equilibrium value of 0.48. All of the above experiments were carried out at 25 °C using a thermostated Cary 17 spectrophotometer.

Kinetics of the Spontaneous Hydrolysis of Sulfinyl Sulfone

11 in 60% Dioxane. The kinetics of the spontaneous hydrolysis of sulfinyl sulfone **11** in 60% dioxane were studied by adding 36 μL of a stock solution of **11** (1×10^{-2} M) in anhydrous dioxane to 3.6 mL of 60% dioxane containing 0.01 M $HClO_4$ and then monitoring the disappearance of the peak due to **11** at 310 nm with time, using a Cary Model 17 spectrophotometer with the cell holder thermostated at 25 °C.

Behavior of Disodium Diphenyl-2,2'-disulfinate (2-Na) Plus Sodium Sulfite in Aqueous Dioxane. A solution of sodium sulfite (2×10^{-3} M) in 60% aqueous dioxane was prepared by adding 7 μL of an aqueous sodium sulfite solution (1.01 M) to 3.6 mL of 60% dioxane in a 1-cm UV cell. Addition to this solution of 32 μL of a stock solution of **2**-Na (1.14×10^{-2} M) in water gave a solution 1.0×10^{-4} M in **2**-Na and 2×10^{-3} M in sulfite. The ultraviolet spectrum of this solution resembled that obtained in the same solvent for **2**-Na without sodium sulfite added. The spectrum remained unchanged over a period of observation of 3 h at 25 °C. The solution in the cell was then acidified by the addition of 60 μL of 12 N H_2SO_4, to give a final $[H^+]$ = 0.10 M. The acidification of the solution led to the formation of a very intense peak at 275 nm due to the H_2SO_3 that was formed on protonation of the sulfite. In order to be able to examine the spectrum of the remaining materials in the solution, the H_2SO_3 was purged from the solution by passing a gentle stream of nitrogen through it for 3 h at room temperature. Examination of the ultraviolet spectrum of the solution at the end of that time showed that it was identical with that obtained upon acidification of **2**-Na in 60% dioxane in the absence of sulfite. In particular *no* absorption peaks at either 296 (thiolsulfonate **3**) or 310 nm (sulfinyl sulfone **11**) were observed.

Acidification of a Concentrated Aqueous Solution of Disodium Diphenyl-2,2'-disulfinate (2-Na). A 0.1 M solution of **2**-Na in water was prepared by dissolving 0.33 g of **2**-Na in 10 mL of water. This was acidified at room temperature with concentrated sulfuric acid until pH <1. A milky solution resulted. This was extracted three times with 10-mL portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate and then concentrated. Addition of hexane to the concentrated extracts gave a white precipitate, 0.16 g, mp 139–140 °C dec. This was shown by infrared examination to consist of cyclic sulfinyl sulfone **11** admixed with some diphenyl-2,2'-disulfinic acid (**2**). Its ultraviolet spectrum showed the λ_{max} at 310 nm characteristic of **11**. A TLC (silica gel) on the chloroform concentrate before the addition of hexane showed no detectable amount of cyclic thiolsulfonate **3**.

Identity of the Product of the Reduction of Diphenyl-2,2'-disulfonyl Chloride (1) with Sulfite Ion. A sample of **1** was reduced with excess sodium sulfite in alkaline aqueous solution in the manner previously described. The amount of **1** and the volume of solution used were such that the final aqueous solution would be 0.075 M in the reduction product of **1**. Dilution of 5 μL of this solution with 3.6 mL of 60% dioxane gave an ultraviolet spectrum resembling that of authentic **2**-Na at the same concentration. This solution was then acidified by the addition of 60 μL of 12 N H_2SO_4. This led to the development of the intense peak at 276 nm associated with the presence of H_2SO_3. The H_2SO_3 was removed by passing a slow stream of nitrogen through the solution for 3 h at room temperature. The ultraviolet spectrum of the resulting solution was identical with that of an acidified solution of **2**-Na of similar concentration and showed no evidence for the presence of any **11** or **3**.

In a second experiment 5 μL of the aqueous solution of the reduction product of **1** was added to 3.6 mL of *anhydrous* dioxane. This led to the precipitation of the excess sulfite left over from the reduction. This was filtered off. Addition of acetic anhydride (36 μL) to the filtrate led to the rapid development of the absorption peak at 310 nm associated with the cyclic sulfinyl sulfone **11**. Its intensity was such as to suggest that essentially all of the reduction product of **1** must be **2**-Na.

Proof that treatment of **2**-Na with excess acetic anhydride in anhydrous dioxane leads to the formation of sulfinyl sulfone **11** had already been demonstrated by the following experiment. In this experiment 32 μL of an aqueous stock solution of **2**-Na (1.14×10^{-2} M) was added to 3.6 mL of anhydrous dioxane, and then 36 μL of acetic anhydride (0.38 mmol) was added. Examination of the ultraviolet absorption spectrum of the solution showed the rapid development of the absorption peak at 310 nm associated with **11**. This peak reached its full intensity in about 5 min. The final intensity corresponded to that expected for effectively quantitative conversion of **2**-Na to **11**.

Reduction of Cyclic Sulfinyl Sulfones 11 and 6 by Sulfite in Acid Solution. The reduction of cyclic sulfinyl sulfone **11** by sulfite in acid was demonstrated indirectly as follows. A sample of disulfinate **2**-Na (0.60 g, 1.82 mmol) and 2.30 g (18.2 mmol) of sodium sulfite were dissolved in 10 mL of water. No change in the ultraviolet absorption spectrum of the solution was observed even after standing at room temperature for 1 h. Addition of 12 N H_2SO_4 to the solution until the pH <1 caused the evolution of some sulfur dioxide and the separation of a second phase as a white cloudy suspension. After stirring the solution at room temperature for 30 min a clear supernatant was obtained. The white precipitate which had separated was collected and was recrystallized from chloroform–hexane to give 0.41 g (88%) of **3**, identical in all respects with the material obtained earlier upon sulfite reduction of disulfonyl chloride **1** followed by acidification and gentle warming (vide supra).

In the experiment with **6**, 0.24 g (1 mmol) of this cyclic sulfinyl sulfone was dissolved in 40 mL of 60% dioxane which had been acidified with 12 N H_2SO_4 to pH <1. Sodium sulfite (3.1 g, 25 mmol) dissolved in 10 mL of water was added slowly with stirring at room temperature. Sufficient sulfuric acid was present so that the pH of the final solution was approximately 1.0. After 5 min the dioxane was removed from the solution through rotary evaporation, and the suspension of organic solid which separated from the now completely aqueous solvent was filtered off and recrystallized from chloroform–hexane to give 0.18 g (81%) of cyclic thiolsulfonate **12**, mp 147–148 °C, identical in all respects with the authentic sample of the same thiolsulfonate prepared earlier (vide supra) by the procedure of Zweig and Hoffman.[11]

Acknowledgments. This research was supported in its initial stages by National Science Foundation Grant MPS 75-19408, and during its later stages by the Robert A. Welch Foundation (Grant D-650).

Registry No.—**1**, 56527-83-4; **2**, 63059-22-3; **2**-Na, 63059-23-4; **3**, 25331-82-2; **5**-Na, 63059-24-5; **6**, 57821-65-5; **7**, 63059-25-6; **8**, 63059-26-7; **9**, 63059-27-8; **10**, 51131-89-6; **11**, 63059-28-9; **12**, 40227-43-8; **13**, 34226-76-1; aniline-2-sulfonic acid, 88-21-1; 2-iodobenzenesulfonyl chloride, 63059-29-0.

References and Notes

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(2) (a) W. L. F. Armarego and E. E. Turner, *J. Chem. Soc.*, 3668 (1956); (b) *ibid.*, 13 (1957).
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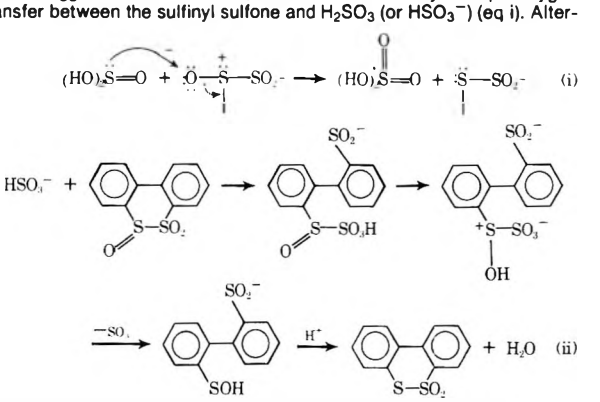
(4) (a) J. L. Kice, G. Guaraldi, and C. G. Venier, *J. Org. Chem.*, **31**, 3561 (1966); (b) J. L. Kice and G. Guaraldi, *ibid.*, **31**, 3568 (1966).
(5) In ref 4a equilibrium constants for sulfinyl sulfone formation from *p*-toluenesulfinic acid were measured at a variety of sulfuric acid concentrations in acetic acid–5% water. While the equilibrium constant for sulfinyl sulfone formation from benzenesulfinic acid was only measured in this particular solvent at $[H_2SO_4]$ = 1.0 M, that experiment and others in acetic acid–1% water at various sulfuric acid concentrations show that without exception K_{eq} for $PhSO_2H$ is 0.35 ± 0.05 K_{eq} for *p*-$CH_3C_6H_4SO_2H$. From this fact and the fact that K_{eq} for p-$CH_3C_6H_4SO_2H$ in acetic acid–5% water–0.10 M H_2SO_4 should be 0.0065, K_{eq} for benzenesulfinic acid in this solution is estimated to be 0.0023.
(6) J. L. Kice and G. Guaraldi, *J. Am. Chem. Soc.*, **89**, 4113 (1967).
(7) Several possibilities for the mechanism of the reactions shown as eq 10 and 11 suggest themselves. First, one could have merely a simple oxygen transfer between the sulfinyl sulfone and H_2SO_3 (or HSO_3^-) (eq i). Alternatively, one could have the reaction sequence outlined below that would be initiated by nucleophilic attack of HSO_3^- on the S=O group of the sulfinyl sulfone (eq ii). The loss of SO_3 from the intermediate $-S^+(OH)SO_3^-$ is reminiscent of the known breakdown of Bunte salts in acid solution,[8] $RS^+(H)SO_3^- \rightarrow RSH + SO_3$.



(i)

(ii)

(8) J. L. Kice, J. M. Anderson, and N. E. Pawlowski, *J. Am. Chem. Soc.*, **88**, 5245 (1966).
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Photocyclization Reactions of Substituted 2,2′-Divinylbiphenyl Derivatives

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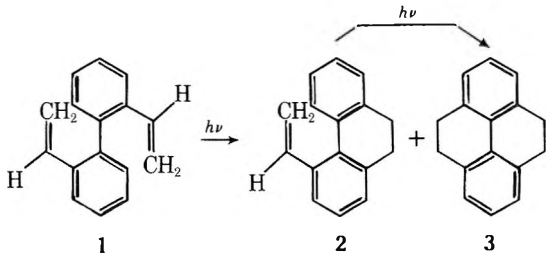
The direct and sensitized photochemistry of substituted 2,2′-divinylbiphenyl derivatives is reported. Direct irradiation of these compounds results in smooth nonoxidative cyclization to tetrahydropyrenes. This reaction may be conveniently viewed as proceeding by a mechanism which involves an initial stilbene–phenanthrene type cyclization, followed by a 1,5-sigmatropic hydrogen shift to give a vinyl-substituted dihydrophenanthrene which is subsequently converted to the tetrahydropyrene system on further irradiation. The photochemistry of several divinylbiphenyls possessing a styryl group was also studied. In contrast to the photocyclizations observed with the simple divinylbiphenyls, these compounds were found to undergo an intramolecular [2 + 2]-cycloaddition reaction. The difference in photobehavior of these systems and the low intersystem crossing efficiency noted is discussed. Calculations by the Hückel molecular orbital method of the sum of the free valence indices in the first excited state (ΣF^*) of the terminal atoms concerned in the photocyclizations were carried out and serve as a guide in predicting the direction of cyclization. The photochemistry of several 2-vinyl-2′-acylbiphenyls was also studied and compared to that encountered in the divinylbiphenyl system.

The photochemical [2 + 2]-cycloaddition reaction has a long history[1] and its utility in the construction of four-membered rings has been amply demonstrated.[2] Similarly, the photocyclization–oxidation reaction of stilbene-like molecules has been widely investigated[3–11] and in many cases has led to the synthesis of a variety of interesting polyaromatic compounds,[12,13] some of which would be tedious to synthesize by other routes.[14] Somewhat related nonoxidative cyclizations have also received wide attention in recent years from both the preparative and mechanistic points of view.[15–22] As part of a general study dealing with intramolecular [2 + 2]-cycloaddition and 6π-electrocyclic reactions, we recently investigated the excited state behavior of several 2,2′-divinylbiphenyl derivatives.[15] During the course of these studies we found that the resulting photochemistry depends not only on the experimental conditions used, but also on the choice of the substituent groups attached to the double bond.[16] In this paper we wish to describe the results of our study and to delineate the effect of the substituent groups and biphenyl geometry on the course of the photoreaction.

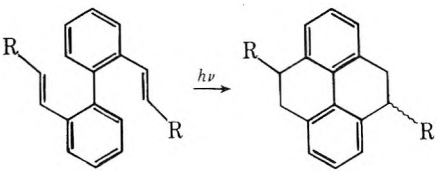
Results

Irradiation of a 0.05 M solution of 2,2′-divinylbiphenyl (1) in benzene with a 450-W Hanovia lamp equipped with a Pyrex filter for 3 h gave a mixture of two products isomeric with starting material. The two isomers could be separated by preparative gas chromatography and are assigned structures **2** and **3** on the basis of their spectral data. The structure of **3** was unambiguously established as 4,5,9,10-tetrahydropyrene (70%), mp 134–135 °C, by comparison with an authentic sample.[23] The minor component was identified as 4-vinyl-9,10-dihydrophenanthrene (**2**) (30%) on the basis of its characteristic NMR spectrum and its quantitative conversion to **3** on further irradiation. The quantum yield for the cyclization of **1** → **2** is 0.042 while that for **2** → **3** is 0.014. The quantum yields were not affected when the irradiation was carried out in the presence of piperylene. The photocyclization of **1** to **2** (and **3**) could also be induced by triplet excitation. Thus, irradiation of a solution of **1** through a uranium glass filter containing sufficient benzophenone to absorb >95% of the incident light gave **2** as well as **3**. In this case, the quantum yield for cyclization was significantly reduced (i.e., $\Phi_{1\rightarrow 2}$ = 0.003 and $\Phi_{2\rightarrow 3}$ = 0.004). These results would tend to indicate that the singlet state of **1** is the reactive state responsible for the cyclization in the direct irradiation experiment.



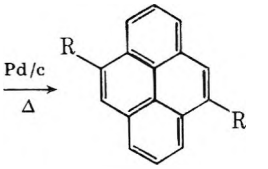
1 **2** **3**

Similar irradiation of 2,2′-biphenyldiacrylonitrile (**4**) afforded 4,5,9,10-tetrahydro-4,9-dicyanopyrene (**5**) (71%), mp 260–262 °C, as the major photoproduct. When the photolysis of dimethyl 2,2′-biphenyldiacrylate (**6**) was conducted in benzene, a mixture of *cis*- and *trans*-4,5,9,10-tetrahydro-4,9-dicarbomethoxypyrene (**7**) was obtained in good yield (60%). Oxidation of photoproducts **5** and **7** to the corresponding 4,9-disubstituted pyrene system (**8**) could be readily achieved by heating **5** and **7** in benzene which contained a catalytic quantity of palladium on carbon.



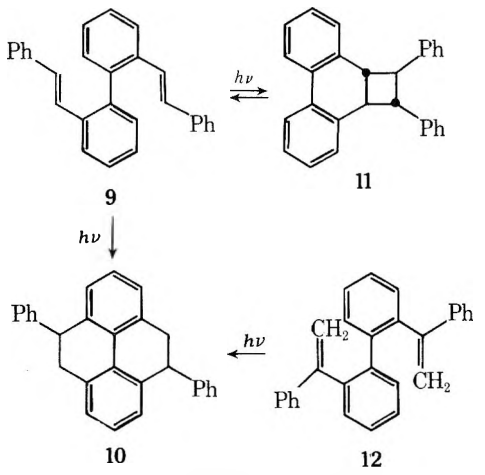
4, R = CN
6, R = CO_2CH_3

5, R = CN
7, R = CO_2CH_3



8a, R = CN
8b, R = CO_2CH_3

Laarhoven and Cuppen had previously reported[24] that the extended photolysis of 2,2′-distyrylbiphenyl (**9**) gave tetrahydro-4,9-diphenylpyrene (**10**) as the thermodynamically controlled photoproduct. Irradiation of **9** for shorter periods of time, however, was reported to give 1,2-diphenylcyclobuta[*l*]phenanthrene (**11**) as the kinetically controlled product[25] which was ultimately converted into **10** on further irradiation.[24] We have confirmed these findings and have also observed that the irradiation of 2,2′-bis(1-phenylvinyl)biphenyl (**12**) gave only **10**, mp 221–213 °C, even under kinetically controlled conditions. It should be pointed out that the irradiation of divinylbiphenyl derivatives **1**, **4**, **6**, and **12** did not lead to any detectable quantities of [2 + 2] internal cycloadducts, even when short irradiation times were used. This

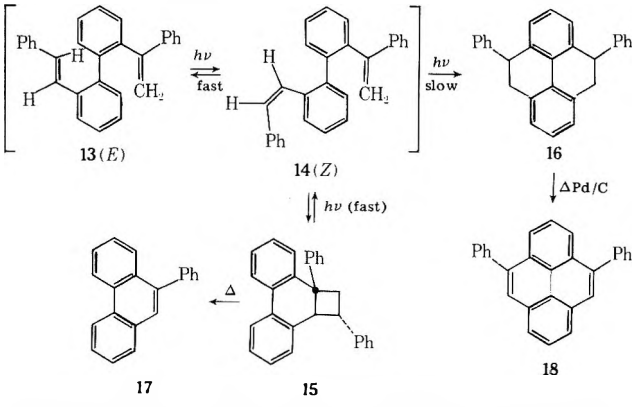


stands in marked contrast to the results of Laarhoven and Cuppen[24] with distyrylbiphenyl system (**9**).

During the course of these studies we found that [2 + 2] cycloaddition is the main reaction which occurs on photoexcitation of the 2-(1-phenylvinyl)-2′-styrylbiphenyl system (**13** or **14**). Thus, irradiation of either the *E* (**13**) or *Z* (**14**) isomer in benzene gave 1,2,2a,10b-tetrahydro-1,2a-diphenylcyclobuta[*l*]phenanthrene (**15**) and 4,5,9,10-tetrahydro-4,10-diphenylpyrene (**16**). Photoequilibration of the *Z* and *E* isomers

$$\mathbf{13} \underset{}{\overset{h\nu}{\rightleftharpoons}} \mathbf{14}$$

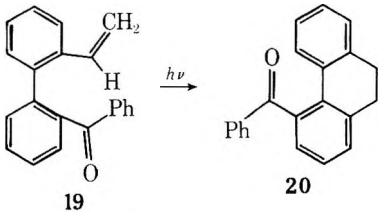
was rapidly established (1:1) before intramolecular cycloaddition occurred. The [2 + 2]-cycloaddition product **15** was identified on the basis of its spectral properties; mass spectrum *m/e* 358 (M^+), 104 (base); UV (methanol) 268 and 300 nm (ε 13 200, 5100); NMR ($CDCl_3$, 100 MHz) τ 7.23 (d, 2 H, *J* = 8.0 Hz), 5.98 (d, 1 H, *J* = 12.0 Hz), 5.63 (td, 1 H, *J* = 12.0 and 8.0 Hz), and 2.21–3.03 (m, 18 H). On further irradiation, this material was converted to tetrahydropyrene **16** in quan-



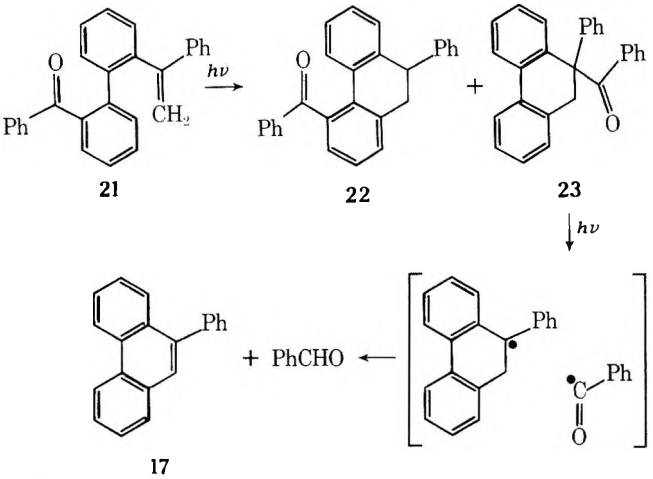
titative yield. Chemical confirmation of the structure of **16** was obtained by its ready oxidation to 4,10-diphenylpyrene (**18**), mp 152–153 °C, on heating with palladium on carbon. When a sample of **15** was subjected to pyrolysis at 150 °C, the major products were 9-phenylphenanthrene (**17**) and polystyrene.

The photochemical results observed with this system are very similar to those encountered by Laarhoven and Cuppen with the 2,2′-distyrylbiphenyl system.[24] Apparently, the photocyclization of **13** (or **14**) to tetrahydropyrene **16** is slow in comparison with the [2 + 2]-cycloaddition reaction. Tetrahydropyrene **16** is only obtained after long irradiation times and its formation can be attributed to a subsequent photocleavage reaction of cyclobutane **15**. These results demonstrate that the [2 + 2] intramolecular photocycloaddition reaction of divinylbiphenyl derivatives only occurs when a stilbene moiety is present in the system.

In view of the extremely interesting substituent effect uncovered during our studies with the divinylbiphenyl system, we felt that it would be worthwhile to determine whether a comparable effect would occur with the related carbonyl system. One of the more common photoreactions of carbonyl compounds is their addition to olefins to form oxetanes, i.e., the Paterno–Buchi reaction.[26,27] Contributions from many laboratories suggest that the cycloaddition of simple phenyl ketones with π bonds proceeds via their n − π* triplet state.[28–33] Ketones with low-lying π–π* states generally do not undergo the Paterno–Buchi reaction,[28] although some exceptions have appeared in the literature.[28,31,34] For example, the irradiation of 2-phenylbenzophenone in the presence of olefins does not lead to oxetanes,[28] presumably because the lowest excited state of this system possesses a π–π* triplet state.[28] However, 3-phenylbenzophenone does undergo efficient cycloaddition with isobutylene (Φ = 0.1),[35] even though this ketone phosphoresces from a π–π* triplet state.[28] Although 2-(o-vinylphenyl)benzophenone and its derivatives would be expected to possess a low-lying π–π^{*3} state, the ready availability of these compounds made it attractive, nonetheless, to examine their photochemical behavior in order to determine whether [2 + 2] cycloaddition would occur. The first system studied was 2-(o-styryl)benzophenone (**19**). Irradiation of **19** with Pyrex filtered light gave no recognizable [2 + 2]-cycloaddition product but instead gave 4-benzoyl-9,10-dihydrophenanthrene (**20**) in high yield.



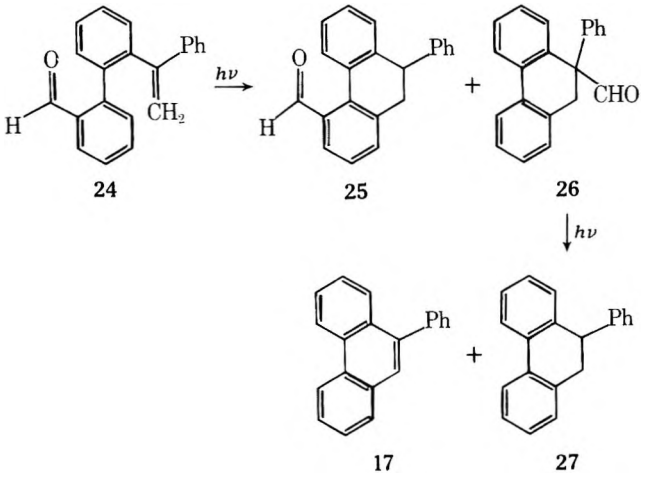
In contrast to the photochemistry of **19**, where only one dihydrophenanthrene was observed, irradiation of 2-[o-(1-phenylvinyl)phenyl]benzophenone (**21**) in benzene with 365-nm light furnished a mixture of two isomeric ketones [**22** (60%) and **23** (20%)]. The structures of these two products were assigned as 4-benzoyl-9-phenyl- (**22**) and 9-benzoyl-9-phenyl-9,10-dihydrophenanthrene (**23**) on the basis of their analytical and spectroscopic data (see Experimental Section for details). Structure **23** was further verified by a photochemical degradation. Photolysis of **23** should cause efficient



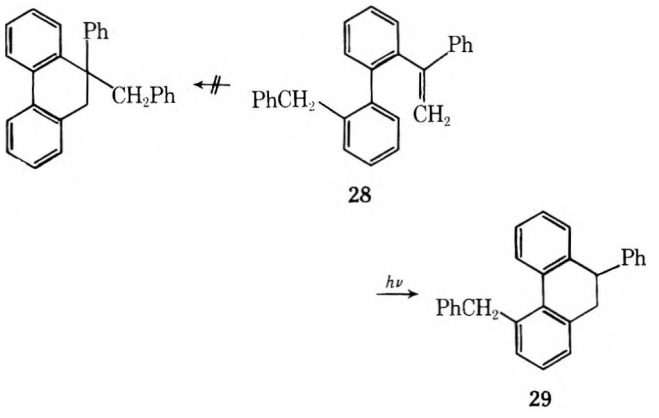
α cleavage and formation of a tight radical pair. Subsequent hydrogen transfer from the 9-phenylphenanthryl radical to the benzoyl radical would be expected to give benzaldehyde and 9-phenylphenanthrene (**17**). Indeed, irradiation of **23** with a low-pressure mercury lamp produced the suspected products in excellent yield. Thus, the photochemical behavior of **23**

provided a simple and effective method of confirming its structure.

We also prepared and irradiated 2′-(1-phenylvinyl)-2-biphenylcarboxaldehyde (**24**) with 365-nm light. The products obtained from this photolysis were 9-phenyl-9,10-dihydro-4-phenanthrenecarboxaldehyde (**25**) (13%) and 9-phenyl-9,10-dihydro-9-phenanthrenecarboxaldehyde (**26**) (50%). The structure of aldehyde **26** was assigned on the basis of its spectroscopic properties (see Experimental Section) and its ready conversion to 9-phenylphenanthrene (**17**) and 9-phenyl-9,10-dihydrophenanthrene (**27**) on irradiation with 2537-Å light.



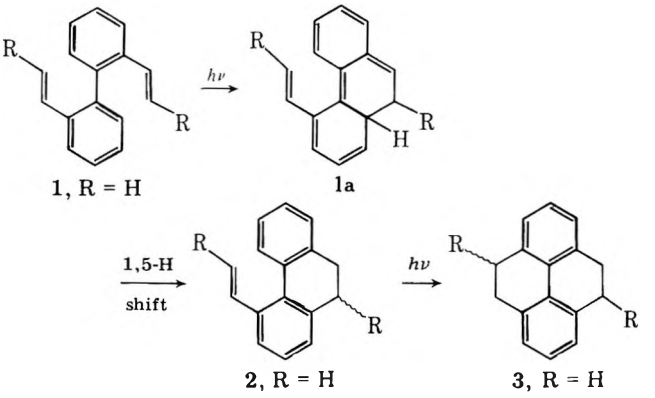
The photocyclization of 2-(1-phenylvinyl)-2′-benzylbiphenyl (**28**) was also studied. In contrast with the results obtained with ketone **21** and aldehyde **24**, this compound afforded a single dihydrophenanthrene (i.e., **29**) whose structure was established as 9-phenyl-9,10-dihydro-4-benzylphenanthrene (**29**), mp 105–106 °C, on the basis of its characteristic



spectral data. It would appear, therefore, that ipso cyclization only occurs when a carbonyl group is present in the 2′-(ortho) position of the biphenyl ring.

Discussion

The most stable conformation of ground-state biphenyl is strongly dependent on the medium. The dihedral angle between the two rings is 40–45° in the gas phase,[36] 20–25° in solution,[37] and 0° in the crystalline state.[38] By contrast, theoretical calculations by Hoffmann[39] predict a planar excited state and some experimental work by Wagner[40] shows that triplet biphenyl prefers to be planar. A planar biphenyl excited state should favor bond formation between the ortho position of the biphenyl ring and an unsaturated 2-substituent. The present study reveals that the irradiation of several 2,2′-divinylbiphenyl derivatives results in a smooth nonoxidative cyclization and represents a convenient route for the preparation of the tetrahydropyrene ring system. This reaction may be conveniently viewed as proceeding by a mechanism which involves an initial stilbene–phenanthrene type cyclization followed by a 1,5-sigmatropic hydrogen shift to give a vinyl-substituted dihydrophenanthrene. On further irradiation, this material is converted to the tetrahydropyrene system. This mechanistic proposal is supported by the isolation of 4-vinyl-9,10-dihydrophenanthrene (**2**) from a short-term irradiation of 2,2′-divinylbiphenyl (**1**).

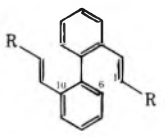
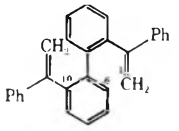
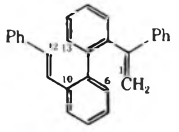
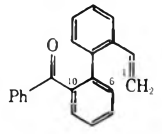
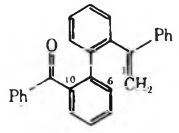
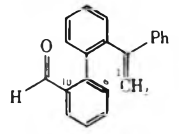
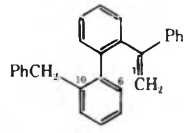


The relative ease of photocyclization of hexatriene-type analogues has been related to the sum of the free-valence indices in the first excited state, ΣF*, at the two positions which become bonded during the cyclization.[41–43] Laarhoven and co-workers showed that only if the sum of free valence indices in the first excited state of the terminal atoms concerned in the photocyclization of stilbene-like compounds exceeds a critical value (unity in this case (i.e., ΣF* > 1.0)) will cyclization occur.[43] In some stilbene-like molecules, photocyclization can occur in a number of possible ways. By using Laarhoven's calculations,[43] one can predict the preferred mode of cyclization in these cases. When more than one mode of cyclization has a value of unity or greater for ΣF* of the terminal atoms concerned in the photocyclization, cyclization usually occurs for the highest calculated value as long as the difference in the values of ΣF* is more than 0.1; otherwise both photocyclizations can occur.[43,44] It seemed that calculation of the ΣF* of the terminal atoms involved in the cyclization of the 2,2′-divinylbiphenyl systems could yield useful information and aid us in predicting the direction of cyclization when multiple modes of cyclization are possible. Using the relation $F^* = \sqrt{3} - \Sigma_s \rho_{rs}^*$ in which ρ_{rs}^* is the π-bond order in the first excited state between the atom r and a neighboring atom s,[45] the ΣF* of the terminal atoms involved in the cyclization was calculated for a number of 2,2′-divinylbiphenyl derivatives. These values are calculated for planar molecules in the usual way and are based on the HMO approximation. All possible modes of cyclization are included in the calculations, and these are outlined in Table I.

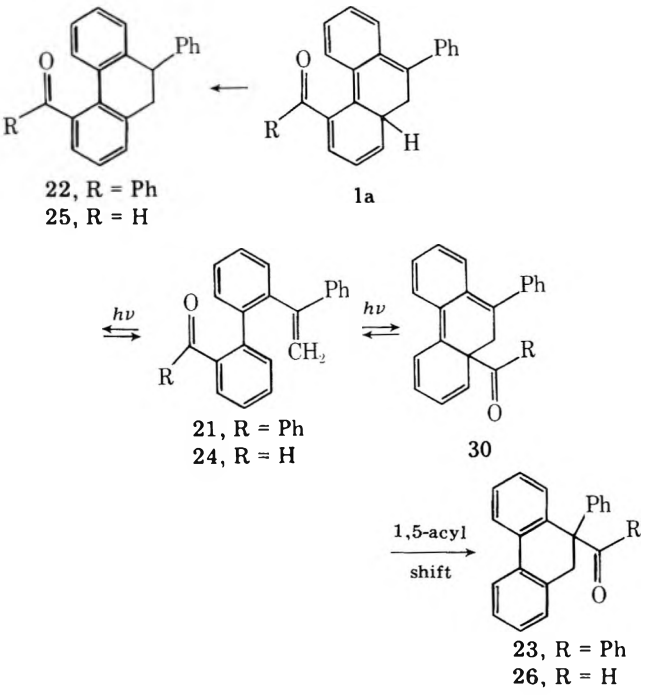
As shown in the table, all compounds with ΣF* > 1.0 undergo cyclization under the influence of light. Of the systems examined, only one, the cyclization of dinitrile **5**, occurs with a value of ΣF* less than unity. This system, however, has a ΣF* which is only slightly less than the critical value, and this exception may be ascribed to the fact that numerical evaluation of ΣF* for compound **5** by the HMO method is a rather rough approximation. Photocyclization of divinylbiphenyl derivatives **1**, **4**, **6**, and **9** at the 1 and 10 positions did not occur as the values of ΣF* at these atoms were much less than the corresponding values at positions 1 and 6 (see Table I). Similarly, structures **12**, **16**, and **19** cyclize only in the direction predicted by the Laarhoven rule.[43]

The rule breaks down, however, with structures **21** and **24**. Calculation of the free valence numbers of the various carbon atoms in the excited state of these systems reveals that the difference between ΣF* is significantly greater than 0.1.

Table I. Results of SHMO Calculations

Compound	ΣF*	Product
 4	R = H 1,6 = 1.454 1,10 = 1.221	3 (obsd) Not obsd
	R = CN 1,6 = 0.979 1,10 = 0.699	8a (obsd) Not obsd
6	R = CO_2CH_3 1,6 = 1.137 1,10 = 0.850	8b (obsd) Not obsd
9	R = Ph 1,6 = 1.022 1,10 = 0.746	10 (obsd) Not obsd
 12	1,6 = 1.525 1,10 = 1.286	10 (obsd) Not obsd
 16	1,6 = 1.437 12,13 = 1.067 1,10 = 1.175 2,12 = 0.809	Obsd Not obsd Not obsd
 19	1,6 = 1.465 1,10 = 1.166	20 (obsd) Not obsd
 21	1,6 = 1.544 1,10 = 1.252	22 (obsd) 23 (obsd)
 24	1,6 = 1.557 1,10 = 1.254	25 (obsd) 26 (obsd)
 28	1,6 = 1.727 1,10 = 1.727	29 (obsd) Not obsd

Hence, photocyclization of **21** and **24** should have given only dihydrophenanthrenes **22** and **25**. Irradiation of these compounds, however, also produced structures **23** and **26**. In fact, structure **26** was the major product obtained from the photolysis of **24**. The most likely mechanism to rationalize the formation of these products involves ipso cyclization to give **30** as a transient intermediate which then undergoes a facile 1,5-acyl shift. The 1,5-sigmatropic shift probably proceeds via a thermally allowed concerted pathway[46,47] since the yield of **23** or **26** was unaffected when the irradiation was carried out in the presence of *n*-dodecanethiol. Lewis and Magyar[48] had previously demonstrated that this thiol is an efficient radical scavenger which is capable of trapping photochemically generated acyl radicals. The absence of benzaldehyde in the above reaction implies that either the benzoyl group is



22, R = Ph
25, R = H

1a

21, R = Ph
24, R = H

30

23, R = Ph
26, R = H

transferred in a concerted fashion or else that geminate recombination of the radical pair is proceeding within a radical cage.

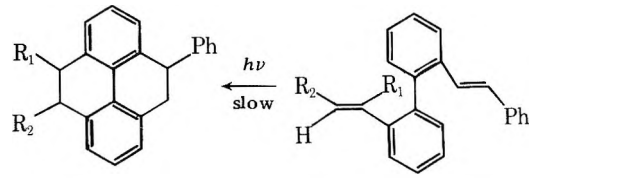
It is not clear why **21** (or **24**) produces a mixture of dihydrophenanthrenes **22** and **23**, whereas the related divinylbiphenyl system **12** cyclizes in only one direction. The slight difference in the magnitude of the free valence numbers (i.e., $\Delta\Sigma F^*$ **21** = 0.292 vs. $\Delta\Sigma F^*$ **12** = 0.239) of the two systems seems to be too small to account for the nonselectivity exhibited by structure **21**. One possibility to account for this nonselectivity is that **21** is polarized in such a direction that the cyclizing atom attached to the carbonyl group may be regarded as being electron deficient. As a result of this polarization, the normally electron-rich ortho position of the excited biphenyl system[49] becomes electron deficient at the position bearing the benzoyl group. This, in turn, creates an electrostatic attraction between the electron-deficient ortho carbon of the biphenyl ring with the electron-rich terminus of the neighboring vinyl group, thereby promoting cyclization between these two atoms. In support of this explanation, we find that the ratio of **22**/**23** is increased on changing the solvent from benzene (3/1) to methanol (1.7/1). The inherent hydrogen bonding capabilities of methanol would be expected to increase the polarization of the carbonyl group in the excited state and thereby promote cyclization on the ortho carbon atom bearing the carbonyl group. Another rationale which could account for the nonselectivity exhibited by structures **21** and **24** is based on the assumption that the initial cyclization step affords cyclohexadienes **1a** and **30** which can regenerate starting material by a retrocyclization reaction. The distribution of products (i.e., **22** or **23**) could then be controlled by the rates of hydrogen or acyl group migration of the transient cyclohexadienes. Thus, the poor ΣF^* correlation encountered with these systems may be related to the fact that the 1,5-acyl shift is faster than the 1,5-hydrogen shift. Further work is needed to distinguish between the above two possibilities.

The finding that 2-(1-phenylvinyl)-2′-benzylbiphenyl (**28**) cyclizes only in one direction, even though the free valence numbers on both ortho positions have the same value, must be related to steric factors. By incorporating a benzyl group on the 2′ position, the concentration of the conformation necessary for ipso cyclization is significantly decreased. The exclusive formation of **29** from **28** is undoubtedly a reflection

of the greater steric interactions involved in ipso cyclization. This phenomenon is not without precedent as other reports in the literature have shown that conformational factors can markedly influence the direction of both photo and thermal electrocyclic reactions.[50-53] Alternatively, the exclusive formation of **29** from **28** may be related to the fact that a 1,5-hydrogen shift of one of the initially formed cyclohexadiene intermediates is much faster than a 1,5-alkyl shift.

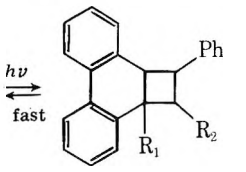
Our inability to detect an oxetane from the photolysis of **21** (or **24**) can be attributed to the π–π^* singlet nature of the excited state. The excited singlet seemingly prefers to cyclize to a dihydrophenanthrene rather than to undergo the Paterno–Buchi reaction. The apparent low intersystem crossing efficiency noted with **21**[54] could either be the result of an exceptionally fast decay process of the singlet state or an especially low rate of intersystem crossing.

One final point worthy of discussion concerns the photochemistry of divinylbiphenyls having an aryl group at the β position. These systems prefer to undergo a fast intramolecular 2 + 2 cycloaddition to give cyclobuta[*l*]phenanthrenes rather than to undergo cyclization to the tetrahydropyrene ring system. Apparently the formation of the tetrahydropyrene is slow in comparison with the formation of the cyclobutane. Only on extended irradiation is the tetrahydropyrene ring produced and its formation can be traced to a subsequent cycloreversion reaction of the initially formed cycloadduct. Calculation of free valence numbers of the various carbon atoms of **9** or **13** in the excited state reveals that the photocyclization should be a favorable process [i.e., $\Sigma F^*_9 = 1.022$ and $\Sigma F^*_{13} = 1.437$ (or 1.067)]. Thus the preferential internal cycloaddition reaction observed with these systems cannot be attributed to an unfavorable cyclization process.



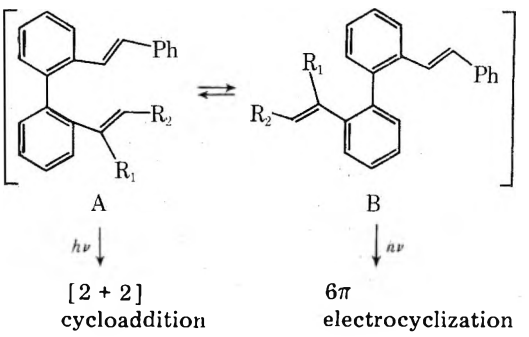
10, R_1 = H, R_2 = Ph
16, R_1 = Ph, R_2 = H

9, R_1 = H, R_2 = Ph
13, R_1 = Ph, R_2 = H



11, R_1 = H, R_2 = Ph
15, R_1 = Ph, R_2 = H

Electronic excitation of these β-aryl substituted divinylbiphenyl derivatives results in energy localization on the stilbene portion of the molecule. Stilbenes are known to undergo 2 + 2 cycloaddition to olefins from the excited singlet state.[55-59] The formation of the cyclobuta[*l*]phenanthrene ring system can be readily ascribed to such a process. When the divinylbiphenyl derivative is devoid of a β-phenyl group, no detectable quantities of a [2 + 2] cycloadduct were found.[60] The distribution of products obtained from the irradiation of these β-aryl substituted divinylbiphenyl derivatives may be related to conformational factors. Two different conformations (A and B) are possible with these systems. One conformation (A) will lead to [2 + 2] cycloaddition while the other conformer (B) will result in cyclization. Lewis and co-workers have previously pointed out that two limiting cases are possible for a situation where two different conformers of a substrate give rise to different photoproducts.[61] In one case, the activation energy for conformational isomerization is lower than that for formation of the products. With this situation,



the ratio of products will depend upon the difference in energy for the transition states leading to the products (Curtin–Hammett principle). In the other case, the activation energy for conformation isomerization is greater than that for formation of the products. For this situation, the ratio of products will depend upon the population of the different conformers and their efficiencies of product formation. If the two conformers of **9** (or **13**) interconvert more rapidly than they react, it follows that the relative distribution of products will depend only on the rates of reaction. According to this argument, the preferential formation of the cyclobuta[*l*]phenanthrene ring system stems from the fact that the 2 + 2 cycloaddition proceeds at a much faster rate than the cyclization reaction. The rapid rate of cycloaddition from conformer A can be ascribed to the close proximity of the excited stilbene moiety and the neighboring vinyl group and the relief of steric crowding which results upon bond closure. It should also be pointed out that the energy barrier for conformational isomerization in the ground and excited state will not necessarily be the same. If conformations A and B are not interconverted in the excited state, then the distribution of products will depend upon the population of A* and B*.[62] The distribution of A* and B* will, in turn, be determined by the ground state equilibrium between the two conformations. Since the 2 + 2 cycloaddition predominates, this reasoning would demand that A be the more stable conformer. The predominance of conformer A could be attributed to the existence of attractive van der Waal forces between the atoms of the aryl-substituted vinyl groups. These weak but effective forces would lead to an overall attractive interaction between the aryl-substituted vinyl groups, much the same as was suggested by Martin in the helicene series.[63] While we consider it instructive to point out the available mechanistic possibilities, the exact situation which operates with these β-aryl substituted divinylbiphenyl derivatives remains to be established.

Experimental Section[64]

Preparation of 2,2′-Biphenyldiacrylonitrile. A solution containing 2.1 g of diphenaldehyde and 6.2 g of cyanomethyltriphenylphosphorane[65] in 200 mL of benzene was heated at reflux for 4 h. The solvent was partially removed and the precipitated triphenyl phosphine oxide was filtered. The resulting crude oil was chromatographed on a 4 × 75 cm Florisil column using a 1:1 pentane–ether mixture as the eluent. The major component isolated (1.1 g, 44%) was a white solid, mp 119–120 °C, which was shown to be a 2:3 mixture of the cis and trans isomers of 2,2′-biphenyldiacrylonitrile (**4**): IR (KBr) 4.53, 6.24, 6.30, 8.40, 10.42, and 13.00 μ; UV (methanol) 223 (ϵ 28 100) and 274 nm (ϵ 32 000); NMR ($CDCl_3$, 100 MHz) τ 4.63 (d, 1 H, J = 12.0 Hz), 4.23 (d, 1 H, J = 16.0 Hz), 3.23 (d, 1 H, J = 12.0 Hz), 3.03 (d, 1 H, J = 16.0 Hz), and 1.80–2.87 (m, 8 H); *m/e* 256 (M^+, base), 228, 179, 178, and 165.

Anal. Calcd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 83.95; H. 4.76; N, 10.86.

Preparation of Dimethyl 2,2′-Biphenyldiacrylate. A solution containing 2.1 g of diphenaldehyde and 7.0 g of carbomethoxymethyltriphenylphosphorane[66] in 200 mL of benzene was heated at reflux for 24 h. The solvent was removed under reduced pressure, and the resulting residue was chromatographed on a 4 × 75 cm Florisil column using a 10% ethyl acetate–benzene mixture as the eluent. The major component isolated was a white solid (1.75 g, 55%) whose structure

was assigned as dimethyl 2,2′-biphenyldiacrylate (**6**): mp 126–127 °C (lit.[67] 123–124 °C); IR (KBr) 5.93, 6.10, 6.30, 6.96, 7.62, 8.40, 10.22, 11.50, and 13.15 μ; UV (methanol) 225 (ε 18:500) and 278 nm (ε 22 500); NMR ($CDCl_3$, 60 MHz) τ 6.35 (s, 6 H), 3.74 (d, 2 H, J = 16.0 Hz), and 2.26–2.94 (m, 10 H); m/e 322 (M^+), 291, 262, 231, 203 (base), 178, and 133.

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.30; H, 5.62.

Preparation of 2,2′-Bis(1-phenylvinyl)biphenyl. To a solution containing 3.57 g of methyltriphenylphosphonium bromide in 75 mL of ether was added 4.3 mL of a 2.3 M n-butyllithium solution at 25 °C. The resulting orange solution was allowed to stir at 25 °C for 20 min prior to the addition of 1.0 g of 2,2′-dibenzoylbiphenyl[68] in 75 mL of ether. The mixture was heated at reflux for 4 days and filtered to remove triphenylphosphine oxide. The residual oil was chromatographed on a 3 × 50 cm Florisil column using a 1:1 pentane–ether mixture as the eluent. The major component isolated contained 900 mg (90%) of 2,2′-bis(1-phenylvinyl)biphenyl (**12**), mp 98–100 °C (lit.[69] 100–101 °C); IR (KBr) 6.22, 6.70, 7.15, 9.41, 11.05, 12.85, and 13.35 μ; UV (methanol) 240 nm (ε 29 300); NMR ($CDCl_3$, 60 MHz) τ 5.07 (d, 2 H, J = 1.5 Hz), 4.67 (d, 2 H, J = 1.5 Hz), and 2.80–3.10 (m, 18 H).

Preparation of 2-(1-Phenylvinyl)-2′-(*Z*)-styrylbiphenyl. A solution containing 2.1 g of diphenylaldehyde, 0.78 g of 2,2-dimethyl-1,3-propanediol, and a trace of p-toluenesulfonic acid in 100 mL of benzene was heated at reflux for 15 h using a Dean–Stark tube to remove the water. The crude oil obtained on removal of the solvent was chromatographed on a 4 × 75 cm Florisil column using a 20% ether–pentane mixture as the eluent. The major component contained 1.3 g (4) of diphenyl monoacetal: IR (neat) 3.40, 5.88, 6.24, 6.81, 7.19, 8.35, 9.05, 9.80, 10.70, 12.05, and 13.10 μ; NMR ($CDCl_3$, 60 MHz) τ 9.40 (s, 3 H), 8.84 (s, 3 H), 6.28–6.99 (m, 4 H), 5.05 (s, 1 H), 1.98–2.98 (m, 8 H), and 0.30 (s, 1 H),

To a solution containing 1.94 g of phenylmethyltriphenylphosphonium chloride[70] in 30 mL of ether was added 2 mL of a 2.5 M n-butyllithium solution at room temperature. The orange solution obtained was allowed to stir at room temperature for 20 min prior to the addition of 1.3 g of the above diphenylaldehyde monoacetal in 20 mL of ether. The solution was stirred at 25 °C for 24 h, filtered, and concentrated under reduced pressure. The resulting oil was taken up in 60 mL of acetone and then 12 mL of a 55% formic acid solution was added. After stirring at 25 °C for 3 days, the solution was diluted with water and extracted with ether. The ether extracts were washed with 10% sodium hydroxide and water, dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and chromatographed on a 3 × 50 cm Florisil column using a 1:1 pentane–ether mixture as the eluent. Removal of the solvent from the major fraction left 905 mg (70%) of 2′-(*Z*)-styryl)-2-biphenylcarboxaldehyde as a pale oil: NMR ($CDCl_3$, 60 MHz) τ 3.82 (d, 1 H, J = 12.0 Hz), 3.60 (d, 1 H, J = 12.0 Hz), 2.03–2.99 (m, 13 H), and 0.21 (s, 1 H).

To a sample containing 284 mg of the above aldehyde was added 0.6 mL of a 1.8 M phenylithium solution. Workup in the normal fashion gave 335 mg (93%) of 2-hydroxybenzyl-2′-(*Z*)-styrylbiphenyl: NMR ($CDCl_3$, 60 MHz) τ 7.83 (br s, 1 H), 4.17–4.50 (m, 1 H), 3.67 (d, J = 2.0 Hz, 2 H), and 2.30–3.30 (m, 18 H). A 362-mg sample of this alcohol in 25 mL of acetone which contained 0.2 mL of Jones reagent was allowed to stir at 25 °C for 5 min. The excess reagent was destroyed by addition of 2-propanol, and the resulting mixture was taken up in 59 mL of water and extracted with ether. The ether extracts were washed with 10% sodium bicarbonate and water, dried over magnesium sulfate, and recrystallized from methanol to give 234 mg (68%) of 2-[o-(*Z*)-styryl)phenyl]benzophenone, mp 85–87 °C; NMR ($CDCl_3$, 60 MHz) τ 3.73 (s, 2 H) and 2.25–3.19 (m, 18 H).

To a solution containing 393 mg of methyltriphenylphosphonium bromide in 20 mL of ether was added 0.44 mL of a 2.5 M n-butyllithium solution at room temperature, followed by 358 mg of 2-[o-(*Z*)-(styryl)phenyl]benzophenone in 20 mL of ether. After stirring at 25 °C for 48 h, the solution was filtered, concentrated under reduced pressure, and purified by thick-layer chromatography using a 20% ether–pentane mixture as the eluent. The major band contained 112 mg (31%) of 2-(1-phenylvinyl)-2′-(*Z*)-styrylbiphenyl (**14**): mp 87–88 °C; IR (KBr) 6.24, 6.95, 7.60, 8.65, 9.05, 9.70, 10.85, and 13.26 μ; UV (methanol) 255 nm (ε 19 500); NMR ($CDCl_3$, 60 MHz) τ 4.83 (d, 1 H, J = 1.5 Hz), 4.59 (d, 1 H, J = 1.5 Hz), 3.86 (d, 1 H, J = 12.0 Hz), 3.61 (d, 1 H, J = 12.0 Hz), 2.62–3.12 (m, 18 H); m/e 358 (M^+) and 255 (base).

Anal. Calcd for $C_{28}H_{22}$: C, 93.81; H, 6.19. Found: C, 93.65; H, 5.88.

Preparation of 2-(1-Phenylvinyl)-2′-(*E*)-styrylbiphenyl. A solution containing 360 mg of 2-(o-(*Z*)-(styryl)phenyl]benzophenone and three crystals of iodine in 50 mL of benzene was heated at reflux for 4 days. Removal of the solvent followed by thick-layer chromatography gave 280 mg (74%) of 2-[o-(*E*)-(styryl)phenyl]benzophenone: mp 111–113 °C; IR (KBr) 603, 6.24, 6.94, 7.82, 8.65, 9.34, 10.38, 10.76, 13.33, 13.97, and 14.35 μ; NMR ($CDCl_3$) 2.47–3.17 (m, 20 H).

To a solution containing 393 mg of methyltriphenylphosphonium bromide in 20 mL of ether was added 0.44 mL of a 2.5 M n-butyllithium solution at room temperature, followed by 358 mg of 2-(o-(*E*)-(styryl)phenyl]benzophenone in 20 mL of ether. After stirring at 25 °C for 48 h, the solution was filtered, concentrated under reduced pressure, and purified on a 1 × 20 cm Florisil column using a 40% ether–pentane mixture as the eluent. The major fraction contained 230 mg (64%) of 2-(1-phenylvinyl)-2′-(*E*)styrylbiphenyl (**13**): mp 80–87 °C; IR (KBr) 6.26, 6.74, 8.55, 9.72, 10.32, 11.08, 13.06, 14.01, and 14.52 μ; UV (methanol) 224 (ε 36 900), 305 (ε 2400), and 315 nm (ε 23 700); NMR ($CDCl_3$, 100 MHz) τ 4.83 (s, 1 H), 4.62 (s, 1 H), and 2.43–3.20 (m, 20 H); m/e 358 (M^+), 257, 181, 178 (base), 126, 104, and 103.

Preparation of 2-[o-(1-Phenylvinyl)phenyl]benzophenone. To a solution containing 4.64 g of methyltriphenylphosphonium bromide in 100 mL of ether was added 5.65 mL of a 2.3 M n-butyllithium solution at room temperature, followed by 3.60 g of 2,2′-dibenzoylbiphenyl in 200 mL of a 1:1 ether–benzene mixture. After stirring for 4 days at 25 °C, the solution was filtered, concentrated under reduced pressure, and chromatographed on a dry column (alumina, 5 × 70 cm) using a 20% ether–pentane mixture as the eluent. Three components were isolated and identified as 2,2′-bis(1-phenylvinyl)biphenyl [500 mg (14%)], 2-[o-(1-phenylvinyl)phenyl]benzophenone [2.03 g (56%)], and recovered starting material. The desired 2-[o-(1-phenylvinyl)phenyl]benzophenone (**21**) was a white solid: mp 111–112 °C; IR (KBr) 6.01, 6.28, 6.75, 6.85, 6.96, 7.62, 7.81, 7.94, 9.97, 10.75, 12.84, 13.32, and 14.14; UV (methanol) 242 nm (ε 26 300); NMR (60 MHz, $CDCl_3$) τ 4.92 (d, 1 H, J = 1.5 Hz), 4.61 (d, 1 H, J = 1.5 Hz), and 2.3–3.0 (m, 18 H); m/e 360 (M^+), 225 (base), 105, and 77.

Anal. Calcd for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 89.95; H, 5.60.

Preparation of 2′-(1-Phenylvinyl)-2-biphenylcarboxaldehyde. To a solution containing 296 mg of diphenaldehyde monoacetal in 15 mL of ether at 0 °C was added 0.6 mL of a 1.8 M phenyllithium solution. After stirring for 30 min at room temperature, the solution was poured over cracked ice which contained 2 drops of hydrochloric acid. The mixture was extracted with ether, and the ether extracts were washed with a 10% sodium bicarbonate solution and water, dried over magnesium sulfate, and concentrated to a pale oil which contained 320 mg (86%) of 2′-(hydroxybenzyl)-2-biphenylcarboxaldehyde acetal: NMR ($CDCl_3$, 60 MHz) τ 9.42 (s, 3 H), 8.84 (s, 3 H), 6.23–6.98 (m, 5 H), 4.86–5.39 (m, 1 H), 4.38–4.53 (m, 1 H), and 2.22–3.08 (m, 13 H).

A solution containing 1.12 g of the above alcohol in 15 mL of pyridine was added to 10 mL of a 1.0 M solution of Cornforth's reagent. The mixture was stirred at room temperature for 15 h, diluted with water, and extracted with ether. The ether extracts were washed with a 5% hydrochloric acid solution, followed by a 10% sodium bicarbonate solution, and then water. After drying over magnesium sulfate, the solvent was removed under reduced pressure to give 882 mg (79%) of 2′-benzoyl-2-biphenylcarboxaldehyde acetal as a pale oil: NMR (60 MHz, $CDCl_3$) τ 9.38 (s, 3 H), 8.71 (s, 3 H), 6.21–6.81 (m, 4 H), 4.87 (s, 1 H), and 2.18–3.03 (m, 13 H). To a solution containing 393 mg of methyltriphenylphosphonium bromide in 20 mL of ether was added 0.44 mL of a 2.5 M n-butyllithium solution, followed by 372 mg of the above ketone. After stirring for 3 days at 25 °C, the solution was filtered, concentrated, and chromatographed on a 2 × 40 cm Florisil column using a 20% ether–pentane mixture as the eluent. The major component contained 285 mg (77%) of 2′-(1-phenylvinyl)-2-biphenylcarboxaldehyde acetal: mp 108–110 °C; NMR τ 9.32 (s, 3 H), 8.72 (s, 3 H), 6.71 (d, 2 H, J = 11.0 Hz), 6.38 (d, 2 H, J = 11.0 Hz), 5.03 (s, 1 H), 4.85 (s, 1 H), and 2.36–3.17 (m, 13 H).

A solution containing 740 mg of the above acetal and 10 mL of a 55% formic acid solution in 50 mL of acetone was stirred at room temperature for 3 days. The solution was extracted with ether, and the ether extracts were washed with 10% sodium hydroxide and water and dried over magnesium sulfate. Removal of the solvent left a crude oil which was purified on a 2 × 40 cm Florosil column using a 20% ether–pentane mixture. The major component isolated from the column was a pale oil (315 mg, 55%) which crystallized on standing, mp 60–62 °C, and whose structure was assigned as 2′-(1-phenylvinyl)-2-biphenylcarboxaldehyde (**24**): IR (KBr) 3.34, 3.45, 3.55, 5.93, 6.23, 6.97, 7.25, 8.40, 9.17, 11.05, 12.10, 13.10, and 14.20 μ; UV (methanol) 235 (ε 25 700) and 292 nm (ε 3200); NMR ($CDCl_3$, 100 MHz) τ 4.67 (s, 1 H), 4.54 (s, 1 H), 2.18–3.24 (m, 13 H), and 0.33 (s, 1 H); m/e 284 (M^+), 255 (base), 241, 240, 239, 179, 178.

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.71; H, 5.69.

Preparation of 2-(1-Phenylvinyl)-2′-benzylbiphenyl. To a mixture containing 190 mg of lithium aluminum hydride and 1.07 g of aluminum chloride in 20 mL of ether was added 600 mg of 2-[o-(1-phenylvinyl)phenyl]benzophenone in 10 mL of ether. The mixture was heated for 1 h at reflux, cooled, and then added to 10 mL of a 20% sulfuric acid solution. The ether layer was separated, washed with 10% aqueous sodium bicarbonate and water, dried over magnesium sulfate, and concentrated under reduced pressure. The pale oil was recrystallized from methanol to give 420 mg (72%) of 2-(1-phenylvinyl)-2′-benzylbiphenyl (**28**): mp 88–89 °C; IR (KBr) 3.31, 6.25, 6.72, 6.94, 7.57, 8.55, 9.32, 9.75, 9.94, 11.06, 12.64, 13.02, 13.33, and 14.30 μ; UV (methanol) 245 nm (ε 17 300); NMR ($CDCl_3$, 60 MHz) τ 6.59 (d, 1 H, J = 15.0 Hz), 6.29 (d, 1 H, J = 15.0 Hz), 4.98 (d, 1 H, J = 1.5 Hz), 4.70 (d, 1 H, J = 1.5 Hz), and 2.63–3.31 (m, 18 H); m/e 346 (M^+), 255 (base), 241, 240, 239, 178, 165, and 91.

Anal. Calcd for $C_{27}H_{22}$: C, 93.60; H, 6.40. Found: C, 93.53; H, 6.42.

Preparation of 2-(o-Styryl)benzophenone. To a solution containing 25.0 g of methyltriphenylphosphonium bromide in 150 mL of ether was added 28.0 mL of a 2.5 M n-butyllithium solution, followed by the addition of 10.2 g of diphenylaldehyde acid methyl ester[71] in 200 mL of ether. After stirring for 24 h at 25 °C, the mixture was filtered, concentrated under reduced pressure, and chromatographed on a 3 × 50 cm Florisil column using a 40% ether–pentane mixture. The major fraction isolated [5.0 g (49%)] was identified as o-styrylbenzoic acid methyl ester: NMR ($CDCl_3$, 60 MHz) τ 6.50 (s, 3 H), 5.00 (dd, 1 H, J = 10.0 and 1.5 Hz), 4.49 (dd, 1 H, J = 18.0 and 1.5 Hz), 3.62 (dd, 1 H, J = 18 and 10.0 Hz), 2.03–2.99 (m, 8 H).

A 4.0-g sample of the above ester was reduced with 360 mg of lithium aluminum hydride in 25 mL of ether. The usual lithium aluminum hydride workup afforded 3.0 g (89%) of o-styrylbenzyl alcohol: NMR ($CDCl_3$, 60 MHz) τ 8.00 (s, 1 H), 5.71 (s, 2 H), 4.98 (dd, 1 H, J = 10.0 and 1.5 Hz), 4.48 (dd, 1 H, J = 18 and 1.5 Hz), 3.66 (dd, 1 H, J = 18.0 and 10.0 Hz), 2.32–3.07 (m, 8 H). To a solution containing 2.16 g of pyridinium chlorochromate in 25 mL of methylene chloride at 25 °C was added 1.05 g of the above alcohol. After stirring for 1.5 h, the mixture was filtered and concentrated under reduced pressure to give 900 mg (86%) of o-styrylbenzaldehyde: NMR ($CDCl_3$) τ 4.96 (d, 1 H, J = 11.0 Hz), 4.40 (d, 1 H, J = 16.0 Hz), 3.67 (dd, 1 H, J = 16.0 and 11.0 Hz), 2.33–2.98 (m, 7 H).

To a solution containing phenylmagnesium bromide (prepared from 1.73 g of bromobenzene and 292 mg of magnesium turnings in 40 mL of ether) was added 2.08 g of the above aldehyde in 40 mL of ether. Normal work-up procedures afforded 2.42 g (85%) of 2-(o-styryl)benzhydrol which was oxidized with Jones reagent to give 62% of 2-(o-styryl)benzophenone (**19**) as a colorless oil: IR (neat) 3.32, 6.01, 6.28, 6.86, 6.95, 7.62, 7.80, 8.69, 9.98, 10.76, 13.01, 13.33, and 14.13 μ; NMR ($CDCl_3$, 100 MHz) τ 5.03 (d, 1 H, J = 10.0 Hz), 4.61 (d, 1 H, J = 16.0 Hz), 3.62 (dd, 1 H, J = 16.0 and 10.0 Hz), and 2.63–3.22 (m, 13 H); m/e 284 (M^+), 105 (base) and 77.

Irradiation of 2,2′-Divinylbiphenyl. A solution containing 150 mg of 2,2′-divinylbiphenyl (**1**) in 150 mL of benzene was irradiated with a 450-W Hanovia lamp equipped with a Pyrex filter sleeve for 18 h. The solvent was removed under reduced pressure, and the crude photolysate was chromatographed on a 1 × 15 cm Florisil column using a 1:1 pentane–ether mixture as the eluent. The major fraction contained 125 mg (85%) of 4,5,9,10-tetrahydropyrene (**3**), mp 134–136 °C (lit.[72] 135–136 °C). The structure of this material was unambiguously established by comparison with an authentic sample. When the irradiation of **1** was carried out for 3 h, a new product was present (30%) and was isolated by preparative gas chromatography (0.5 in. × 4 ft 3% SE-30 on Chromosorb W at 160 °C) and shown to be 4-vinyl-9,10-dihydrophenanthrene (**2**) on the basis of the following data: IR (neat) 6.15, 6.32, 6.72, 6.90, 7.08, 7.94, 9.94, 10.88, 12.45, and 13.40 μ; UV (methanol) 244 (ε 17 200) and 274 nm (ε 14 700); NMR ($CDCl_3$, 60 MHz) τ 7.26 (s, 4 H), 4.75 (dd, 1 H, J = 11.0 and 1.5 Hz), 4.32 (dd, 1 H, J = 18.0 and 1.5 Hz), and 2.28–3.20 (m, 8 H); m/e 206 (M^+ and base). Further irradiation of this material afforded 4,5,9,10-tetrahydropyrene (**3**).

Irradiation of 2,2′-Biphenyldiacrylonitrile. A solution containing 160 mg of 2,2′-biphenyldiacrylonitrile (**4**) in 125 mL of benzene was irradiated through a Corex filter sleeve for 5 h. Removal of the solvent followed by chromatography on a 1 × 15 cm Florisil column with a 20% ethyl acetate–benzene mixture gave 114 mg (71%) of 4,5,9,10-tetrahydro-4,9-dicyanopyrene (**5**) as a pale-yellow solid: mp 258–260 °C; IR (KBr) 4.43, 6.90, 7.75, 8.05, 8.45, 9.10, 10.00, 12.35, and 13.52 μ; UV (methanol) 231 (ε 9800), 267 (ε 14 900), 277 (ε 17 000), and 290 nm (ε 11 700); NMR ($CDCl_3$, 100 MHz) τ 6.83 (d, 2 H, J = 7.0 Hz), 5.73 (t, 1 H, J = 7.0 Hz), and 2.57–2.78 (m, 6 H); m/e 256 (M^+ and base). The structure of this material was verified heating a 120-mg sample with 10 mg of 5% paladium on carbon in 10 mL of toluene at 160 °C for 20 h. Separation of the catalyst followed by removal of the solvent gave 4,9-dicyanopyrene (**8a**) as a yellow solid: mp 392–397 °C (lit.[73] mp 405–406 °C); IR (KBr) 4.48, 6.70, 6.90, 8.20, 10.88, 11.20, 12.50, and 13.90 μ; UV (methanol) 243, 268, 280, 333, and 348 nm (ε 10 900, 3100, 6300, 1900, and 2900); m/e 252 (M^+ and base).

Irradiation of Dimethyl 2,2′-Biphenyldiacrylate. A 410-mg sample of **6** in 125 mL of benzene was irradiated through a Corex filter sleeve for 7 h. Removal of the solvent followed by chromatography on a 2 × 40 cm Florisil column using a 10% ethyl acetate–benzene mixture afforded 246 mg (60%) of 4,5,9,10-tetrahydro-4,9-dicarbomethoxypyrene (**7**), mp 122–129 °C. This material was a 2:1 mixture of isomers as evidenced by examination of the NMR spectrum (100 MHz, $CDCl_3$) τ 6.71–7.19 (m, 4 H), 6.57 and 6.47 (s, 6 H total), 6.17–6.37 (m, 2 H), and 3.20 (s, 6 H); IR (KBr) 5.75, 6.67, 7.00, 7.88, 8.35, 9.01, 9.42, 12.35, and 14.00 μ; UV (methanol) 268 (ε 14 200), 278 (ε 16 900), and 290 nm (ε 12 000); m/e 322 (M^+) and 203 (base). This material was oxidized with 5% palladium on charcoal at 160 °C in toluene (24 h) to give 4,9-dicarbomethoxypyrene (**8b**): mp 239–240 °C; IR (KBr) 5.74, 6.75, 7.00, 7.92, 8.38, 9.46, 11.00, 12.30, and 14.00 μ; UV (methanol) 243 (ε 46 400), 271 (ε 18 600), 282 (ε 29 400), and 346 nm (ε 15 900); m/e 318 (M^+ and base).

Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43. Found: C, 75.36; H, 4.43.

Irradiation of 2,2′-Bis(1-phenylvinyl)biphenyl. A 200-mg sample of **12** in 140 mL of benzene was irradiated through a Corex filter sleeve for 4 h. Removal of the solvent followed by chromatography through a 1 × 20 cm Florisil column with a 1:1 benzene–pentane mixture gave 75 mg (38%) of 4,5,9,10-tetrahydro-4,9-diphenylpyrene (**10**), mp 211–213 °C (lit.[24] 213–215 °C). This material was compared with an authentic sample synthesized according to the procedure of Laarhoven and Cuppen.[24]

Irradiation of 2-(1-Phenylvinyl)-2′-styrylbiphenyl. A solution containing 150 mg of either the (*E*) or (*Z*) isomer of 2-(1-phenylvinyl)-2′-styrylbiphenyl (**13** or **14**) in 350 mL of benzene was irradiated through Pyrex for 16 h. Removal of the solvent followed by chromatography on a 1 × 12 cm Florosil column using a 5% ether–pentane mixture gave 120 mg of 4,5,9,10-tetrahydro-4,10-diphenylpyrene (**16**), mp 152–158 °C, as a mixture of stereoisomers: IR (KBr) 6.30, 6.75, 6.94, 7.74, 8.69, 9.33, 9.74, 12.70, 13.08, 13.63, and 14.25 μ; UV (methanol) 272 (ε 13 200), 282 (ε 14 900), and 294 nm (ε 10 400); NMR ($CDCl_3$, 100 MHz) τ 6.67–6.85 (d, 4 H, J = 8.0 Hz), 5.70 (t, 2 H, J = 8.0 Hz), and 2.08–3.22 (m, 16 H); m/e 358 (M^+ and base). This material was oxidized with 5% palladium on carbon at 160 °C for 16 h to give 4,10-diphenylpyrene (**18**): mp 152–153 °C; IR (KBr) 6.32, 6.75, 6.98, 7.37, 9.11, 9.35, 11.25, 11.89, 12.61, 12.95, 13.83, and 14.33 μ; UV (methanol) 244 (ε 43 200), 279 (ε 40 100), 315 (ε 10 200), 328 (ε 19 800), and 344 nm (ε 26 000); m/e 354 (M^+), 225, 133, 131, 89 (base), and 73.

Anal. Calcd for $C_{28}H_{18}$: C, 94.88; H, 5.12. Found: C, 94.49; H, 5.04.

The irradiation of the 2-(1-phenylvinyl)-2′-styrylbiphenyl system was also carried out for a much shorter period of time. A 150-mg sample of either (*E*)-**13** or (*Z*)-**14** in 140 mL of benzene was irradiated through a Pyrex filter sleeve for 40 min. Removal of the solvent followed by thick-layer chromatography using a 1% ether–pentane mixture resulted in the separation of three bands. The two minor components were recovered starting material (42%) [(*Z*) and (*E*) mixture (1:1)], 4,5,9,10-tetrahydro-4,10-diphenylpyrene (**16**) (5 mg, 3%), and 82 mg (55%) of 1,2,2a,10b-tetrahydro-1,2a-diphenylcyclobuta[*l*]phenanthrene (**15**): mp 147–148 °C; IR (KBr) 6.25, 6.72, 6.95, 8.36, 9.15, 9.31, 9.68, 10.24, 10.98, 12.73, 13.24, 13.51, and 14.14 μ; UV (methanol) 268 (ε 13 200 and 300 nm (ε 5080); NMR ($CDCl_3$, 100 MHz) τ 7.23 (d, 2 H, J = 8.0 Hz), 5.98 (d, 1 H, J = 12.0 Hz), 5.63 (td, 1 H, J = 12.0 and 8.0 Hz) and 2.21–3.03 (m, 18 H); m/e 358 (M^+), 104 (base), and 77.

Anal. Calcd for $C_{28}H_{22}$: C, 93.81; H, 6.19. Found: C, 93.77; H, 6.19.

Photolysis of 1,2,2a,10b-tetrahydro-1,2a-diphenylcyclobuta[*l*]-phenanthrene (**15**) in benzene through Pyrex resulted in the quantitative formation of 4,5,9,10-tetrahydro-4,10-diphenylpyrene (**16**). Thermolysis of **15** at 150 °C for 48 h, on the other hand, resulted in the formation of 9-phenylphenanthrene (**17**) and polystyrene.

Irradiation of (*E*,*E*)-2,2′-Distyrylbiphenyl. A 200-mg sample of **9** in 140 mL of benzene was irradiated through Pyrex for 64 h. Removal of the solvent followed by chromatography on a 2 × 20 cm Florosil column using a 1:1 benzene–hexane mixture gave 105 mg (52%) of 4,5,9,10-tetrahydro-4,9-diphenylpyrene (**10**), mp 211–213

°C (lit.[24] 213–215 °C). When the irradiation was carried out for 1 h, the major component isolated from the thick-layer plate (135 mg, 68%) was 1,2,2a,10b-tetrahydro-1,2-diphenylcyclobuta[*l*]phenanthrene (**11**), mp 136–137 °C (lit.[24] 136–137 °C), whose spectral properties were identical with those reported in the literature.[24]

Irradiation of 2-[*o*-(1-Phenylvinyl)phenyl]benzophenone. A solution containing 140 mg of **21** in 275 mL of benzene was irradiated through a Vycor filter sleeve for 22 h. Removal of the solvent followed by thick-layer chromatography using a 20% ether–pentane mixture gave 9-phenylphenanthrene (**17**) (16 mg (10%) and 4-benzoyl-9-phenyl-9,10-dihydrophenanthrene (**22**) [85 mg (60%)]: mp 116–117 °C; IR (KBr) 6.04, 6.30, 6.72, 6.92, 7.61, 7.82, 8.38, 8.65, 9.88, 10.10, 10.87, 11.47, 12.30, 12.61, 13.02, and 13.06 μ; UV (methanol) 255 nm (ε 21 100); NMR ($CDCl_3$, 100 MHz) τ 6.79 and 6.77 (two overlapping doublets, 2 H, J = 7.0 Hz), 5.84 (t, 1 H, J = 7.0 Hz), and 2.48–3.20 (m, 17 H); *m/e* 360 (M^+), 254, 202, and 105 (base).

Anal. Calcd for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 89.94; H, 5.60.

The irradiation of **21** was also carried out with wavelength of light >365 nm. A 300-mg sample of **21** in 410 mL of benzene was irradiated through a uranium glass filter for 60 h. Removal of the solvent followed by chromatography on a 2 × 40 cm silica gel column using a 20% ether–pentane mixture gave 185 mg of 4-benzoyl-9-phenyl-9,10-dihydrophenanthrene (**22**) as well as 60 mg (20%) of 9-benzoyl-9-phenyl-9,10-dihydrophenanthrene (**23**): mp 147–148 °C; IR (KBr) 5.98. 6.74, 6.92, 7.93, 8.24, 10.90, 13.05, 13.25, and 14.09 μ; UV (methanol) 260 nm (ε 18 300); NMR (100 MHz, $CDCl_3$) τ 6.32 (s, 2 H) and 2.42–3.47 (m, 18 H). When europium shift reagent was added, the singlet at τ 6.32 was converted to an AB quartet (J_{AB} = 14.0 Hz); *m/e* 358 (M^+), 256, 126 (base), 119, 105, and 98.

Anal. Calcd for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 89.65; H, 5.47.

The ratio of **22** and **23** did not change when the irradiation of **21** was carried out in the presence of 1-dodecanethiol. Further irradiation of **23** with 2537-Å light resulted in the formation of 9-phenylphenanthrene (**17**) and benzaldehyde.

Irradiation of 2′-(1-Phenylvinyl)-2-biphenylcarboxaldehyde. A 100-mg sample of **24** in 350 mL of benzene was irradiated through a Pyrex filter sleeve for 4.5 h. Removal of the sovlent followed by thick-layer chromatography using a 20% ether–pentane mixture gave three bands which were identified as 9-phenyl-9,10-dihydrophenanthrene (**27**) [58 mg (58%)], 9-phenylphenanthrene (**17**) [12 mg (1)] and 9-phenyl-9,10-dihydro-4-phenanthrenecarboxaldehyde (**25**) [10 mg (10%)]. The first two products were identified by comparison with authentic samples. The assignment of the third component as **25** rests on its analytical and spectral data: mp 116–117 °C; IR (KBr) 5.96, 6.29, 6.94, 7.28, 8.15, 8.63, 9.33, 10.27, 12.64, 13.16, 13.64, and 14.24 μ; UV (methanol) 243 (ε 16 600), 269 (ε 10 600), and 324 nm (ε 5300); NMR ($CDCl_3$, 100 MHz) τ 6.65–6.81 (two overlapping doublets, 2 H, J = 7.0 Hz), 5.67–5.84 (t, 1 H, J = 7.0 Hz), 2.40–2.98 (m, 11 H), 1.98–2.10 (m, 1 H), and −0.37 (s, 1 H); *m/e* 284 (M^+ and base) 283, 255, 178, 91, and 77.

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.35; H, 5.66.

The photolysis of **24** was also carried out using light of wavelength >365 nm. A 80-mg sample of **24** in 140 mL of benzene was irradiated through a uranium glass filter for 28 h. Removal of the solvent followed by thick-layer chromatography using a 3% ether–pentane mixture gave a mixture of 9-phenyl-9,10-dihydro-4-phenanthrenecarboxaldehyde [(**25**) (10 mg (13%)] and 9-phenyl-9,10-dihydro-9-phenanthrenecarboxaldehyde (**26**) [40 mg (50%)]: mp 111–112 °C; IR (KBr) 5.81, 6.75, 6.97, 9.17, 10.53, 12.14, 12.99, 13.39, and 14.13 μ; UV (methanol) 269 (ε 6500) and 300 nm (ε 1300); NMR ($CDCl_3$, 100 MHz) τ 6.60 (d, 1 H, J = 15.0 Hz), 6.38 (d, 1 H, J = 15.0 Hz), 1.88–3.06 (m, 13 H), and −0.11 (s, 1 H); *m/e* 284 (M^+) 255 (base), 178, 146, and 126.

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.68; H, 5.55.

On further photolysis using 2537-Å light, **26** was converted to 9-phenylphenanthrene (**17**) and 9-phenyl-9,10-dihydrophenanthrene (**27**).

Irradiation of 2-(1-Phenylvinyl)-2′-benzylbiphenyl. A 100-mg sample of **28** in 140-mL of benzene was irradiated through a Pyrex filter sleeve for 48 h. Removal of the solvent followed by chromatography on a 1 × 10 cm silica column using a 20% ether–pentane mixture as the eluent gave 9-phenyl-9,10-dihydro-4-benzylphenanthrene (**29**) as the only detectable photoproduct: mp 105–106 °C; IR (KBr) 6.27, 6.72, 6.92, 7.80, 8,70, 10.61, 12.66, 12.89, 13.39, and 14.30 μ; UV (methanol) 265 nm (ε 16 100); NMR ($CDCl_3$, 60 MHz) τ 6.83 (d, 2 H, J = 7.0 Hz), 5.90 (t, 1 H, J = 7.0 Hz), 5.62 (s, 2 H), and 2.63–3.07 (m, 17 H); *m/e* 346 (M^+ and base).

Anal. Calcd for $C_{27}H_{22}$: C, 93.60; H, 6.40. Found: C, 93.55; H, 6.44.

Irradiation of 2-(o-Styryl)benzophenone. A solution containing 80 mg of **19** in 140 mL of benzene was irradiated through a Pyrex filter sleeve for 24 h. Removal of the solvent followed by chromatography on a 1 × 10 cm neutral alumina column using a 1:1 pentane–ether mixture as the eluent gave 4-benzoyl-9,10-dihydrophenanthrene (**20**) [60 mg (75%)] as the major product: IR (neat) 3.50, 6.01, 6.25, 6.96, 7.85, 8.61, 8.96, 9.96, 11.11, 12.76, 13.46, and 14.08 μ; UV (methanol) 253 (ε 26 900) and 293 nm (ε 5900); NMR (100 MHz, $CDCl_3$) τ 7.03 (s, 4 H) and 2.28–3.13 (m, 12 H); *m/e* 284 (M^+), 283 (base), 255, 207, 179, 178, 105, and 77.

Quantum Yield Determination. Quantitative measurements were made on a rotating assembly with a series of 2537- or 3130-Å lamps in a Rayonet reactor. Samples in 13-mm Pyrex or quartz ampules were placed in holders on the assembly approximately 6 cm from the light source. All studies were made at room temperature. Samples were degassed to 10^{-4} mm in several freeze-pump-thaw cycles and then sealed. Benzophenone–benzhydrol solutions were used as the chemical actinometer.[74] After irradiation, the degree of reaction was determined by quantitative NMR or vapor-phase chromatography. The conversions were run to 15% or less. In no case was the amount of product formed affected by added piperylene. The quencher was present in concentrations sufficiently high to suppress established triplet processes.[75] Sensitization experiments used benzophenone and were made on a rotating assembly with a central light source (internal water-cooled mercury arc lamp, Hanovia Type L-450W) equipped with a uranium filter sleeve. The concentrations were such that benzophenone absorbed greater than 98% of the light.

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Registry no.—**1**, 34919-47-6; **2**, 55006-42-3; *cis*-**4**, 63104-60-9; *trans*-**4**, 63104-61-0; **5**, 55006-99-0; **6**, 55006-97-8; *cis*-**7**, 55007-00-6; *trans*-**7**, 55007-01-7; **8a**, 55006-40-1; **8b**, 55006-41-2; **9**, 33510-35-9; **12**, 55006-98-9; **13**, 63104-62-1; **14**, 63104-63-2; **15**, 63104-64-3; *cis*-**16**, 63104-65-4; *trans*-**16**, 63104-66-5; **18**, 63104-67-6; **19**, 63104-68-7; **20**, 63104-69-8; **21**, 63104-70-1; **22**, 63104-71-2; **23**, 63104-72-3; **24**, 63104-73-4; **25**, 63104-74-5; **26**, 63104-75-6; **28**, 63104-76-7; **29**, 63104-77-8; diphenaldehyde, 1210-05-5; cyanomethyltriphenylphosphorane, 63104-78-9; carbomethoxymethyltriphenylphosphorane, 63104-79-0; methyltriphenylphosphonium bromide, 1779-49-3; 2,2′-dibenzoylbiphenyl, 24018-00-6; 2,2-dimethyl-1,3-propanediol, 126-30-7; diphenyl monoacetal, 63104-80-3; phenylmethyltriphenylphosphonium chloride, 1100-88-5; 2′-((*Z*)-styryl)-2-biphenylcarboxaldehyde, 63104-81-4; 2-hydroxybenzyl-2′-(*Z*)-styrylbiphenyl, 63104-82-5; 2-[*o*-(*Z*)-(styryl)phenyl]benzophenone, 63104-83-6; 2[o-(*E*)-(styryl)phenyl]benzophenone, 63104-84-7; 2′-(hydroxylbenzyl)-2-biphenylcarboxaldehyde acetal, 63104-85-8; 2′-benzoyl-2-biphenylcarboxaldehyde acetal, 63104-86-9; 2′-(1-phenylvinyl)-2-biphenylcarboxaldehyde acetal, 63104-87-0; diphenylaldehyde acid methyl ester, 16231-67-7; *o*-styrylbenzoic acid methyl ester, 63104-88-1; o-styrylbenzyl alcohol, 4393-04-8; *o*-styrylbenzaldehyde, 63104-89-2; bromobenzene, 108-86-1.

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Dipolar Micelles. 5. Micellar Effects on the Hydrolysis of Neutral and Charged Esters

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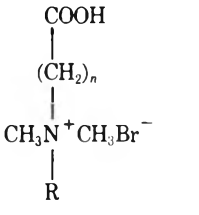
The specific base catalyzed hydrolyses of positively charged and neutral esters in three betainelike micelles of structures I–III, and five dipolar micelles IV–VIII, have been studied. These comprised nine different esters: $C_{10}H_{21}N^+(CH_3)_2ZBr^-$, Z = 2-(*p*-nitrobenzoyloxy)ethyl (CPNBA), Z = 3-(*p*-nitrobenzoyloxy)propyl (HCPNBA), Z = 3-(2,4-dinitrophenyloxycarbonyl)propyl (DNPDE$^+$); *p*-nitrophenyl acetate (PNPA); *p*-nitrophenyl hexanoate (PNPH); *p*-nitrophenyl decanoate (PNPD); 2,4-dinitrophenyl acetate (DNPA); 2,4-dinitrophenyl decanoate (DNPD); and decyl *p*-nitrobenzoate (DPNBA). Study has shown that the second-order rate coefficients of PNPA, PNPH, and PNPD enhance with increasing concentration of premicelle aggregates (subunits) and decrease in the presence of micelles. The betainelike micelles exhibit inhibitory effect on rates of hydrolyses of most substrates included in this study. The inhibitory efficiency was found to depend on the positions of both the reaction site and the carboxylate anion of the zwitterionic micelle. It is suggested that proximity of microenvironmental factors affects primarily the course of hydrolyses on the micellar surface.

In parts 3 and 4[1,2] we have shown that proximity and microenvironmental factors are important in determining the catalytic efficiency of micelle-forming cationic surfactants containing hydroxy head groups at various positions around the cationic surface. It is well known that reactions which occur at the micellar surface are highly affected by the hy-

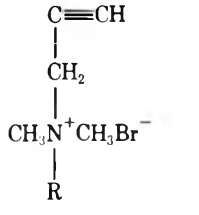
drophilic–lyophilic mode of the system. Therefore, the substrate–micelle intracomplexes may serve as attractive models[3-7] for a systematic study of reaction courses at the interfaces of biological systems.

Present study concerns the kinetic effects of dipolar micelles I–VIII on the hydrolyses of various esters A–E. The models included here were designed to furnish deeper insight on effects of conformation and electrostatic interactions on the catalytic reactivity of micelles. In view of the differences in the mechanistic routes between the micelles of the type discussed earlier in part 4[2] and those of I–VIII presented here, more information on reaction sites and structural effects is expected.

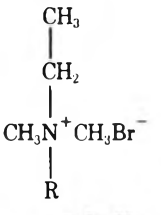
Surface Active Compounds



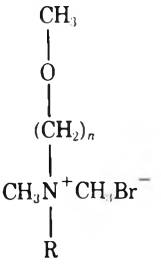
I, R = $C_{10}H_{21}$; n = 1
Ia, R = CH_3; n = 1
II, R = $C_{10}H_{21}$; n = 2
III, R = $C_{10}H_{21}$; n = 3



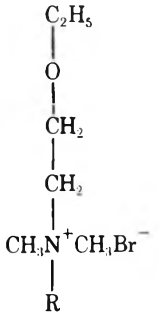
IV, R = $C_{10}H_{21}$
IVa, R = CH_3



V, R = $C_{10}H_{21}$

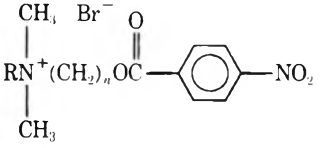


VI, R = $C_{10}H_{21}$, n = 1
VII, R = $C_{10}H_{21}$, n = 2

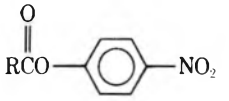


VIII, R = $C_{10}H_{21}$

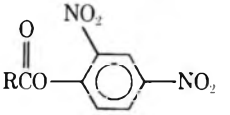
Esters



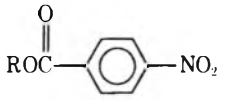
A: CPNBA, n = 2; R = $C_{10}H_{21}$
HCPNBA, n = 3; R = $C_{10}H_{21}$



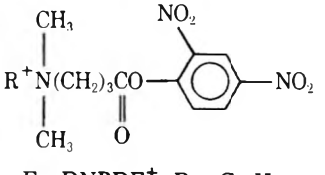
B: PNPA, R = CH_3
PNPH, R = C_5H_{11}
PNPD, R = C_9H_{19}



C: DNPA, R = CH_3
DNPD, R = C_9H_{19}



D: DPNBA, R = $C_{10}H_{21}$



E: DNPDE$^+$, R = $C_{10}H_{21}$

Experimental Section

Micelle Forming Agents. Compounds I–VIII were prepared according to procedures i or ii described in part 3[1] as outlined below:

(i) $CH_3(CH_2)_n(CH_3)_2N + Br(CH_2)_mX \rightarrow CH_3(CH_2)_n(CH_3)_2N^+(CH_2)_mX\ Br^-$

(ii) $CH_3(CH_2)_nBr + N(CH_3)_2(CH_2)_mX \rightarrow CH_3(CH_2)_nN^+(CH_3)_2(CH_2)_mX\ Br^-$

The preparation of *N,N*-dimethyldecylamine used in method i is according to Clarke et al.[8] Compounds I and III were prepared from the appropriate bromoesters (method i) and the esters formed were hydrolyzed either during the quaternization step (compound I) or in the final step with aqueous hydrobromic acid. The synthesis of II (method ii) is accompanied by a large amount of elimination product and the yield of the compound is only 10%.

***N,N*-Dimethyl-*N*-decyl-*N*-2-carboxyethylammonium Bromide (II).** Decyl bromide (48 g) was added to ethyl 3-dimethylaminopropionate (21.5 g). The solution was allowed to stand at room temperature for 2 days only, and the precipitate removed by filtration, followed by washing with ether (mp 55–70 °C).

After several recrystallizations from methanol–ether the quaternary ethyl ester of II melted at 65 °C. The ester hydrolyzed in aqueous HBr solution pH 1 at 50 °C over a period of 1 week followed by lyophilization. The residue was recrystallized from acetone and dried. For analytical properties see Table I.

Esters. All the esters were prepared as described[1,2] and purified prior to their use.

Kinetic Measurements. The hydrolyses of *p*-nitrobenzoate esters were followed by monitoring the release of *p*-nitrobenzoate anion at 250–260 nm as previously described.[2] A Unicam SP800 recording spectrophotometer with scale expansion was used. The temperature of 30 °C in the cell was maintained by circulation of water from an external thermostated bath. All the reactions were performed in a 0.05 M carbonate buffer at a pH range of 9.5–10.5, and in an ionic strength of 0.8 M (KBr). The concentration of esters in the equilibrated cell was 5×10^{-5} M. The second-order rate constants are assembled in Tables II and III. The plots of second-order rate coefficients of the short-chain esters against concentration of micelle-forming surfactants are presented in Figures 1–3.

Results and Discussion

From Figures 1–3 it can be seen that the rate constants of short-chain phenyl esters tend to increase first, and then decrease gradually as the detergent concentrations increase.[9a] The kinetic cmc values at the reaction maxima were found to be higher than those determined by the surface tension method. The corresponding cmc values of micelles I, IV, and V at 0.8 M (KCl) are 4–6 $\times 10^{-3}$, 9 $\times 10^{-3}$, and 5 $\times 10^{-3}$ M.

Scheme I describes in outline the intermediary species involved in the hydrolytic processes. In this scheme M and $(m)_x$ are the average concentrations of micelle units and subunits, respectively, and K_1 and K_2 are the corresponding association constants of the substrate.

At low concentrations of detergent and below the cmc the rate of hydrolysis depends on $(m)_x$ concentration (eq 1), while

Scheme I

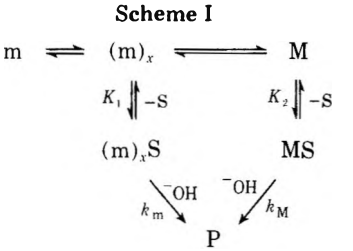


Table I. Analysis and Physical Constants of Compounds II, III, IV, IVa, VI, and VIII

Compd	Registry no.	Mp, °C	Method	Formula	Analysis C Calcd	C Found	H Calcd	H Found	N Calcd	N Found	Br Calcd	Br Found
II[b]	26543-24-8	138–140	ii	$C_{15}H_{32}NO_2Br$	53.25	53.11	9.46	9.44	4.19	4.09	23.67	23.82
III[c]	62851-20-1	92–93	ii	$C_{16}H_{34}NO_2Br$	54.54	54.58	9.65	9.47	3.97	4.14	22.72	22.81
IV[d]	62851-21-2	76	i	$C_{15}H_{30}NBr$	59.21	59.42	9.87	9.81	4.61	4.61	26.32	26.42
IVa[e,b]	7505-53-5	182	i	$C_6H_{12}NBr$	40.45	40.14	6.74	6.67	7.68	7.83	44.94	44.90
VI[a]	62851-22-3	99	ii	$C_{14}H_{32}NOBr$	54.19	53.71	10.32	10.16				
VIII[b]	62851-23-4	124	ii	$C_{16}H_{36}NOBr$	56.80	56.51	10.65	10.51	4.14	4.40	23.67	23.40

Recrystallized from: [a] methanol–ether; [b] acetone; [c] acetone–ether; [d] acetone–ethyl acetate; [e] methanol.

Table II. Rate Constants k_m, k_M (s^{-1} M^{-1}) and Association Constants of Substrates (PNPA, PNPH, DNPA) with Micelles III, IV, and V[a]

Micelles		Esters PNPA	PNPH	DNPA
	k_{OH}	12.1	7.9	64.9
III	Kinetic cmc	0.01	0.01	0.01
	k_{cmc}	24	13.8	12.0
	k_e	19	8.3	12.8
	k_m	62	60.4	390
	K_S		162	
	K_M		2.0	
IV	Kinetic cmc	0.02	0.02	0.03
	k_{cmc}	35	25.9	138
	k_e	90	79	15
	k_m	38	14.7	296
	K_S	74	178	43.8
	K_M	7.5	2.1	71
V[b]	Kinetic cmc	0.008	0.01	0.01
	k_{cmc}	24.8	10.5	130
	k_e	145		60
	k_m	41		301
	K_S	37	272	
	K_M	6.7	1.9	

[a] At 30 °C, μ = 0.8 M (KBr). [b] Registry no.: V, 39995-56-7.

at concentrations above the cmc the quantity of $(m)_x$ remains constant and the reaction rate varies with the micellar concentration (M) only (eq 2).

$$k_{obsd} = (k_{OH} + k_m Kem)^{-}OH/(1 + Kem) \ldots \quad (1)$$

$$Kem = K_1(m)_x = K_1(m/n)$$

where m is the detergent concentration based on monomers, and n is the average aggregation number of the subunits in the solution. k_{OH} denotes the second-order rate constant in the bulk solution, and k_m denotes the rate constant in the subunits.

$$k_{obsd} = [k_{cmc} + k_M K_S(m - cmc)]^{-}OH/[1 + K_S(m - cmc)] \ldots \quad (2)$$

$$K_S(m - cmc) = K_2M = K_2(m - cmc)/n'$$

where k_{cmc} is the second-order rate constant of the ester hydrolysis at the cmc, and k_M is the second-order rate constant of the substrate–micelle complex.

The parameters in eq 1 and 2 were derived by fitting the experimental plots to the theoretical ones, using a nonlinear least-squares program.

From Table II it can be noted that the ratio of the apparent association constants (K_e, K_s) varied in the range of 0.05–3.9. A ratio >1 does not indicate a better binding of the substrate to the subunit than to the micelle, since the two systems differ in their aggregation numbers. On the assumption that $n' > n$ in the three micelles III, IV, and V, it follows that the

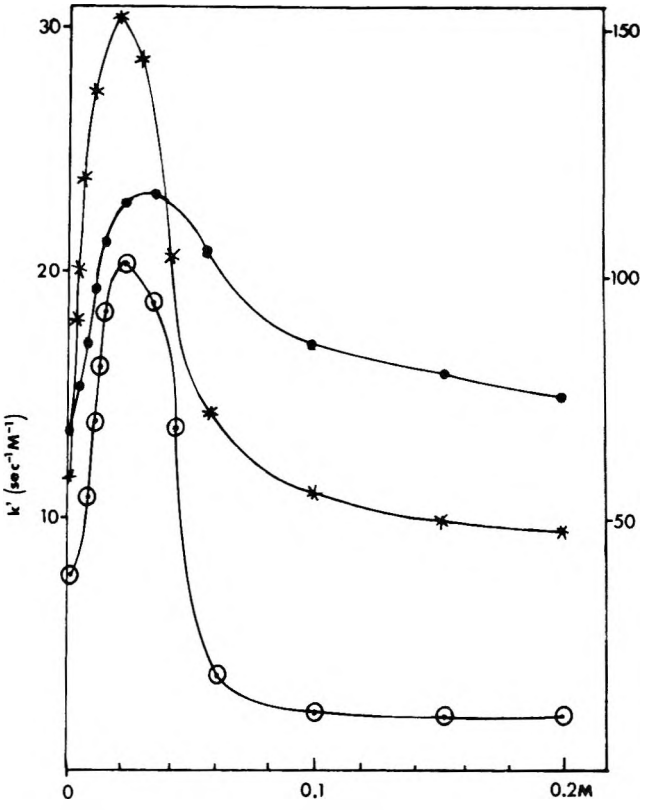


Figure 1. Second-order rate dependence of PNPH (⊙–⊙) and PNPA (★–★) (left-hand ordinate) and DNPA (●–●) (right-hand ordinate) on the concentration of micelle-forming agent (IV): T = 30 °C, μ = 0.8 M (KBr).

binding capacity of micelle's unit is greater than that of the premicelle aggregates. As anticipated, the binding of PNPH to the micellar phase compared with PNPA and DNPA is most efficient due to the greater extent of hydrophobic interactions. The data also indicate that micellar effects of III, IV, and V cannot be accommodated with those produced by other types of cationic micelles recorded in the literature.[10,11]

From Figures 1, 2, and 3 it is apparent that the effect of micelle III, IV, and V on the reaction rates above the cmc is that of an inhibition. Moreover, the better the penetration of the esters into the hydrophobic region of the micelle the greater the inhibitory effects. This is inferred from the decreasing ordering in the relative rates (k_{OH}/k_M) of PNPH, PNPA, and DNPA.

The above mentioned phenomenon is in contrast with the well-known behavior of cationic micelles, which accelerate the reaction rates of anionic nucleophiles due to the electrostatic stabilization of the transition state. Therefore, it can be assumed that in the case of the latter micelles, steric perturbations of the micellar head groups should be attributed to the

Table III. Second-Order Rate Constants k_M (s^{-1} M^{-1}) of Long-Chain Esters with Micelles I–VIII

Micelles	Esters					
	DPNBA	CPNBA	HCPNBA	DNPD	DNPDE+	PNPD
H_2O		13.0	1.7		1688	
I[b]	0.023	9.13	1.08	4.0	910	0.56
II		6.6	1.1	20	1950	2.05
III	0.020	9.3	1.4	20	2100	1.78
IV	0.022	19.5	1.91	19	2100	1.62
V	0.025	11.9	1.8	11.7	2200	1.43
VI	0.021	12.5	2.0	20.5	1533	2.88
VII[c]	0.025	13.9	1.55			1.43
VIII	0.023	14.4	2.0	11.1	1280	1.40

[a] At 30 °C, μ = 0.8 M (KBr). [b] Registry no.: I, 39995-54-5. [c] Registry no.: VII, 61063-28-3.

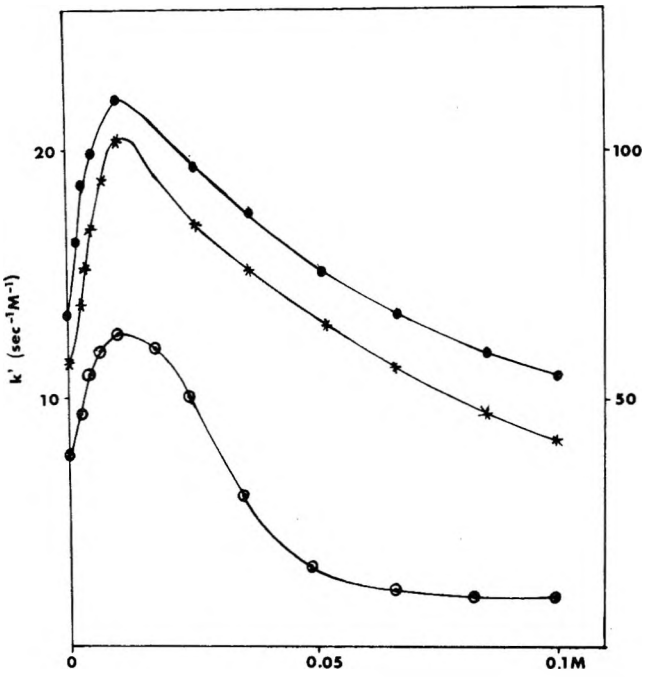


Figure 2. Second-order rate dependence of PNPH (⊙–⊙) and PNPA (★–★) (left-hand ordinate) and OPDNPA (●–●) (right-hand ordinate) on the concentration of micelle-forming agent (III): T = 30 °C, μ = 0.8 M (KBr).

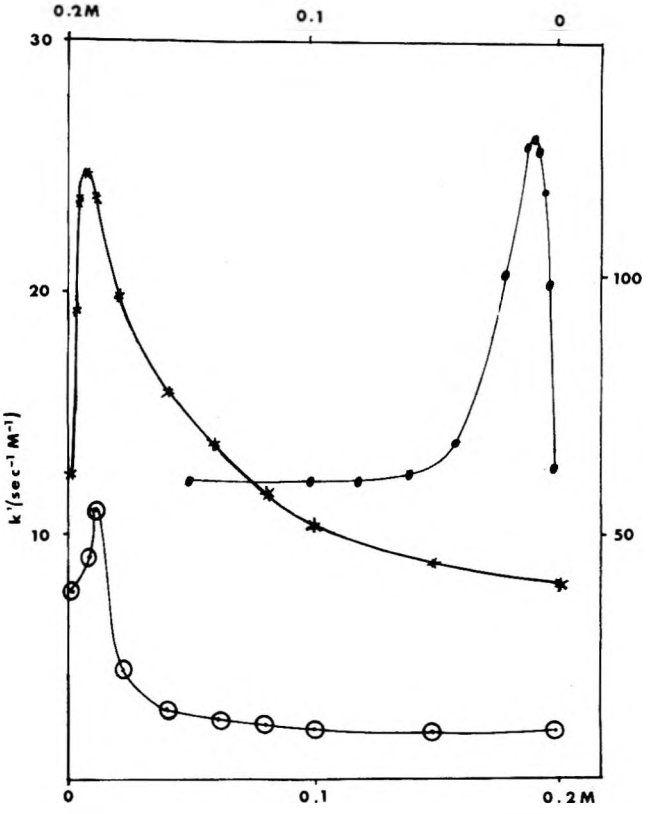


Figure 3. Second-order rate dependence of PNPH (⊙–⊙) and PNPA (★–★) (left-hand ordinate and lower abscissa) and DNPA (●–●) (left-hand ordinate, upper abscissa) in the presence of micelle-forming agent (V): T = 30 °C, μ = 0.8 M (KBr).

decrease in reaction rates. This factor must dominate the electrostatic effects of the positively charged surface.

In addition, the data recorded in Table III indicate that both polar and negatively charged head groups also exert an influence on the reaction rates. Accordingly, at various regions on the surface, the shielding and electrostatic effects contribute unequally to the microenvironment at the reaction site of the substrate. Hence, it seems that the reactivity of esters at the micellar surface depends mainly on the locality of the reaction site and on steric factors. Corroboration of this view is shown, thus: (a) It is most likely that hydrophobic interactions orient the reaction centers of both PNPD and PNPH to reside near the positively charged onium groups of micelles III, IV, and V. On the other hand, the electrostatic interactions of the functional head groups of the latter micelles with the surface seems to be negligible. This is adduced from the relative rate of PNPD in the betaine-like micelles I, II, and III (Table III). Consequently, the similarity in the rate coefficients between PNPD and PNPH in the presence of micelles III, IV, and V (see Tables II and III) can be related to the closeness of the microenvironment effect on the reaction sites of the two esters. (b) Although the rate constants (k_M) of DNPA and PNPA decrease as the micelle concentration increases above the cmc, the rate of PNPA only is suppressed below its value in water. This is reflected also in their K_s values (see micelle IV) and the origin of this behavior could stem from the difference in the position of the two esters on the surface. The molecules of DNPA are assumed to cluster around the water-rich region of the micelle and should conceivably be less affected than those of PNPA, which tend to penetrate into the interior region of the micelle.

The observed premicelle-induced augmentation in reaction rates could be interpreted in similar terms. In fact the subunits of III, IV, and V display kinetic characteristics which are peculiar to cationic micelles and the relative k_m/k_{OH} values lie in the range of 1.8–7.5 (Table II). This clearly indicates that the aliphatic head groups exert greater influence on the closed surface of the micelle rather than on the subunits. The differences between the systems could spring from differences in (a) shielding capacities, (b) surface shapes, (c) modes of binding, and (d) the effective charges. These reflect virtually all microenvironmental differences at the reaction sites.

The kinetic effects as displayed by the subunits of III, IV, and V (Table II) also indicate that substrate reactivity does not depend on the binding constants K_s. This again suggests

that orientation of the reaction site in a subunit system is a more important factor than the extent of the substrate interaction.

The increase in reaction rate of PNPA in the presence of IVa by a factor of 2.3 ($k = 28\ s^{-1}\ M^{-1}$) is worthy of note. The measurements were taken in the range 0.05–0.2 M, showing no dependence on concentration. The reaction rate of PNPA under similar conditions with Ia was unaffected. This emphasizes the contribution of electrostatic effect of both negative and positive ions on the specific base hydrolysis of esters.

The rate enhancement of anionic nucleophiles in cationic micelles was recently proposed to be due to hydrophobic desolvation of ion pairs.[9b] Our data presented above could not be accommodated with that proposal, since the low hydrophobic environment of the subunit actually increases substrate reactivity, whereas the high hydrophobic environment of the micelle decreases the reactivity.

Effect of Zwitterionic Micelles. An inspection of Table III reveals inconsistency in the kinetic effects of carboxylate anions (I, II, III) on the hydrolysis of the different esters. Substrates bearing good leaving groups, such as in DNPD, $DNPDE^+$, and PNPD, are inhibited by micelles of the type I, whereas the ester CPNBA is inhibited mainly by micelle I. Substrate of the kind of DPNBA is quite unaffected by zwitterionic micelles. The carboxylate-induced rate retardation in alkaline hydrolysis can be explained in terms of electrostatic interactions similar to that described for other micellar and bimolecular systems.[12–15]

The remarkable increase in reactivity of the nucleophilic reactions in cationic surfactant could be attributed to: (a) the effect of binding of the reactants to the micellar surface, which increases the effective concentration of the reacting species and as a consequence its proximity effects;[16,17] (b) electrostatic interactions between the negatively charged transition state and the micelle surface, which enhanced its stabilization relative to that of the ground state.[18,19] Following these considerations anionic micelles are to be expected to exert the opposite effect on reaction rates. However, the charge characteristic in zwitterionic micelles is not clear. There are three possibilities which must be reckoned. First, that zwitterionic micelles could affect the reaction rate like neutral micelles to retard the reaction rate. This could be envisioned either on the basis of the ground state (a decrease in binding of reactants) or on the basis of the transition state (a decrease in electrostatic stabilization) as compared to the situation in cationic micelles. Second, zwitterionic micelles could behave like cationic micelles in accelerating the reaction rates. This was actually the case when cyanide ion was added to pyridinium ion in the presence of dodecyldimethylammoniopropanesulfonate.[18a] Third, zwitterionic micelles may behave like anionic detergents which inhibit the reaction rate in alkaline hydrolysis, since 70–80% of the positive charge on the cationic group should be neutralized by the counterions[20] at high ionic strength (0.8 M).

The data presented here point out that additional factors are also responsible for the varied reactivity of zwitterionic micelles. The basic hydrolyses of DNPD and PNPD in the three zwitterionic micelles I, II, and III reveal the importance of the location of the reaction site relative to the positively and negatively charged groups on the micellar surface. The case of the latter esters in the presence of micelle I is that the site of reaction and of carboxylate anion are very close and therefore electrostatic interactions should destabilize the emerging negatively charged transition state of the ester, and dominate the stabilization effects induced by the cationic group. In the presence of zwitterionic micelles II and III the carboxylate anion is located more in the region of the bulk solution and thus the electrostatic stabilization of the transition state due to the positively charged surface is more pronounced, as compared to micelle I.

The proximity of the carboxylate group in the betaine series[21] to that of the ammonium head group is inferred from physical measurements. This is borne out also from the kinetic data. However, it might be quite different for the zwitterionic micelles II and III.

The significance of the location of the reaction site in the zwitterionic micelles is also noted in other types of esters. The anticipated inhibitory effect of micelle III on the hydrolysis of $DNPDE^+$ was not experimentally observed. In fact (see Table III), the relative rates of $DNPDE^+$ in the zwitterionic micelles I, II, and III resemble those of PNPD and DNPD, suggesting analogy between the latter and the former. Thus, it can be concluded that the reaction site in $DNPDE^+$ is most probably on or near the surface rather than in the bulk. Moreover, the tendency of aromatic compounds to solubilize on the surface of cationic micelles is well documented.[22–25] It is permissible, therefore, to conclude that $DNPDE^+$ exists in a folded conformation and that the phenyl moiety occupies a position between the positively charged groups.

On the basis of kinetic salt effects we have inferred earlier that this sort of conformation actually exists in the case of CPNBA, HCPNBA, and $DNPDE^+$. Accordingly, the above-mentioned effects of the zwitterionic micelles on HCPNBA and CPNBA appear plausible. However, some differences could be observed upon comparing the latter with $DNPDE^+$: (a) All three zwitterionic detergents, I, II, and III, exert diminishing effects on rates of reaction of HCPNBA and CPNBA (compared to micelle V), but this is not the case with $DNPDE^+$. (b) The rate constant of HCPNBA is affected in the presence of micelles I and II, but in the case of $DNPDE^+$ only micelle I exhibited an inhibitory effect. (c) In the hydrolysis of CPNBA only micelle II was the most effective one. These kinetic differences could be attributed to small conformation variation in the folded forms of the esters, pointing the closeness of the reaction site to the carboxylate anion. The micellar effects of I, II, and III are rather modest and could also originate either from microscopic changes in the dielectric constant of the medium or from changes in solvation of the transition state. It could also be due to changes in the steric interactions within the micelles, but they all must be small.

On comparison between the rate constants of compounds V, VI, and VII, only little sensitivity to the polar groups along the surfactant chain was observed.

The absence of an inhibitory effect in the case of DPNBA in the presence of micelle I appeared rather unexpected at first glance, since it was thought to be similar to that of PNPD and DNPD. However, the electrostatic interactions of the charged groups in the zwitterionic micelle with the attacking nucleophile and the leaving group in the transition state of DPNBA relative to PNPD may account for the dissimilar effects in the esters.

More work on the transition state level is warranted toward this end.

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Registry No.—PNPA, 830-03-5; PNPH, 956-75-2; DNPA, 4232-27-3; DPNBA, 6500-30-7; CPNBA, 62851-24-5; HCPNBA, 62851-25-6; DNPD, 61063-34-1; $DNPDE^+$, 62905-89-9; PNPD, 1956-09-8.

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A New Synthesis of Benzo[*a*]pyrene. 7,10-Dimethylbenzo[*a*]pyrene[1]

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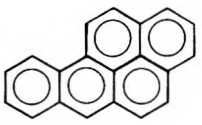
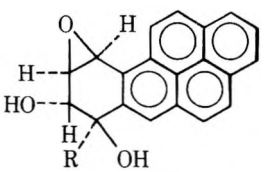
1-Acetylpyrene was reacted with the lithium enolate of ethyl acetate to yield the hydroxy ester which was dehydrated to 3-(1-pyrenyl)-2-butenoic acid. Reduction produced 3-(1-pyrenyl)butanoic acid which was reduced by $LiAlH_4$ to 3-(1-pyrenyl)butanol. Mesylation, cyanation, and hydrolysis afforded 4-(1-pyrenyl)pentanoic acid. This acid was produced in 15% yield but in one step by alkylation of pyrene with γ-valerolactone. Cyclization with HF produced 7-keto-10-methyl-7,8,9,10-tetrahydrobenzo[*a*]pyrene from which 10-methylbenzo[*a*]pyrene was produced by reduction and dehydrogenation and 9,10-dimethylbenzo[*a*]pyrene by reaction with methyllithium followed by dehydration and dehydrogenation. Alternately 7,10-dimethylbenzo[*a*]pyrene was synthesized by reaction of 1-bromopyrene with 2,5-dimethylfurar. (via 1-pyryne) to yield 7,10-dihydro-7,10-dimethyl-7,10-epoxybenzo[*a*]-pyrene which on reduction and acid-catalyzed dehydration yielded 7,10-dimethylbenzo[*a*]pyrene. The fact that 10-methylbenzo[*a*]pyrene is inactive as a carcinogen is discussed in terms of the effect of the 10-methyl group on the metabolism involved.

The metabolism of benzo[*a*]pyrene, **1**, in relation to carcinogenicity and mutagenicity has long interested scientists. Recently, the hypothesis has been advanced that one (or more) of the isomeric 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenes, **2**, is the ultimate carcinogen, and/or mutagen.[3] Presumably, epoxidation[4] of 1 to yield the 7,8-



1



2, R = H
4, R = CH_3

epoxide occurs first, followed by hydration to trans-7,8-diol which is then epoxized to **2**. Thus three enzyme-catalyzed processes occur consecutively to yield (presumably) the ultimate carcinogenic species.

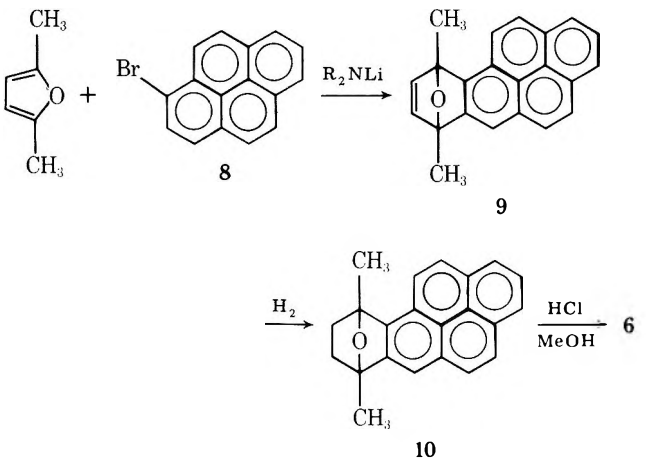
In studies in the benz[*a*]anthracene series, we have hypothesized that the carcinogenic activity of many substituted benz[*a*]anthracenes can be rationalized if it is assumed that: (a) detoxification occurs by metabolic attack at position 7; and (b) carcinogenic activity arises by metabolism which is initiated by attack at position 5.[5,6] Each of these metabolic pathways can be blocked (or altered) by substitution of a methyl or fluoro group at the position involved. For example, 7,12-dimethylbenz[*a*]anthracene is a potent carcinogen but 5,7,12-trimethylbenz[*a*]anthracene[7] and 7,12-dimethyl-5-fluorobenz[*a*]anthracene[7,8] are inactive, probably because in each the 5 position is blocked.

Because of the results in the benz[*a*]anthracene series we became interested to find out if the current hypothesis concerning the ultimate carcinogen in the benzo[*a*]pyrene series could be tested by determining the carcinogenic activity of benzo[*a*]pyrenes having methyl groups in the benz ring.

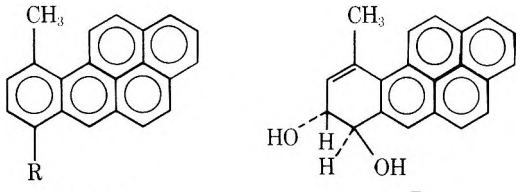
For example, if a methyl group were substituted at the 7 position of benzo[*a*]pyrene would this block the epoxidation at the 7,8 position and render the compound inactive? Since 7-methylbenzo[*a*]pyrene, **3**, has been reported to be carcinogenic,[9] evidently the epoxidation at the 7–8 bond can occur as well as the hydration of the 7,8-oxide to the 7-methyl-7,8-*trans*-diol. The latter could then be epoxidized at the 9–10 bond to yield a 7,8-dihydroxy-9,10-epoxy-7-methyl-7,8,9,10-tetrahydrobenzo[*a*]pyrene, **4**, which would be a corcinogenic substance analogous to the product, **2**, formed from **1**. The above reasoning assumes that the carcinogenic activity of **3** is due to the same type of metabolic processes responsible for the activation of **1**.

Accordingly, we wished to know if 10-methylbenzo[*a*]pyrene, **5**, and 7,10-dimethylbenzo[*a*]pyrene, **6**, would be carcinogenic. We have been informed that after 16 months, **5** has produced no tumors and hence must be considered inactive as a carcinogen.[7] One can assume that **5** is capable of being epoxidized and the epoxide hydrated to *trans*-7,8-dihydro-7,8-dihydroxy-10-methylbenzo[*a*]pyrene, **7**, but epoxidation at the 9,10 position is either blocked or the epoxide, if formed, does not interact with DNA as does **2**. Further experiments

Scheme I



to sort out the possibilities are in order. We will be glad to supply quantities of **5** and **6** to interested researchers. Tests

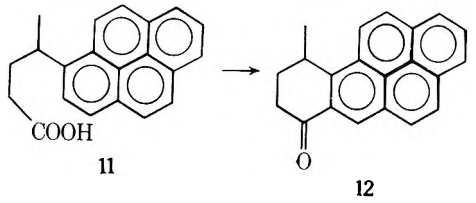


5, R = H
6, R = CH_3

on **6** have been initiated[7] but it is too early to assess its activity. Presumably it will prove inactive because of the blocking effect of the methyl group at the 10 position.

7,10-Dimethylbenzo[*a*]pyrene, **6**, was synthesized by a route (Scheme I) involving condensation of 1,2-pyryne with 2,5-dimethylfuran. A similar condensation with furan failed because of metallation.[11]

Improvements in the synthesis of **5**[10] included a one-step, time-saving condensation of pyrene with γ-valerolactone[12] to form **11**, a route superior to others despite the 15% yield.



Cyclization of **11** to 7-keto-10-methyl-7,8,9,10-tetrahydrobenzo[*a*]pyrene, **12**, followed by conventional chemistry led to the synthesis of both **5** and **6**.

Experimental Section[13]

4-(1-Pyrenyl)pentanoic Acid, 11. This compound was prepared essentially as described[10] from 1-acetylpyrene except that the homologation of 3-(1-pyrenyl)-butanoic acid was accomplished by reduction to 3-(1-pyrenyl)butanol (*m/e* 274)[14] with $LiAlH_4$ in benzene–ether (reflux, 6 h) in almost quantitative yield (single spot on TLC) followed by conversion (almost quantitatively) to the mesylate (*m/e* 352)[14] by treatment with mesyl chloride in CH_2Cl_2–$(C_2H_5)_3N$ at 0 °C for 75 min. To a solution of 37.1 g (0.1 mol) of mesylate and 1.5 g of Aliquat 336[15] in 150 mL of benzene was added a solution of 40 g of KCN in 100 mL of water. The mixture was refluxed and well stirred for 48 h. After removing solvent from the washed benzene layer, a solution of the residue (single spot on TLC different from mesylate) in 100 mL of ethanol and 100 mL of 40% KOH was refluxed for 20 h. Since the crude acid, **11**, produced melted at 126–128 °C and after recrystallization from benzene–acetic acid at 129.5–130.5 °C (lit.[10] mp 135–136 °C of purified **11**) evidently a polymorphic form was at hand. The overall yield from 3-(1-pyrenyl)butanoic acid was 80.7%. Our procedure represents an improvement of the literature method[10] in that larger amounts of material can be more easily processed and the overall yield of pure acid is better.

In another synthesis of **11**, 16.2 g of $AlCl_3$ was added during 5–10 min to a well-stirred mixture of 20.2 g of commercial pyrene[16] and 100 mL of *o*-dichlorobenzene followed by 8.0 g of freshly distilled γ-valerolactone. The reaction mixture was gradually heated to 50–55 °C, held there for 48 h, and poured after cooling into ice–HCl. After removal of solvent by steam distillation an ether solution of the products was extracted with water and then 3% NaOH. Acidification of the alkaline extract gave 8 g of crude **11**. The methyl ester was prepared, distilled, and chromatographed over silica gel to yield 4.2 g of methyl ester (single spot on TLC). Hydrolysis and recrystallization of the acid from benzene–petroleum ether, 30–60 °C, afforded 3.7 g of colorless **11**, mp 130–131 °C (lit.[10] mp 135–136 °C, a polymorphic form as we never got a melting point higher than 130–131 °C). An overall yield of 15.3% based on valerolactone was obtained. The yield of pure **11** was smaller if the Friedel–Crafts reaction was run at 120 °C for 4 h.

3-(1-Pyrenyl)butanoic Acid. To an ether solution of 0.22 mol of methyllithium (2 M) was added 30.8 g of 2,2,6,6-tetramethylpiperidine[17] followed after 5 min at 0 °C with 100 mL of pure THF. To this solution at −78 °C was added 19.3 g of ethyl acetate[18] during 5 min followed after 15 min with a solution of 50 g (0.21 mol) of 1-acetylpyrene[10] in 250 mL of THF added during 20 min. After 45 min at −78 °C the reaction mixture was treated with dilute HCl. A conventional workup yielded crude hydroxy ester which was heated with 350 mL of toluene and 0.5 g of toluenesulfonic acid for 5 h, the water formed being removed by distillation. Alkaline hydrolysis afforded 44 g (89% based on recovery of 8 g (16%) of 1-acetylpyrene) of 3-(1-pyrenyl)-2-butenoic acid, mp 228–232 °C (lit.[19] mp 233 °C). Catalytic hydrogenation of 4 g of acid in 40 mL of THF over 150 mg of PtO_2 (Engelhard) for 4 h at 50 psi afforded 3.2 g (80%) of 3-(1-pyrenyl)butanoic acid, mp 177–178 °C (lit.[10] mp 177–178 °C), after crystallization from benzene.

7-Keto-10-methyl-7,8,9,10-tetryhydrobenzo[*a*]pyrene, 12. To 250 mL of HF in a polyethylene bottle was added 24.0 g of **11** with stirring. After 30 min the HF was evaporated in a rapid stream of N_2 and the residue was treated with aqueous $NaHCO_3$ and filtered. The neutral product was recrystallized from benzene–petroleum ether to yield 15.2 g of **12**, mp 154–159 °C (combined yield 97%). Recrystallization afforded pure **12** mp 162–163 °C (lit.[10] mp 162–163 °C) with little loss. More than 30 min contact with HF gave lower yields.

10-Methylbenzo[*a*]pyrene, 5. The conversion of **12** to **5**, mp 188–190 °C, was accomplished essentially as described[10] in 41% overall yield. When the aromatization of the secondary alcohol was effected by heating at 300–360 °C for 30 min over 5% rhodium-on-alumina[20] the yield was 51%. Pure **5**, mp 192–193 °C (lit.[10] mp 190–190.8 °C), was obtained with little loss by vacuum sublimation.

7,10-Dimethylbenzo[*a*]pyrene, 6. A solution of lithio *N*-cyclohexylisopropylamine prepared by treating 3.5 g (0.025 mol) of amine in 50 mL of THF with an equivalent of butyllithium in hexane was added over 15 min to a stirred solution of 6.7 g of 1-bromopyrene[21] and 11.5 g of 2,5-dimethylfuran in 100 mL of THF at room temperature. After refluxing for 4 h the mixture was poured on ice–HCl. A benzene–ether extract of the products was washed with water and saturated NaCl solution and dried by passing over $MgSO_4$. After removal of solvent the residue was triturated with 30–60 °C petroleum ether. The solid obtained (1.4 g) contained nitrogen and was discarded. Recrystallization of the material from the filtrate yielded 1.1 g of **9**, mp 167–168 °C. Column chromatography of the material from the mother liquors afforded first 1.5 g of pyrene and then 1.2 g of **9** (total yield 33%): mp 167–168 °C; *m/e* 296, NMR ($CDCl_3$, $(CH_3)_4Si$, ppm) 127 (s, 3, CH_3), 144 (s, 3 H, CH_3), 413–441 (m, 2 H, CH=CH), 467–504 (m, 8 H, ArH).[22] Anal. Calcd for $C_{22}H_{16}O$: C, 89.1; H, 5.4. Found:[23] C, 88.8, H, 5.4.

About the same yield was obtained when 2,2,6,6-tetramethylpiperidine[17] was used in place of cyclohexylisopropylamine. This reaction failed when run in glyme or when lithium hexamethyl disilazane was used in THF.

A solution of 0.80 g of **9** in 30 mL of THF was reduced over PtO_2 at 15 psi for 1 h to yield a yellow solid (*m/e* 298) which was suspended in 50 mL of methanol saturated with HCl. After heating at reflux for 2.5 h the solvent was removed under reduced pressure and the residue was triturated with saturated Na_2CO_3 and filtered. Recrystallization of the solid from acetic acid yielded crude **6** in 87% yield. Sublimation afforded pure **6** as a bright yellow solid: mp 167–168 °C with little loss; *m/e* 280; NMR ($CDCl_3$) 176 (s, 3, $ArCH_3$), 196 (s, 3, $ArCH_3$), 434–568 ppm (m, 10, ArH). Anal. Calcd for $C_{22}H_{16}$: C, 94.1; H, 5.8. Found:[23] C, 94.3; H, 5.7.

Alternately, a sample of **6** was prepared by reaction of **12** with

methyllithium in ether–benzene, followed by dehydration of the tertiary alcohol formed and aromatization at 300–330 °C for 30 min over Rh-on-Al_2O_3.[20] The melting point and mixture melting point of **6** prepared by the two routes was 167–168 °C.

Registry No.—**1**, 50-32-8; **5**, 63104-32-5; **6**, 63104-33-6; **8**, 1714-29-0; **9**, 63104-34-7; **11**, 63104-35-8; **12**, 63104-36-9; 3-(1-pyrenyl)butanol, 63104-37-0; 3-(1-pyrenyl)butanol mesylate, 63104-38-1; mesyl chloride, 124-63-0; 3-(1-pyrenyl)butanoic acid, 63104-39-2; ethyl acetate, 141-78-6; 1-acetylpyrene, 3264-21-9; 3-(1-pyrenyl)-2-butenoic acid, 63104-40-5; 2,5-dimethylfuran, 625-86-5.

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(2) Postdoctoral Research Associate.
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(14) We thank Mr. R. Weisenberger for the mass spectral determinations.
(15) Methyltricapyrlammonium chloride obtained from the McKerson Corp., 3016 Fourth Ave. S., Minneapolis, Minn.
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(23) Microanalyses by M-H-W Laboratories Garden City, Mich. 48135.

Isonicotinyloxycarbonyl, a Novel Amino Protecting Group for Peptide Synthesis[1]

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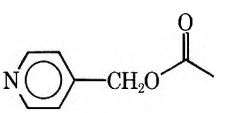
The isonicotinyloxycarbonyl (iNoc) group is an acid-stable protecting group for the protection of the ϵ-amino group of lysine. iNoc can be removed by reduction with Zn under mild acidic conditions or by catalytic hydrogenation. The combined physical and chemical properties of iNoc offer unique advantages for its use as a lysine protecting group.

We[2] and others[3,4] have observed undesired loss of the benzyloxycarbonyl protecting group used for the protection of the ϵ-amino group of lysine during acid-catalyzed removal of the α-amine protecting group, *tert*-butyloxycarbonyl. Methods for more selective removal of the *tert*-butyloxycarbonyl group in the presence of benzyloxycarbonyl have been proposed.[5] Protecting groups for lysine of greater acid stability[6] or more acid labile α-amino protecting groups[7] have been used to avoid these problems. The former approach has been successfully used in solid-phase peptide synthesis.[6] For a variety of reasons it is less satisfactory for synthesis in solution.[8] These improvements still rely on kinetic differences in the rates of removal of two acid labile protecting groups cleaved by different mechanisms. Cleavage of the more labile protecting groups generally proceeds predominantly via an S_N1 pathway, while the more stable protecting groups follow an S_N2 pathway. Thus, modifications in removal conditions by the introduction of nucleophilic scavengers or solvent changes may result in a loss of selectivity. We have noted such decreased selectivity for removal of the *tert*-butyloxycarbonyl group in the presence of the benzyloxycarbonyl group.[9] For this reason, we preferred an ϵ-amino lysine protecting group which is completely stable to acid, but which can be smoothly removed under mild conditions, for instance, reductively. Such a protecting group would assure absolute stability when the *tert*-butyloxycarbonyl is cleaved with acid. Conversely, such an ϵ-amino protecting group could be removed reductively without affecting a butyloxycarbonyl group.

Although kinetic selectivity for protecting group removal has, for example, been successfully applied in a synthesis of human insulin,[10] there are advantages to tactics based on a choice of protecting groups removed by chemically different methods. The known protecting groups which would offer chemical selectivity do not fulfill all of our other requirements for a lysine protecting group.[11] We have discussed our criteria in detail elsewhere.[8] These include (1) stability under conditions employed in peptide synthesis, (2) removal under unique and mild chemical conditions, (3) stability under conditions for the removal of other protecting groups, and (4) capability to increase rather than decrease the solubility of large peptides in polar solvents.

The isonicotinyloxycarbonyl protecting group (1) appeared



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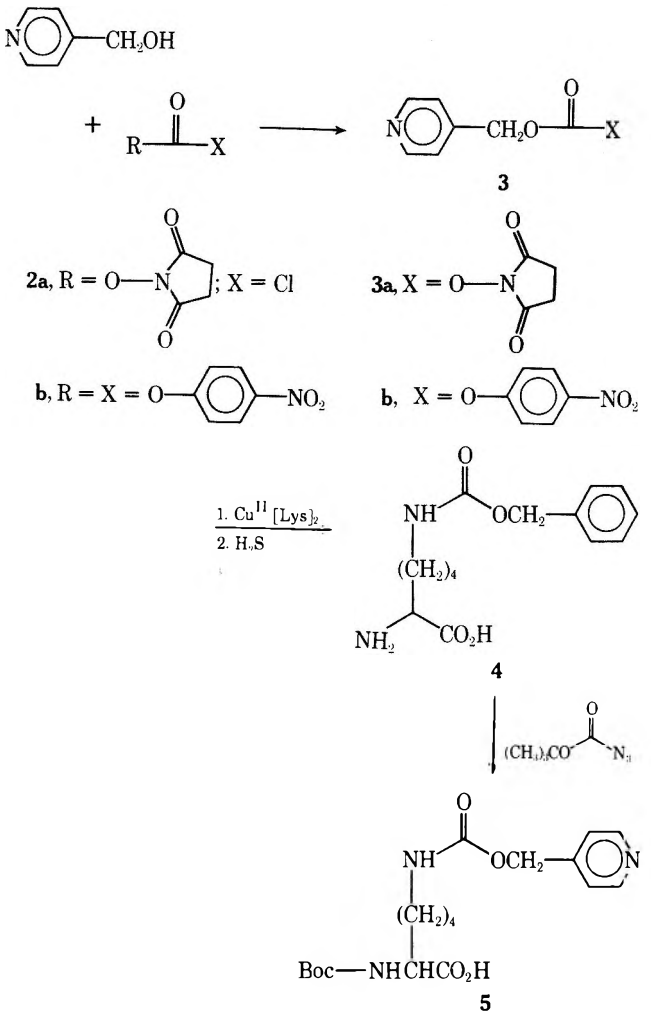
to offer the desired combination of properties to meet these criteria. The pyridine ring should make **1** highly stable under acidic conditions, while facilitating reductive removal, as was the case for the carboxyl protecting, 4-picolyl esters of Young.[12]

Isonicotinyl *p*-nitrophenyl carbonate (**3b**) was prepared by the reaction of bis(nitrophenyl) carbonate (**2b**) with 4-hydroxymethylpyridine in the presence of *N*-methylmorpholine

Scheme I



(Scheme I). The *p*-nitrophenol salt of **3b** of purity satisfactory for the synthesis of 4 was obtained on evaporation of the reaction solution. Our earlier studies had utilized isonicotinyl *N*-succinimido carbonate (**3a**). This reagent is more difficult to prepare and is less stable than **3b**. Either reagent can be used in reaction with the copper(II) complex of lysine to give N^{ϵ}-iNoc-Lys (4). N^{α}-Boc-N^{ϵ}-iNoc-Lys (**5**) was prepared by reaction of 4 with either *tert*-butyl succinimido carbonate or *tert*-butyl azidoformate.

The isonicotinyloxycarbonyl group can be selectively removed from *5* by the action of either zinc dust in aqueous acetic acid or by catalytic hydrogenation using 5% Pd/C, giving clean conversion to α-Boc-Lys. In contrast, treatment of **5** with anhydrous HF for 1 h at 18 °C results in a clean conversion to ϵ-iNoc-Lys (4) with no detectable lysine being formed. The stability of ϵ-iNoc-Lys under a variety of conditions commonly encountered in peptide synthesis is summarized in Table I. It is clear that this protecting group can be safely employed in synthetic tactics involving any acid labile protecting group, except possibly those requiring HBr for removal. The data in this table also give a view of the range of conditions under which the protecting group may be removed. Thus, complete removal of iNoc can be expected with zinc under acidic but not basic conditions. Sn(II) is found to be too weak a reducing agent to remove iNoc. A more precise definition of the ease of reduction of iNoc was obtained by studies using cyclic voltametry. Two sharp reduction waves were observed at −1.95 and −2.25 V (relative to Ag/AgCl). Controlled potential electrolysis at −2.02 V indicated a two-electron reduction from which 4-picoline and lysine were isolated. Reduction at −2.35 V resulted in a lower yield of lysine, suggesting that the wave at −2.25 V represents a side reaction. The reduction potential

Table I. Stability of the Isonicotinyloxycarbonyl Group

Reagent or conditions	Time, h	Stability[a]
HF (liquid) (18 °C)	1	Stable
HCl/ethyl acetate (satd) (20 °C)	1	Stable
Trifluoroacetic acid (20 °C)	1	Stable
HCl/ethyl acetate (satd) + 10% mercaptoethanol (20 °C)	1	Stable
HBr/acetic acid (30%) (20 °C)	1	~10% removal
Zn (dust) bicarbonate 0.1 N pH 8 (20 °C)	1	~10% removal
50% aqueous acetic acid (100 °C)	0.5	Stable
$SnCl_2$ in 50% aqueous acetic acid	1	Stable
Zn dust (HCl activated) in 50% acetic acid	1.5	Complete removal

[a] Determined by TLC analysis of total reaction.

of −1.95 V for the iNoc group is more positive than that required for the removal of the benzyloxycarbonyl group (−2.90 V).[13]

An example of the removal of the iNoc protecting group from ϵ-iNoc-Lys[3]–substance P is described in the Experimental Section, for illustrative purposes. None of the amino acids present in this peptide show any reaction under the conditions for protecting group removal. The use of the iNoc protecting group has also been reported for the synthesis of somatostatin[14] and analogues.[15] The stability of the indole of tryptophan was also demonstrated by removal of the protecting group of ϵ-iNoc-Lys (Zn/50% aqueous HOAc) in the presence of an equimolar amount of Boc-Trp-Ser-Tyr-OEt. No detectable change occurred in the UV absorbance of the peptide at 280 mμ. We have observed oxidation of sulfur-containing peptides if high-speed stirring is used in the presence of air and zinc dust. Cysteine is oxidized to cysteic acid and methionine to the sulfone. This process may be metal catalyzed. Under optimal conditions for protecting group removal (as described in the Experimental Section), no side reactions have been observed with any of the genetically coded amino acids.

Use of the isonicotinyloxycarbonyl protecting group would appear to offer a solution to the problems which have been encountered when benzyloxycarbonyl has been used for the protection of the ϵ-amine of lysine. It is stable to most of the conditions commonly employed in peptide synthesis, including the strongly acidic conditions often employed for removal of peptides from resin supports in the solid-phase method. The new protecting group is cleanly removed under mild conditions, which can be safely applied in the presence of all functional groups commonly encountered in peptide synthesis. The presence of a basic functionality also offers potential advantages for purification of products by electrophoresis or ion-exchange chromatography, as emphasized by Young et al. in the use of picolyl esters.[12,16] In our experience, the isonicotinyloxycarbonyl protected peptides have shown favorable solubility properties, often a crucial practical consideration in the synthesis of large molecules by classical methods.

Experimental Section

Preparation of Isonicotinyl *p*-Nitrophenyl Carbonate (3b). (a) Bis(*p*-nitrophenyl) carbonate (152 g, 0.67 mol) was dissolved in 1600 mL of methylene chloride. A solution of 4-pyridylcarbinol (63.5 g, 0.58 mol) (azeotropically dried using benzene to remove water of hydration) in 500 mL of methylene chloride was added dropwise over 30 min with stirring, followed by a solution of *N*-methylmorpholine (50 g) in 150 mL of methylene chloride. The sclution was allowed to stir for 2.5 days. TLC (silica gel, $CHCl_3$) showed that this length of time is required for complete reaction. The resulting solution was washed as follows: two 2-L portions of H_2O, one 2-L portion of 0.1 N

H_2SO_4, four 2-L portions of saturated $NaHCO_3$, and one 2-L portion of saturated NaCl. The organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness in vacuo. The solid residue was dissolved in a minimum of warm (30 °C) ethyl acetate. The free base of isonicotinyl *p*-nitrophenyl carbonate crystallized on standing overnight, 53 g, mp 104–106 °C. (Anal. Calcd for $C_{13}H_{10}N_2O_5$: C, 56.93; H, 3.68; N, 10.22. Found: C, 56.80; H, 3.69; N, 10.16.) Addition of hexane to the supernatant gave 45 g of the nitrophenol salt (mp 112–113 °C). Further addition of hexane gave a third crop, which was also the nitrophenol salt (37 g). The total yield from these three crops was 76%. The NMR and IR spectra of both the free base and nitrophenol salt were consistent with the assigned structures.

(b) 4-Pyridylcarbinol (13.12 g, 0.12 mol), which was azeotropically dried with benzene, and bis(*p*-nitrophenyl) carbonate (27.2 g, 0.12 mol) were dissolved in 200 mL of CH_2Cl_2 and the mixture was stirred for 3 days at 20 °C. The mixture was filtered to remove a small amount of insoluble material and the solution was evaporated to dryness. The foamy solid was dissolved in 500 mL of ethyl acetate and crystallized by the addition of about 200 mL of hexane to give 26.2 g (80% yield) of the *p*-nitrophenyl salt of **3b** (mp 108–111 °C).

Preparation of ε-iNoc-Lys (4). A solution of 7.44 g (0.044 mol) of $CuCl_2 \cdot 2H_2O$ in 160 mL of H_2O was added to a solution of 14.56 g (0.08 mol) of L-lysine hydrochloride in 160 mL of H_2O, and the solution was adjusted to pH 9.5 by the addition of 50% aqueous NaOH. Isonicotinyl *p*-nitrophenyl carbonate (22 g, 0.08 mol) was added over a period of 20 min, with stirring. The reaction mixture was stirred at 20 °C for 26 h (heavy precipitate, vigorous stirring required), after which acetic acid was added to pH 7.2. The copper complex of ε-isonicotinyloxycarbonyl lysine was isolated by filtration and washed with H_2O (slow filtration). This material was dissolved in 10% aqueous acetic acid (900 mL) and treated with H_2S to precipitate CuS. The mixture was filtered through Celite and the filtrate evaporated to dryness in vacuo. The product (22 g) contains small amounts of free lysine and *p*-nitrophenol. This material (20 g) was dissolved in water (150 mL) and sufficient Dowex 1 × 2 (OH^-) added to obtain pH 6.6, thus adsorbing residual *p*-nitrophenol. The solution was applied to a 1400-mL column of IRC-50 (NH_4^+) and eluted with 20% ethanol in 0.1 N NH_4OAc. The first four ninhydrin positive fractions (500 mL each) contained a single component as indicated by TLC (silica gel, $CHCl_3$–MeOH–H_2O, 50:40:10). These were combined and evaporated to dryness in vacuo, and the residue was crystallized from water–ethanol to yield 13.3 g (47%), mp 235–236 °C, $[\alpha]^{24}_D$ −7.32° (c 0.7, 2 N HOAc). Anal. Calcd for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.45; H, 6.79; N, 14.93. *Note*: If the copper complex of ε-iNOC-Lys is thoroughly washed with water, clean product is obtained by crystallization of the free ε-iNoc-Lys without ion exchange chromatography. Thorough washing is made difficult, however, by the physical nature of the complex.

***N*-α-Boc-ε-iNoc-Lys (5).** ε-iNoc-Lys (24 g, 0.085 mol) was suspended in 645 mL of dimethylformamide. Tetramethylguanidine (9.89 g, 0.086 mol) was added, followed by dropwise addition of *tert*-butyl azidoformate (12.12 g, 0.085 mol) over a period of 45 min, with stirring. An additional 9.89 g of tetramethylguanidine was added, and the solution was stirred 18 h at 20 °C. The resulting solution was evaporated to dryness in vacuo at a temperature below 35 °C and the residue dissolved in 300 mL of H_2O. The solution was adjusted to pH 4.2 (product oils out) by the addition of dilute H_2SO_4 and flushed with a stream of nitrogen in a hood for a period of 1 h. The mixture was extracted four times with ethyl acetate (400 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo to a small volume. When crystals started to form the evaporation was stopped and the solution heated to dissolve the crystals. Product crystallized on standing at room temperature overnight. After filtration, the crystals were washed with cold ethyl acetate–hexane and dried in vacuo at 20 °C (22.5 g). A second crop gave an additional 5.4 g: total yield 86%; mp 130–131 °C; $[\alpha]^{24}_D$ 7.49° (*c* 0.6, 2 N HOAc). Anal. Calcd for $C_{18}H_{27}N_3O_6$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.62; H, 6.90; N, 10.72.

Example of Removal of the iNoc Protecting Group. Synthesis of Substance P. Arg-Pro-Lys(iNoc)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2[17] (298 mg) was dissolved in 3 mL of 50% aqueous acetic acid, and 300 mg of HCl-activated zinc dust[18] was added. The reaction was stirred at room temperature for 1.5 h, at which time an aliquot (5 μL) was removed, diluted to 100 μL with water, and treated with H_2S to remove Zn(II). TLC analysis (silica gel using $CHCl_3$–MeOH–2% aqueous NaCl 55:40:10) indicated a single product and about 25% remaining starting peptide. The remaining reaction solution was diluted with 3 mL of 50% aqueous acetic acid, and an additional 300 mg of zinc dust was added. After stirring an additional 1.5 h, TLC analysis as above showed complete conversion to substance P. No by-products were detected by TLC. The remaining zinc dust was separated by decantation and washed several times with 50% aqueous acetic acid by decantation. The combined solution and washes were diluted to a volume of 20 mL and Zn(II) precipitated as ZnS by treatment with H_2S. ZnS was removed by centrifugation and washed five times with 10-mL portions of 50% aqueous acetic acid. The combined solution and washes were evaporated to dryness in vacuo, and the gummy residue was triturated with ethyl acetate to give a solid which was dried in vacuo to give 239 mg (90%) of substance P. Amino acid analysis after enzymatic degradation using pronase and aminopeptidase-M showed: $Lys_{1.02}$, $Arg_{0.99}$, $Glx_{2.08}$,[19] $Pro_{2.01}$, $Gly_{1.03}$, $Met_{0.93}$, $Leu_{0.99}$, $Phe_{1.96}$. ε-iNoc-Lys, which is eluted at the same time as histidine on the short column of the amino acid analyzer, was not detectable in the hydrolyzate.

Electrolysis of ε-iNoc-Lys. A cyclic voltammogram of ε-iNoc-Lys was obtained using a cyclic universal programmer, Model PAR 175, and a coulometer, Model PAR 179 (Princeton Applied Research Corp.). Two sharp reduction waves at epc = −1.95 and −2.25 V (vs. Ag/AgCl) were measured at a hanging mercury drop electrode in 0.1 M tetra-*n*-butylammonium iodide in 80% DMF and 20% H_2O. For controlled potential electrolysis, ε-iNoc-Lys (0.101 g, 35×10^{-4} mol) was dissolved in a mixture of H_2O (5 mL) and 0.1 M tetrabutylammonium iodide in DMF (25 mL). A mercury pool (10 mL) was used as cathode and a platinum wire was used as anode with an Ag/AgCl reference electrode. Electrolysis at −2.02 V for 40 min resulted in precipitation of lysine (1.16×10^{-4} mol), 64% as determined by amino acid analysis. Amino acid analysis of the solution showed an additional 3.7×10^{-5} mol of lysine (total lysine, 84%) and 10^{-5} mol of unreacted ε-iNoc-Lys. Gas chromatographic analysis of the solution showed the presence of 4-picoline. A similar electrolysis at −2.35 V gave only 20–25% yield of lysine.

Removal of iNoc by Hydrogenation. *N*-α-Boc-ε-iNoc-Lys (5) (10 mg) was dissolved in 1 mL of 5% aqueous acetic acid. Pd/C (10%; 10 mg) was added, the suspension was purged with nitrogen, and hydrogen was bubbled through the solution for 10 min. Analysis by TLC showed complete removal of the iNoc protecting group.

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Registry No.—**1**, 1007-48-3; **3b**, 32919-24-7; **4**, 42561-68-2; **5**, 42417-16-3; bis(*p*-nitrophenyl) carbonate, 5070-13-3; 4-pyridylcarbinol, 586-95-8; L-lysine hydrochloride, 10098-89-2.

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Structure Analysis of the Nucleoside Disaccharide Antibiotic Anthelmycin by Carbon-13 Nuclear Magnetic Resonance Spectroscopy. A Structural Revision of Hikizimycin and Its Identity with Anthelmycin[1]

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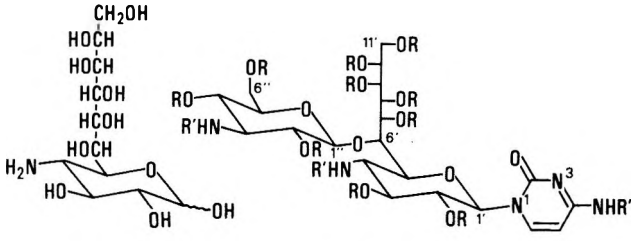
The ^{13}C NMR spectral analysis of the nucleoside disaccharide antibiotic anthelmycin, its derivatives, and several synthetic hexopyranosyl nucleoside models was used to confirm structure **2a** for the antibiotic. The structure of hikizimycin is identical with that of anthelmycin.

Anthemycin and hikizimycin are nucleoside disaccharide $C_{21}H_{37}N_5O_{14}$ antibiotics elaborated by *Streptomyces longissimus*[2] and *Streptomyces* A-5,[3] respectively. Earlier structural studies on these two antibiotics revealed that each is constituted from a 3-amino-3-deoxy-D-glucopyranose (kanosamine) residue β-glycosidically attached to an aminoundecose, $C_{11}H_{23}NO_{10}$, which in turn forms a β-nucleoside linkage with N(1) of a cytosine residue.[4,5] The aminoundecose, hikosamine (1), has the 4-amino-4-deoxy-D-glucopyranoside system in its structure.[6] From an evaluation of the periodate oxidation behavior of *N,N'*-diacetylhikizimycin, Uchida suggested the linkage of kanosamine was to position 2′ of the hikosamine moiety of hikizimycin.[7] The polyol side-chain configuration followed from the isolation of D-glycero-D-galactoheptose after oxidative cleavage of the C(4)–C(5) bond of 1.[7] This structure proposal for hikizimycin also was claimed



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2a R=R′=H
2b R=R′=Ac
2c R=H, R′=Ac

to be supported by an analysis of the ^{13}C NMR spectrum of the antibiotic.[8]

The possible identity of anthelmycin and hikizimycin was intimated by the presence of common structural features in the two natural products. Comparison of the ^{13}C NMR spectra of anthelmycin and hikizimycin at the same pH as well as of their *N,N'*-diacetyl derivatives now established that the two antibiotics are identical. However, a preliminary analysis of the ^{13}C NMR spectra of anthelmycin and its peracetate (**2b**) excluded position 2′ of the hikosamine moiety as the site of attachment of the 3-amino-3-deoxy-D-glucopyranose unit. The need for an unambiguous structure determination of anthelmycin and hence a structure revision of hikizimycin became mandatory. Recently, our chemical degradative studies performed on anthelmycin combined with mass spectrometry of suitable derivatives thereof resulted in the correct structure assignment for anthelmycin, in which the 3-amino-3-deoxy-D-glucopyranose is linked to position 6′ of the hikosamine moiety as represented by **2a**.[1a] As a consequence, the structure of hikizimycin also is illustrated by **2a**.

The complete assignment of the ^{13}C NMR spectrum of anthelmycin has been performed utilizing appropriate hexopyranosyl nucleoside models and several hydrolysis products and derivatives of the antibiotic. In this communication the ^{13}C NMR analysis of these compounds, independently establishing structure **2a** for anthelmycin, is presented.

The carbon resonances of the cytosyl residue of anthelmycin are recognized easily from cytosyl nucleosides recorded in the literature.[9,10] The signals of the kanosamine moiety can be selected by comparison with the resonances of methyl-3-amino-3-deoxy-β-D-glucopyranoside (**3**). An exact duplication of the resonances of **3** is not observed in the spectrum of anthelmycin (**2a**) in the free amine form (Table II). Deviations which approach 2 ppm are noted for carbons 1″, 2″, and 3″. These differences, however, vanish in strong acid solution, confirming the correct selection of resonances for this residue. The disparity in chemical shifts at high pH reflects probably conformational effects which are disrupted upon amine protonation.

The remaining resonances arise from the hikosamine moiety of the antibiotic. In view of the 4-amino-4-deoxy-β-D-glucopyranoside substructure in this fragment, an examination of simpler models was undertaken to provide a basis for signal assignment and for the determination of the linkage site between the two sugar residues of anthelmycin. The β-nucleoside compounds **4a**, **5a**, **6a**, **7a**, **8a**, and **9** along with the acetyl derivatives **4b–8b** were synthesized[11] employing standard literature procedures.[12] All δ values of these compounds are listed in Table I.

Internal comparison of compounds **4a–8a** allows a self-consistent assignment of all resonances. The glucopyranose signals of **4a** and **5a** are nearly identical, indicating that β-linked cytosyl and uracyl moieties exert equivalent effects. The 2′-OCH_3 derivative **8a** and the 3′-OCH_3 derivative **6a** differentiate the C(2′), C(3′), and C(5′) resonances of **4a–8a**. Methylation causes downfield shift increments of 9.5 and 9.4 ppm for C(2′) and C(3′) of **8a** and **6a**, respectively, leaving neighboring carbon centers minimally affected.[13] The replacement of the 4′-hydroxy group of **6a** with an amino or

Table I. ^{13}C Chemical Shifts of Glucopyranosyl Nucleosides[a,i]

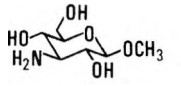
	4a[b]	5a[b]	6a[b]	7a[b]	8a[c]	9[b,f]	4b[d,g]	5b[d,g]	6b[d,g]	7b[e,g]	7c[b,g]	8b[d,g]
C(2)	159.1	153.0	158.8	157.2	152.3	159.1	154.9	150.6	155.4	154.1	158.3	151.3
C(4)	167.1	167.0	166.8	165.2	162.5	167.2	163.0	162.8	163.0	162.4	166.4	162.4
C(5)	98.1	104.0	98.0	97.0	102.2	98.2	97.8	103.9	98.0	96.2	97.4	103.1
C(6)	143.1	143.0	142.9	141.4	140.0	143.2	144.3	139.2	145.0	145.5	142.2	136.9
C(1′)	84.7	83.9	84.6	83.9	83.4	84.8	81.2	80.4	81.4[h]	80.6	84.5	82.4
C(2′)	72.3	72.3	71.8	71.9	81.8	72.3	70.5	69.5	72.3	70.8	72.9	79.1
C(3′)	77.5	77.1	86.9	76.8	78.3	77.4	72.6	72.8	81.9[h]	72.6	75.3	74.7
C(4′)	70.4	70.2	69.7	52.8	71.1	70.4[h]	67.8	67.9	69.2	49.1	52.4	68.3
C(5′)	79.8	79.7	79.6	79.7	80.4	78.9	75.1	74.9	75.1	75.0	79.0	74.6
C(6′)	61.3	61.7	61.5	61.3	62.3	69.9[h]	61.6	61.7	62.1	62.7	61.9	61.9

[a] Chemical shifts expressed on the Me_4Si scale. Secondary references are listed in the Experimental Section. [b] Deuterium oxide solution. [c] Acetone-d_6 solution. [d] Deuteriochloroform solution. [e] Dimethyl-d_6 sulfoxide solution. [f] The resonances of C(1″)–C(6″) of this compound are 103.8, 74.3, 77.2, 70.8, 76.8, and 62.0 ppm, respectively. [g] Carbonyl and methyl resonances of the acetyl function of this substance are not reported. [h] Signals in any vertical column may be interchanged. [i] Registry no.: **4a**, 3319-89-9; **4b**, 3180-75-4; **5a**, 3180-77-6; **5b**, 3180-73-2; **6a**, 62973-63-1; **6b**, 62973-66-4; **7a**, 22212-28-8; **7b**, 22176-13-2; **7c**, 21209-53-0; **8a**, 62973-64-2; **8b**, 62973-67-5; **9**, 62973-65-3.

acetamido function (cf. **6a** with **7a** and **6a** with **7c**, respectively) results in well-characterized shift modifications of the relevant carbon resonances.[14,15]

Comparison of the spectra of **4a** or **5a** with that of methyl-β-D-glucopyranoside[16] reveals fair agreement of the shift values of C(2′), C(3′), C(4′), and C(6′). However, aside from the expected upfield shift of the C(1′) resonance in the nucleoside, C(5′) suffers a 3-ppm downfield shift. This behavior, common to all substances in Table I, is analogous to that observed between adenosyl-β-D-xylopyranoside and methyl-β-D-xylopyranoside.[17] The spectra of several adenosyl α- and β-hexopyranosides show that the replacement of a methyl group by the heterobase does not lead only to unique perturbation of C(5′), but also of C(3′) and C(2′) depending on the nature of the sugar residue.[17,18]

The peracetates **4b**–**8b** show regular shift perturbations with respect to the parent nucleosides. Carbons 3′ and 5′ experience shielding increments of 4.3 ± 0.7 and 4.6 ± 0.2 ppm, respectively, from the acetyl functions on flanking carbon centers. Carbons 2′ and 4′ of **4a**, **5a**, and **8a** respond to a single adjacent acetyl group with 2.3 ± 0.5 and 2.6 ± 0.2 ppm



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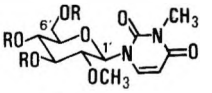
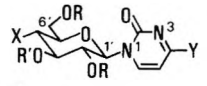
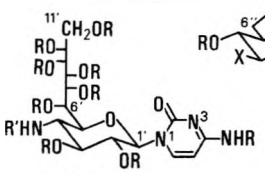


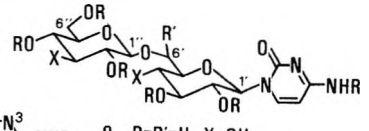
8a R=H
8b R=Ac



4a R=R′=H, X=OH, Y=NH_2
4b R=R′=Ac, X=OAc, Y=NHAc
5a R=R′=H, X=OH, Y=OH
5b R=R′=Ac, X=OAc, Y=OH
6a R=H, R′=Me, X=OH, Y=NH_2
6b R=Ac, R′=Me, X=OAc, Y=NHAc
7a R=R′=H, X=Y=NH_2
7b R=R′=Ac, X=Y=NHAc
7c R=R′=H, X=NHAc, Y=NH_2



11a R=R′=H
11b R=R′=Ac
11c R=H, R′=Ac



9 R=R′=H, X=OH
10a R=H, R′=CH_2OH, X=NHAc
10b R=Ac, R′=CH_2OAc, X=NHAc

shielding increments and the anomeric carbon resonances of **4a**, **5a**, **6a**, and **7a** are shielded 3.3 ± 0.2 ppm by a 2′-*O*-acetyl function. In the conversion of **8a** to **8b** the anomeric carbon is insulated from the direct effect of *O*-acetylation and, therefore, shifts minimally.

The unassigned carbon resonances of **2a** contain signals corresponding closely to those of C(1′), C(2′), C(3′), and C(4′) of 4-amino-4-deoxy-β-D-glucopyranosyl nucleoside **7a**, suggesting the absence of glycosidic substitution at C(2′) and C(3′). A similar shift relationship is observed between *N*,*N*′-diacetylanthelmycin (**2c**) and **7c**. The spectrum of hikosaminylcytosine (**11a**), an acid hydrolysis product of anthelmycin (**2a**), substantiates partially this view by eliminating the possibility of a 3′-O-glycosidic linkage. Equivalent C(1′)–C(4′) resonances of **11a** and **2a** are found at both high and low pH. The large upfield resonance shift of carbon centers situated β to primary amine functions, which are incurred upon N-protonation, identify unambiguously C(3′) and C(5′) of these substances.[19,20] The C(3′) δ value, equal to that of C(3′) in model **7a**, demands an unsubstituted 3′-hydroxyl group.

The 80.2-ppm signal in the spectrum of **2a** is a reasonable value for C(2′), if the 2′ oxygen is involved in a glycosidic linkage [cf. C(2′) of 81.8 ppm in the spectrum of 2′-*O*-methyl nucleoside **8a**]. This possibility may be dismissed by the shift response of C(1′) of the antibiotic **2a**, its *N*,*N*′-diacetyl derivative **2a**, and of the *N*,*N*′-diacetyl derivative of **11a** accompanying peracetylation. The C(1′) resonance is shielded in excess of 3 ppm in each case. This fact, in conjunction with the acetylation results of models **4a**–**8a** summarized above, is incompatible with a 2′-O-glycosidic linkage for anthelmycin. The almost identical C(1′) signals of **2a** and **11a** (and **2c** and **11c**) further refute a 2′ linkage by analogy with the shielding difference of the C(1) resonance of β-D-glucopyranose and 2-*O*-glucopyranosyl-β-D-glucopyranose (β-sophorose).[13]

Upon allocation of the resonances of the C(1′)–C(5′) fragment of **2a**, **11a**, and their corresponding *N*-acetyl derivatives **2c** and **11c** the assignment of the remaining six side-chain carbons of **11a** was achieved by comparison of the shift values of D-mannitol.[21,22] The isolation of D-glycero-D-galacto-heptose[7] dictated the choice of this model, which reflects the polyol side-chain stereochemistry of the undecose moiety of anthelmycin (≡ hikizimycin). The good resonance correlation of the terminal four-carbon residue of **2c** and **11c** with those of D-mannitol and the shielding experienced by the C(5′) signal of **2c** with respect to **11c** are explained best by attachment of the 3-acetamido-3-deoxy-β-D-glucopyranoside substituent to position 6′ in **2c**. This interpretation is corrobo-

Table II. ^{13}C Chemical Shifts of Anthelmycin, Hikosaminylcytosine, and Models[a,b,g]

	2a[c] pH >11	2a[c] pH <1	3[c] pH >11	3[c] pH <1	2b[d]	2c[c]	11a[c] pH >11	11a[c] pH <1	11b[d]	11c[c]	10a[c]	10b[d]
C(2)	157.6	148.8			155.1	157.4	157.8	148.2	155.6	159.2	159.1	155.2
C(4)	165.5	159.3			162.7	165.9	165.7	158.8	163.2	167.2	167.1	162.9
C(5)	96.6	96.1			97.3	98.0	96.6	95.9	97.6	98.2	98.8	98.0
C(6)	141.8	144.2			145.3	143.6	141.9	144.1	145.2	143.0	144.5	144.7
C(1′)	84.1	82.6			80.9	85.3	83.9	82.6	81.6	85.0	84.6	81.2
C(2′)	71.7	70.7			69.6	72.7	71.4[e]	71.9	69.3	72.7	72.8	70.7
C(3′)	77.2	72.3[e]			72.8	75.7	78.0	72.3	73.1	75.7	75.4	72.8
C(4′)	53.0	54.2			49.9	53.4	53.5	54.5	49.6	54.3	53.1	50.2
C(5′)	79.1	72.0[e]			80.6	77.9	78.8	72.3	79.0	79.1	79.3	79.0
C(6′)	80.2	79.5			73.9	80.8	71.2	70.7	68.0[e]	70.5	81.5	76.0
C(7′)	68.2[e]	67.0			67.7[e]	69.2	68.2[f]	69.0	67.5[e]	70.2	61.2	62.8
C(8′)	69.2[e,f]	68.2[f]			67.7[e]	69.6	68.4[f]	67.5[e]	67.2[e]	69.2		
C(9′)	69.5[f]	68.8[f]			67.7[e]	69.8	69.4	67.7[e]	66.9[e]	69.2		
C(10′)	71.3	71.0			67.1[e]	72.0	71.3[e]	71.2	66.0	72.1		
C(11′)	63.1	63.1			61.9	64.5	63.1	63.1	62.1	64.4		
C(1″)	105.0	103.0	103.3	103.0	101.7	106.1					105.0	101.0
C(2″)	74.0	69.5	72.8	69.3	71.4	73.0					73.1	71.9
C(3″)	58.5	57.3	56.9	57.1	53.0	58.0					58.2	53.2
C(4″)	69.8	65.5	69.7	65.8	68.4	69.2					69.3	69.0
C(5″)	77.8	76.8	76.8	76.8	73.6	78.2					78.2	73.4
C(6″)	61.1	59.8	60.9	59.9	61.9	61.9					62.1	62.5

[a] Chemical shifts expressed on the Me_4Si scale. Secondary references are listed in the Experimental Section. [b] The carbonyl and methyl resonances of the acetyl derivatives are not individually assigned and are not reported. [c] Deuterium oxide solution. [d] Deuteriochloroform solution. [e,f] Assignments in any vertical column may be interchanged. [g] Registry no.: **2a**, 12706-94-4; **2b**, 62990-71-0; **2c**, 62990-72-1; **3**, 14133-36-9; **10a**, 63018-04-2; **10b**, 62973-68-6; **11a**, 58976-11-7; **11b**, 58933-70-3; **11c**, 63016-79-5.

rated by the observed 0.9-ppm upfield shift of the C(5′) resonance in the 6′-O-substituted nucleoside 9 (synthesized from β-gentiobiose) with respect to C(5′) of **4a**. Consequently, *N,N′*-diacetylanthelmycin is represented by structure **2c** and anthelmycin by **2a**. This conclusion is supported further by the isolation of **10a** as one of the products of periodate oxidation of **2c** and subsequent borohydride reduction. The carbon shifts of **10a** and its peracetate **10b**, listed in Table II, are consistent with this structure.

The ^{13}C NMR data of hikizimycin (≡ anthelmycin) (**2a**) and hikosaminylcytosine (**11a**) reported by Uchida et al.[8] are in reality the values corresponding to their hydrobromide[23] and hydrochloride[23] salts, respectively. Spectral comparisons between neutral and protonated amine species seem, in part, to be the reason for the previous erroneous structure assignment.[8]

Experimental Section

The ^{13}C NMR spectra of compounds reported in Table I and **2a**, **10a**, **11b**, and **11c** of Table II were recorded on a Bruker HX-90E spectrometer operating at 22.63 MHz or a Bruker WP-60 spectrometer operating at 15.08 MHz in the Fourier transform mode. Me_4Si as internal standard was used for spectra taken in deuteriochloroform solution and Me_4Si as external standard for the spectra recorded in deuterium oxide solution (0.05–0.50 M).

The spectra of **10b** and **11a** were recorded on a JEOL PFT-100 spectrometer operating at 25.03 MHz in the Fourier transform mode. Compound **11a** was examined in deuterium oxide solution containing 2% dioxane as internal reference and **10b** in deuteriochloroform solution. The spectra of **2a**, **2b**, and **3** were recorded on a Varian DP-60 spectrometer operating at 15.08 MHz in the Fourier transform mode. Compounds **2a** and **3** were examined in deuterium oxide solution containing dioxane as internal reference; **2b** was recorded in deuteriochloroform solution. All chemical shifts are expressed on the Me_4Si scale by the use of the relationship: $\delta_{Me_4Si} = \delta_{p\text{-dioxane}} + 66.3$ ppm = $\delta_{CDCl_3} + 76.9$ ppm.

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(23) These compounds were prepared by Dr. K. Uchida in the laboratory of one of the present authors (B. C. Das).

1,N^2-Ethenoguanine and N^2,3-Ethenoguanine. Synthesis and Comparison of the Electronic Spectral Properties of These Linear and Angular Triheterocycles Related to the Y Bases

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We have shown that the reaction of guanosine with chloroacetaldehyde in aqueous solution in the physiological pH range yields 1,N^2-ethenoguanosine (5,9-dihydro-9-oxo-3-β-D-ribofuranosylimidazo[1,2-*a*]purine). This compound could be hydrolyzed to 1,N^2-ethenoguanine (5,9-dihydro-9-oxoimidazo[1,2-*a*]purine), which was also prepared authentically by hydriodic acid treatment of the glyoxal–guanine adduct. The 1,N^2-ethenoguanine, which is an unsubstituted (at N-4, C-6, and C-7) Y-type base, is not fluorescent under the same conditions at which the 4-methyl compounds fluoresce. By contrast, the isomeric and angular N^2,3-ethenoguanine (8,9-dihydro-9-oxoimidazo[2,1-*b*]purine) is fluorescent ($\lambda_{excitation}$ 262 nm, $\lambda_{emission}$ 410 nm). The N^2,3-ethenoguanine synthesis was initiated by the reaction of chloroacetaldehyde with O^6-benzylguanine, O^6-methylguanine, and 2-amino-6-benzylthiopurine, followed by hydrogenolysis or hydrolysis, hydrolysis, and oxidation and hydrolysis, respectively. The reaction of guanosine is indicative of the damage that can result from the action of the mutagen chloroacetaldehyde on guanosine derivatives under physiological pH conditions.

The reaction of chloroacetaldehyde in aqueous solution with adenine- and cytosine-containing compounds[1,2] to produce 1,N^6- and 3,N^4-etheno-bridged compounds, respectively, has found wide application.[3,4] Interest stems from the biological activity generally evident at the nucleoside, nucleotide, and coenzyme level and from the species responsible for the fluorescence emission properties.[5,6] The crystal and molecular structures of suitable derivatives have been determined.[7,8] We agree with Kochetkov, Shibaev, and Kost[1] that in the pH range most favorable for reaction at 37 °C of chloroacetaldehyde with adenosine (pH 4.5) and cytidine (pH 3.5), guanosine is not reactive.[2] When chloroacetaldehyde was used in this laboratory to modify tRNA in aqueous solution at different selected pHs,[9] guanosine as well as cytidine and adenosine residues appeared to be undergoing attack at pH 6.3,[10] within the optimum range for retention of tRNA tertiary structure.[11]

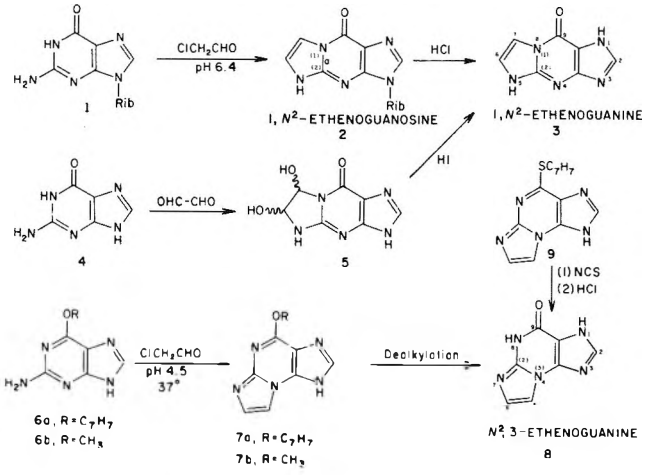
Since chloroacetaldehyde is known to be mutagenic[12,13] and is one of the likely liver metabolites of vinyl chloride, its reaction with guanosine under physiological conditions was of particular interest. Moreover, the possible development of fluorescence due to the formation of an additional ring suggested the value of product comparison with the fluorescent natural nucleosides Y[14–27] (wybutosine, Y-Wyo)[28] and Yt[29–31] (wyosine, Wyo)[28] and corresponding bases related to guanine.[32]

The reaction of guanosine (**1**) with chloroacetaldehyde in aqueous solution at 37 °C was followed by the development of ultraviolet absorption at 305 nm over a period of hours and over a pH range from 6.5 to 4.5. At pH 6.5 the reaction rate is significant, but is still less than one-third that of adenosine with chloroacetaldehyde under the same conditions. The relative reaction rate for the guanosine reaction falls off sharply with decreasing pH and is practically negligible at pH 4.5. A preparative reaction was run at carefully controlled pH (6.40 ± 0.05), monitored by comparison of the ultraviolet absorption intensities at λ_{max} 272 and 254 nm, and, for the optimum conversion, halted when these became equal. 1,N^2-Ethenoguanosine (**2**) was isolated from the reaction mixture by chromatography on cellulose followed by high performance liquid chromatography on cation exchange resin. The elemental analysis and the mass spectrum were consistent with the introduction of an etheno bridge, which was also indicated by the pair of doublets (6-H or 7-H, δ 7.43 or 7.62, J_{67} = 2.5 Hz, along with 2-H, δ 8.16) for the etheno protons in the NMR spectrum. The linear (1,N^2-etheno) (**2**) rather than angular (N^2,3-etheno) tricyclic structure was assigned to the guanosine–chloroacetaldehyde product, inter alia, by the close similarity of its ultraviolet spectra (Figure 1) with those of 5,9-dihydro-6-methyl-9-oxo-3-β-D-ribofuranosyl-5*H*-imidazo[1,2-*a*]purine (**2**, with CH_3 at C-6)[31] in acidic, neutral, and basic media. The 5-H (**2**) rather than the 4-H tautomeric form was indicated by the close similarity of the ultraviolet absorption spectra, in acidic and neutral media, of the product with those of 5,9-dihydro-5,6-dimethyl-9-oxo-3-β-D-ribofuranosylimidazo[1,2-*a*]purine (**2**, with CH_3 at N-5 and C-6),[31] locked in the "5-H" form by the methyl substituent. The chemical shift of δ 7.43 in the product **2** could be assigned to the 7-H not only by comparison with the δ 7.36 and 7.43 values for the 7-H in the 6-methyl and 5,6-dimethyl models, respectively,[31] but, positively, by the observed reduction in intensity of the δ 7.43 signal relative to that of δ 7.62 when α-deuterio-enriched chloroacetaldehyde, e.g., $ClCD_2CHO$, was used in the reaction with guanosine. This method of NMR assignment based upon deuterium labeling had proved effective for the adenosine and cytidine reaction products with chloroacetaldehyde.[6–8,33]

The deribosidation of 1,N^2-ethenoguanosine (**2**) was effected by acid hydrolysis to produce 1,N^2-ethenoguanine (**3**). Guanine (**4**) itself did not react with chloroacetaldehyde under the conditions specified for the conversion of guanosine to the etheno-bridged product. However, compound **3** could be obtained unequivocally by treating the adduct formed from guanine and glyoxal (**5**, the tautomeric form is written conventionally)[34] with 47% hydriodic acid at 55–60 °C for 5–6 days. The elemental analysis and the mass spectrum were satisfactory for the indicated product **3**. NMR assignments for the hydriodide of **3** are comparable with those for compound **2** except for the signal for 2-H, which experienced a downfield shift of δ 1.2, suggestive of N-1/N-3 as the site of protonation. A similar downfield shift of δ 1.3 was observed for the signal of the corresponding 8-H upon conversion of guanosine to 7-methylguanosine.[35,36] Preference for the tautomeric form (1-H, 5-H) shown in **3** is adduced from comparison of the ultraviolet absorption spectra in acidic, neutral, and basic media (Figure 1) with those of models,[31] but the representation is not intended to be exclusive. All of the assembled data clearly support the structure assignment of the base as 1,N^2-ethenoguanine (5,9-dihydro-9-oxoimidazo[1,2-*a*]purine) (**3**) and the riboside as 1,N^2-ethenoguanosine (5,9-dihydro-9-oxo-3-β-D-ribofuranosylimidazo[1,2-*a*]purine) (**2**).

Despite structural similarities to the fluorescent Y bases and nucleosides, 1,N^2-ethenoguanine (**3**) is only weakly fluorescent and 1,N^2-ethenoguanosine (**2**) is nonfluorescent. The major structural difference is the fixed N-4 substitution in the natural Y series vs. the mobile 5-H in our synthetic series. We therefore decided to synthesize N^2,3-ethenoguanine, which contains the etheno bridge in an angular tricyclic system, for comparison of its spectroscopic properties—especially possible fluorescence emission—with those of its isomer **3**.

In order to increase the basicity (nucleophilicity) of the guanine ring system and to hinder sterically the reaction of chloroacetaldehyde at N-1, we selected O^6-benzylguanine (**6a**)[37] as the precursor of the angular system. The reaction of **6a** with chloroacetaldehyde in dilute solution proceeded smoothly at 37 °C and at pH 4.5, the optimal pH for adenosine. The O^6-benzyl-N^2,3-ethenoguanine (9-benzyloxyimidazo[2,1-*b*]purine) (**7a**) thus obtained was readily converted to N^2,3-ethenoguanine (8,9-dihydro-9-oxoimidazo[2,1-*b*]-purine) (**8**) by hydrolysis with 2 M hydrochloric acid or by hydrogenolysis over palladized charcoal.[38] Similarly, N^2,3-etheno-O^6-methylguanine (**7b**) was prepared from O^6-methylguanine[39] and was hydrolyzed by heating with concentrated hydrochloric acid on a steam bath to produce N^2,3-ethenoguanine (**8**). Consideration of the versatility of thioalkyl groups for subsequent transformations led us to prepare 6-benzylthio-N^2,3-ethenoguanine (**9**) from 2-amino-6-benzylthiopurine,[40,41] again with chloroacetaldehyde in dilute solution at 37 °C and pH controlled at 4.0–4.5. The conversion of **9** to **8** was accomplished by oxidation with *N*-



chlorosuccinimide followed by hydrolysis with hydrochloric acid.

The NMR spectra of **7a, 7b,** and **9** are characterized in the aromatic region by the presence of a singlet for 2-H and a pair of doublets for the etheno protons 5-H and 6-H. The latter signals are separated by about 0.4 ppm. The three protons, 2-H, 5-H, and 6-H, respectively, exhibit similar chemical shifts in **7a, 7b,** and **9**. The NMR spectra of the hydrochloride salts of **7a** and **7b** were almost identical for the 2, 5, and 6 protons. The spectra of the hydrochlorides prepared from **6a** and **6b** by reaction with $ClCD_2CHO$ lacked the signal at δ 8.38 for the 5-H, and the signal at δ 8.08 for the 6-H collapsed to a singlet with formal replacement of 5-H by 5-D. These assignments were carried over to the free bases (**7a,b**). We observed downfield shifts of 0.4–0.7 ppm for the 2-, 5-, and 6-H's and an increase in the J_{56} value from 1.5 to 2.6 for the etheno protons when **7a** and **7b** were converted to their hydrochlorides. The 6 proton was shifted maximally, which suggests that N-7 is the site of protonation in these compounds. Comparable shifts had been observed in the NMR spectrum of 3,N^4-ethenocytidine hydrochloride compared with that of the free

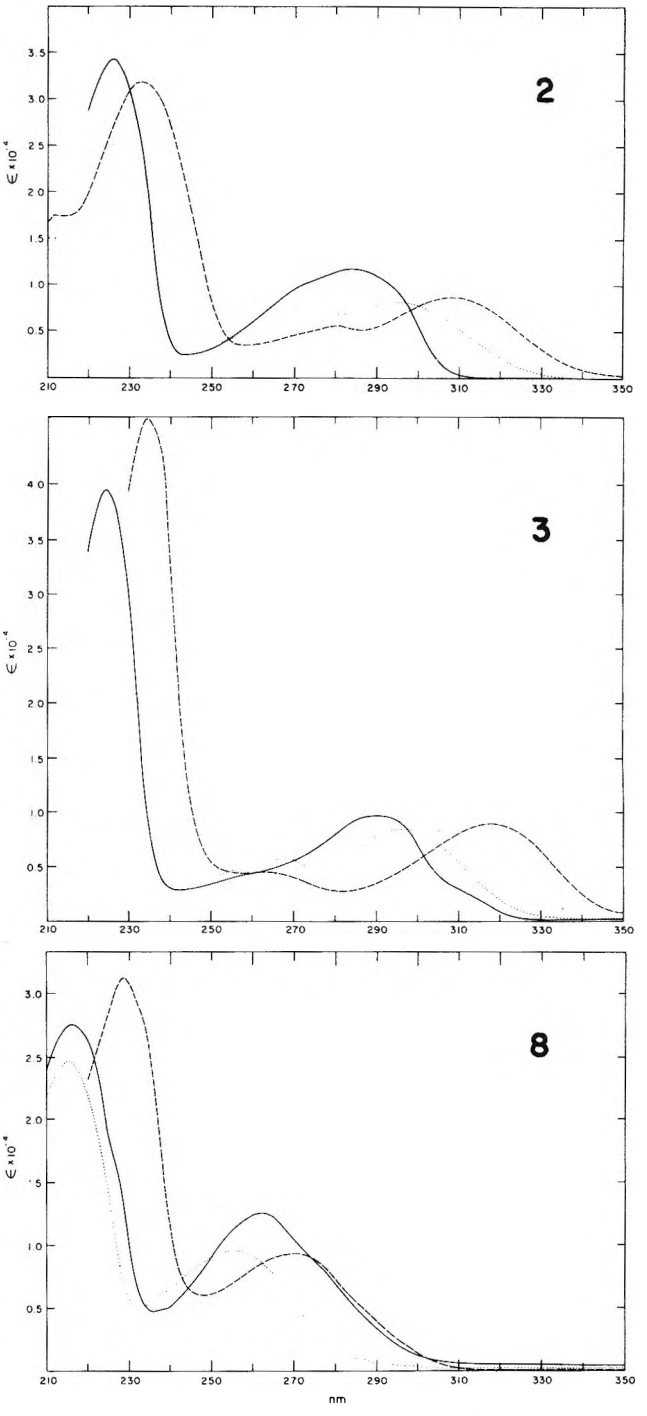


Figure 1. The UV spectra of 1,N^2-ethenoguanosine (**2**), 1,N^2-ethenoguanine (**3**), and N^2,3-ethenoguanine (**8**) in aqueous 0.05 M phosphate buffer, pH 7 (—), 0.1 N HCl (· · ·), and 0.1 N NaOH (- - -).

base.[6] The NMR spectrum of the angular ethenoguanine, 8,9-dihydro-9-oxoimidazo[2,1-*b*]purine (**8**), in the aromatic region showed parallel chemical shifts, that is, increasing δ following the order 6-H, 5-H, and 2-H (see Experimental Section), which were assigned conveniently by conversion of the 5-D precursors to the 5-deuterio-**8**.

Tricyclic aromatic and heteroaromatic systems of the linear type generally exhibit lower energy electronic transitions than their angular isomers.[42,43] This is true also for 1,N^2-ethenoguanosine (**2**) and 1,N^2-ethenoguanine (**3**) compared with N^2,3-ethenoguanine (**8**). The low-energy bands in the ultraviolet spectra (Figure 1) of the angular isomer **8** are shifted 30–50 nm toward shorter wavelength from those of the linear pair (**2, 3**). What is most impressive is the finding that the

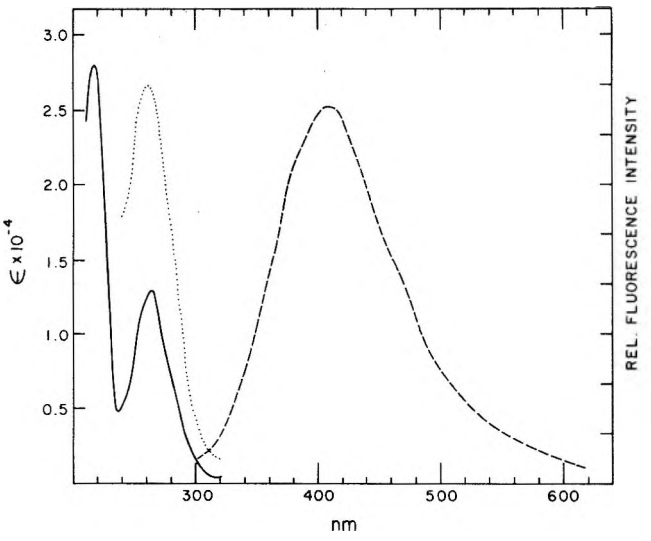


Figure 2. Ultraviolet absorption (—), corrected fluorescence excitation (···), and corrected fluorescence emission (- - -) spectra of N^2,3-ethenoguanine (8) in water, pH 6.8.

N^2,3-ethenoguanine (8) is *fluorescent*, whereas the linear 1,N^2-ethenoguanosine (2) is not. The fluorescence emission maximum is observed at 410 nm when compound 8 is irradiated near 280 nm.

A study of the fluorescence behavior of N^2,3-ethenoguanine (8) in solvents of decreasing polarity (water, ethanol, dioxane) showed the corrected excitation maxima to be consistent with the corresponding UV maxima (Table I, Figure 2). Although the wavelength of the emission maxima did not change significantly with decreasing solvent polarity, the relative quantum yields and fluorescence lifetimes showed substantial increases in going from water to ethanol to dioxane. Similar changes in emission characteristics have been observed with other fluorescent guanine derivatives.[44] Evleth and Lerner[45] indicate that theoretical analysis reasonably rationalizes the photophysical properties of 1,N^6-ethenoadenine (ε-adenine) by demonstrating a relationship with the highly fluorescent indolizines, whereas the relationship between a Y base and the indolizines is much less well characterized and only a vague relationship is found to exist. Neither 1,N^2-ethenoguanine (3) (5-H tautomer as opposed to the 4-CH_3 substitution in a Y base) nor N^2,3-ethenoguanine (2) has been subjected to analogous theoretical treatment as yet.

In conclusion, we have achieved a better understanding of the slow reaction of chloroacetaldehyde with guanosine under physiological conditions (pH ca. 6.4) and have established the structure of the major product formed in the reaction. This pH may be selected for the reaction of chloroacetaldehyde with more complex molecules containing guanosine. Where both guanosine and adenosine units are present and stereochemically available, both can react at pH 6.4. We have also produced a fluorescent derivative of guanine, namely N^2,3-ethenoguanine (8), that should possess, in protonated form, hydrogen-bonding characteristics like guanine and, as the base, hydrogen-bonding characteristics like a 3-substituted xanthine.

Experimental Section

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. The NMR spectra were recorded by Mr. Steven Silber on a Varian Associates HA-100 spectrometer using tetramethylsilane as an internal standard. The ultraviolet spectra were obtained on a Beckman Acta MVI spectrophotometer. Corrected fluorescence emission and fluorescence excitation spectra were acquired on a Spex Fluorolog spectrofluorometer. All fluorescence measurements were made at room temperature (22 °C). The fluorescence measured for each solution was normalized for differences among the samples in optical density at the exciting wavelength and is therefore a quantitative representation of quantum efficiencies relative to quinine taken as 0.7.[46]

Table I. Fluorescence Emission and Excitation Data for 8

Solvent	Emission[a] λ_{max}, nm	Excitation[b] λ, nm	τ,[c] ns	Φ rel[d]
H_2O (pH 6.8)	410	262 (UV 262)	1.38 ± 0.01	0.03
EtOH	400	263 (UV 263)	2.23 ± 0.02	0.12
Dioxane	400	270 (UV 265)	2.73 ± 0.01	0.26

[a] Fluorescence emission spectra were measured with excitation at 280 nm, and corrected curves were obtained using correction factors supplied with the Fluorolog. [b] Corrected excitation spectra were recorded directly by holding emission at 415 nm. [c] Fluorescence lifetimes were measured by phase only. [d] Determined using corrected emission spectra by comparison with quinine sulfate (in 0.1 N H_2SO_4), which has a quantum yield of 0.7.[45]

Quantum efficiencies were obtained by using corrected spectral areas and also by means of a spectrofluorometer described by Weber et al.[47] The values obtained by the two methods were comparable. Fluorescence lifetimes were measured by Dr. David Jameson on a Model SLM subnanosecond spectrofluorometer. Thin-layer chromatography was carried out on Eastman chromagram sheets of cellulose or silica gel, with or without fluorescent indicator. After development of the chromatograms, spots were located with the aid of an ultraviolet lamp. The solvent systems employed were: solvent 1, 1-butanol–water (86:14); solvent 2, 2-propanol–water (7:3); solvent 3, ethyl acetate–1-propanol–2-propanol–water (4:2:1:2); solvent 4, water; solvent 5, chloroform–ethanol (80:20); solvent 6, chloroform–ethanol (70:30).

Preparative high performance liquid chromatography (HPLC) was done using a Chromatronix pump and UV detector and a Hewlett-Packard recorder equipped with a unit to provide automatic zero suppression. Glass columns designed by Drs. L. Kirkegaard and D. Cole, University of Illinois, were packed with suitable resins for the separations involved. Microanalyses were performed by Mr. Joseph Nemeth and associates, who also weighed samples for quantitative electronic absorption spectra. Low-resolution mass spectra were obtained by Mr. J. Wrona on a Varian-Mat CH-5 spectrometer coupled with a 6201 computer and STATOS recorder.

pH Profile of the Reaction of Chloroacetaldehyde with Adenosine and Guanosine. A solution of 35 mg (0.125 mmol) of guanosine in 35 mL of 0.5 M sodium acetate buffer (for pH 4.5 and 5.5) or potassium phosphate buffer (for pH 6.4) and 1 mL of 2 M aqueous chloroacetaldehyde solution was stirred in a stoppered flask at 37 °C. A similar arrangement was used for adenosine, with controls for buffer and chloroacetaldehyde and buffer blanks. Aliquots (1 mL) were taken at constant intervals, made up to 50 mL with 0.01 M NaOH, and the spectra were recorded. Absorption values corresponding to the formation of 1,N^6-ethenoadenosine (290 nm, ε 3700) and 1,N^2-ethenoguanosine (305 nm, ε 8600)[48] were corrected for buffer and chloroacetaldehyde blank to give A_{obsd}. Percentage of products formed ($A_{obsd}/A_{prod} \times 100$) was plotted against time in hours to obtain a semiquantitative comparison of reaction rates.

All chloroacetaldehyde reactions must be run in a well-ventilated hood, employing adequate precaution against exposure to any part of the body.[12,13]

1,N^2-Ethenoguanosine (5,9-Dihydro-9-oxo-3-β-D-ribofuranosylimidazo[1,2-*a*]purine) (2). Guanosine (1) (850 mg, 3 mmol) and sodium chloride (3 g) in 750 mL of water were stirred magnetically under nitrogen at 37 °C bath temperature. After most of the guanosine had dissolved (~30 min), 20 mL of 2 M aqueous chloroacetaldehyde solution was added and the pH was carefully maintained between 6.35 and 6.45 using 0.2 M aqueous sodium hydroxide solution in the reservoir of a pH stat. Progress of the reaction was monitored using UV spectra at pH 7. The reaction was stopped when the absorption intensities at λ_{max} 272 and 254 nm became equal. Depending on the concentration of the particular batch of the chloroacetaldehyde and small variations in maintaining the pH and temperature of the reaction, it may take 3–7 days to reach this optimum point. Formation of 1,N^2-ethenoguanosine could be detected by TLC on cellulose in solvents 4 and 3 used successively. At the optimum point a 5-μL spot of the reaction mixture gave a faintly observable nonfluorescent spot

of ethenoguanosine (R_f 0.5, Guo R_f 0.4 in solvent 3). A comparison of NMR signal intensities at δ 7.94 (8-H of Guo) with those at 7.43 or 7.62 (etheno doublets in ε-Guo) in the NMR spectrum of the reaction mixture suggested the presence of about 45% ε-guanosine and 55% unreacted guanosine at the optimum point.

For isolation of 1,N^2-ethenoguanosine, the reaction mixture was evaporated to a syrup at 37 °C under vacuum, dissolved in 200 mL of water, and the aqueous solution was washed three times with equal volumes of ether. The aqueous layer was then concentrated to a small volume, adsorbed over 1 g of cellulose (CF-11), and chromatographed on 500 g of cellulose (column size, 6.4 × 1000 cm) in solvent 1 to yield 50 mg of crude ε-guanosine and 50 mg of a guanosine and ε-guanosine mixture. The latter was rechromatographed on cellulose in solvent 3 to yield an additional 20 mg of ε-guanosine (70 mg isolated, 7.5%, or 17% yield based on the amount of unreacted guanosine). An analytical sample was obtained after three recrystallizations from water (60 °C) as microneedles, mp 252–253 °C (determined on a hot stage microscope). A better yield of very pure product could be obtained by a preliminary purification on a short cellulose column in solvent 1 followed by HPLC on cation exchange resin Aminex A-5 (Bio-Rad) at 50 °C (column 1.3 × 76.2 cm, 0.1 M ammonium formate, pH 4.1, 0.60 mL/min): NMR [$(CD_3)_2SO$] δ 5.85 (d, 1, J = 5 Hz, anomeric H), 7.43 and 7.62 (d, J = 2.5 Hz, etheno H's), 8.16 (s, 1, 2-H); λ_{max} (0.1 M HCl) 222 nm (ε 26 500), 272 (8200), 295 (8300); λ_{max} (pH 7.0) 227 (34 400), 284 (11 900); λ_{max} (0.1 M NaOH) 233 (32 000), 280 (5750), 308 (8840); mass spectrum (70 eV) m/e 175 (base peak), 307 (M^+).

Anal. Calcd for $C_{12}H_{13}N_5O_5$: C, 46.91; H, 4.26; N, 22.79. Found: C, 46.86; H, 4.29; N, 22.86.

1,N^2-Ethenoguanine (5,9-Dihydro-9-oxoimidazo[1,2-a]-purine) (3). The glyoxal–guanine adduct 5[34] (1.4 g crude, 7 mmol) and hydriodic acid (30 mL, 47%) were stirred magnetically in a stoppered flask at 55–60 °C. The reaction was followed by UV in 0.1 M NaOH until the maximum at 284 nm, due to the glyoxal adduct, was completely replaced by that of the ε-guanine near 315 nm. The reaction was complete in 5–6 days when most of the product precipitated. The mixture was cooled overnight and filtered to yield 820 mg of a cream-colored solid. On concentration, the mother liquor yielded an additional 200 mg (total yield 1.02 g, 41%) of the 1,N^2-ethenoguanine hydriodide, mp > 300 °C. The compound was dissolved in boiling water, and the pH was adjusted to 6–7, causing the crystallization of 0.51 g of the free base·$\frac{1}{4}H_2O$, mp > 290 °C. Anhydrous free base for analysis was obtained by special drying at >200 °C: λ_{max} (0.1 M HCl) 221 nm (ε 29 000), 268 (5750), 295 (8450); λ_{max} (pH 7.0) 224 (39 700), 290 (9700); λ_{max} (0.1 M NaOH) 234 (46 200), 262 (4500), 318 (8900); mass spectrum (70 and 10 eV) m/e 175 (M^+, base peak).

Anal. Calcd for $C_7H_5N_5O$: C, 48.02; H, 2.88; N, 39.98. Found: C, 48.11; H, 3.03; N, 40.00.

The *hydriodide* had the following NMR spectrum [$(CD_3)_2SO$]: δ 7.66 (d, 1, J_{67} = 2.6 Hz, 6- or 7-H), 7.79 (d, 1, J_{67} = 2.6 Hz, 7- or 6-H), 9.37 (s, 1, 2-H), 11.45 (br NH protons, exchanged by D_2O).

Anal. Calcd for $C_7H_6IN_5O$: C, 27.74; H, 2.00; N, 23.11. Found: C, 27.41; H, 1.95; N, 22.45.

Conversion of 1,N^2-Ethenoguanosine (2) to 1,N^2-Ethenoguanine (3). 1,N^2-Ethenoguanosine (10 mg) was treated with 5 mL of 2 M HCl on a steam bath for 1 h. The product was identified as 1,N^2-ethenoguanine by comparison of its UV spectra in acid, base, and neutral media, by co-chromatography with an authentic sample on cellulose TLC plates in two solvent systems (2 and 4), and by its mass spectrum (70 and 10 eV): m/e 175 (M^+, base peak), with no peaks above 175.

***O^6*-Benzyl-N^2,3-ethenoguanine (9-Benzyloxyimidazo[2,1-*b*]purine) (7a).** O^6-Benzylguanine[37] [NMR[$(CD_3)_2SO$] δ 5.5 (s, 2, CH_2), 6.25 (br s, 2, NH_2, exchanged by D_2O), 7.3–7.6 (m, 5, C_6H_5), 7.83 (s, 1, 8-H); λ_{max} (0.1 M HCl) 233 nm (sh) (ε 5200), 287 (11 000); λ_{max} (pH 7) 239 (7800), 281 (8200); λ_{max} (0.1 M NaOH) 245 (sh) (4600), 284 (8500)] (241 mg, 1 mmol) in 20 mL of 75% aqueous ethanol was treated with 2 mL of 2 M aqueous chloroacetaldehyde solution at pH 4.0–4.5 and 37 °C bath temperature. The reaction was complete in 50–60 h. The mixture was evaporated, the residue was triturated with 5 mL of water, the pH was adjusted to neutral, and the precipitated free base was collected by filtration; 250 mg (94%). Recrystallization from aqueous ethanol provided 220 mg of very fine shiny crystals, mp 243–244 °C: NMR (hydrochloride) [$(CD_3)_2SO$] δ 5.74 (s, 2, CH_2), 7.25–7.7 (m, 5, C_6H_5), 8.08 (d, 1, J_{56} = 2.6 Hz, 6-H), 8.38 (d, 1, J_{56} = 2.6 Hz, 5-H), 8.68 (s, 1, 2-H); NMR (free base) [$(CD_3)_2SO$] δ 5.58 (s, 2, CH_2), 7.30–7.65 (m, 5, C_6H_5), 7.38 (d, 1, J_{56} = 1.5 Hz, 6-H), 7.84 (d, 1, J_{56} = 1.5 Hz, 5-H), 8.20 (s, 1, 2-H); λ_{max} (0.1 M HCl) 216 nm (ε 34 400), 266 (14 950); λ_{max} (pH 7.0) 219 (29 050), 273 (10 550); λ_{max} (0.1 M NaOH) 225 (32 500), 276 (9450); mass spectrum (10 eV) m/e (rel abundance) 265 (M^+), 175 (100); (70 eV) 265 (M^+), 175 (99) (M^+ −91 + 1), and 91 (100) (tropylium ion).

Anal. Calcd for $C_{14}H_{11}N_5O$: C, 63.39; H, 4.18; N, 26.40. Found: C, 63.48; H, 4.14; N, 26.63.

***N^2*,3-Etheno-*O^6*-methylguanine (9-Methoxyimidazo[2,1-*b*]purine) (7b).** O^6-Methylguanine[39] [NMR[$(CD_3)_2SO$] δ 3.97 (s, 3, CH_3), 7.82 (s, 1, 8-H)] (200 mg, 1.2 mmol) suspended in 12 mL of aqueous ethanol (60%) was treated with 1.5 mL of 2 M aqueous chloroacetaldehyde solution at pH 4.0–4.5 and 37 °C bath temperature and the product was isolated as in the reaction of O^6-benzyl-N^2,3-ethenoguanine. Recrystallization from a large excess of boiling water afforded 185 mg (81%) of fine white crystals ($\frac{1}{4}$ H_2O), mp 228–230 °C. Special drying above 110 °C provided the anhydrous free base for analysis: NMR (hydrochloride) [$(CD_3)_2SO$] δ 4.24 (s, 3, CH_3), 8.06 (d, 1, J_{56} = 2.6 Hz, 6-H), 8.38 (d, 1, J_{56} = 2.6 Hz, 5-H), 8.67 (s, 1, 2-H); NMR (free base) [$(CD_3)_2SO$] δ 4.1 (s, 3, CH_3), 7.44 (d, 1, J_{56} = 1.6 Hz, 6-H), 7.86 (d, 1, J_{56} = 1.6 Hz, 5-H), 8.29 (s, 1, 2-H); λ_{max} (0.1 M HCl) 215 nm (ε 26 850), 264–269 (br) (12 200); λ_{max} (pH 7.0) 221 (24 500), 272 (9900); λ_{max} (0.1 M NaOH) 225 (29 550), 275 (8800); mass spectrum (70 and 10 eV) m/e 189 (M^+ and base peak).

Anal. Calcd for $C_8H_7N_5O$: C, 50.79; H, 3.73; N, 37.02. Found: C, 50.69; H, 3.81; N, 37.47.

N^2,3-Ethenoguanine (8,9-Dihydro-9-oxoimidazo[2,1-*b*]-purine) (8). O^6-Benzyl-N^2,3-ethenoguanine (7a) (100 mg) was treated with 10 mL of 2 M hydrochloric acid on a steam bath for 1 h. The solution was evaporated to dryness and the residue was triturated with ether and filtered. The solid was dissolved in boiling water, the pH was adjusted to 6–7, and the free base ($\frac{1}{4}$ H_2O) crystallized: yield, 58 mg (88%) of white crystals; mp > 290 °C; NMR (hydrochloride) [$(CD_3)_2SO$] δ 7.61 (d, 1, J_{56} = 2.2 Hz, 6-H), 8.02 (d, 1, J_{56} = 2.2 Hz, 5-H), 8.38 (s, 1, 2-H); λ_{max} (0.1 M HCl) 215 nm (ε 25 000), 256 (9650); λ_{max} (pH 7.0) 216 (28 200), 262 (12 850); λ_{max} (0.1 M NaOH) 229 (32 000), 270 (9600); mass spectrum (10 and 70 eV) 175 (M^+, base peak). Anhydrous free base was obtained for analysis by special drying >200 °C.

Anal. Calcd for $C_7H_5N_5O$: C, 48.02; H, 2.88; N, 39.98. Found: C, 47.93; H, 2.80; N, 39.92.

Debenzylation of *O^6*-Benzyl-N^2,3-ethenoguanine by Catalytic Hydrogenolysis. O^6-Benzyl-N^2,3-ethenoguanine (7a) hydrochloride (100 mg) was hydrogenated at 25 °C and 1 atm in the presence of 10% Pd/C in 10 mL of absolute ethanol for 11 h. The mixture was diluted with 100 mL of 75% aqueous ethanol and filtered. The filtrate was evaporated to dryness, and the residue was recrystallized from a large excess of boiling water at neutral pH to yield 45 mg (68%) of N^2,3-ethenoguanine (8) identical in all respects with that obtained by acid hydrolysis of **7a**.

Demethylation of 7b. N^2,3-Etheno-O^6-methylgaunine (**7b**) was converted quantitatively to N^2,3-ethenoguanine on heating with concentrated HCl on a steam bath for 24 h. The product was identified by comparison of its UV, NMR, and mass spectra (see above).

6-Benzylthio-N^2,3-ethenoguanine (9-Benzylthioimidazo-[2,1-*b*]purine) (9). 2-Amino-6-benzylthiopurine[40,41] [NMR [$(CD_3)_2SO$] δ 4.54 (s, 2, CH_2), 6.38 (br s, 2, Pu-NH_2, exchanged by D_2O), 7.2–7.6 (m, 5, C_6H_5), 7.88 (s, 1, 8-H)] (600 mg, 2.34 mmol) was treated with 3.5 mL of 2 M aqueous chloroacetaldehyde solution in 60 mL of 75% aqueous ethanol at pH 4–4.5 and 37 °C bath temperature. The reaction was complete in 6–7 days. The pH was adjusted to neutral using 1 M $NaHCO_3$ solution, and the precipitated product was filtered, washed with water twice, and dried to yield an off-white powder (626 mg, 93%). It was recrystallized from a large excess of boiling water to give shiny cream-colored, fine crystals: mp 295 °C; NMR [$(CD_3)_2SO$ + DCl] δ 4.74 (s, 2, CH_2), 7.2–7.7 (m, 5, C_6H_5), 8.14 (d, 1, J_{56} = 2.4 Hz, 6-H), 8.38 (d, 1, J_{56} = 2.4 Hz, 5-H), 8.7 (s, 1, 2-H); NMR (free base) [$(CD_3)_2SO$] δ 4.67 (s, 2, CH_2), 7.2–7.55 (m, 5, C_6H_5), 7.61 (d, 1, J_{56} = 1.5 Hz, 6-H), 7.97 (d, 1, J_{56} = 1.5 Hz, 5-H), 8.26 (s, 1, 2-H); λ_{max} (0.1 M HCl) 301 nm (24 700); λ_{max} (pH 7.0) 302 (14 100); λ_{max} (0.1 M NaOH) 248 (14 800), 300 (18 800); mass spectrum (10 eV) m/e (rel abundance) 281 (M^+ and base peak); (70 eV) 281 (60) (M^+), 248 (60) ($M - SH)^+$, 91 (100).

Anal. Calcd for $C_{14}H_{11}N_5S$: C, 59.77; H, 3.94; N, 24.89. Found: C, 59.68; H, 3.90; N, 24.99.

Conversion of 6-Benzylthio-N^2,3-ethenoguanine to N^2,3-Ethenoguanine. 6-Benzylthio-N^2,3-ethenoguanine (**9**) (17 mg) was treated with 24 mg of *N*-chlorosuccinimide in 5 mL of aqueous methanol (80%) at 50–60 °C. In <1 h a highly fluorescent solution resulted. The reaction was allowed to proceed overnight, the solution was evaporated to dryness, and the residue was purified by chromatography over a short silica gel column in solvent 6. The fractions containing the oxidized compound (UV detection) were pooled and evaporated. The residue was treated with 2 N HCl overnight on a steam bath. The product was purified by HPLC on cation exchange

resin Aminex A-5 (Bio-Rad) at 50 °C (column 1.3 × 76.2 cm, 0.1 M ammonium formate, pH 4.1, 0.60 mL/min) and was identified as N^2,3-ethenoguanine by its HPLC elution volume, UV, and mass spectrum.

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Registry No.—**1**, 118-00-3; **2**, 62462-38-8; **3**, 56287-13-9; **3** HI, 62962-38-3; **5**, 21323-76-2; **6a**, 19916-73-5; **6b**, 20535-83-5; **7a**, 62962-39-4; **7a** HCl, 62991-00-8; **7b**, 62962-40-7; **7b** HCl, 62962-41-8; **8**, 62962-42-9; **8** HCl, 62962-43-0; **9**, 62990-98-1; **9** HCl, 62991-01-9; chloroacetaldehyde, 107-20-0; 2-amino-6-benzylthiopurine, 1874-58-4.

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(48) It was found that the guanosine–chloroacetaldehyde reaction produces additional products in smaller quantities, so that minor contributions of these products to the absorption intensity at 305 nm are possible. The development of some fluorescence was observed during the course of the reaction; however, compound **2** isolated from the reaction is not fluorescent under the conditions described.

Substituent Control of the Regiospecificity of Trifluoroacetic Acid Addition to an Allene

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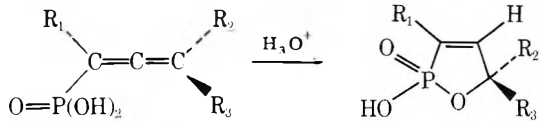
Electrophilic additions to allenes can occur with attachment of the electrophile to either the central or terminal carbons of the allene linkage. Such reagents as sulfenyl halides,[1a] molecular halogens,[1b] and mercury salts[1c] seem to add regiospecifically and stereospecifically to the central atom, while hydrogen halide addition[1d] and acid-catalyzed hydration[1e] generally occur with terminal orientation.[1f]

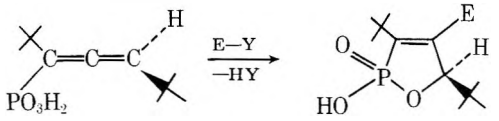
We recently found[2] that allenic phosphonic acids (**1**) with alkyl substituents for *both* R_2 and R_3 undergo facile Brønsted acid-catalyzed cyclization to give oxaphospholenes (**2**). This



1a, $R_1 = R_3 = t\text{-}C_4H_9$; $R_2 = H$
b, $R_1 = t\text{-}C_4H_9$; $R_2 = R_3 = CH_3$

2

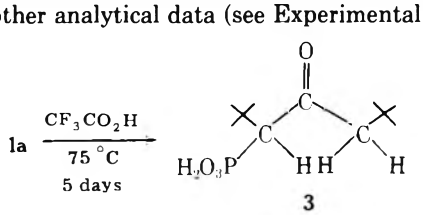
reaction can be visualized as "unusual" central protonation followed with attack by internal nucleophile. In contrast, compounds with R_2 and/or R_3 = H completely resisted cyclization. For example, **1a** ($R_1 = R_3 =$ *tert*-butyl, R_2 = H) was unchanged after 11 days at 90 °C in 2 M HCl (aqueous dioxane).[2] More powerful electrophiles such as bromine or mercuric acetate *did* effect the cyclization of **1a**, giving 4-substituted oxaphospholenes.[3] When these cyclizations were carried out with optically pure (*R*)-(−)-**1a**, the oxaphospholenes were formed with stereospecificity ranging from >41 (EY = Br_2) to 86% [EY = $Hg(OAc)_2$].[3]



1a

Continuing our search for a Brønsted acid capable of cyclizing **1a**, we examined the effectiveness of trifluoroacetic acid (TFA).[4] Not unexpectedly, **1b**[2] (R_1 = *tert*-butyl, $R_2 = R_3 = CH_3$) in TFA (127 mg/mL) underwent nearly quantitative cyclization to **2b**[2] during 16 h at 60 °C. But when **1a** was subjected to similar conditions, the reaction took an unwanted detour.

The reaction of **1a** with TFA at 75.0 °C, which could be conveniently monitored by ^1H NMR, resulted in conversion[5] to a new compound. This product is assigned structure **3** on the basis of its ^1H NMR spectrum [δ (TFA-d_1): 1.11 (s, 9 H), 1.30 (s, 9 H), 2.80 (s, 2 H), 3.60 (d, J = 21 Hz, 1 H), 11.30 (s, 3 H[6])] and other analytical data (see Experimental Section).

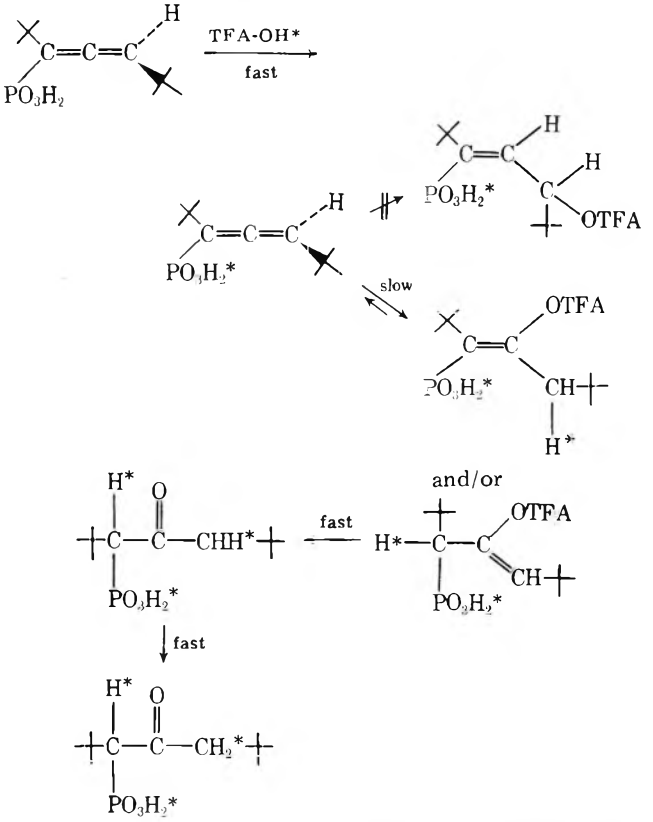


3

The formation of **3** followed first-order kinetics, with $k_{75.0°C} = (4.8 \pm 0.1) \times 10^{-4}$ min^{-1} ($t_{1/2}$ = 24 h). Evidence that **3** did *not* arise *via* **2a**[7] came from the observation that the latter was totally unchanged after 4 days in TFA at 75 °C. Further, **3** itself was stable during further heating in TFA.

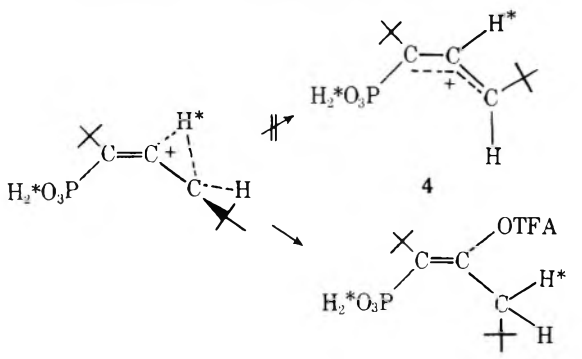
Treatment of **1a** with deuterio-TFA at 75.0 °C resulted in the formation of **3**-d_5, with no trace of the methylene or methine protons detectable at any time during the reaction. The rate of this reaction was notably slower than in TFA–OH, the solvent deuterium isotope (k_H/k_D) being 7.4 ± 0.7.[8] A control experiment with **3** in TFA-d_1 at 75.0 °C showed rapid exchange of the methylene protons ($t_{1/2}$ < 5.5 h),[8] and slow exchange of the methine proton ($t_{1/2} \sim 70$ h).[8] The allenic proton doublet of **1a** (δ5.62, J = 14 Hz) appeared to exchange about as rapidly as the methine proton in **3**.[9] Not unexpectedly, optically pure **1a**,[3] $[\alpha]^{25}_D$ −73.7° (*c* 0.0435 g/mL, TFA), gave **3** of much reduced rotation ($[\alpha]^{25}_D$ −1.2°, c 0.0386, TFA). Unfortunately, because of the developing color of the reaction mixture,[5] it was not possible to measure the rate of loss of optical activity, which should exceed the rate of **1a** → **3**.[10]

The most straightforward mechanism consistent with the above data is shown below. The rate-determining step of this



mechanism involves terminal electrophilic addition of TFA, exactly opposite to the course of protonation with **1b** (vide supra). We conclude that it will not be possible to cyclize allenic phosphonic acids with Brønsted acids unless the terminal carbon readily accommodates a positive charge (e.g., $R_2 = R_3$ = alkyl). If just one of the positions is substituted, the molecule will be highly resistant toward protonation, but in the presence of sufficiently strong Brønsted acids it will undergo terminal, rather than central, attack. It is somewhat surprising that twisting of the protonated allene linkage to give relatively stable allylic ion **4** does *not* occur, indicating that the activa-

tion barrier for the twist must exceed the barrier for trifluoroacetate addition to the central carbon atom.



Experimental Section

The instrumentation used in this work has been previously described.[2,3,7]

Preparation of 3. A 303-mg sample of phosphonic acid **1a**[7] in 5.8 mL of TFA was heated to 75 °C for 5 days, after which ^{1}H NMR indicated no starting material and ~85% pure **3**.[5] The burgandy colored solution was rotary evaporated, dissolved in 5 mL of benzene, then rotary evaporated again. The dark semisolid residue was recrystallized four times from minimum benzene to give 137 mg (42%) of colorless **3**, mp 167–168 °C. Its ^{1}H NMR spectrum is given in the text: IR (KBr) 1720 cm^{-1}; MS (20 eV) *m/e* (rel absorbance) 250 (13), 179 (12), 152 (97), 137 (100), 122 (47), 99 (52), 57 (48).

Anal. Calcd for $C_{11}H_{23}O_4P$: C, 52.78; H, 9.26. Found: C, 52.76; H, 9.20.

Kinetics measurements were done by ^{1}H NMR integration of the intensity of the doublet in **1a** compared to the doublet in **3**. In the case of TFA-d_1, ^{1}H NMR peak heights in the *tert*-butyl region were used.

Registry No.—**1a**, 42087-76-3; **3**, 63088-99-3; TFA, 76-05-1.

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(4) MCB reagent, used without further drying.
(5) Although <15% of other products were indicated by ^{1}H NMR (weak singlets at δ 0.99 and 1.41), the reaction mixture became burgandy colored during the reaction due to a small component of acid-catalyzed polymerization.
(6) The excess OH integration is due to adventitious water in the TFA-d_1.
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(8) Precision estimated to be ±10%.
(9) As the doublet at δ 5.62 decayed, due both to exchange and conversion to **3**, another weak multiplet appeared at δ 5.74. No such absorptions were observed in the TFA–OH reaction.[10]
(10) TFA containing 9% (w/w) water shows a slightly increased rate of coloring,[5] but the rate of hydration is depressed by 75%. When TFA containing 42% (w/w) trifluoroacetic anhydride is used, **1a** (δ 5.62, d, J = 14 Hz) is rapidly converted at 25 °C to a closely related compound (presumably the mixed anhydride) with δ 5.73, d, J = 15.5 Hz.[9] This solution gives no **3** (or its anhydide) after 3 days at 75 °C, nor does it show any coloring.[5]

Micellar Effects on the Monohalogenation of *n*-Pentyl Phenyl Ether

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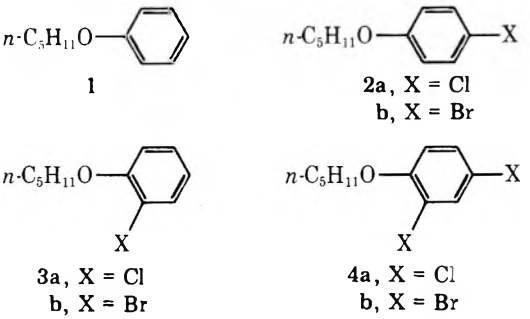
Micellar catalysis of organic reactions has been studied with numerous and diverse systems.[1] However, the synthetic application of micellar catalysis has received limited attention,[2] although stereochemical control has been the subject of several investigations.[3] If a substrate with several potential reaction sites is solubilized by a micelle in a specific manner, it is conceivable that some control of regioselectivity might accompany micellar catalysis of a given reaction.

We have examined the ability of micellar catalysis to influence the regioselectivity of two electrophilic aromatic substitution reactions of *n*-pentyl phenyl ether (**1**).[4] Ether **1**



1; **2a**, X = Cl; **b**, X = Br; **3a**, X = Cl; **b**, X = Br; **4a**, X = Cl; **b**, X = Br

was monochlorinated with chlorine and hypochlorous acid in aqueous micellar sodium lauryl sulfate (NaLS) and was monobrominated with bromine in aqueous micellar NaLS, sodium laurate (NaL), and cetyltrimethylammonium bromide (CTABr), and the ratios of para (**2**) to ortho (**3**) products were determined.[5] For each run, the concentration of **1**, halogenating agent, and micelle was 2.0×10^{-4} M. After the reaction period, the ether product mixture was isolated by one of two methods. In the first, the micellar solution was eluted through a column of ion-exchange resin (Dowex 2-X8 for NaLS and Bio-Rex 70 for CTABr runs). The surfactant and organic material both were retained by the column, and the latter was recovered by elution with methanol and ether. In the second method, organic material was extracted into hexane as surfactant was precipitated by the slow addition of calcium chloride (for NaLS and NaL runs) or sodium perchlorate (for CTABr runs) to a vigorously stirred mixture of micellar solution and hexane. Recoveries by the two methods were comparable, but the latter was quicker and therefore preferred.

The isolated product mixtures were analyzed by GLC after the addition of a hydrocarbon internal standard. For each run where recovery based on starting material was <90%, a control demonstrated that para (**2**) and ortho (**3**) products do not fractionate on isolation.

Ether **1** also was monohalogenated with chlorine and bromine in water. For these runs the concentration of **1** was 6.7×10^{-5} M (saturated solution) and that of halogenating agent 4.0×10^{-5} M, and standard extraction procedures were used for isolation of products, which were analyzed by GLC. The results of all halogenation runs are given in Table I. For any run, no more than a trace, if any, of 2,4-disubstituted product **4** was detected.

Ultraviolet (UV) spectroscopy was used to assess the microenvironments of chlorine, bromine, and **1** in micellar media. A comparison of the UV spectra of chlorine and bromine in micellar NaLS with those in water and heptane led to the conclusion that in micellar NaLS chlorine and bromine do not reside in the micelle hydrocarbon core, but rather in an aqueous environment; the same is assumed for hypochlorous acid. It is further assumed that in micellar NaL and CTABr bromine resides in an aqueous environment. An analogous comparison of the spectra of **1** in micellar NaLS, NaL, and CTABr with those in water, heptane, and 40:60 (v/v) water–dioxane led only to the conclusion that in the micellar media the phenoxy group of **1** does not reside in the bulk aqueous phase. Furthermore, by UV spectroscopy it was demonstrated

Table I. Results of Monohalogenation of *n*-Pentyl Phenyl Ether (1) at 22 ± 3 °C

Run[a]	Solvent[b]	Halogenating agent[c]	Reaction time, h	% recovery of 1 + 2 + 3[d,e]	% yield of 2 + 3[d,f]	*p*/*o* ratio[g] (2/3)
1	aq NaLS	Cl_2	90	95	93	3.1
2	aq NaLS	Cl_2	90	94	94	3.1
3	aq NaLS	HOCl	68	98	98	2.6
4	aq NaLS	HOCl	90	74	71	2.5
5	H_2O	Cl_2	20		15	1.6
6	H_2O	Cl_2	20		10	1.7
7	aq NaLS	Br_2	40	80	79	114
8	aq NaLS	Br_2	40	70	70	108
9	aq NaL	Br_2	68	98	92	24
10	aq NaL	Br_2	68	86	80	22
11	aq CTABr	Br_2	68	70	65	31
12	aq CTABr	Br_2	68	78	73	30
13	H_2O	Br_2	5		16	20
14	H_2O	Br_2	5		21	21

[a] Concentration of 1 was 6.7×10^{-5} M for runs in H_2O and 2.0×10^{-4} M for all other runs. [b] Aqueous micellar solutions were 2.0×10^{-4} M in micelles. [c] Concentration was 4.0×10^{-5} M for runs in H_2O and 2.0×10^{-4} M for all other runs. [d] For runs in micellar media, based on original amount of 1 and determined by GLC analysis using an internal standard. [e] Not determined for runs in H_2O. [f] For runs in H_2O, based on GLC analysis of recovered mixture of **1**, **2**, and **3**. [g] Determined by GLC analysis.

that 1 was completely solubilized in the runs in micellar media.

The results of Table I clearly indicate that micellar catalysis can affect the regioselectivity of monohalogenation. For 1 with chlorine in water, the para/ortho ratio (**2a/3a**) was 1.6 (runs 5 and 6), and that in micellar NaLS was 3.1 (runs 1 and 2). Likewise, with hypochlorous acid the para/ortho ratio of 2.6 in micellar NaLS (runs 3 and 4) is higher than the ratio of 1.41[6a] for anisole in water.[7]

For runs with bromine an effect on the para/ortho ratio (**2b/3b**) was observed with two of the three micellar media used. The para/ortho ratio of 111 (runs 7 and 8) obtained in NaLS is much greater than the ratio of 20 (runs 13 and 14) in water. In micellar NaL and CTABr ratios of 23 (runs 9 and 10) and 30 (runs 11 and 12), respectively, were obtained. The para/ortho ratio for each run in NaLS and CTABr is a minimum value for micellar-catalyzed monohalogenation, since some of the reaction undoubtedly proceeds in the bulk aqueous phase where the para/ortho ratio is lower.

On solubilization of 1 by a micelle, the phenoxy group most likely resides near the micelle surface, and the lipophilic *n*-pentyl chain extends into the hydrocarbon core. With this orientation for **1**, the ortho positions relative to the para position might be sterically shielded from the halogenating agent. As a result, for 1 solubilized by a micelle the fraction of substitution at the para position would be greater than that for 1 in water. The results of Table I are consistent with shielding of the ortho positions at the reactive sites for halogenation in NaLS and CTABr micelles, but not at that site in a NaL micelle. Alternatively, the results in micellar NaL are consistent with bromination which occurs almost totally in the bulk aqueous phase, but this is unlikely. In addition to those outlined above, the results must reflect additional medium and electrostatic factors,[9] but their effects are difficult to assess.

The results indicate that micellar catalysis has a potential application in the control of regioselectivity in organic synthesis, and we are pursuing this further.

Experimental Section

All melting and boiling points are uncorrected. Routine GLC analyses and preparative separations were performed on two columns: column A, 5 ft × ¼ in. stainless steel packed with 3% SE-30 on 100–120 mesh Varaport 30; and column B, 4.5 ft × ¼ in. aluminum packed with 3% SE-30 on 80–100 mesh Chromosorb W. The GLC analyses of product mixtures from the runs of Table I were performed on column C, 8 ft × ¼ in. aluminum packed with 8% SE-30 on 60–80 mesh Chromosorb W AW DMCS. Column oven temperatures of 150 and 180 °C, respectively, were used for chlorination and bromination product analyses. Ultraviolet spectra were obtained with a Beckman DB ultraviolet spectrophotometer and quartz 1-cm cuvettes and with a Cary 14 recording spectrophotometer and quartz 1-cm cuvettes or 10-cm cylindrical cells. Critical micelle concentrations (cmc) were determined by the ring method with a Cahn RM-2 electrobalance and surface tension accessory. Spectral grade dioxane and heptane (Mallinckrodt) were used for UV spectra, and tetrahydrofuran (THF) was distilled from lithium hydride before use. Combustion analyses were performed by Huffman Laboratories, Wheatridge, Colo., and by Galbraith Labororatories, Knoxville, Tenn.

Sodium Lauryl Sulfate (NaLS). Attempts to purify several commerical samples of NaLS were unsuccessful. The cmc of purified commercial material was $\leq 5 \times 10^{-3}$ M with serious hysteresis (lit.[10a] 8.1×10^{-3} M). Therefore NaLS was prepared as follows.

In standard fashion with methanol and sulfuric acid as catalyst lauric acid (Aldrich) was converted to methyl laurate, bp 93–95 °C (0.5 mm). By GLC analysis (column A) the ester was 99.8% pure, and it was reduced in THF with $LiAlH_4$ to give lauryl alcohol, bp 98–100 °C (0.03 mm), mp 24–25 °C. By GLC analysis (column B) this material was homogeneous, and with the procedure of Sandler and Karo,[11] 24.7 g (0.133 mol) of it was converted to laurylsulfuric acid with 11.2 g (0.140 mol) of SO_3 (Sulfan, Baker). Then the crude acid was added to an ice-cold solution of 5.6 g (0.14 mol) of NaOH in 130 mL of water followed by 500 mL of ice-cold methanol. The resultant solid was collected by filtration and recrystallized from methanol. Then a methanol solution of this material was decolorized three times with Norit and evaporated to leave NaLS with a cmc of 5.5×10^{-3} M with serious hysteresis. This NaLS was dissolved in a minimum amount of water at 25 °C, and the solution was cooled to 8 °C. The material which crystallized had a cmc of 6.3×10^{-3} M with only slight hysteresis, and it was combined with NaLS of similar purity from two parallel preparations starting with a total of 316 g of lauryl alcohol. The combined material was recrystallized from water and then from absolute ethanol to yield 107 g (20%) of NaLS with a cmc of 7.1×10^{-3} M with no hysteresis (lit.[10a] 8.1×10^{-3} M).

Sodium Laurate (NaL). A total of 300 g (1.50 mol) of lauric acid (Aldrich) was converted to its sodium salt following an established procedure.[12] The resulting crude material was recrystallized from methanol three times to give NaL with a cmc of 1×10^{-2} M (lit.[13] 2.4×10^{-2} M). This material was slurried twice in ether and once in hexane to give 86.0 g (26%) of NaL with a cmc of 2.1×10^{-2} M with slight hysteresis.

Cetyltrimethylammonium Bromide (CTABr). A 75.0-g portion of CTABr (Aldrich) was washed with hexane and recrystallized from methanol. Two crops were collected, 39.5 g total, and each had a cmc of 9.1×10^{-4} M with no hysteresis (lit.[10b] 9.2×10^{-4} M).

***n*-Pentyl Phenyl Ether (1) and Substituted *n*-Pentyl Phenyl Ethers (2, 3, and 4).** Each of the ethers was prepared by a standard Williamson procedure[14] using the appropriate combination of *n*-pentyl bromide and phenol or substituted phenol. In each preparation fractional distillation gave purified material which was homogeneous

Table II.[a] Physical Properties of Ethers 1, 2, 3, and 4

Ether	Registry no.	Bp, °C
1[b]	2050-04-6	94–96 (23 mm)
2a[c]	51241-40-8	113–115 (0.5 mm)
2b[a]	30752-18-2	81–83 (0.05 mm)
3a[d]	51241-39-5	78–80 (0.1 mm)
3b[a]	60376-60-8	85–87 (0.1 mm)
4a[a]	63076-61-9	118–120 (0.1 mm)
4b[e]	63076-62-0	106–108 (0.01 mm)

[a] Satisfactory analytical data (±0.3% for C and H) were reported for all new compounds listed in the table. [b] Reference 4. [c] B. Jones, *J. Chem. Soc.*, 1831 (1935). [d] E. M. Van Duzee and H. Atkins, *J. Am. Chem. Soc.*, **57**, 147 (1935). [e] S. J. Branch and B. Jones, *J. Chem. Soc.*, 2921 (1955).

by GLC analysis (column A). Table II gives the physical data of the ethers prepared.

Halogenation of *n*-Pentyl Phenyl Ether (1) with Chlorine, Hypochlorous Acid, and Bromine in Aqueous Micellar Media (Runs 1–4 and 7–12). Chlorine (Matheson) and bromine (Mallinckrodt) were used as received, and hypochlorous acid was prepared as described by Brauer.[15] Halogenating agents were added to reaction mixtures as aqueous solutions standardized (ca. 0.005 M) with sodium thiosulfate–potassium iodide.[16] For each run the total volume was 500 mL, and the concentration of 1, micelle, and halogenating agent was 2.0×10^{-4} M. The following is the general procedure used.

All glassware to be exposed to micellar solution was cleaned with $Na_2Cr_2O_7$–H_2SO_4 cleaning solution and rinsed in sequence with water, dilute ammonia, and water. To a 1-L Erlenmeyer flask was added 16.4 mg (0.100 mmol) of 1. Then an amount of surfactant was added in the form of a stock solution, which on subsequent dilution to 500 mL gave a micelle concentration of 2.0×10^{-4} M (see below). The exact volume (ca. 20 mL) of standarized aqueous halogenating solution needed to give a final concentration of 2.0×10^{-4} M was calculated, and the micellar solution was diluted with water to 500 mL minus this volume. After the reaction mixture was swirled to dissolve 1, the calculated volume of halogenating agent solution was added, and the mixture was swirled again and allowed to sit (in the dark for brominations) at room temperature (22 ± 3 °C). After the appropriate period, products were isolated by one of the two methods described below.

The amount of surfactant necessary to give a micelle concentration of 2.0×10^{-4} M was calculated using the cmc and aggregation number[1c] (62 for NaLS, 56 for NaL, and 61 for CTABr). A micelle concentration of 2.0×10^{-4} M corresponds to concentrations of 1.95×10^{-2}, 2.22×10^{-2}, and 1.31×10^{-2} M for NaLS, NaL, and CTABr, respectively.

Isolation of Products from Micellar Media. Two methods were used. In the first, a 5-in. aqueous bed of ion-exchange resin was prepared in a 1-in. (o.d.) glass column and washed with 550 mL of methanol followed by 1 L of water. Dowex 2-X8 (chloride form, 20–50 mesh) was used for NaLS solutions and Bio-Rex 70 (sodium form, 80–100 mesh) for CTABr solutions. The micellar reaction mixture was passed through the column three to four times until there was no visual residual surface activity. In this process organic material also was retained by the resin, and it was recovered by elution with 200 mL of methanol followed by 100 mL of ether. Rotary evaporation of the combined eluates left an oil which was extracted into hexane. The resulting hexane solution was dried over Na_2SO_4, and rotary evaporation yielded the product mixture.

In the second, extraction of the product mixture into hexane was facilitated by precipitation of the surfactant. The lauryl sulfate ion of NaLS and the laurate ion of NaL were precipitated with $CaCl_2$ and the cetyltrimethylammonium ion of CTABr with $NaClO_4$. To a vigorously stirred mixture of 500 mL of micellar solution and 150 mL of hexane was added a molar equivalent of precipitating agent dissolved in 30 mL of water. Stirring was continued for 10 min, the hexane layer was separated, and the aqueous layer including precipitate was extracted three times in the same manner using 100-mL portions of hexane. The combined hexane extracts were dried over Na_2SO_4, and rotary evaporation yielded the product mixture.

Analysis of Product Mixtures Isolated from Micellar Media. To each product mixture was added a known weight of 1-phenyldecane as internal standard, and analysis was performed by GLC. Appropriate known mixtures of 1, 2, 3, 4, and 1-phenyldecane were analyzed by GLC, and correction factors for differences in thermal conductivity were calculated relative to the internal standard and used in quantitation of analyses. For integration the cut-and-weigh method was employed with Keuffel and Esser Albanene tracing paper.

The product mixtures isolated from runs in aqueous NaLS contained small amounts of lauryl alcohol. The retention time of 2a was identical with that of this material, so product mixtures from runs 1, 2, 3, and 4 were treated as follows after the addition of 1-phenyldecane in order to convert lauryl alcohol into lauryl acetate, which did not interfere with the GLC analysis. To a solution of the product mixture and internal standard in 10 mL of THF were added 1 mL each of pyridine and acetyl chloride. The resulting mixture was stirred for 2 h at room temperature and diluted with 10 mL of methanol. After 10 min at room temperature the mixture was concentrated by rotary evaporation and extracted with hexane. The resulting hexane solution was washed with 5 mL of 5% aqueous NaOH followed by 5 mL of water and was then dried over Na_2SO_4 and rotary evaporated to leave the product mixture for analysis.

Product mixtures isolated from runs 9 and 10 in aqueous NaL contained small amounts of lauric acid, which had a retention time identical with that of 3b. Therefore, after the addition of internal standard, lauric acid was removed by extraction of a hexane solution with 10% aqueous NaOH. Then the solution was washed with water, dried over Na_2SO_4, and rotary evaporated to leave the product mixture for analysis.

For each run where <90% (based on internal standard) of total ether was recovered in form of 1, 2, and 3, a control demonstrated that 2 and 3 do not fractionate during isolation.

Halogenation of *n*-Pentyl Phenyl Ether (1) with Chlorine and Bromine in Water (Runs 5, 6, 13, and 14). A saturated solution of 1 (6.7×10^{-5} M) was prepared by stirring an excess of 1 with water at room temperature for 2 h. The solution was allowed to stand overnight and was then separated from undissolved ether. To a 500-mL portion of this solution was added 2.0×10^{-5} mol of chlorine in the form of 2.27 mL of a 8.82×10^{-3} M aqueous solution, and to another 500-mL portion was added 2.0×10^{-5} mol of bromine in the form of 4.94 mL of a 4.05×10^{-3} M aqueous solution. Each mixture was swirled and allowed to sit at room temperature for the appropriate reaction period. Then it was quenched with Na_2SO_3, saturated with NaCl, and extracted with three 100-mL portions of hexane. The combined extracts were dried over Na_2SO_4 and rotary evaporated to give the product mixture, which was analyzed by GLC. For integration the cut-and-weigh method was used, and correction factors for differences in thermal conductivity were used in quantitation of analyses.

Ultraviolet Spectroscopy of *n*-Pentyl Phenyl Ether (1). The spectrum of a 2.0×10^{-4} M solution of 1 in heptane displayed absorption maxima at 278 (ϵ 1899) and 272 nm (ϵ 2045) and in 40:60 (v/v) water–dioxane at 278 (ϵ 1454) and 272 nm (ϵ 1763).

The spectrum of a 1.05×10^{-4} M solution of 1 in a 1.95×10^{-2} M aqueous solution of NaLS (micelle concentration of 2.0×10^{-4} M) displayed absorption maxima at 278 (ϵ 1231), 272 (ϵ 1550), and 220 nm (ϵ 7406).[17] Then 7.9 mg (0.048 mmol) of 1 was added to 200 mL of the same NaLS solution, and the mixture was shaken periodically for 2 h and allowed to sit overnight. A sample was withdrawn with the exclusion of any undissolved 1 at the surface and its spectrum recorded. The absorbance of the absorption maximum at 272 nm was 0.377 with 1-cm cuvettes, and this corresponds to a concentration of 2.4×10^{-4} M. Therefore, for runs 1–4 it can be concluded that the 16.4-mg (0.100 mmol) portion of 1 was completely dissolved in the 500 mL of 1.95×10^{-2} M aqueous NaLS.

Solutions were prepared in 2.22×10^{-2} M NaL and 1.31×10^{-2} M CTABr with amounts of 1 that would give each a concentration of 2.0×10^{-4} M if all of 1 dissolved, and absorbance values of the maximum at 272 nm with 1-cm cuvettes were 0.304 and 0.327, respectively. If it is assumed that the molar extinction coefficients for 1 at 272 nm in NaL and CTABr are the same as that for 1 in NaLS, then it can be calculated that 1 is almost if not completely solubilized in both solutions. The spectrum of the NaL solution displayed maxima at 278 (ϵ 1236) and 272 nm (ϵ 1523) and that of the CTABr solution maxima at 279 (ϵ 1378) and 272 nm (ϵ 1630).

The spectrum of a 2.56×10^{-5} M solution of 1 in water displayed absorption maxima at 275 (ϵ 985), 268 (ϵ 1204), and 218 nm (ϵ 6337). Then a saturated aqueous solution of 1 was prepared, and a sample was withdrawn with exclusion of undissolved 1 at the surface and its spectrum recorded. The absorbance of the maximum at 268 nm was 0.081 with 1-cm cuvettes, and this corresponds to a concentration of 6.7×10^{-5} M.

Ultraviolet Spectroscopy of Chlorine and Bromine. Spectra were obtained for 5×10^{-3} M solutions of chlorine in water, aqueous NaLS, 40:60 (v/v) water–dioxane, and heptane. The concentration of NaLS was 0.32 M, which corresponds to a micelle concentration

of 5.0×10^{-3} M. The following absorption maxima (nm) were observed: for water, 292 (ε 24); for aqueous NaLS, 290 (ε 37); for aqueous dioxane, 306 (ε 55); and for heptane, 330 (ε 258).

Spectra were obtained for 2.0×10^{-4} M solutions of bromine in water, aqueous NaLS, and heptane. The concentration of NaLS was 1.95×10^{-2} M, which corresponds to a micelle concentration of 2.0×10^{-4} M. The following absorption maxima (nm) were observed: for water, 260 (shoulder, ε 83) and 392 (ε 82); for aqueous NaLS, 260 (shoulder, ε 66) and 392 (ε 76); and for heptane, 417 (ε 157).

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Registry No.—NaLS, 151-21-3; NaL, 629-25-4; CTABr, 57-09-0; lauric acid, 143-07-7; methyl laurate, 111-82-0; lauryl alcohol, 112-53-8; laurylsulfuric acid, 151-41-7.

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(5) In a related study Breslow and co-workers[6] have examined the influence of cyclodextrins on the regioselectivity of anisole monochlorination in aqueous hypochlorous acid.

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(7) A comparison with different substrates is being made, but it can be reasonably assumed that in aqueous hypochlorous acid 1 would give a para/ortho ratio very close to that reported for anisole. Monochlorination of **1**, *n*-nonyl phenyl ether, and *n*-dodecyl phenyl ether in 40:60 (v/v) water–dioxane with hypochlorous acid gave para/ortho ratios of 3.2, 3.3, and 3.6, respectively.[8] These results indicate that in a homogeneous nonmicellar medium the para/ortho ratio is influenced only slightly by chain length.

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(17) A short-wavelength absorption maximum at 220 nm is reported here, but analogous maxima are not for those spectra above and for most of those below due to instrumental limitations (Beckman DB) in the short-wavelength region.

Quinazolines and 1,4-Benzodiazepines. 80.[1] 1-Hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, a Hydroxamic Acid via an Amidine *N*-Oxide

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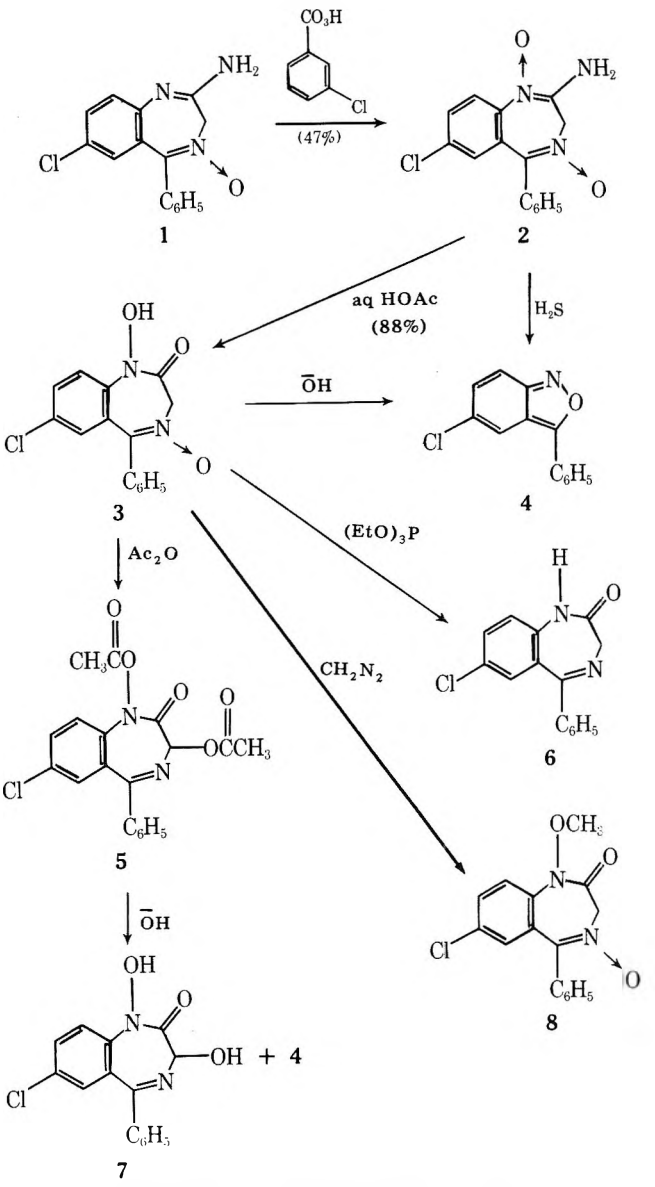
We wish to record the preparation of a novel class of 1,4-benzodiazepines which contain oxygenated nitrogen atoms in position 1. Also of interest was the preparation of the amidine *N*-oxide[2] **2** by peracid oxidation of amidine **1**[3] and the efficient hydrolysis of compound **2** to the hydroxamic acid **3**.

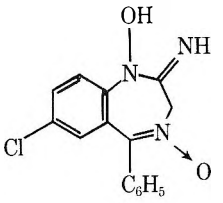
When a solution of 7-chloro-2-amino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**1**)[4] in methylene chloride was treated with a slight excess of *m*-chloroperbenzoic acid at room temperature, oxidation was complete in minutes and the amidine *N*-oxide **2** was readily isolated, as yellow prisms, in 47% yield (Scheme I). Compound **2** was soluble in both dilute aqueous acids and bases, and was very susceptible to hydrolysis. For example, if a solution of **2** in aqueous acetic acid was allowed to stand at room temperature, the insoluble hydroxamic acid **3** precipitated and was obtained in 88% yield. Mild treatment of **2** with anhydrous hydrogen sulfide afforded a complex mixture from which only 5-chloro-3-phenyl-2,1-benzisoxazole[5] (**4**) was isolated (49%). The same degradation product **4** was obtained (87% yield) when the hydroxamic acid **3** was dissolved in 1 N sodium hydroxide at room temperature. An attempt to deoxygenate the 4-oxide function of **3** with triethyl phosphite resulted in a simultaneous reduction of the hydroxamic acid to the lactam–imine, compound **6**,[6] which was isolated in 24% yield. The acidic character of the hydroxamic acid was evident by the smooth O-methylation of **3** with diazomethane to give **8**. When **3** was heated in acetic anhydride, the 1,3-diacetoxy derivative **5** was obtained. Mild alkaline hydrolysis of **5** afforded a mixture of the 1,3-dihydroxy compound **7** and the 2,1-benzisoxaole **4**, which again indicated the destabilizing influence of the 1-hydroxy substituent on the benzodiazepine ring toward cleavage by nucleophiles.

Scheme I



A comparison of the NMR and UV spectra of **2** and **3** indicated that none of the hydroxyamidine tautomer **9** exists in

solution. Compound **3** served as a model for the tautomeric structure **9**. The hydroxyl proton of **3** appeared at δ 11.07 in



9

the NMR spectrum, while the spectrum of **2** showed an NH_2 signal at δ 7.9–8.4; the methylene protons in position 3 of **3** were nonequivalent, appearing as a broad AB quartet, while the methylene group in both **1** and **2** appeared as singlets. Furthermore, the UV spectrum of **2** was quite different than that of **3**.

Experimental Section[7]

2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 1,4-Dioxide (2). To a stirred suspension of 6.80 g (24.0 mmol) of 7-chloro-2-amino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**1**)[4] in 70 mL of methylene chloride, chilled in an ice bath, was added in portions 5.90 g (28.8 mmol) of *m*-chloroperbenzoic acid (technical grade, 85%). The ice bath was removed and stirring was continued for 0.5 h. A brown solution was formed and a starch–iodide test indicated little or no remaining peracid. Triethylamine (5 mL, 35 mmol) was added and the precipitated solids were collected to give 3.4 g (47%) of **2**, mp 211 °C dec. Recrystallization from ethanol afforded yellow prisms: mp 221 °C; IR (KBr) 3400–3060 (br) and 1548 cm^{-1}; NMR (Me_2SO-d_6) δ 4.78 (s, 2, CH_2), 6.90 (d, 1, H-6), 7.47 (m, 5, C_6H_5), 7.57 (q, 1, H-8), 8.14 (d, 1, H-9), and 7.9–8.4 (br, 2, NH_2); UV max (2-PrOH) 220 nm (sh, ε 19 000), 244 (18 750), 288 (26 700), and 370 (sh, 1310); mass spectrum *m/e* 301 (M^+).

Anal. Calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.92. Found: C, 59.79; H, 4.38; N, 14.10.

Diacetic Acid Salt of 2. A solution of 4.0 g (13.3 mmol) of **2** in 15 mL of glacial acetic acid was diluted with 70 mL of ether. Colorless prisms which crystallized were collected. The weight was 4.9 g (88%), mp 145–148 °C dec, UV spectrum identical with that of **2**.

Anal. Calcd for $C_{15}H_{12}ClN_3O_2{\cdot}2C_2H_4O_2$: C, 54.10; H, 4.78; N, 9.96. Found: C, 54.22; H, 4.91; N, 9.89.

7-Chloro-1,3-dihydro-1-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (3). A solution of 8.0 g (26.6 mmol) of **2** in 100 mL of 50% aqueous acetic acid was diluted with 200 mL of water and left at room temperature overnight. The solids which precipitated were collected, in two crops, to give 7.0 g (88%) of the desired product, mp 212–213 °C dec. Recrystallization from ethyl acetate afforded yellow prisms: mp 219–220 °C dec; IR (KBr) 2950–2370 (salt bands) and 1700 cm^{-1} (carbonyl); UV max (2-PrOH) 243 nm (ε 26 800) and 311 (9620); NMR (Me_2SO-d_6) δ 4.50 and 4.80 (br s, 1 each, CH_2), 6.97 (d, 1, 6-H), 7.4–7.8 (m, 7, arom) and 11.07 (s, 1, OH); mass spectrum *m/e* 302 (M^+).

Anal. Calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.52; H, 3.66; N, 9.25. Found: C, 59.55; H, 3.68; N, 9.15.

5-Chloro-3-phenyl-2,1-benzisoxazole (4).[5] **(a) From 2.** Into a stirred suspension of 151 mg (0.5 mmol) of **2** in 5 mL of tetrahydrofuran at room temperature was introduced a stream of hydrogen sulfide gas for 15 min. The reaction mixture was separated by preparative thin-layer chromatography on silica gel. The main band (R_f 0.75 in 10% ether–benzene) was collected by elution with 10% methanol–ethyl acetate. Crystallization from methanol of the residue, after removal of solvents, gave 50 mg (49%) of yellow needles, mp 113–114 °C. This material was identical with a known sample of **4**[5] by TLC, IR, and mixture melting point.

(b) From 3. A solution of 0.3 g (1.0 mmol) of **3** in 10 mL of 1 N aqueous sodium hydroxide was left at room temperature overnight. Yellow needles that formed were collected and washed with water. The yield was 200 mg (87%), mp 111–113 °C. This material was identified by TLC, IR, and mixture melting point as **4**.

In a separate experiment, a solution of **3** in tetrahydrofuran was saturated with concentrated hydrochloric acid and left at room temperature overnight. The 2,1-benzisoxazole **4** again was isolated in high yield.

7-Chloro-1,3-diacetoxy-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (5). A suspension of 3.0 g (10 mmol) of **3** in 8 mL of acetic anhydride was heated gently on a steam bath for 2 h; a clear solution formed after 5 min. On cooling, **5**, which crystallized as prisms, was collected and washed with benzene followed by hexane. It weighed 3.1 g (80%), mp 197–199 °C. Recrystallization from tetrahydrofuran–petroleum ether afforded colorless prisms; mp 196–198 °C; IR (KBr) 1810, 1755, and 1725 cm^{-1}; NMR (DMF-d_7) δ 2.29 (s, 3, 3-$OCOCH_3$), 2.39 (s, 3, 1-$OCOCH_3$), 6.17 (s, 1, CHOAc), and 7.5–8.0 (m, 8, arom); UV max (CH_3CN) 231 nm (ε 31 000), 253 (sh, 16 700), and 309 (sh, 2120); mass spectrum *m/e* 386 (M^+).

Anal. Calcd for $C_{19}H_{15}ClN_2O_5$: C, 59.00; H, 3.91; N, 7.24; Cl, 9.17. Found: C, 59.18; H, 3.87; N, 7.38; Cl, 9.04.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (6).[6] **Reduction of 3 with Triethyl Phosphite.** A suspension of 0.3 g (1.0 mmol) of **3** in 2 mL of triethyl phosphite was heated on a steam bath for 2.5 h. A clear solution gradually formed. The reaction mixture was separated by preparative thin-layer chromatography on silica gel. The main band (R_f 0.71 in ethyl acetate) was collected, eluted with 10% methanol in ethyl acetate, and evaporated. Crystallization of the residue from ethyl acetate–ether gave 65 mg (24%) of **6** as colorless prisms, mp 209–211 °C. This material was identified as **6**[6] by TLC, IR, and mixture melting point.

7-Chloro-1,3-dihydro-1,3-dihydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7). To a solution of 0.77 g (2.0 mmol) of **5** in 10 mL of tetrahydrofuran at room temperature was added 6 mL of 1 N aqueous sodium hydroxide. The two-phase mixture was stirred vigorously overnight. Tetrahydrofuran was evaporated. The aqueous layer was further basified to pH 11 with 0.1 N aqueous sodium hydroxide and extracted with methylene chloride. The organic layer was separated, dried, and evaporated. Crystallization of the residue from methanol gave 90 mg (20%) of 5-chloro-3-phenyl-2,1-benzisoxazole (**4**) as yellow needles, mp 109–111 °C. This material was identified as **4** by TLC, IR, and mixture melting point.

The aqueous layer was acidified with acetic acid and extracted with methylene chloride. The organic layer was separated, dried, and evaporated. Crystallization of the residue from ether gave 140 mg of crude **7**, which on recrystallization from ethanol–water gave 75 mg (23%) of cream prisms; mp 176–178 °C dec; IR (KBr) 3240–3110 (br) and 1687 cm^{-1}; UV max (2-PrOH) 233 nm (ε 28 200), 260 (sh, 16 900), and 324 (2240); NMR (Me_2SO-d_6) δ 4.69 (d, J = 9 Hz, 1, 3-OH), 6.34 (d, J = 9 Hz, 1, CH), 7.15 (m, 1, 6-H), 7.41 (m, 5, C_6H_5), 7.61 (m, 2, 8-H and 9-H), and 10.77 (s, 1, NOH); mass spectrum *m/e* 302 (M^+).

Anal. Calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.52; H, 3.66; N, 9.25. Found: C, 59.38; H, 3.80; N, 9.27.

7-Chloro-1,3-dihydro-1-methoxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (8). To a stirred solution of 6.2 g (22 mmol) of **3** in 250 mL of tetrahydrofuran at room temperature was added, in portions, an ethereal solution of diazomethane until gas evolution ceased. A few drops of acetic acid were added to decompose excess diazomethane. Solvents were evaporated. Crystallization of the residue from ethyl acetate gave 2.7 g of crude **8**. Recrystallization from ethyl acetate afforded 1.8 g (34%) of colorless prisms: mp 195–197 °C; IR (KBr) 1718 and 1240 cm^{-1}; NMR ($CDCl_3$) δ 3.81 (s, 3, OCH_3); mass spectrum *m/e* 316 (M^+).

Anal. Calcd for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; N, 8.84. Found: C, 60.61; H, 4.27; N, 9.09.

Acknowledgment. We thank Dr. S. Kasparek for a search of the literature and Dr. R. P. W. Scott and his staff in our Physical Chemistry Department, in particular, Dr. W. Benz for mass spectra, Dr. F. Scheidl for elemental analyses, Dr. V. Toome for UV measurements, Mr. S. Traiman for IR spectra, and Dr. T. Williams for NMR spectra.

Registry No.—**1**, 7722-15-8; **2**, 63076-85-7; **2** diacetic acid salt, 63076-86-8; **3**, 63076-87-9; **4**, 719-64-2; **5**, 63076-88-0; **6**, 1088-11-5; **7**, 63076-89-1; **8**, 63076-90-4.

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Synthesis of Acylcyclopropanes and Oxiranes from Vinylsulfonium Salts and Lithium Enolates

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Unsaturated onium salts have great synthetic utility as Michael acceptors and dipolarophiles as well as ylide precursors.[1,2] Of the salts, vinylphosphonium salts have been widely used for synthesis of heterocyclic compounds via Michael additions and subsequent Wittig reactions.[3] However, similar application of vinylsulfonium salts to synthetic chemistry has not been reported except for a few reactions with active methylene compounds such as malononitrile and diethyl malonate to give cyclopropanes.[4] Accordingly, in order to get further information on reactivities of vinylsulfonium salts, we have investigated the reaction between the salts and lithium enolates.

Dimethylstyrylsulfonium perchlorate (**2a**) was allowed to react with lithium acetophenone enolate (**1a**) in THF–DMF at room temperature to give *trans*-1-benzoyl-2-phenylcyclopropane (**3a**) in 70% yield. A similar reaction between other vinylsulfonium salts **2** and lithium enolates **1** gave the corresponding *trans*-acylcyclopropanes **3** in good yield (Table I).

On the other hand, similar treatment of **2** with other lithium enolates **4** produced oxiranes **5**, but none of the expected acylcyclopropanes were detected except for the reaction of **2a** with **4b** (Table II). The reaction of **2a** with lithium *p*-chloropropiophenone enolate (**4b**) gave *trans*-1-*p*-chlorobenzoyl-1-methyl-2-phenylcyclopropane (**3e**) in 66% yield instead of the oxirane corresponding to **5c**. For the establishment of the structure of **5a**, treatment of **5a** with Raney Ni gave 2,4-diphenyl-3-methyl-1-pentene (**6**) in 85% yield. The pentene **6** would be formed by ring opening of the oxirane, followed by dehydration.[6]

The formation of acylcyclopropanes **3** and oxiranes **5** would be considered as follows: The reaction of vinylsulfonium salts **2** with enolate anion **1** or **4** give betain A and/or ylide B. The betain A would easily decompose to acylcyclopropanes **3** with elimination of dimethyl sulfide. On the other hand, oxiranes **5** might be formed by the intramolecular reaction of the ylide B with the carbonyl group. Although the products depend on the substituents of lithium enolates, the difference of the two pathways is not clear at this stage.

Finally these results indicate that vinylsulfonium salts are versatile reagents, since selective formation of acylcyclopropanes and oxiranes is possible by the choice of nucleophiles.

Experimental Section

General. Melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. IR, ^{1}H NMR, and mass spectra were obtained on a JASCO IR-E spectrometer, JEOR LMN-3H-60 and JNM-ps-100 spectrometer, and a Hitachi RMU-6E spectrometer, respectively.

Materials. Dimethylstyrylsulfonium perchlorate (**2a**) and dimethylisobutenylsulfonium perchlorate (**2b**) were prepared by the reaction of corresponding methyl *trans*-vinyl sulfides with methyl iodide in the presence of silver perchlorate. Trimethylsilyl enol ethers of acetophenone, *p*-chloroacetophenone, propiophenone, and diethyl ketone were prepared from the corresponding ketones and trimethylsilyl chloride according to the established method.[7]

Reaction of Vinylsulfonium Salts with Lithium Enolates. General Procedure A. To a solution of 12 mmol of methyllithium in 30 mL of dry THF was added an equimolar amount of trimethylsilyl enol ether of ketone with stirring under cooling. After 1 h, 10 mmol of vinylsulfonium salt in 30 mL of dry DMF was added dropwise, and allowed to stand at room temperature for 12–20 h. The reaction mixture was treated with 20 mL of water, extracted with chloroform, dried over sodium sulfate, and distilled in vacuo. This procedure was applied to the reactions of lithium enolates **1a, 1b, 4a,** and **4c.**

General Procedure B. To a solution of 12 mmol of lithium diisopropylamide in 30 mL of dry THF was added an equimolar amount of ketone with stirring at −78 °C. After 1 h, 10 mmol of vinylsulfonium salt in 30 mL of dry DMF was added dropwise. The reaction mixture was warmed to room temperature and allowed to stand for 15 h. The following workup method was similar to the procedure A. This procedure was applied to the reactions of lithium enolate **4b.**

***trans*-1-Benzoyl-2-phenylcyclopropane** (3a): mp 48.5–51.5 °C (lit.[5a] mp 45.5–50 °C); IR (Nujol) 1650 cm^{-1}; mass spectrum (70 eV) *m/e* 222 (M^+); NMR ($CDCl_3$) δ 1.41–1.64 (m, 1), 1.76–2.02 (m, 1), 2.56–3.00 (m, 2), 7.00–7.60 (m, 8, aromatic), 7.84–8.04 (m, 2, aromatic).

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.36; H, 6.09.

***trans*-1-Benzoyl-2-isopropylcyclopropane (3b):** bp 122–123 °C (10 mm); IR (neat) 1650 cm^{-1}; mass spectrum (70 eV) *m/e* 188 (M^+); NMR ($CDCl_3$) δ 1.02 (d, 6, 2 CH_3, J = 6.1 Hz), 1.08–1.18 (m, 1), 1.36–1.56 (m, 2), 1.80 (m, 1), 2.36–2.60 (m, 1), 7.16–7.60 (m, 3, aromatic), 7.88–8.08 (m, 2, aromatic).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.96; H, 8.81.

***trans*-1-*p*-Chlorobenzoyl-2-phenylcyclopropane (3c):** bp 142–144 °C (1.5 mm); IR (neat) 1660 cm^{-1}; mass spectrum (70 eV)

Table I. Synthesis of Acylcyclopropanes from Vinylsulfonium Salts and Lithium Enolates

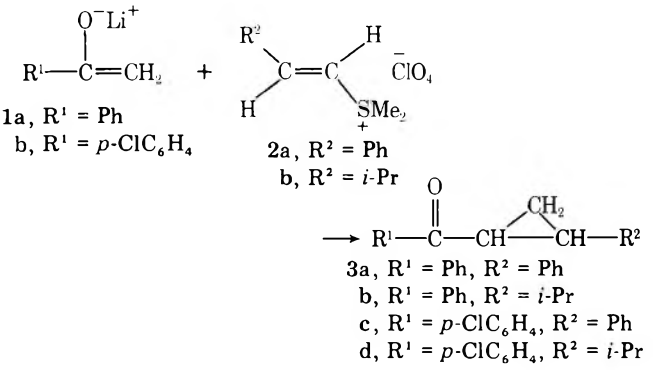
Enolate	Registry no.	Sulfonium salts	Registry no.	Reaction time, h	Product[a]	Registry no.	Yield, %
1a	35249-09-3	**2a**	38066-22-7	12	**3a**	1145-92-2	70
1a		**2b**	63016-90-0	17	**3b**	63016-91-1	80
1b	63016-88-6	**2a**		17	**3c**	63016-92-2	42
1b		**2b**		20	**3d**	63016-93-3	67

[a] All products were trans; **3a** and **3b** were identified with authentic samples and literature data.[5] The structure of **3c** and **3d** were confirmed by the NMR data, which were similar to those of **3a** and **3b,** respectively.

Table II. Synthesis of Oxiranes from Vinylsulfonium Salts and Lithium Enolates

Enolate	Registry no.	Sulfonium salt	Reaction time, h	Product[a]	Registry no.	Yield, %
4a	57204-88-3	**2a**	12	**5a**	63016-95-5	69
4a		**2b**	19	**5b**	63016-96-6	61
4b	63016-94-4	**2b**	15	**5c**	63016-97-7	37
4c	61501-43-7	**2a**	15	**5d**	63016-98-8	45
4c		**2b**	15	**5e**	63016-99-9	36

[a] Although the products may exist as four diastereoisomeric racemates, all the products gave only one peak on GLC and it was difficult to determine how many diastereomers they include.



1a, R^1 = Ph
b, R^1 = *p*-ClC_6H_4

2a, R^2 = Ph
b, R^2 = *i*-Pr

3a, R^1 = Ph, R^2 = Ph
b, R^1 = Ph, R^2 = *i*-Pr
c, R^1 = *p*-ClC_6H_4, R^2 = Ph
d, R^1 = *p*-ClC_6H_4, R^2 = *i*-Pr

m/e 256 (M^+); NMR ($CDCl_3$) δ 1.40–1.68 (m, 1), 1.72–2.40 (m, 1), 2.56–2.92 (m, 2), 7.04–7.48 (m, 7, aromatic), 7.80–8.00 (m, 2, aromatic).

Anal. Calcd for $C_{16}H_{13}OCl$: C, 74.85; H, 5.07; Cl, 13.84. Found: C, 74.95; H, 5.11; Cl, 13.74.

***trans*-1-*p*-Chlorobenzoyl-2-isopropylcyclopropane (3d):** bp 128–130 °C (2 mm); IR (neat) 1660 cm^{-1}; mass spectrum (70 eV) *m/e* 222 (M^+); NMR ($CDCl_3$) δ 1.03 (d, 6, 2 CH_3, *J* = 6.1 Hz), 0.92–1.20 (m, 1), 1.40–1.56 (m, 2), 1.64–1.88 (m, 1), 2.32–2.52 (m, 1), 7.20–7.58 (m, 2, aromatic), 7.82–8.08 (m, 2, aromatic).

Anal. Calcd for $C_{13}H_{15}OCl$: C, 70.11; H, 6.74; Cl, 15.96. Found: C, 70.28; H, 6.89; Cl, 16.20.

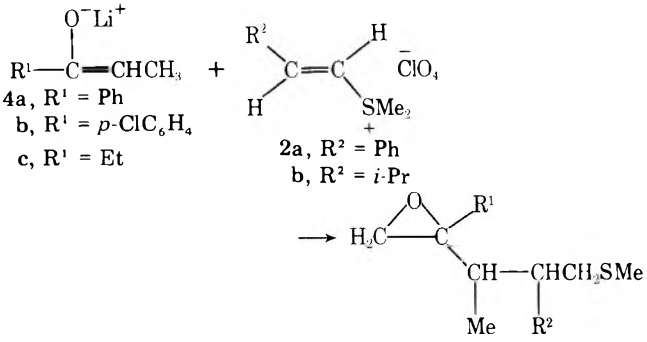
***trans*-1-*p*-Chlorobenzoyl-1-methyl-2-phenylcyclopropane (3e).** NMR analysis confirmed that the phenyl group is trans to the *p*-chlorobenzoyl group:[4a] bp 163–165 °C (1 mm); IR (neat) 1660 cm^{-1}; mass spectrum (70 eV) *m/e* 270 (M^+); NMR ($CDCl_3$) δ 1.16 (s, 3, CH_3), 1.28 (d of d, 1, *J* = 4.5 and 6.8 Hz), 1.95 (d of d, 1, *J* = 4.5 and 9.1 Hz), 2.66 (d of d, 1, *J* = 6.8 and 9.1 Hz), 7.08–7.48 (m, 7, aromatic), 7.60–7.80 (m, 2, aromatic).

Anal. Calcd for $C_{17}H_{15}OCl$: C, 75.42; H, 5.55; Cl, 13.12. Found: C, 75.12; H, 5.63; Cl, 13.43.

2,4-Diphenyl-3-methyl-5-methylthio-1-pentene oxide (5a): bp 155–158 °C (2 mm); IR (neat) 1280, 1250, 1220, 1150, 1070, 1020, 930, 905, 830, 760 cm^{-1}; mass spectrum (70 eV) *m/e* 298 (M^+), 151 ($PhCHCH_2SMe^+$), 147 ($H_2\overline{COC}(Ph)CHMe^+$); NMR ($CDCl_3$) δ 1.12 (d, 3, CH_3, *J* = 7.5 Hz), 1.80 (s, 3, SCH_3), 2.10–2.50 (m, 1), 2.55–2.96 (m, 5), 7.00–7.45 (m, 10, aromatic).

Anal. Calcd for $C_{19}H_{22}OS$: C, 76.48; H, 7.43; S, 10.73. Found: C, 76.65; H, 7.46; S, 10.69.

2-Phenyl-3-methyl-4-isopropyl-5-methyl-thio-1-pentene oxide (5b): bp 133–135 °C (2 mm); IR (neat) 1280, 1250, 1230, 1150, 1100, 1020, 940, 910, 830, 760 cm^{-1}; mass spectrum (70 eV) *m/e* 264 (M^+), 147 ($H_2\overline{COC}(Ph)CHMe^+$), 117 (*i*-$PrCHCH_2SMe^+$); NMR ($CDCl_3$) δ 0.80 (d, 6, 2 CH_3, *J* = 6.1 Hz), 1.04 (d, 3, CH_3, *J* = 7.6 Hz), 1.54 (m, 1, *J* = 6.1 Hz), 1.90 (s, 3, SCH_3), 1.80–2.14 (m, 2), 2.22 (d, 2, CH_2SMe, *J* = 5.8 Hz), 2.78 (d, 1, *J* = 5.3 Hz), 2.97 (d, 1, *J* = 5.3 Hz), 7.20–7.48 (m, 5, aromatic).



4a, R^1 = Ph
b, R^1 = *p*-ClC_6H_4
c, R^1 = Et

2a, R^2 = Ph
b, R^2 = *i*-Pr

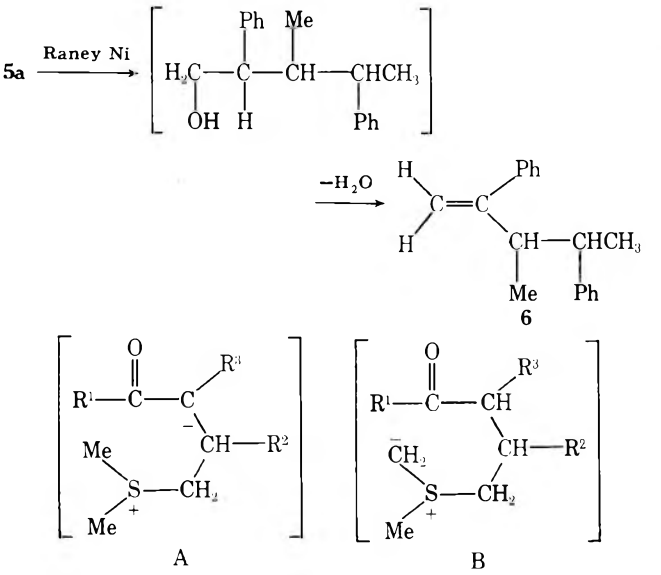
5a, R^1 = Ph, R^2 = Ph
b, R^1 = Ph, R^2 = *i*-Pr
c, R^1 = *p*-ClC_6H_4, R^2 = *i*-Pr
d, R^1 = Et, R^2 = Ph
e, R^1 = Et, R^2 = *i*-Pr

Anal. Calcd for $C_{16}H_{24}OS$: C, 72.69; H, 9.15; S, 12.11. Found: C, 72.29; H, 9.11; S, 11.77.

2-*p*-Chlorophenyl-3-methyl-4-isopropyl-5-methylthio-1-pentene oxide (5c): bp 122–124 °C (1 mm); IR (neat) 1250, 1150, 1090, 1005, 950, 830, 750 cm^{-1}; mass spectrum (70 eV) *m/e* 298 (M^+), 181 ($H_2COC(CHMe)C_6H_4Cl$-*p*$^+$), 116 (*i*-$PrCCH_2SMe^+$); NMR ($CDCl_3$) δ 0.85 (d, 6, 2 CH_3, *J* = 7.6 Hz), 1.02 (d, 3, CH_3, *J* = 6.1 Hz), 1.50–2.08 (m, 3), 1.97 (s, 3, SCH_3) 2.32–2.72 (m, 3, CH_2SMe and HHCOC), 3.68 (d, 1, HHCOC, *J* = 6.0 Hz), 7.05–7.50 (m, 4, aromatic).

Anal. Calcd for $C_{16}H_{23}OSCl$: C, 64.32; H, 7.71 Found: C, 64.05; H, 7.81.

2-Ethyl-3-methyl-4-phenyl-5-methylthio-1-pentene oxide (5d): bp 147–150 °C (4 mm); IR (neat) 1280, 1150, 1110, 1070, 910, 830, 760 cm^{-1}; mass spectrum (70 eV) *m/e* 250 (M^+), 151 ($PhCHCH_2SMe^+$); NMR ($CDCl_3$) δ 0.78 (t, 3, CH_3, *J* = 7.6 Hz), 0.98 (d, 3, CH_3, *J* = 7.3 Hz), 1.22 (m, 1), 1.58 (q, 2, CH_2CH_3, *J* = 7.6 Hz), 1.92 (s, 3, SCH_3), 2.22 (m, 1), 2.48 (s, 2), 2.84 (s, 2), 7.02–7.44 (m, 5, aromatic).



6

A B

Anal. Calcd for $C_{15}H_{22}OS$: C, 71.97; H, 8.86; S, 12.78. Found: C, 71.75; H, 9.13; S, 12.43.

2-Ethyl-3-methyl-4-isopropyl-5-methylthio-1-pentene oxide (5e): bp 133–135 °C (15 mm); IR (neat) 1280, 1240, 1190, 1090, 1030, 950, 815, 750 cm^{-1}; mass spectrum (70 eV) *m/e* 216 (M^+), 99 ($H_2COC(Et)CHMe^+$); NMR ($CDCl_3$) δ 0.82–1.20 (m, 12, 4 CH_3), 1.34–1.96 (m, 5), 2.08 (s, 3, SCH_3), 2.42 (d, 2, CH_2SMe, *J* = 5.3 Hz), 2.56 (d, 1, *J* = 4.5 Hz), 2.62 (d, 1, *J* = 4.5 Hz).

Anal. Calcd for $C_{12}H_{24}OS$: C, 66.63, H, 11.18; S, 14.79. Found: C, 66.78; H, 11.35; S, 14.70.

2,4-Diphenyl-3-methyl-1-pentene (6). The suspension of 1.5 g of **5a** and Raney Ni in 30 mL of EtOH was refluxed for 11 h and Raney Ni was filtrated off. After removal of solvent, the residue was chromatographed on alumina (benzene–hexane, 1:1) to give 0.8 g of **6:** bp 60–62 °C (1.5 mm); IR (neat) 1615, 900 cm^{-1}; mass spectrum (70 eV) *m/e* 236 (M^+); NMR ($CDCl_3$) δ 1.04 (d, 3, CH_3, *J* = 6.1 Hz), 1.11 (d, 3, CH_3, *J* = 6.1 Hz), 2.68–3.16 (m, 2), 5.08 (d, 1, *J* = 15.2 Hz), 5.26 (d, 1, *J* = 15.2 Hz), 7.04–7.48 (m, 10, aromatic).

Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.07; H, 8.40.

Registry No.—3e, 63017-00-5; **6,** 63017-01-6; *trans*-1-phenyl-2-methylthioethane, 15436-06-3; *trans*-1-methylthio-3-methylbut-1-ene, 25650-52-6; methyllithium, 917-54-4; 1-trimethylsilyloxy-1-phenylethene, 13735-81-4; 1-trimethylsilyloxy-1-*p*-chlorophenylethene, 58518-76-6; 1-trimethylsilyloxy-1-phenylpropene, 37471-46-8; 3-trimethylsilyloxy-pent-α-ene, 17510-47-3; lithium diisopropylamide, 4111-54-0; 4′-chloropropiophenone, 6285-05-8; methyl iodide, 74-88-4.

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Micellar-Catalyzed Reaction of Hydroxamic Acids

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Micellar catalysis has attracted considerable interest[1-4] with regard to fundamental studies of catalysis and mechanism and for its relationship to enzymatic processes. The hydrolysis of amide-like substances is of interest because of their relationship to peptides. There seems to be only one report[5] of micellar catalysis of amide hydrolysis and that is only a very small catalysis in the base-catalyzed hydrolysis of *N*-methyl-*p*-nitroacetanilide by cationic micelles; the corresponding *p*-H and *p*-methoxy anilide reaction rates were slightly decreased by the surfactant.

Considerable modification of the leaving group in the hydrolysis reaction results from substitution of a hydroxamic acid for an amide. The electronegative hydroxyl in place of hydrogen will result in a better leaving group, i.e., the expelled species is a weaker base. Such substitution might lead to a significant change in reactivity in a micellar system. The data reported here demonstrate that respectable anionic micellar catalysis for the acid-catalyzed hydrolysis of octanohydroxamic acid does occur. (Mechanistic studies of the acidic hydrolysis of hydroxamic acids have been reported.[6]) The kinetic measurements are summarized in Table I. Examination of the effect of hydrochloric acid concentration[7] and of the temperature and sodium chloride concentration[8] on the critical micelle concentration (cmc) of sodium dodecyl sulfate suggests a cmc of 10^{-3} M for the conditions listed in Table I. Rate increases should occur near and above, but not below, the cmc for micellar catalysis. This is shown in Table I for sodium dodecyl sulfate. In addition, rate data for reaction in the presence of the simple salts sodium chloride and sodium *p*-toluenesulfonate (Table I) show that very little rate effect can be attributed to simple salt effects.

A standard kinetic scheme[1] for micellar catalysis is shown in Scheme I, where M and S are micelle and substrate, re-

Scheme I

$$\begin{array}{ccc} \mathrm{M} + \mathrm{S} & \overset{K}{\rightleftharpoons} & \mathrm{MS} \\ \downarrow k_o & & \downarrow k_m \\ \text{products} & & \text{products} \end{array}$$

spectively, and k_o and k_m are the rate constants for product formation outside and within the micelle, respectively. This model leads to the relationship[1]

$$\frac{1}{k_0 - k_1} = \frac{1}{k_0 - k_m} + \left(\frac{1}{k_0 - k_m}\right)\left(\frac{N}{K(C_D - \mathrm{cmc})}\right)$$

in which k_1 is the observed pseudo-rate constant, K is an equilibrium constant, N is the micellar aggregation number, and C_D is the total surfactant concentration. A graph of the left side of this equation vs. $1/(C_D - \mathrm{cmc})$ in which the cmc is taken as 10^{-3} M and C_D is in the range 0.01–0.06 M is a good linear plot within experimental error. (The standard deviation of the slope is 1.8% of the slope, correlation coefficient 0.9998.) Evaluation of the slope and intercept yields $k_m = 44.8 \times 10^{-5}$ s^{-1} and $K/N = 119$. The catalytic ratio k_m/k_o is 9.74.

Table II shows the effect of sodium dodecyl sulfate on the rate of acidic hydrolysis of phenylacetohydroxamic acid. The catalytic effect is similar, although considerably reduced in magnitude, under comparable conditions to that observed with octanohydroxamic acid (Table I). This indicates, as would be anticipated,[1] that micellar effects vary as a function of substrate structure.

The hydrolysis mechanism in the micellar environment might be expected to be analogous to that[6] in the absence of micelles with the micelles performing either or both of two functions.[1] The first function is an orientation effect in which the micelle attracts the neutral substrate and a reagent, such as H_3O^+, of charge opposite to the charge of the micelle. The other mode of action is micellar stabilization of a transition state of charge opposite to that of the micelle relative to its stabilization of the reagent, in turn relative to stabilization by water, leading to rate enhancement.

Table II. Kinetic Data for Hydrolysis of $PhCH_2CONHOH$ in 0.314 N HCl at 55.0 °C with SDS[a]

SDS, M[b]	$10^5 k$[c]	SDS, M[b]	$10^5 k$[c]
0	4.89	0.04	11.1
10^{-4}	5.28	0.16	19.4
10^{-3}	6.19	0.32	17.6
0.02	6.06		

[a] Sodium dodecyl sulfate. [b] Ambient temperature, three significant figures. [c] Average pseudo-first-order constant, s^{-1}; initial concentration of phenylacetohydroxamic was 5×10^{-4} M.

Experimental Section

Octanohydroxamic acid, mp 77.8–78.3 °C (lit.[9] 78–79 °C), was prepared from methyl octanoate according to the general procedure described before.[6] Phenylacetohydroxamic acid has been described previously.[10] Sodium dodecyl sulfate was purified according to literature[1] procedures. Solutions of sodium dodecyl sulfate and hydrochloric acid were prepared within several hours of use and stored in the cold to prevent hydrolysis of the sodium dodecyl sulfate (the half-life[11] of sodium dodecyl sulfate in 0.1 N HCl, 50 °C, at concentrations above its cmc is 7 days). Mallinckrodt analytical reagent sodium chloride and Eastman sodium *p*-toluenesulfonate (97% minimum of the sulfonate, 1% maximum of H_2O) were used as received.

The kinetic measurements were made by the spectrophotometric method reported previously[6] except that sufficient acidity had to be maintained in the ferric chloride solutions to prevent precipitation in the presence of sodium dodecyl sulfate. Beer's law was shown to hold for the ferric ion–hydroxamate complex under these conditions.

Acknowledgment. The support of the Western Michigan University Faculty Research Fund is greatly appreciated.

Registry No.—Sodium dodecyl sulfate, 151-21-3; sodium *p*-toluenesulfonate, 657-84-1; octanohydroxamic acid, 7377-03-9; phenylacetohydroxamic acid, 5330-97-2.

Table I. Kinetic Data for Hydrolysis of $CH_3(CH_2)_6CONHOH$ in 0.203 N HCl at 50.7 °C with Various Salts

Salt	None	SDS[a]	SDS	SDS	SDS	SDS	SDS
Concn[b]		10^{-4}	10^{-3}	0.01	0.02	0.04	0.06
$10^5 k$[c]	4.60	4.68	6.96	25.2	32.3	37.7	40.1
Salt		NaCl		NaCl	NaTs[d]		NaTs
Concn[b]		0.01		0.06	0.01		0.06
$10^5 k$[c]		4.85		4.86	4.87		5.00

[a] Sodium dodecyl sulfate. [b] Molarity, ambient temperature, three significant figures. [c] Average pseudo-first-order constant, s^{-1}; initial concentration of octanohydroxamic acid was 5×10^{-4} M. [d] Sodium *p*-toluenesulfonate.

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Deamination of 2-Phenyl-2-(2-methoxyphenyl)-ethylamine

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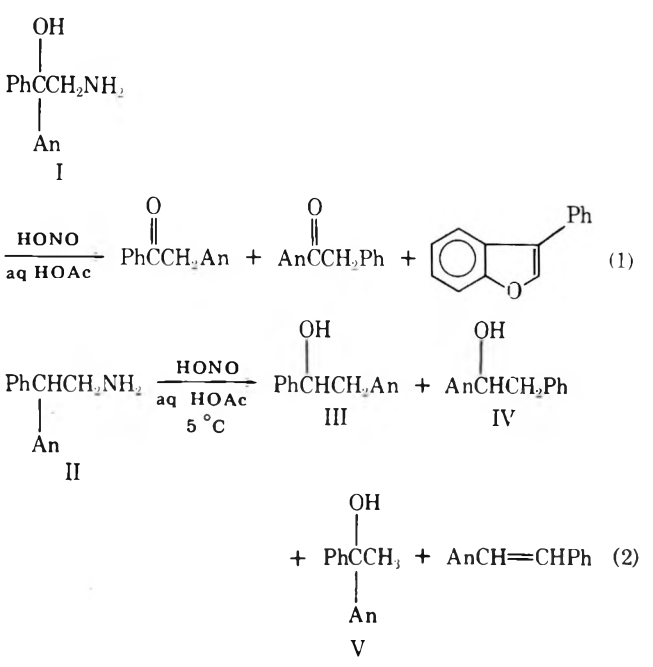
Previously we reported[1] the results of deamination of amino alcohol I, which demonstrated the first example of *o*-MeO-5 participation[2] in such rearrangements (eq 1). We now report the deamination of the related amine II (eq 2).



Ph = C_6H_5; An = *o*-$C_6H_4OCH_3$

Treatment of the hydrochloride of II with sodium nitrite in aqueous acetic acid at 5 °C produced (after treatment of the reaction mixture with lithium aluminum hydride to cleave any acetates) alcohols III,[3,4] IV,[3,5,6] a minor amount (<5%) of V,[7] and an alkene fraction consisting of *o*-methoxystilbenes.[5,8,9] There is no indication of *o*-MeO-5 participation in the present case, in direct contrast to the deamination of I.

Typical migratory aptitudes of aryl groups in such reactions of diarylethylamines (Ph = 1.00) are *p*-tolyl, 1.18,[10] and *p*-anisyl, 1.44.[11] Such results have been interpreted in terms of ground-state conformational control in both amino alcohol and amine cases.[12,13] The migratory ability of the *o*-anisyl group in various rearrangements has been shown to be <1.[1,14,15,16] In the present case, the migratory ratio for the *o*-anisyl group (III/IV by ^{1}H NMR analysis) is 2.67. This appears to be substantially the highest migratory aptitude observed for any aryl group in reactions of this kind, for reasons about which we can only speculate at this time. Furthermore, we find no evidence of *o*-MeO-5 participation in the present case. We are attempting experiments designed to provide information about ground-state conformations in diarylethylamines and diarylethyl amino alcohols and thus yield some insight into the reasons for the observed migration tendencies.

Experimental Section

2-Methoxybenzophenone. Addition of phenylmagnesium bromide to o-methoxybenzaldehyde (Aldrich Chemical Co., Inc.), followed by oxidation of the crude product with Jones reagent in benzene (48 h reflux), provided 2-methoxybenzophenone: mp 36–37 °C (lit.[17] mp 39 °C).

2-Phenyl-2-(2-methoxyphenyl)ethanal (VI). 1-Phenyl-1-(2-methoxyphenyl)ethene[18] was prepared by treatment of 2-methoxybenzophenone with methylmagnesium iodide in tetrahydrofuran, followed by dehydration of the alcohol product (V[7]) with H_2SO_4 (pH 1) during workup: yield 89%; bp 120–125 °C (2 Torr). H_2O_2 (30%, 21 mL) was added dropwise to formic acid (97%, 100 mL) and the solution was allowed to stand for 1 h. Then a solution of the alkene[18] (31.0 g) in benzene (100 mL) was added dropwise and the mixture was stirred overnight. The layers were separated and the benzene layer was extracted with water, saturated $NaHCO_3$, and water, and dried. The benzene was removed at reduced pressure and the aldehyde was distilled: yield 23.7 g (71%); bp 135 °C (~1 Torr) [lit.[19] bp 198–200 °C (16 Torr)]; IR (neat) 2715, 1723 cm^{-1}; NMR ($CDCl_3$) δ 3.62 (3 H, s, OCH_3), 5.05 (1 H, d, J = 3 Hz, CH), 7.19 (9 H, m, ArH), 9.83 (1 H, d, J = 3 Hz, CHO).

2-Phenyl-2-(2-methoxyphenyl)ethanal Oxime (VII). A mixture of aldehyde VI (8 g), hydroxylamine hydrochloride (8 g), sodium hydroxide (8 g), water (160 mL), and ethanol (150 mL) was heated at reflux for 1 h. Standard workup yielded 3.4 g of the oxime: mp 112–114 °C; IR ($CHCl_3$) 3200, 1245, 1039 cm^{-1}; NMR ($CDCl_3$) δ 3.69 (3 H, s, OCH_3), 5.25 (1 H, d, J = 8 Hz, CH), 7.2 (9 H, m, ArH), 7.83 (1 H, d, J = 8 Hz, CHN), 8.70 (1 H, s, OH).

2-Phenyl-2-(2-methoxyphenyl)ethylamine Hydrochloride (II HCl). Oxime VII was reduced with lithium aluminum hydride in refluxing diethyl ether for 24 h. Saturated Na_2SO_4 was added dropwise to quench the reaction. The ether layer was dried ($MgSO_4$) and then saturated with anhydrous HCl. The crystals of II HCl which formed were recrystallized from ethanol–acetone: mp 215–217 °C; IR (KBr) 3400, 1245, 1030, 908 cm^{-1}; NMR (free base, $CDCl_3$) δ 3.25 (2 H, d, J = 8 Hz, CH_2), 3.74 (3 H, s, OCH_3), ~3.74 (2 H, br s, NH_2), 4.50 (1 H, t, J = 8 Hz. CH), 7.25 (9 H, m, ArH).

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.78; N, 5.31; Cl, 13.44. Found: C, 68.60; H, 7.04; N, 4.93; Cl, 13.44.

Deamination Reactions. In a typical run 40 mg of amine hydrochloride II HCl and 40 mg of $NaNO_2$ were dissolved in 10 mL of 50% acetic acid and allowed to stand for 4 h at 5 °C. Then 1 mL of saturated NH_2SO_3H was added, followed by 15 mL of 6 N NaOH. The reaction mixture was extracted with CH_2Cl_2 (three 10-mL portions) and the combined extracts were dried ($MgSO_4$). Solvent was removed at reduced pressure and 30 mL of anhydrous ether was added. Then ~50 mg of lithium aluminum hydride was added to cleave any acetates. The reaction was quenched with saturated Na_2SO_4, and the aqueous layer was extracted with CH_2Cl_2 (three 10-mL portions). The combined organic layers were dried and solvent was removed at reduced pressure to leave an oil, which was diluted with 1 mL of diethyl ether and chromatographed on thick-layer silica gel plates with acetone–benzene (1:99). The alcohol fraction was removed and analyzed by ^{1}H NMR using the methoxyl singlets (solvent $CDCl_3$, δ 3.70 for III, 3.65 for IV, 3.42 for V) at expanded sweep width for quantification. Duplicate runs gave the same results.

A similar run with 328 mg of II HCl (1.24 mmol) and 390 mg of $NaNO_2$ but without the $LiAlH_4$ treatment allowed isolation of 113 mg (0.497 mmol) of mixed alcohols, 46.2 mg (0.143 mmol) of mixed acetates, and 61.4 mg (0.290 mmol) of an alkene fraction which appeared by ^{1}H NMR to be a mixture of *o*-methoxystilbenes;[5,8,9] net recovery, 75%.

The alkene fraction isolated above was subjected to the deamination conditions and shown to be unchanged; the alcohols were also shown to be stable to the reaction conditions, as judged by TLC and ^{1}H NMR.

Acknowledgment. We wish to thank Dr. Edward Rosenberg for helpful discussions and suggestions.

Registry No.—II, 63059-14-3; II HCl, 51431-51-7; III, 30314-63-7; IV, 22817-10-3; V, 32250-84-3; VI, 63059-15-4; VII, 63059-16-5; 1-phenyl-1-(2-methoxyphenyl)ethene, 24892-80-6; 2-methoxybenzophenone, 2553-04-0.

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Mass Spectrometry of Alkenyl and Aryl Thiolacetates

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The mass spectra of alkenyl and aryl thiol acetates were studied in connection with our investigations of the photochemistry of these compounds.[1,2,3] The three important fragmentation mechanisms involve cleavage of the sulfur carbonyl carbon bond as shown by paths a, b, and c in Schemes I and II. Homolysis of this bond is also the primary photochemical reaction.

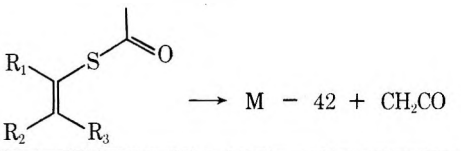
Path a, which involves the simultaneous dissociation of the sulfur–carbonyl carbon bond and the transfer to the sulfur fragment of the α-hydrogen atom, may occur by a four-centered mechanism to form ketene and the vinyl thiol radical cations or by a six-centered mechanism to form ketene and thioaldehyde radical cations (Scheme III).

For alkyl vinyl thioethers, the six-centered hydrogen-atom transfer is highly favored over the four-centered mechanism as ion cyclotron resonance spectroscopy has been used to show that deuterium is transferred from the β carbon of the alkyl side chain to the sulfur fragment to form thioaldehyde radical cations in preference to vinyl thiol radical cations by a 9:1 ratio.[4]

In the mass spectra of four saturated alkyl thioacetates, namely methyl, ethyl, propyl, and isobutyl thiolacetate, we observed no M − 42 ions. In contrast, the seven alkenyl thiolacetates which we studied formed the M − 42 ion in relative abundances ranging from 5 to 100% as shown in Table I.

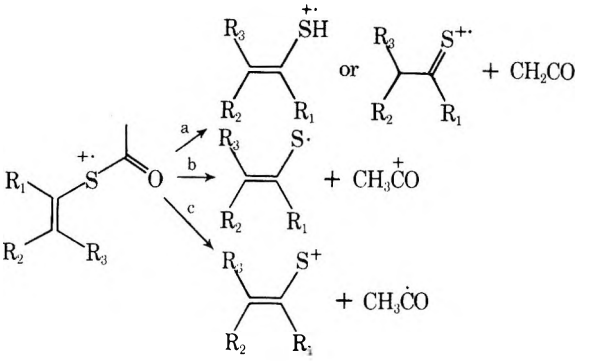
In saturated esters the six-centered hydrogen-atom transfer is structurally precluded, but the four-centered mechanism is possible. Thus, the absence of the M − 42 ions for the saturated alkyl thiolacetates coupled with the ICR work on alkyl vinyl thiol ethers indicates the six-centered mechanism is probably responsible for the formation of the M − 42 ions from the alkenyl thiolacetates.

Table I

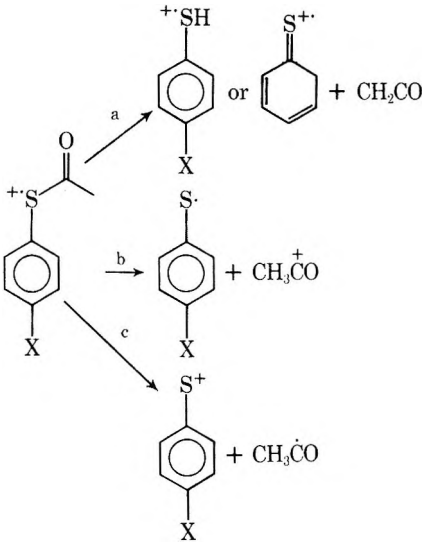


R_1	R_2	R_3	Registry no.	Rel abundance M − 42, %
H	H	H	10340-63-3	5
H	CH_3	CH_3	63059-17-6	70
H	$(CH_3)_3C$	H	63059-18-7	17
H	C_6H_5	H	52214-53-6	78
H	CH_3	H	63059-19-8	10
	$(CH_2)_3$	H	16214-69-0	38
	$(CH_2)_4$	H	15783-82-0	100

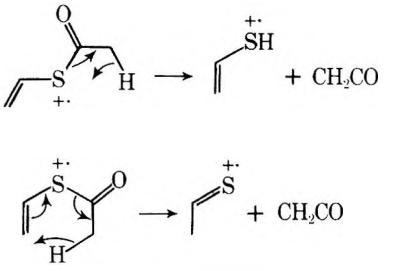
Scheme I



Scheme II



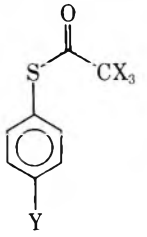
Scheme III



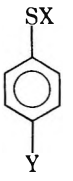
The two cyclic enethiolacetates, cyclopentenyl thiolacetate (1) and cyclohexenyl thiolacetate (2), display relative abundances of the M − 42 ion of 38 and 100%, respectively. If the transition state for the formation of these M − 42 ions were four centered, then the relative abundances of the ions should

be independent of ring size. The observed difference in the relative abundances of the M − 42 ions may reflect the fact that in the transition state for the six-centered mechanism the 5–6 ring junction for **1** is less stable than the 6–6 ring junction for **2**.

Phenyl thiolacetate (**3**) and the 4-methoxy, 4-dimethylamino, 4-chloro, and 4-methyl analogues all lost ketene from the parent ion to form M − 42 ions. Phenyl thiolacetate-d_3 (**4**) and 4-toluene thiolacetate-d_3 (**5**) lose ketene-d_2 from the parent ions to form ions at *m/e* 111 and 125, respectively. As discussed below, these spectra show that deuterium has been transferred from the acetyl group to the benzene ring carbons either by the six-centered mechanism directly or by the thiol intermediate formed by the four-centered mechanism.



3, X = Y = H
4, X = D; Y = H
5, X = D; Y = CH_3
9, X = H; Y = CH_3



6, X = Y = H
7, X = D; Y = H
8, X = H; Y = CH_3

Thiophenol **6** and **3** form the same ions below *m/e* 110, although ions derived directly from *m/e* 110 are more intense for **6** than for **3**.

The cyclopentadiene radical cation appears at *m/e* 66 in the spectra of **6** and **3** and at *m/e* 67 in the spectra of the thiophenol-*s*-d_1 (**7**) and **4**. 4-Toluene thiol (**8**) and 4-toluene thiolacetate (**9**) form analogous, but less intense, ions at *m/e* 80, while **5** forms the deuterated ion at *m/e* 81. These ions arise from loss of CS from the 2,4-cyclohexadienethione radical cations which would be formed in the six-centered fragmentation of the aryl thiolacetates.

The phenyl cation is partially deuterated in the spectra of **7** and **4** and appears at *m/e* 77 and 78. The analogous ion at *m/e* 91 is the most intense ion in the spectrum of **8** and is very intense for **9**. **5** shows large peaks at *m/e* 91 and 92.

Deuterated and nondeuterated thiophene radical cations appear at *m/e* 85/84 in a ratio of 2:1 for both **7** and **4**. This scrambling of deuterium in **7** from sulfur onto the benzene ring before the loss of acetylene[5] and also before other fragmentations[6,7] represents complete randomization and is evidence for the interconversion of the thiophenol and 2,4-cyclohexadiene thione ions. Therefore, interpretation of the loss of ketene for the aryl thiolacetates in terms of whether a four- or six-centered mechanism is operative is precluded.

Photolysis of **3** produces **6**, which was thought to arise from the secondary photolysis of diphenyl disulfide.[8,9] However, **6** could be formed either by abstraction of a hydrogen atom from the acetyl group by the thiyl radical produced from photocleavage of the *S*-acyl bond or by transfer of a hydrogen atom from the acetyl group to the ortho carbon atom prior to photocleavage of the *S*-acyl bond.

In order to test these possibilities of hydrogen-atom transfer from the acetyl group, **4** and **5** were irradiated in cyclohexane for 3 h at 254 nm. Products were isolated by gas chromatography of the photolysis mixture after removal of solvent. The photolysis of **4** produced deuterium-free diphenyl disulfide and deuterium-free **6**. The deuterium label of **7** is not lost under the gas chromatographic isolation procedure employed. Likewise, **5** photolyzed to deuterium-free 4,4′-ditolyl disulfide. Thus, **6** is not formed by hydrogen-atom transfer from the acetyl group.

In summary, the ICR evidence for the transfer of the β-hydrogen atom of alkyl vinyl sulfides, the lack of M − 42 ions in the spectra of saturated alkyl thiolacetates, and the difference in intensity of M − 42 ions for **1** and **2** indicate that hydrogen-atom transfer from the acetyl group to the sulfur fragment occurs by a six-centered mechanism for alkenyl thiolacetates. However, the interconversion between cyclohexadienethione and thiophenol radical cations precludes distinguishing between four- and six-centered mechanism for arene thiolacetates. The analogy between the photochemistry and mass spectra of arene thiolacetates is limited to simple cleavage of the *S*-acyl bond and does not extend to the transfer of hydrogen from the acetyl group to the sulfur entity.

Experimental Section

Mass spectra were obtained on a Hitachi-Perkin Elmer RMU-6 spectrometer at 70 eV. Gas chromatography was performed on a Hewlett-Packard Model 700 gas chromatograph equipped with a thermal conductivity detector and a 20 ft × 1/8 in. OV-225 column. Thiol esters were prepared according to literature procedures as listed: methyl thiolacetate,[10] ethyl thiolacetate,[11] propyl thiolacetate,[11] isobutyl thiolacetate,[11] vinyl thiolacetate,[12] isobutenyl thiolacetate,[12] β-*tert*-butyl vinyl thiolacetate,[13] cyclopentenyl thiolacetate[16] (**1**), cyclohexenyl thiolacetate[16] (**2**), phenyl thiolacetate[17] (**3**), 4-methoxyphenyl thiolacetate,[17] 4-dimethylaminophenyl thiolacetate,[18] 4-chlorophenyl thiolacetate,[17] 4-toluene thiolacetate[17] (**9**). Structure assignments were confirmed by NMR and IR spectra. Phenyl thiolacetate-d_3 (**4**) and 4-toluene thiolacetate-d_3 (**5**) were prepared from the thiol and acetic-d_3 acid using dicyclohexylcarbodiimide.[11] Photochemistry of the deuterated esters was conducted exactly as previously reported.[2]

Supplementary Material Available: A table of mass spectra data for compounds which are not reported in the literature (1 page). Ordering information is given on any current masthead page.

Registry No.—$CH_3CH_2SCOCH_3$, 625-60-5; $(CH_3)_2CHCH_2SCHOCH_3$, 2432-37-3; 4-Cl-$C_6H_4SCOCH_3$, 21021-60-3; 4-$CH_3OC_6H_4SCOCH_3$, 60787-31-7; $C_6H_5SCOCD_3$, 60860-51-7; 4-$CH_3C_6H_4SCOCD_3$, 60860-52-8.

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Synthesis of Aryl Alkynes. 1. 2-Ethyl-4-methoxyphenylacetylene

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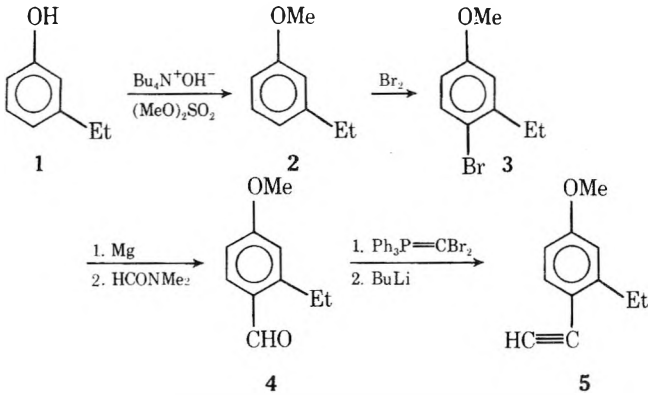
While many aryl alkenes and alkanes have been synthesized for study as potential synthetic estrogens,[2] no systematic

Scheme I



endeavor to synthesize phenylacetylene derivatives for such application has been documented. The synthesis of 2-ethyl-4-methoxyphenylacetylene (5) is reported. It is a precursor for a series of alkynes to be synthesized for study of structure–estrogenic activity relationships in such compounds.

Synthetic Approach

Scheme I summarizes the synthesis of the title compound 5. Two convenient starting materials, 3-ethylphenol (1) and 3-methoxyacetophenone, are readily available. Phase-transfer-catalyzed methylation of 1 provided quantitatively 3-methoxyethylbenzene (2). Similar high yields of 2 are obtained by Clemmenson reduction of the acetophenone. Attempts to obtain 2 from 3-methoxybenzaldehyde via Wittig reaction with triphenylmethylenephosphorane and subsequent hydrogenation of 3-methoxystyrene are unsatisfactory.

Two methods for carbonylation were studied. Bromination of 2 yielded exclusively 4-bromo-3-ethylanisole (3), underscoring the applicability of partial rate factors to this electrophilic aromatic substitution.[3] (The position of bromination was confirmed by conversion to the known 2-ethyl-4-methoxybenzoic acid.[4]) Grignard reaction with *N*,*N*-dimethylformamide yields 2-ethyl-4-methoxybenzaldehyde (4). Friedel–Crafts reaction (Cl_2CHOCH_3 and $TiCl_4$)[5] of 2 is unsatisfactory, as an isomeric mixture of aldehydes results.

Ethinylation, the final conversion, was first attempted using the method of Oliver and Walton.[6] In this procedure an arylcopper reagent couples with iodoethinyl(trimethyl)silane to give an arylethinyl(trimethyl)silane, which may be quantitatively desilylated by treatment with alkali. In our hands this conversion failed, and 3-ethyl-4-iodoanisole was isolated. Steric factors often hinder organocopper reactions,[7] and in this case the *o*-ethyl group probably facilitated exchange over ethinylation. Ethinylation was achieved using the two-step method of Corey and Fuchs (Wittig reaction followed by alkyllithium-promoted rearrangement).[8]

Experimental Section

All reagents were suitably purified before use. Anhydrous $MgSO_4$ served as the drying agent. Boiling points are uncorrected. Infrared spectra of thin films were recorded on the Beckman IR-10 and calibrated using the 6.24-μm band of polystyrene. NMR spectra of dilute solutions in Silanor-C were recorded on the Varian T60 spectrometer. Standard spectral notations apply. X-ray data were obtained using the Picker x-ray fluorescence spectrometer.

3-Ethylanisole (2). To a slurry of NaOH (20 g, 0.5 mol) and tetrabutylammonium hydroxide (10 mol %) in 100 mL of H_2O was added dropwise a solution of 3-ethylphenol (1, Aldrich Chemical Co., 30.5 g, 0.25 mol) in 50 mL of H_2O. To the resulting solution was added dropwise 30 mL of dimethyl sulfate (0.3 mol). Rapid, exothermic reaction ensued. After stirring 2 h, separation of the organic layer, extraction of the aqueous layer with CH_2Cl_2, drying and concentration, distillation afforded 31.2 g (95%) of 2 as a colorless oil: bp 70–71 °C (9 Torr); lit.[9] bp 74 °C (10 Torr); IR (film) 1600, 1480, 1260, 1150, 1030, 865, 770, and 680 cm^{-1}; NMR ($CDCl_3$) δ 6.9 (m, 4, phenyl), 3.8 (s, 3, OCH_3), 2.55 (quartet, 2, J = 8 Hz, $-CH_2CH_3$), 1.2 (t, 3, J = 8 Hz, $-CH_2CH_3$).

2-Ethyl-4-methoxybromobenzene (3). A slurry of 2 (6.8 g, 0.05 mol) and 0.1 g of iron filings in 50 mL of CCl_4 was stirred and cooled in an ice–salt bath as a solution of bromine (2.9 mL, 0.055 mol) in 20 mL of CCl_4 was added dropwise over 3 h. After stirring 3 h, the mixture was poured into water and worked up. Drying and concentration gave 9.6 g (90%) of 3 as a colorless oil: bp 79–80 °C (0.5 Torr); IR (film) 1590, 1570, 1470, 1235, 1135, 1005, 860, 840, and 790 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (doubled doublets, 1, J = 1 and 2 Hz, phenyl), 6.7 (m, 2, phenyl), 3.7 (s, 3, OCH_3), 2.75 (quartet, 2, J = 8 Hz, $-CH_2CH_3$), 1.2 (t, 3, J = 8 Hz, $-CH_2CH_3$); x-ray fluorescence K α-Br 29.96°, K β-Br 26.79°.

Anal. Calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.16; Br, 37.15. Found: C, 50.49; H, 5.25; Br, 37.09.

2-Ethyl-4-methoxybenzaldehyde (4). To magnesium turnings (1.6 g, 0.065 g-atom) in 30 mL of anhydrous ether was added a solution of 4.3 g of ethyl bromide (0.04 mol) and 4.3 g of 3 (0.02 mol) in 50 mL of anhydrous ether. After refluxing for 1 h an ethereal solution of 4.3 mL (0.06 mol) of *N*,*N*-dimethylformamide was added with external cooling. After 1 h it was decomposed with aqueous NH_4Cl. After separation the aqueous layer was extracted twice with ether. Combined ethereal extracts were washed and dried. Concentration and distillation gave 3.1 g (94%) of colorless liquid: bp 107–108 °C (2.5 Torr); IR (film) 2720, 1690, 1610, 1240, 900, and 810 cm^{-1}; NMR ($CDCl_3$) δ 10.3 (s, –CHO), 7.7 (d, 1, J = 7 Hz, phenyl), 6.7 (m, 2, phenyl), 3.8 (s, 3, $-OCH_3$), 2.6 (quartet, 2, J = 8 Hz, $-CH_2CH_3$) and 1.1 (t, 3, J = 8 Hz, $-CH_2CH_3$).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.12; H, 7.39.

2-Ethyl-4-methoxyphenylacetylene (5). A mixture of Zn powder (2.62 g, 0.04 g atom), 10.5 g of triphenylphosphine (0.04 mol), 13.3 g of CBr_4 (0.04 mol), and 300 mL of CH_2Cl_2 was stirred under Ar for 24 h. After the dropwise addition of 3.3 g of 4 (0.02 mol) the mixture was stirred an additional 2 h. Addition of 1.2 L of pentane, filtration, and evaporation of solvents gave dibromo-2-(2′-ethyl-4′-methoxyphenyl)ethene. Insoluble material was reworked by additional cycles of CH_2Cl_2 extraction–pentane precipitation to maximize yield of dibromoolefin to 5.5 g (86%). This yellow liquid was used without further purification.

A solution of 5.5 g of dibromoolefin in 60 mL of THF was cooled to −78 °C (dry ice–acetone) and *n*-butyllithium (44 mL, 0.8934 M) was added dropwise. After 1 h at −78 °C, the reaction was warmed to room temperature and poured into 200 mL of water. The alkyne was extracted with pentane. Distillation afforded 2.5 g (80%) of clear colorless liquid: bp 112–113 °C (7.5 Torr); IR (film) 3300, 2100, 1605, 1490, 1235, 1030, and 640 cm^{-1}; NMR ($CDCl_3$) δ 6.8 (m, 3, phenyl), 3.7 (s, 3, OCH_3), 2.95 (s, 1, C≡CH), 2.7 (quartet, 2, J = 8 Hz, $-CH_2CH_3$), 1.2 (t, 3, J = 8 Hz, $-CH_2CH_3$).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.62; H, 7.64.

Registry No.—1, 620-17-7; 2, 10568-38-4; 3, 34881-44-2; 4, 6161-69-9; 5, 62929-98-0; dibromo-2-(2′-ethyl-4′-methoxyphenyl)ethene, 62929-99-1.

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Synthesis of Olefins via Reduction–Decyanation of β,γ-Unsaturated Nitriles

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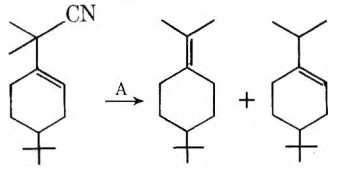
As part of a program aimed at developing methodology for the synthesis of natural products, we are examining dual uses of the cyano function as an activating and leaving group. We

Table I. Variations in Olefin Isomer Ratio with Changing Reaction Conditions

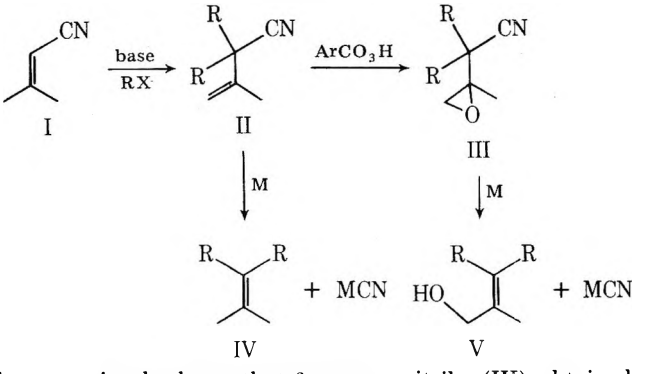


2b 3b 4b

A	3b (rel %)[a]	4b (rel %)[a]	% yield[b]
Na, NH_3, −33 °C	20	80	95
Li, NH_3, −33 °C	20	80	85
Ca, NH_3, −33 °C	20	80	94
Li, NH_3, EtOH, −33 °C	35	65	
Li, NH_3, *t*-BuOH, −33 °C	40	60	
Li, NH_3, *t*-BuOH, −78 °C	30	70	95
Na, NH_3, *t*-BuOH, −33 °C	50	50	99
K, C_6H_6, 80 °C	20	80	99
Na, naphthalene, −78 °C	15	85	
Li, THF, HMPA, 25 °C	20	80	90

[a] Analyzed by gas chromatography. [b] Crude product.

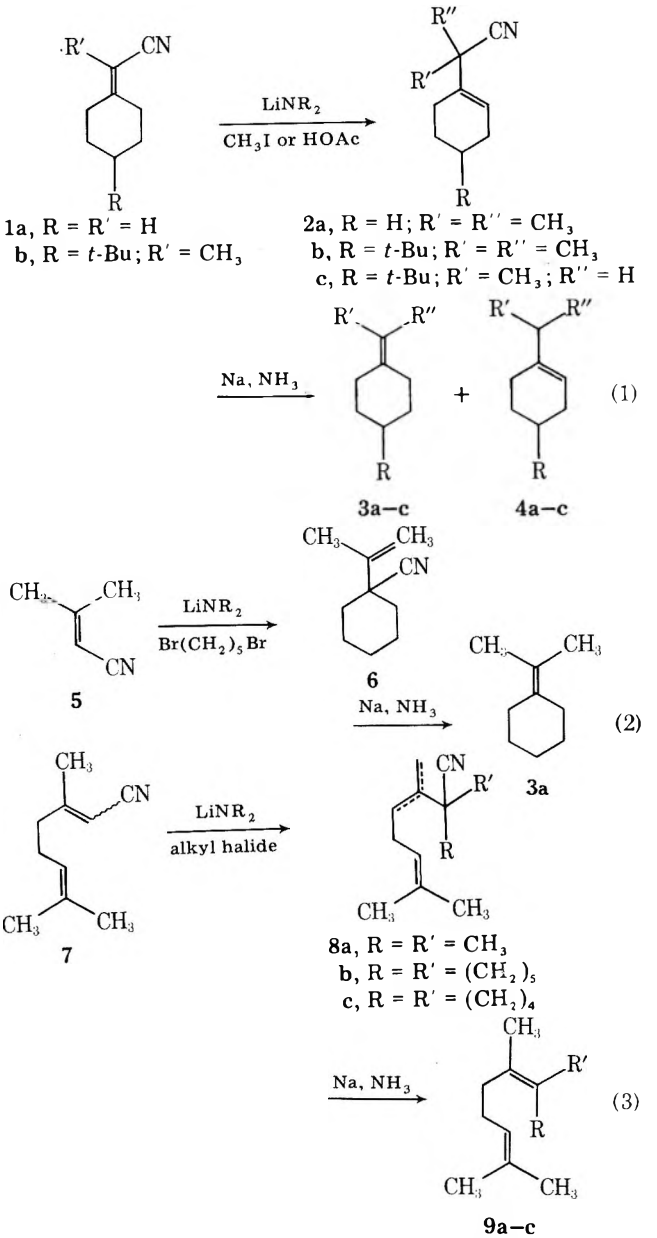
Scheme I



have previously shown that β,γ-epoxy nitriles (III), obtained according to Scheme I, undergo smooth reduction–elimination to allylic alcohols (V) upon treatment with dissolving metals.[1] In this report we describe related work involving the reduction–decyanation of β,γ-unsaturated nitriles (II) to give olefins (IV).

We first explored the synthesis of isopropylidenecyclohexanes **3a** and **3b** from the cyclohexylideneacetonitriles **1a** and **1b** (eq 1). Methylation using lithium diisopropylamide and methyl iodide in THF–HMPA gave the requisite β,γ-unsaturated nitriles **1a** and **2b**.[1] Nitrile **2a** underwent reduction with sodium in ammonia to a 1:2 mixture of the exocyclic and endocyclic olefin isomers **3a** and **4a**.[2] When reduction was carried out in the presence of *tert*-butyl alcohol, a 1:1 mixture of these olefins was obtained. The 4-*tert*-butyl derivative **2b** behaved analogously. Reduction using sodium in ammonia afforded a 1:4 mixture of olefins **3b**[3] and **4b** without added alcohol and a 1:1 mixture in the presence of *tert*-butyl alcohol. Attempts to increase the proportion of isopropylidene isomer **3** by changes in reducing metal, proton source, solvent, and temperature were unpromising. Some representative trials are shown in Table I.

Interestingly, reduction of the monomethylated cyclohexenylacetonitrile **2c** yielded cyclohexene **4c**[4] exclusively. These findings suggested to us that the reduction–decyanation of allylic cyano compounds tends toward thermodynamic control,[5] especially in the absence of an added proton source. Therefore, an alternative approach to isopropylidenecycloalkanes and related olefins starting from isopropenyl-substituted nitriles such as **6** seemed worth pursuing. Here, we would expect the isopropylidene isomer **3a** to be the more stable of the two possible olefin products. In fact, this expectation was fully realized. Alkylation of β,β-dimethylacrylonitrile (**5**)[6] with 1,5-dibromopentane followed by reduction of the resulting nitrile **6** with sodium in ammonia afforded isopropylidenecyclohexane (**3a**) containing 5% of the isopropenyl isomer (eq 2).



1a, R = R′ = H
b, R = *t*-Bu; R′ = CH_3

2a, R = H; R′ = R″ = CH_3
b, R = *t*-Bu; R′ = R″ = CH_3
c, R = *t*-Bu; R′ = CH_3; R″ = H

3a–c 4a–c (1)

5 6 3a (2)

7 8a, R = R′ = CH_3
b, R = R′ = $(CH_2)_5$
c, R = R′ = $(CH_2)_4$

9a–c (3)

The readily available mixture of gerano- and neronitriles (**7**)[7] could be similarly alkylated to the dimethyl- (**8a**), cyclohexyl- (**8b**), and cyclopentyl-substituted (**8c**) unsaturated nitriles (eq 3). These intermediates were obtained as mixtures of double bond isomers judged by NMR analysis to contain principally the *E* isomers. Reduction with sodium in ammonia then yielded the isomerically pure tetrasubstituted olefins **9a, 9b,** and **9c** in high yield.

The foregoing results show that allylic cyano compounds, conveniently prepared by alkylation of conjugated nitriles, serve as useful precursors to olefins. The regiochemistry of the reduction process appears to favor the more highly substituted and/or more stable double bond isomer, although additional studies are needed to establish the controlling factors. Finally, synthetic applications based on the use of α,ω-dihalides as the alkylating agents leading to cycloalkylidene olefins such as **3a, 9b,** and **9c** may find use in connection with bisabolenes[8] and related natural products.

Experimental Section[9]

2-(4-*tert*-Butylcyclohexylidene)propanenitrile (1b). To a

Table II. Unsaturated Nitriles

Nitrile[a]	Registry no.	% yield	NMR, ppm CH_3	NMR, ppm Vinylic H(s)
1b	63089-63-4	97	1.85 (s) 0.85 (s)	
2b	63089-64-5	98	1.45 (s) 0.88 (s)	5.8–6.0
2c	63089-65-6	98	1.26 (d, J = 6 Hz) 0.88 (s)	5.6–5.9
6	63089-66-7	82	1.90 (s)	5.26 (s) 5.00 (m)
8a		98	1.49 (s) 1.62 (s) 1.70 (s)	4.9 5.23 5.05–5.35

[a] Satisfactory analytical data (C, H, N) for all compounds were submitted for review.

Table III. Olefins

Olefin(s)[c]	Registry no.	% yield	NMR CH_3	NMR Vinylic H
4c	15822-49-8	92	0.88 (s) 0.90 (t, J = 8 Hz)	5.3–5.6
3a	5749-72-4	91	1.68 (s)	
4b[a]	63089-67-8	93	0.90 (s) 1.0 (d, J = 14 Hz)	5.3–5.5
9a	63089-68-9	94	1.62 (s)	5.0–5.3
9b	63089-69-0	78[b]	1.65 (s)	4.9–5.3
9c	63089-70-3	88[b]	1.61 (s)	4.9–5.3

[a] Obtained from acid treatment of **3b, 4b** mixture. [b] Overall yield from conjugated nitrile **7.** [c] Satisfactory analytical data for all compounds except **4c** and **3a** were submitted for review.

stirred suspension of 0.83 g (20 mmol) of sodium hydride in 15 mL of 1,2-dimethoxyethane (DME) was added 3.5 mL (20 mmol) of 2-(diethylphosphono)propanenitrile in 5 mL of DME.[10] The mixture was stirred at reflux until cessation of hydrogen evolution, whereupon 1.25 g (9.9 mmol) of 4-*tert*-butylcyclohexanone in 10 mL of DME was added and reflux was continued for 20 h. The cooled mixture was poured into water and the product was isolated by ether extraction and chromatographed on alumina to give 1.58 g (97%) of nitrile **1b,** mp 66–67 °C (Table II).

General Alkylation Procedure. To a solution of lithium diisopropylamide (prepared from 1.25 mL of diisopropylamine in 150 mL of tetrahydrofuran, 3.6 mL of 2.2 M *n*-butyllithium, and 1.8 mL of hexamethylphosphoramide) at −78 °C was added 3.4 mmol of conjugated nitrile in 20 mL of tetrahydrofuran.[1,11] After 15 min, 8 mmol of methyl iodide or 4 mmol of α,ω-dibromide was added and the stirred mixture was allowed to reach room temperature over a 2-h period. Water was added and the alkylated unsaturated nitriles (**2b, 6,** and **8a**) were isolated by ether extraction and purified by short-path distillation. These results are shown in Table II. Nitriles **8b** and **8c** were reduced directly without purification.

2-(4-*tert*-Butyl-1-cyclohexenyl)propanenitrile (2c). To a solution of lithium diisopropylamide (prepared from 0.8 mL of diisopropylamine in 10 mL of tetrahydrofuran, 2.3 mL of 2.2 M *n*-butyllithium, and 1.0 mL of hexamethylphosphoric triamide) at −78 °C was added 0.64 g of nitrile **1c.** After 15 min, 0.6 mL of glacial acetic acid was added.[11] The solution was allowed to reach room temperature, water was added, and the product was isolated by ether extraction to give 0.63 g (98%) of deconjugated nitrile **2c,** bp 70°C at 0.05 Torr (Table II).

General Reduction Procedures. To a stirred solution of 10 mg-atoms of sodium in 25 mL of refluxing ammonia contained in a three-neck flask equipped with a cold finger condenser charged with dry ice–acetone slurry was added a solution of 1 mmol of nitrile in 2–3 mL of tetrahydrofuran. After sitrring for 1 h, the mixture was treated with solid ammonium chloride to discharge the blue color. The ammonia was allowed to evaporate, 25 mL of water was added, and the olefin products (**4c, 3a, 9a, 9b,** and **9c**) were isolated by hexane extraction and purified by short-path distillation. The results are shown in Table III.

Equilibration of Olefins 3b and 4b.[12] A solution of 0.18 g of a 55:45 mixture of olefins **3b** and **4b** in 10 mL of 5% sulfuric acid in acetic acid was stirred at room temperature for 1 h. The acid was neutralized with 10% sodium hydroxide and the product was isolated by hexane extraction, affording 0.17 g (93%) of a 95:5 mixture of **4b** and **3b,** bp 70 °C (bath temperature) at 15 mm.

Acknowledgments. We are indebted to the National Science Foundation for support of this work through a research grant (CHE75-07777). We also thank the Dow Chemical Co. for a fellowship award to R.B. A generous sample of gerano- and neronitriles was provided by Robert Dahill, Givaudan Corp., Clifton, N.J.

Registry No.—**3b,** 14033-75-1; **8a** isomer I, 63089-71-4; **8a** isomer II, 63089-72-5; **8b** isomer I, 63122-45-2; **8b** isomer II, 63089-73-6; **8c** isomer I, 63089-74-7; **8c** isomer II, 63089-75-8; 2-(diethylphosphono)propanenitrile, 29668-61-9; 4-*tert*-butylcyclohexanone, 98-53-3.

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(9) The apparatus described by W. S. Johnson and W. P. Schneider ["Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132] was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with water, saturated brine solution, and drying the extracts over anhydrous sodium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Nuclear magnetic resonance spectra were recorded with Varian T-60 or Perkin Elmer R20B spectrometers. Signals are reported as the chemical shift downfield from tetramethylsilane (Me_4Si) in parts per million (ppm) of the applied field. Coupling constants are reported in hertz (Hz).
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Coordinative Role of Alkali Cations in Organic Synthesis. 2. The Chalcone–Flavanone System

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Coordination of alkali cations (M) with neutral organic nucleophiles is now well known,[1-3] and the effect of such interactions on the methylation of kojic acid with dimethyl sulfate has been reported.[4] Significantly, the mechanism of organic reactions involving caustic alkalies and alkali salts is always discussed by considering only the anionic part of the inorganic species.[5] It is demonstrated in this paper that a full mechanism of such reactions cannot be written until the interactive behavior of the cationic counterpart is also discussed, for there is no reason why a cation should be inert when negatively charged or polarized species are involved in the reaction. To illustrate this point, we describe the condensation of 2-hydroxyacetophenone (HAP) with benzaldehyde (BLD) to produce chalcone and cyclization of the latter to produce flavanone as a function of the nature and concentration of the caustic alkalies. In the following, notations such as E, E_4, and

Table I. Yield of Chalcone with Different Alkalies under Different Conditions

Medium of synthesis	Reaction mixture (MOH:BLD:HAP)	% yield KOH	NaOH	LiOH
E	3:1:1	5	10	16
E_4	3:1:1	40	52	91
	5:1:1	66	85	93[a]
	9:1:1	85	90	92[a]
E_{25}	3:1:1	35	48	70
E_{50}	3:1:1	15	20	30
E_{75}	3:1:1	SR[b]	SR	SR

[a] Undissolved portion of the alkali decanted before acidification of the reaction mixture. [b] SR, slight reaction.

E_{25} used for the reaction media denote ethanol, ethanol–water (96:4) and ethanol–water (75:25), respectively.

Experimental Section

Synthesis of Chalcone. HAP (2.5 mL) and BLD (2.55 mL) were added to 30 mL of the reaction medium (Table I) in a conical flask. Weighed solid caustic alkali was added. The reaction mixture was shaken constantly until alkali dissolved (20–30 min) and the orange-red solution produced crystals of metal chalconate. When LiOH in E or E_4 was used, slight warming of the reaction mixture was necessary to produce the orange-red solution; Li^+–chalconate does not crystallize. The reaction mixture was set aside for 4 h and neutralized with 1 N HCl. The crude chalcone was collected, washed three times with 10–20-mL lots of water, dried at room temperature, and weighed. The yield of the crude chalcone (mp 85–7 °C) obtained under different conditions is shown in Table I. The crude product was recrystallized from E_4 (mp 90 °C) before further work.

Synthesis of Chalcone in the Absence of M. KOH (2 mmol, 0.11 g) in 2 mL of E_4 was treated with dicyclohexyl-18-crown-6 (4 mmol, 1.48 g) to obtain the naked hydroxide.[6] HAP (0.7 mmol, 0.092 g) in 1 mL of E_4 was then added and the reaction mixture was swirled for 5–10 min. BLD (0.7 mmol, 0.72 g) dissolved in 1 mL of E_4 was added and the reaction mixture was set aside for 4 h. On acidification with 1 N HCl, the solution produced only the reactants, although in the absence of the crown ether such a reaction mixture produced the chalcone in about 40% yield (Table I).

Cyclization of Chalcone. Cyclization experiments were carried out by two methods.

(a) **Weight Technique.** Chalcone (0.224 g) was added to 10 mL of alkali solution in E_{75} and set aside at room temperature (20–22 °C) for the desired time period as indicated in Table II. The colorless flavanone was collected, dried, and weighed. Although ethanol present in the medium solubilizes a fraction of the product, nonetheless it had to be used to prevent cocrystallization of chalcone from the hydrolysis of M^+–chalconate in the equilibrium:

$$\text{chalcone} \rightleftharpoons M^+\text{–chalconate} \rightleftharpoons \text{flavanone}$$

The relative results with different alkalies are shown in Table II.

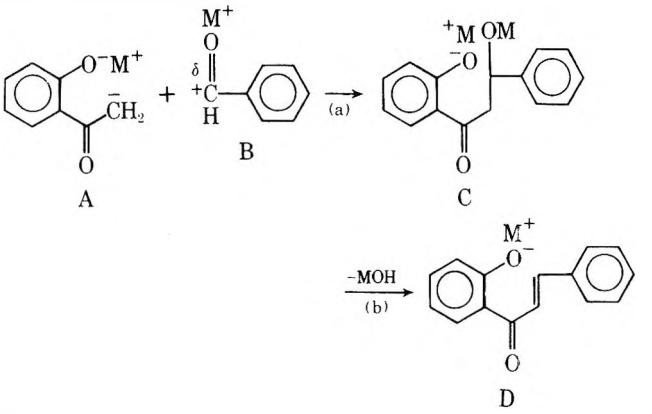
(b) **pH-Metric Technique.** Four 10-mL lots of E_{50} were adjusted at pH 11 using LiOH, NaOH, KOH, and Bu_4NOH. The yellow ethanolic solution of the chalcone (0.1 mL of 1%) was added to each. The time required for the decolorization of the color was taken as an indication of the efficiency of the different cations toward cyclization of the chalcone at a given OH ion concentration.

Results and Discussion

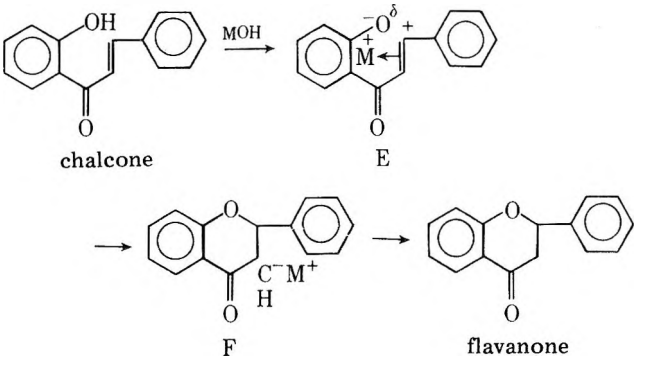
Synthesis of Chalcone. The results shown in Table I show that the yield of the chalcone is the highest in E_4, with the yield enhanced in the order of KOH, NaOH, and LiOH and as the concentration of alkali was increased. This indicates that synthesis is favored as charge density and concentration of M increase, which in turn means that M coordinates with the carbonyl of BLD as shown for B in the Scheme I; the degree of the carbonium character in B and hence of its condensation with A is expected to be in accordance with the strength of the BLD→M^+ bond and hence the charge density of M. Coordination of M with aromatic aldehydes in known[7–9] and for Li with BLD is confirmed by the fact that solubility of LiOH in E_4 (under N_2) is significantly enhanced with BLD.

Scheme I

Synthesis of chalcone

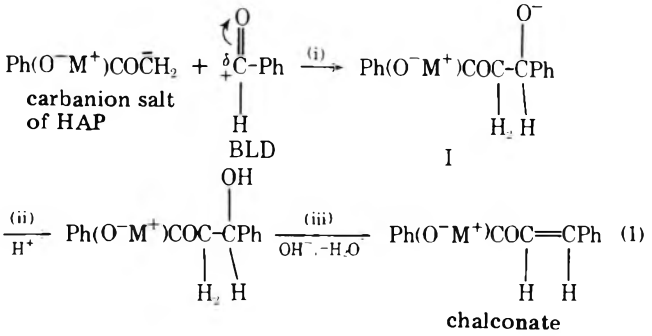


Cyclization of chalcone



The basic role of M during synthesis is confirmed by the observation that condensation fails to take place when the K of the alkali is concealed from the reaction mixture using the crown ether. When the reaction medium is dehydrated, condensation does not take place. Some water in the medium is therefore necessary, for ionic reactions are involved. Also, the yield of chalcone decreases as water in the medium exceeds 4% (Table I), indicating that water weakens the BLD→M^+ bond, diminishes the carbonium character of B, and hinders its condensation with A.

Mechanism of Condensation. The condensation mechanism is usually[10] written as shown in eq 1. With an increase



in concentration of alkali, protonation of I and hence yield of the chalconate should decrease. However, we note that the yield of the latter (e.g., in E_4, Table I) increases with the amount of alkali used. This indicates that the route of synthesis is not via steps i to iii but via a and b shown in Scheme I. The latter mechanism explains how excess alkali favors the yield of the chalconate by enhancing the carbonium character of B, by favoring "acid-catalyzed" elimination of MOH from C, and by stabilizing the product of the latter, D, against cyclization through strengthening the M^+–phenoxide ion pair; the term "acid catalyzed" has been used for elimination of

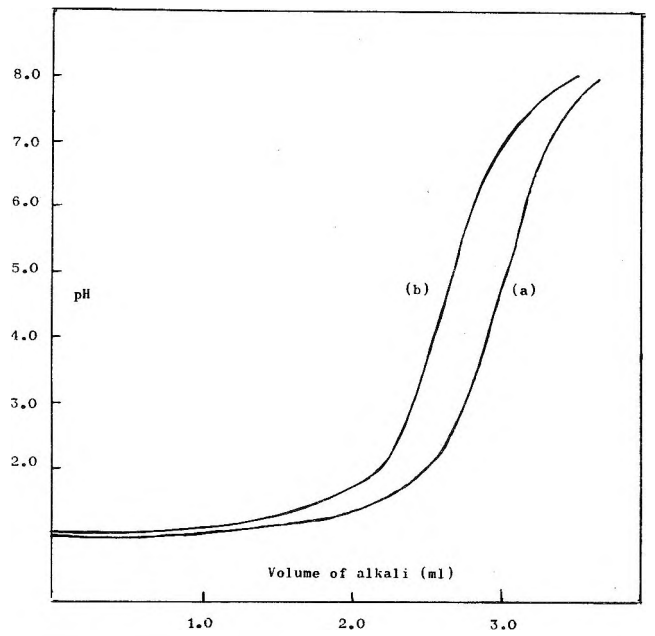


Figure 1. pH metric curves of $HClO_4$–Bu_4NOH systems in alcoholic medium when ionic strength (0.06 M) was maintained with $Bu_4N^+I^-$: (a) in the absence of chalcone, and (b) in the presence of chalcone (0.005 M).

Table II. Efficiency of Different Alkalies toward Cyclization of Chalcone (Medium of Work, E_{75}; Alkali:Chalcone, 1:1)

Molar concn of each reactant, M	Time of contact, h	% cyclization KOH	NaOH	LiOH
0.1	2	72[a]	68[a]	Nil[b]
	5	82	80	Nil
	20	86	86	Nil
0.03	2	75	71	Li^+–$Chal^-$ + flavanone[c]
	5	87	88	92[d]
	20	90	90	Flavanone + Li^+–$Chal^-$
0.01	2	78	76	Flavanone Li^+–$Chal^-$
	5	88	88	94
	20	92	93	94[d,e]

[a] In the earlier stages of the reaction NaOH and KOH are even less efficient; for a contact period of 30 min, % cyclization with KOH (70) and NaOH (61) is as shown in parentheses. [b] Li^+–chalconate only was recovered. [c] Products are shown in the order of relative yield. [d] A few crystals of Li^+–chalconate were present. [e] Contamination by Li^+–chalconate shows that decyclization of the product also starts taking place due to an extended period of contact of the latter with LiOH.

MOH because the proton eliminated as MOH is polarized indirectly by M^+ which is a Lewis acid.

Cyclization of Chalcone. Very dilute (4×10^{-4} M) solutions of chalcone at pH 11 are cyclized by LiOH, NaOH, KOH, and Bu_4NOH in 54, 38, 23, and 18 min, respectively. This indicates that the anion of M^+–chalconate cyclizes rapidly as the charge density of M decreases and the strength of the M^+–phenoxide ion pair loosens. The results in Table II also indicate that at high concentration (0.1 M) cyclization is favored in the order LiOH, NaOH, and KOH and as the alkali/chalcone ratio is decreased. However, at intermediate concentrations (e.g., 0.03 M) efficiency of the alkalies is in the order KOH, NaOH, and LiOH. This can be attributed to M^+–π interaction as shown for E in Scheme I, an interaction which fails to contribute toward the stability of the M^+–chalconate at high dilution (4×10^{-4} M) and goes undetected at high concentrations (0.1 M) due to a dominating contribution of the M^+–phenoxide ion pair. The following observation confirms the activity of unsaturation of the aliphatic part in E.

When $HClO_4$ is titrated in the pH range 2 to 8 (where the chalcone does not ionize) in the presence and absence of chalcone employing NaOH and Bu_4NOH as alkalies, chalcone is found to decrease the concentration of $HClO_4$ but only in the case of Bu_4NOH (see Figure 1). This shows that a neutral molecule of chalcone deprotonates $HClO_4$ to become itself protonated in the cavity through M^+–π bonds as with M^+ in E. The "encapsulated" proton can be replaced by the small-sized Na^+ during titration but not by the bulky Bu_4N^+ which competes unfavorably on steric as well as charge-density grounds. If protonation should have taken place outside the cavity, say at the carbonyl group, then both the alkalies could deprotonate the H^+–chalcone complex successfully.

Mechanism of Cyclization. The mechanism of the cyclization is also described in Scheme I. The M^+–π interaction in E enhances the carbonium character at the β carbon and also loosens the $-O^-M^+$ ion pair. The phenoxy anion so destabilized attacks the β carbon to produce the closed-ring labile carbanion salt (F). The latter hydrolyzes easily to produce the flavanone.

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Registry No.—HAP, 582-24-1; BLD, 100-52-7; chalcone, 94-41-7; flavanone, 487-26-3.

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Photochemical Reactions of Aromatic Compounds. 27.[1] Stereospecific Photocycloaddition of *cis*- and *trans*-1-Methoxypropenes to 2-Naphthonitrile

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The photocycloadditions of olefinic compounds and furan to aromatic nitriles usually occur in a stereoselective manner[2-4] and have been discussed in terms of exciplexes. In a previous paper,[2a] we reported that irradiation of 2-naphthonitrile (1) and alkyl vinyl ethers at 313 nm exclusively gives endo [2 + 2] cycloadduct **5a**, whereas that at >280 nm for a longer time results in formation of a cyclobutene compound **3** as a main product. In this note, we report the stereospecific photocycloadditions of *cis*- and *trans*-1-methoxypropenes (**4c** and **4t**) to 2-naphthonitrile (**1**).

Table I. ^{1}H NMR Spectra of 5 and 6[a]

Registry no.	Compd	δ (multiplicity) H-1	H-4	H-5	H-7	H-8	CH_3	OCH_3	Coupling constant, Hz $J_{1,8}$	$J_{7,8}$	J_{8,CH_3}
62930-47-6	**5c**	3.79 (d)	6.50 (AB quartet)	5.68	4.38 (d)	2.88 (m)	0.81 (d)	3.42 (s)	9.5	8.0	7.5
62961-30-2	**5t**	2.87 (d)	6.59 (AB quartet)	5.63	3.90 (d)	2.52 (m)	1.14 (d)	3.44 (s)	9.5	8.5	6.5
62961-31-3	**6c**	3.48 (d)	6.50 (AB quartet)	5.70	3.81 (d)	2.66 (m)	1.14 (d)	3.53 (s)	8.5	6.5	7.0
62961-32-4	**6t**[b]	*c*	6.34 (AB quartet)	5.76	3.90 *c*	3.20 (m)	0.87 (d)	3.37 (s)	*c*	c	7.0

[a] In CCl_4 using tetramethylsilane as internal standard. Aromatic resonances [δ 7.9–8.5 (m, 4 H)] are omitted. [b] The spectrum was obtained by subtracting the signals of **5t** from the spectrum of a mixture of **5t** and **6t**. [c] Not determined.

Table II. Rate Constants (k_q) for Quenching of 2-Naphthonitrile Fluorescence by Enol Ethers[a]

Registry no.	Enol ether	Adiabatic IP, eV	$k_q\tau$, M^{-1}	k_q, $M^{-1}s^{-1}$	log k_q
109-92-2	**2**[b]	8.49[h]	0.46	4.17×10^7	7.62
116-11-0	**7**[c]		1.43	1.29×10^8	8.11
110-87-2	**8**[d]	8.34[i]	2.46	2.22×10^8	8.35
4696-26-8	**9t**[e]		12.2	1.10×10^9	9.04
4696-25-7	**9c**[f]	8.04[h]	25.3	2.28×10^9	9.36
17574-84-4	**10**[g]	7.65[h]	93.9	8.46×10^9	9.93

[a] Concentration of **1**, 1.5×10^{-4} M in air-saturated cyclohexane. [b] Ethyl vinyl ether. [c] 2-Methoxypropene. [d] Dihydropyran. [e] *trans*-1-Ethoxypropene. [f] *cis*-1-Ethoxypropene. [g] 1-Methoxy-2-methylpropene. [h] N. E. Schore and N. J. Turro, *J. Am. Chem. Soc.*, **97**, 2482 (1975). [i] K. Watanabe, T. Nakayama, and J. R. Mottl, *J. Quant. Spectrosc. Radiat. Transfer*, **2**, 369 (1962).

Results and Discussion

Irradiation of a benzene solution containing **1** and **4c** through Pyrex with a high-pressure mercury arc gave **5c** and **6c** in ca. 7:3 ratio in quantitative yield. Similarly, irradiation of **1** and **4t** gave **5t** and **6t** in ca. 4:1 ratio. VPC and NMR analyses of the photolysates showed that any other 1:1 adducts were not formed. Irradiation for a longer time resulted only in the slight change of the **5** to **6** ratio.

From NMR and mass spectra, all the products were confirmed to have an identical skeletal arrangement. By means of VPC–mass analyses, they were found to reveal essentially identical mass spectra, the weak parent peak at *m/e* 225 and the strong fragment peaks at *m/e* 153 and 72. The UV spectra of **5c** and **5t** were characteristic of the 1,2-dihydronaphthalene chromophore.[5]

The NMR spectra of the four adducts were very similar. They consisted of an AB quartet of olefinic protons, a sharp singlet of methoxy protons, a sharp doublet of methyl protons, and two sets of doublets and a multiplet of three methine protons. The couplings of the methine protons were readily analyzed by the first-order analyses and double irradiation experiments. In the case of **5c**, for example, the doublets at δ 0.31, 3.79, and 4.38 were collapsed into singlets by irradiation at δ 2.88 (m), respectively, thus confirming the vicinal couplings of the proton (H-8) attaching to methyl-substituted carbon with the other methine protons (H-1 and H-7). The NMR data are listed in Table I. The configurations of the cyclobutane ring were determined by comparing the chemical shifts of H-7, H-8, and methyl protons of the four cycloadducts; molecular models show that the protons located in the endo direction must be shielded by the anisotropic effects of the benzene ring and/or the double bond, unlike the corresponding protons located in the exo direction.

When **5c** and **6c** were heated at 300 ± 10 °C, **4c** and **4t** were obtained in 9:1 ratio. Similarly, the thermolysis of **5t** gave **4c** and **4t** in 1:4 ratio. Moreover, the direct photolysis of **5c** or **5t** in the presence of a triplet quencher[6] gave **4c** or **4t** each in >95% specificity. The thermal decomposition of cyclobutane compounds usually favors stereochemical retention in formation of olefins[7] and the Woodward–Hoffmann rule predicts that the concerted $[2_s + 2_s]$ cycloreversion is allowed in the electronically excited state.[8] Therefore, these results provide further support for the structures assigned.

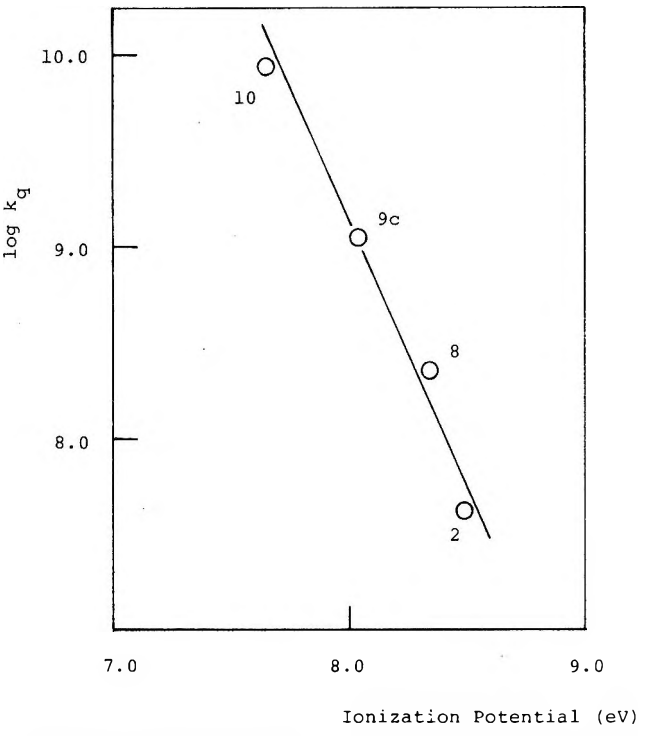
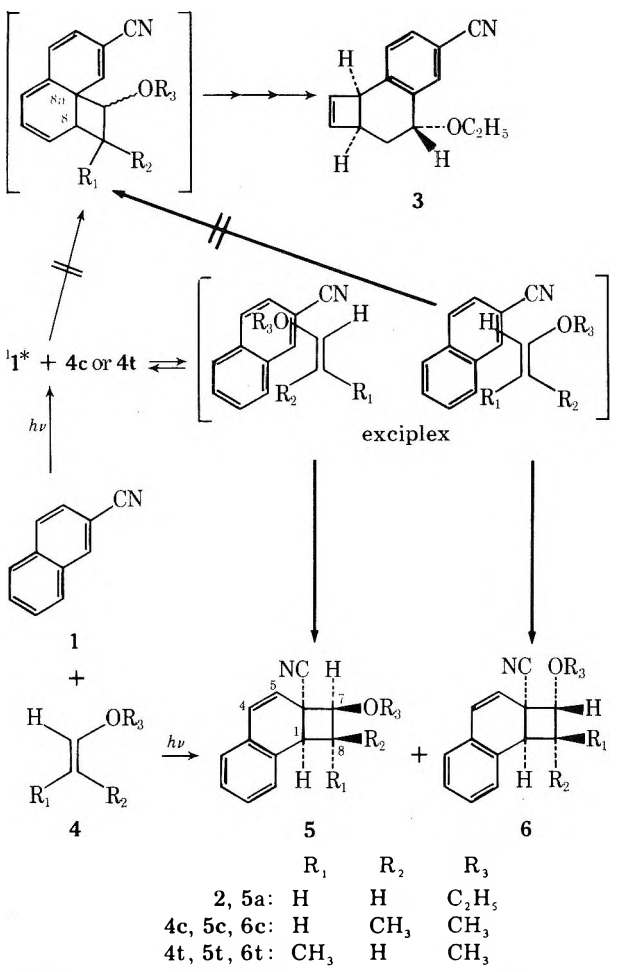


Figure 1. Correlation of log k_q vs. adiabatic ionization potential of enol ethers (abstracted from Table II).

The fluorescence of **1** was quenched by various enol ethers and the quenching rates increase with the decrease of the ionization potentials of enol ethers (Table II and Figure 1). The values of k_q were obtained from the Stern–Volmer slopes ($k_q\tau$) and the lifetime of excited singlet **1** (τ = 11 ns).[9] The

Scheme I



linear correlation of log k_q vs. ionization potentials suggests a charge transfer mechanism for the fluorescence quenching. Fluorescence quenching by 1-methoxy-2-methylpropene was accompanied by the appearance of an exciplex emission (λ_{max} 435 ± 5 nm) with an isoemissive point at 418 nm. Moreover, the photocycloadditions of **4c** and **4t** were quenched by pyridine, but not at all by piperylene. This result provides evidence for the exciplex intermediacy, since pyridine is a good quencher for exciplexes involving **1**, but does not quench **1** fluorescence.[1] Therefore, the $_{\pi}2_s + _{\pi}2_s$ photocycloaddition of **4c** and **4t** proceeds in a concerted manner via singlet exciplexes.

It is noteworthy that **5c** and **5t** possessing the *endo*-methoxy group predominate over **6c** and **6t**, respectively. This endoselective orientation of the methoxy group reflects favorable configuration of the exciplexes.

In contrast to the photocycloaddition of **2** to **1**, that of **4c,t** gave the "exo" adduct **6c,t** even to minor extents, but not such adducts as **3**; steric effects of the methyl group of **4c,t** allow the approach of **4c,t** in the exo orientation of the methoxy group and inhibit the addition to the C(8)–C(8a) bond of **1** (Scheme I).

Experimental Section

The following instruments were used for spectral measurements: ^{1}H NMR, Hitachi R-24 (60 MHz) and JEOL JNM JS-100 (100 MHz); IR, Hitachi EPI-S2; UV, Hitachi 124; mass spectra, Hitachi RMU-6E; fluorescence spectra, Hitachi MPF-2A. VPC–mass analyses were carried out on a Hitachi RMS-4 machine. VPC was carried out on a Shimadzu GC-2C equipped with a flame ionization detector using a column of Ucon oil LB-550X (5% on Celite 545, 1.5 m) at 160 °C or PEG 20M (20% on Celite 545, 3 m) at 100 °C. 2-Naphthonitrile was obtained from tokyo Kasei and was purified by vacuum distillation and recrystallization from hexane. *cis*- and *trans*-1-Methoxypropenes were prepared according to the method cited in literature[10] and were separated by preparative VPC using a column of PEG 6000. The purities were over 95%. Methyl isobutenyl ether was prepared by the method of Böhme and Bentler.[11] All the enol ethers were distilled from anhydrous potassium carbonate before use.

Photoreaction with *cis*-1-Methoxypropene (4c). A solution of **1** (0.3 g, 2 mmol) and **4c** (3 mL) in 30 mL of benzene placed in a Pyrex glass tube was irradiated with an Eikosha PIH-300 high-pressure mercury arc for 10 h at ambient temperature. After removal of solvent and excess **4c**, the residual oil was chromatographed on silica gel using mixtures of benzene–hexane as eluent. After recovery of 50 mg of **1**, further elution gave 200 mg of **5c**: mp 65–66 °C; IR (CCl_4) 2240, 1150 cm^{-1}; UV (cyclohexane) λ_{max} 275 sh (ϵ 6300), 267 nm (6800); mass spectrum *m/e* 225 (M^+).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.84; H, 6.65; N, 6.16.

Further elution gave 150 mg of a mixture of **5c** and **6c**, from which 30 mg of **5c** crystallized out. Repeated chromatography of the mixture gave ca. 50 mg of **6c**, including a small amount of **5c** which was an oil. On storage of this mixture in a refrigerator it did not solidify.

Photoreaction with *trans*-1-Methoxypropene (4t). In a similar way, a benzene solution (30 mL) of **1** (0.3 g, 2 mmol) and **4t** (3 mL) was irradiated for 10 h. Column chromatography of the photolysate on silica gel gave 60 mg of **1** and 230 mg of **5t**, which was recrystallized from methanol: mp 127.5–129 °C; IR (CCl_4) 2240, 1150 cm^{-1}; UV (cyclohexane) λ_{max} 277 sh (5300), 268 nm (5800); mass spectrum *m/e* 225 (M^+).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.75; H, 6.71; N, 6.08.

Further elution gave ca. 100 mg of a mixture of **5t** and **6t**, from which 30 mg of **5t** crystallized out. Repeated chromatography of the mixture gave only a mixture enriched by **6t**, which did not solidify on storage in a refrigerator.

Photolysis of 5c and 5t. A solution of **5c** or **5t** (10 mg) and ferrocene (5 mg) in 1 mL of acetonitrile placed in a Pyrex tube was irradiated with a high-pressure mercury arc. During the course of the irradiation, the photolysate was analyzed by VPC at 5-min intervals for the initial 30 min; it was found that **1** and **4c** or **4t** increased linearly with the disappearance of **5c** or **5t**. Irradiation for 1 h resulted in the complete decomposition of **5c** or **5t**.

Quenching Experiments. Solutions of 0.05 M **1** and 0.5 M **4c** or **4t** in ethyl acetate and in pyridine were prepared. Another solution of 0.05 M **1**, 0.5 M **4c** or **4t**, and 0.05 M piperylene in ethyl acetate was also prepared. Irradiation was carried out for 2 mL of each solution through an aqueous potassium biphthalate solution (>300 nm) with a high-pressure mercury arc using a merry-go-round apparatus. The photolysates were analyzed by VPC; it was found that irradiation for 30 min resulted in ca. 20% conversion of **1** for ethyl acetate solutions, independently of the presence and absence of piperylene, while any products could not be detected for pyridine solutions.

Registry No.—**1**, 613-46-7; **4c**, 4188-68-5; **4t**, 4188-69-6.

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Regarding Polarizability Effects of Hydrocarbon Substituents on Base Strengths in Solution[1]

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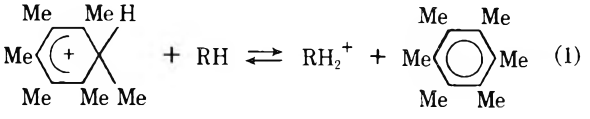
Hydrocarbon substituent effects play many and varied roles in chemistry. In spite of much effort, the understanding of these effects has remained a substantial challenge.[2] In proton-transfer (and similar) equilibria, the substitution of hydrogen by alkyl groups is expected to act to stabilize positive charge. No exceptions are known in gas-phase proton-transfer equilibria.[3] In solution, there are numerous exceptions, even when the alkyl substituent is introduced at relatively large distances from the site of protonation. For example, a 4-methyl substituent decreases (not increases) the basicity of quinuclidine by 0.11 pK_a units in water.[4]

We wish to report important new comparisons of hydrocarbon substituent effects on proton-transfer equilibria in the gas phase and in aqueous solution. These comparisons establish that the intrinsic ability of hydrocarbon substituents to stabilize positive charge by polarizability,[5,6] inductive, and conjugative interactions is observed with appropriate carbon bases almost quantitatively in aqueous solutions. That is, for proton-transfer reactions such as eq 1, the effects of hydrocarbon substituents in B are influenced in a very minor way by aqueous solvent. The result has important consequences in showing that polarizability effects of hydrocarbon substituents can be a major effect, even *in aqueous solution* in appropriate cases (e.g., reaction 1). In other words, polarizability effects cannot be regarded as an isolated curiosity of gas-phase chemistry.[7]



(1)

The latter impression has arisen because, for example, the phenyl (or cyclohexyl) substituent in anilinium ion (or cyclohexylammonium ion) stabilizes the gaseous cation by polarization by about 7 kcal/mol more than does a methyl substituent in methylammonium ion.[3] In aqueous solution, however, there is little or no such effect.[3] Polarizability effects of hydrocarbon substituents in ammonium (and oxonium[8]) ions are generally virtually completely attenuated by hydroxylic (or other hydrogen-bond acceptor) solvents.[3] The dispersal to solvent of cationic charge through the formation of hydrogen bonds between the hydrogen-bond acceptor solvent and the NH^+ and OH^+ solvation sites has been proposed to account for the high degree of attenuation of hydrocarbon substituent polarizability effects in these ions.[3,7-10] Inductive (dipolar) and conjugative effects of hydrocarbon substituents are less attenuated by such solvation interactions,[3,11,12] since the stabilization by polarization falls off especially rapidly with the distance of charge dispersal ($1/r^4$ in the simple electrostatic model[5,6]).

Our present results are of interest in providing critical new evidence for the above concept of substituent–solvent interactive effects. It has been well recognized[13] that delocalized aryl carbocations and their unsaturated hydrocarbon precursors form weak to negligible hydrogen bonds to acceptors, e.g., $(H_2O)_n$. Thus the principal mechanism of cationic charge dispersal to aqueous solvent is evidently absent for such cations. The expected consequence is indeed that which is observed for reaction 1; namely, the hydrocarbon subsituent effect (polarizability, inductive, and conjugative effects in total) is nearly the same in the aqueous solution as is observed in the gas phase.

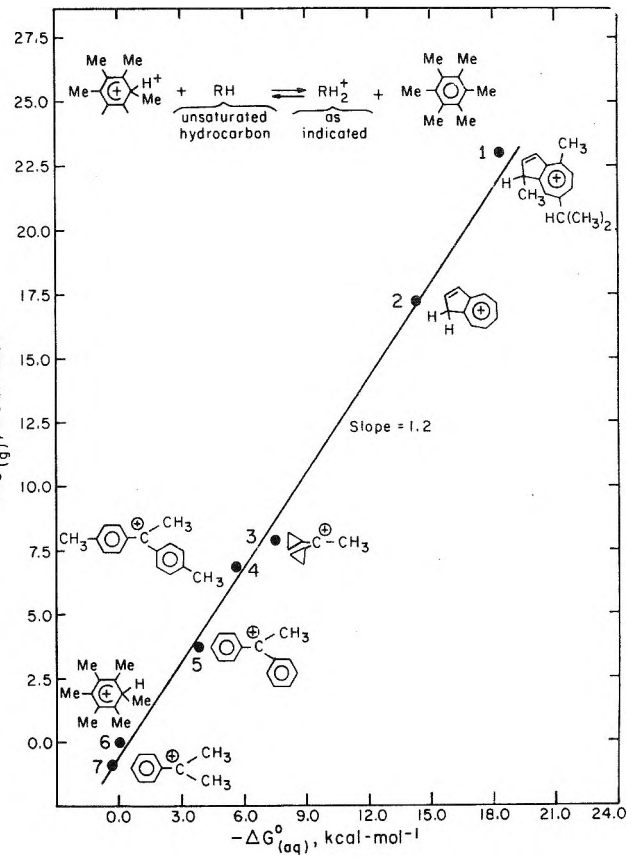


Figure 1. Comparison of gaseous and aqueous phase base strengths of hydrocarbon bases.

The present report represents an extension, now including alkyl substituents (points 1 and 4 in Figure 1) and cyclopropyl substituents (point 3 in Figure 1), of our earlier report[14] that carbon bases (which protonate to give delocalized aryl carbocations) are accompanied by structural effects on protonation which are approximately quantitatively equal in the gas phase and in aqueous solution. The results are shown in Figure 1, which plots for reaction 1 $\Delta G^\circ_{(g)}$ vs. $\Delta G^\circ_{(aq)}$. The linear regression line has a slope of 1.2, which is not significantly different from unity in view of uncertainties in acidity function behavior (specifically between H'_R[15] and H_c[16]) on which the $\Delta G^\circ_{(aq)}$ values are based.[17] It should be noted, however, for the pair guaiazulene and azulene, which both protonate in dilute acid, that there is very little uncertainty of this nature. The $\Delta G^\circ_{(aq)}$ value for 1,1-dicyclopropylethylene is based upon our UV measurements in H_3PO_4 ($pK_{R+} + -7.5$) using the H'_R scale reported by Arnett.[18]

The results for the 1,1-dicyclopropylethylene are significant in the present context. In the gas phase cyclopropylamine is 3.1 kcal/mol stronger base than aniline.[19] In aqueous solution the cyclopropylamine is not relatively less basic, but is in fact 6.1 kcal/mol stronger than aniline. However, as shown in Figure 1, 1,1-dicyclopropylethylene is approximately a 4 kcal/mol stronger base than 1,1-diphenylethylene in the gas phase and *in aqueous solution.* It is generally accepted that the base strength of aniline is decreased by 5–6 kcal/mol by conjugation in the free-base form.[3] In aqueous solution, the principal cause of the 6.1 lower basic strength of aniline than cyclopropyl amine may be attributed to this conjugation, since there is little preferential stabilization by polarization of the

hydrated anilinium ion over that of the hydrated cyclopropylammonium ion.

In the gas phase, however, anilinium ion is more stabilized than cyclopropylammonium ion by the polarization effect, which tends to offset the "resonance" effect in aniline. Thus there is a substantial increase (~3 kcal) in the gas-phase base strength of aniline compared to cyclopropylamine. In the carbocations, greater polarization stabilization by phenyl than cyclopropyl also presumably occurs (as well as the π electron delocalization, which favors the dicyclopropylethyl cation), but in the absence of the hydrogen-bonding solvation the relative combination of polarization and resonance effects in the carbocations is not changed in solution compared to the gas phase.

Finally, we call attention to the wide variety of sizes, shapes, and carbon content (8–17) of the carbocations involved in Figure 1, as well as the nearly 25-kcal range of structural effects, as evidence supporting the ideas expressed on cation solvation. The methods used for the gas-phase equilibrium constant determinations have been described in detail.[21]

Registry No.—1,2,3,4-Tetramethylbenzene, 488-23-3; hexamethylbenzene, 87-85-4; guaiazulene, 489-84-9; azulene, 275-51-4; 1,1-dicyclopropylethylene, 822-93-5; 1,2-di-*p*-tolylethylene, 2919-20-2; 1,1-diphenylethylene, 530-48-3; (1-methylethenyl)benzene, 98-83-9.

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Approaches to the Mitomycins. Photochemistry of Aminoquinones

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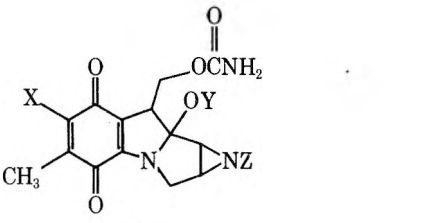
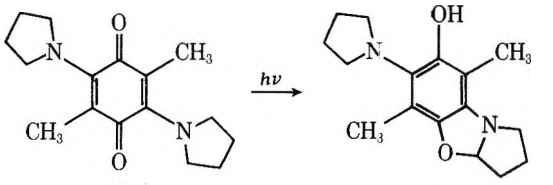
The mitomycin antibiotics (**1**) have been the subject of a wide variety of synthetic endeavors.[1] Very little experimentation has been described that deals with the problem of the introduction of oxygen functionality at the α carbon of the pyrrolidine ring. Toward this goal, we have examined a method for obtaining α-oxygenated aminohydroquinones that was discovered by Cameron and Giles.[2] Readily prepared aminoquinones are photooxidized by an intramolecular oxygen insertion, e.g., **2** → **3**.

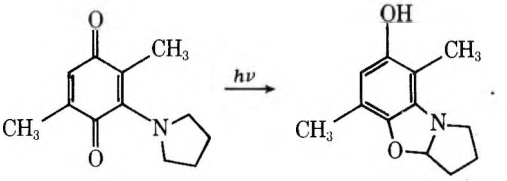


1

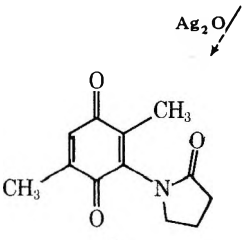


2 **3**

In our work, a model aminoquinone **4** was prepared by using a tenfold dilution of the conventional conditions for the condensation of pyrrolidine and xyloquinone to form a bis adduct. The photolysis of **4** with a sunlamp to produce **5** proceeded cleanly, although isolation of **5** in high yield was not possible.



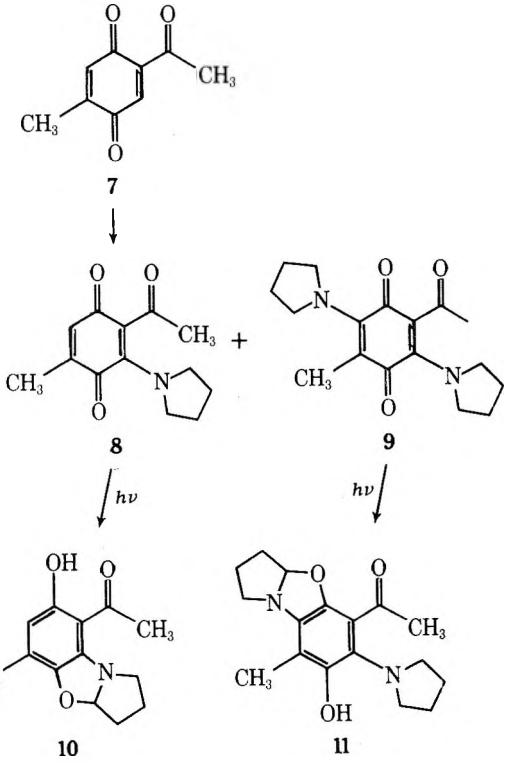
4 **5**



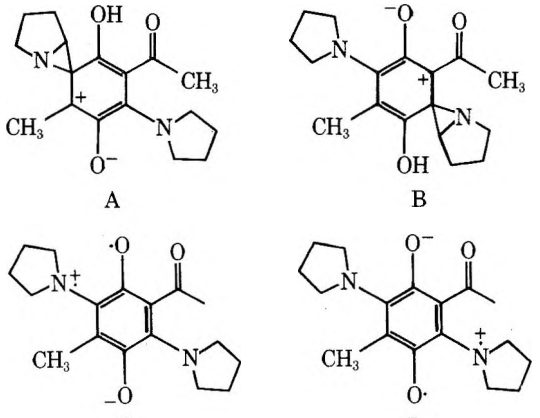
6

These insertion products are characterized by the appearance of a downfield methine hydrogen in their NMR spectra and the disappearance of quinone carbonyls in their IR spectra. Oxidation of photoproduct **5** with silver oxide yielded pyrrolidone–quinone **6**, a derivative with the heterocyclic α carbon in the desired oxidation state. Lactam **6** was characterized by its unambiguous NMR, by its carbonyl band at 5.78 μm, and by its UV λ_{max} 273 nm. This maximum is shifted almost 30 nm to longer wavelength compared to **4**, presumably because of lesser stabilization of the ground state of the chromophore.

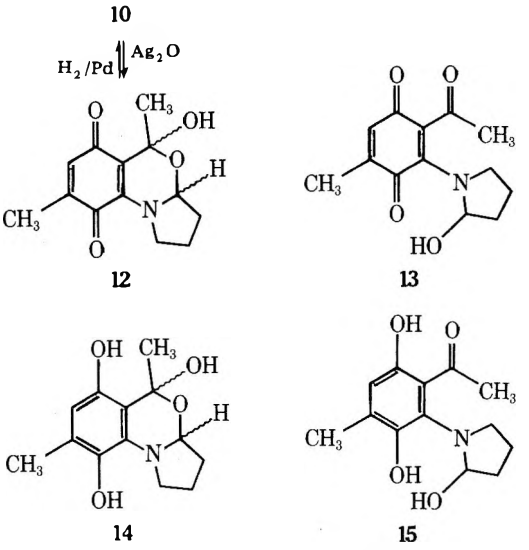
We chose to study next the amine adducts 8 and 9, either of which was available from the known quinone 7, depending on the conditions of pyrrolidine addition. If a lactam could be



formed, one could plan carbon–carbon forming reactions where the oxygen could remain at the desired angular position. Photolysis of 8 afforded 10 in a clean process, whereas 9 yielded 11. That dissimilar pyrrolidines had photocyclized was established by the absence of a strongly H-bonded acetyl band at 1625 cm^{-1} in the IR of 11 which was present in 10. In both products the characteristic methine protons were observed in the NMR. The positional selectivity in the photolysis of 9 can be rationalized by invoking a mechanism for the reaction suggested by Orlando and Bose.[3] The suggestion was made that polar, spirocyclic intermediates such as A or B are involved. It is clear that a polar transition state leading to the latter would be destabilized by having a carbon with carbonium ion character adjacent to a carbonyl. Or, if a charge transfer initiates the reaction, a species such as C would be more stable than D. Furthermore, the intermediate in the photolysis of 8 would require an unfavorable juxtaposition of carbonium ion character and the acetyl group. Thus, the qualitative observation that its photolysis was slower by at least a factor of 4 compared to 9 is also interpretable.

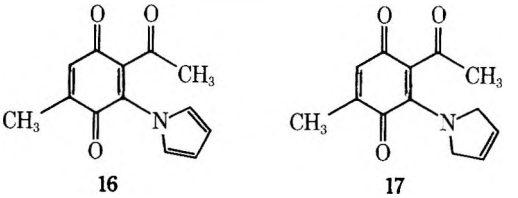


To convert the pyrrolidine α carbon from the masked aldehyde oxidation state to the lactam level, photoproduct 10 was treated with Ag_2O. The structure assigned to the product is that of oxazine 12. The assignment rests on the reappearance of quinone characteristics in the NMR (allylic coupling of CH_3 and vinyl H) along with the maintenance of the characteristic downfield methine of the oxypyrroldine ring. Further, the side-chain acetyl has been masked as shown by disappearance of its carbonyl peak in the IR and a shift of its CH_3 resonance in the NMR to δ 1.76. Although one would not expect a single epimer to form in this hemiacetal, there is no definitive evidence to suggest that a mixture was obtained. In NMR spectra of the crude oxidation product, the peaks for the methine H and the acetal CH_3 were not as sharp as in purified material. Clearly, the desired intermediate 13 had attacked the reactive acetyl faster than carbinolamine could be oxidized, and the equilibrium concentration of 13 must be too low for an oxidation to lactam at a usable rate. Other oxidants were no more useful at producing uncyclized products. In an effort to prepare 14, which could have been expected to



be in equilibrium with 15, the oxazine 12 was subjected to catalytic hydrogenation. A clean conversion back to 10 was accomplished.

In a further variation, the condensation of Δ^3-pyrroline with quinone 7 was attempted. In previous work with quinones of lower oxidation potential, Lown had reported the addition to be uneventful.[4] However, in our hands. a spontaneous dehydrogenation of the initial adduct took place, affording pyrrole–quinone 16. This is the first example of a pyrrole with



N-quinone substitution. The normal event in the reaction of pyrroles and quinones is α-pyrrole substitution.[5] Thus, we rule out an explanation for the formation of 16, where there is a prior conversion of Δ^3-pyrroline to pyrrole followed by addition. Instead, we hypothesize that 17 must undergo an intramolecular dehydrogenation–hydrogenation reaction. Photolysis of this pyrroloquinone did not yield an oxygen insertion product.

Experimental Section[6]

3-*N*-Pyrrolidine-2,5-xyloquinone (4). To a stirred solution of 0.200 g (1.469 mmol) of xyloquinone in 40 mL of ethanol was added 0.238 g (3.346 mmol) of pyrrolidine. The mixture, protected from light but not air, immediately darkened and after 6 h, excess amine was

removed by vacuum distillation. Preparative silica plate workup ($CHCl_3$) resulted in the isolation of 0.150 g (50%) of paste-like product **4**: UV (ethanol) λ_{max} 245 nm (log ϵ 4.4); IR ($CHCl_3$) 6.08, 6.40 (br) μm; NMR ($CDCl_3$) δ −1.88 (br s, pyrrolidino CCH_2C), 1.95 (d, J = 1.5 Hz, CH_3), 2.03 (s, CH_3), 2.8–3.2 (br, pyrrolidino NCH_2).

5,8-Dimethyl-1,2,3,3a-tetrahydropyrrolo[2,1-*b*]benzoxazol-7-ol (5). A solution of 0.150 g (0.73 mmol) of aminated quinone **4** in oxygen-free benzene was exposed to a sunlamp under a stream of nitrogen. The dark solution rapidly became colorless, the benzene was removed by vacuum distillation, and this gave the yellow photoproduct (80%): NMR ($CDCl_3$) δ 1.95 (br s, pyrrolidino CCH_2C), 2.05 (s, CH_3), 2.14 (s, ArMe), 2.8–3.5 (m, NCH_2), 5.85 (q, NCHOAr), 6.20 (s, ArH).

3-*N*-(2-Oxypyrrolidino)-2,5-xyloquinone (6). The photoproduct **5** (0.120 g, mmol) was placed in a 100-mL flask with 50 mL of benzene, 0.160 g of silver oxide, and 10 mL of water. The reaction mixture was stirred for 3.5 at 40 °C, after which the silver oxide was removed by suction filtration through a Celite column. Preparative silica plate workup ($CHCl_3$–acetone; 4:1) resulted in the isolation of 0.05 g (42%) of a reddish-purple paste **6.**

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.97; N, 6.39. Found C, 64.60; H, 7.09; N, 5.57.

UV (ethanol) λ_{max} 225, 273 (log ϵ 4.57, 4.44); IR ($CHCl_3$) 5.78, 6.08 μm; NMR ($CDCl_3$) δ 1.83 (pyrrolidino CH_2), 2.0 (br s, pyrrolidino $COCH_2$), 2.07 (d, J = 1.5 Hz, CH_3), 2.16 (s, CH_3), 2.9–3.7 (m, NCH_2), 6.50 (q, J = 1.5 Hz, vinyl H).

2-Acetyl-3-*N*-pyrrolidino-5-methyl-1,4-benzoquinone (8). To 0.36 g (1.8 mmol) of cupric acetate in 30 mL of methanol and 0.168 g (2.4 mmol) of pyrrolidine was added 0.200 g (1.22 mmol) of quinone **7** in 20 mL of methanol.[7] This was allowed to stir at room temperature in an aluminum foil wrapped 100-mL round-bottom flask with the surface well exposed to air for 20 min, at which time the solvent was removed. Workup involved putting the crude residue on preparative silica plates and eluting with chloroform. A dark red band was isolated from the plates (R_f 0.25) and 0.207 g (64%) of **8** was recovered as a paste: IR ($CHCl_3$) 3.38, 6.00, 6.09, 6.32, 6.75, 7.00, 7.35, 7.60, 9.15, 10.10 μm; UV (ethanol) λ_{max} 285 nm (ϵ 8700), (16 600), 480 (3300); NMR ($CDCl_3$) δ 183–2.18 (br, m, 4 H), 2.00 (d, 3 H, J = 1.5 Hz), 2.57 (s, 3 H), 3.37–3.68 (br, m, 4 H), 6.50 (q, 1 H, J = 1.5 Hz).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.90; H, 6.43; N, 6.00. Found: C, 66.60; H, 6.56; N, 5.63.

2-Acetyl-3,5-di-*N*-pyrrolidino-5-methyl-1,4-benzoquinone (9). Only a disubstituted product (25%) could be isolated if the time in the above-described reaction was extended 30 min: IR ($CHCl_3$) 3.45, 6.10, 6.19, 6.68, 6.92, 7.14, 7.64, 9.19 μm; UV (ethanol) λ_{max} 273 nm (ϵ 7200), 325 (7830), 375 sh (2685), 495 (716); NMR ($CDCl_3$) δ 1.80–2.17 (br, m, 8 H), 2.02 (s, 3 H), 2.51 (s, 3 H), 3.55–4.04 (br, m, 8 H).

8-Acetyl-1,2,3-3a-tetrahydro-5-methylpyrrolo[2,1-b]benzoxazol-7-ol (10). A stirred solution of 0.94 g (0.403 mmol) of red aminoquinone **8** in 150 mL of distilled benzene purged with nitrogen was irradiated for 90 min with a GE 250-W sunlamp. Silica preparative plate chromatography of the concentrated residue ($CHCl_3$–EtOAc, 20:80) yielded 0.910 g (96.8%) of yellow phenol as an oil: IR ($CHCl_3$) 2.79, 3.42, 6.13, 6.20, 7.01, 7.91, 8.50, 9.35, 9.80, 10.80 μm; UV (ethanol) λ_{max} 225 nm (ϵ 13 900), 286 (11 700), 398 (4600); NMR ($CDCl_3$) δ 1.73–2.52 (br, m, 4 H), 2.21 (s, 3 H), 2.75 (s, 3 H), 2.90–4.28 (br, m, 2 H), 5.90–6.08 (br, m, 1 H), 6.44 (s, 1 H), 13.30 (s, 1 H, ex).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 67.00; H, 6.45; N, 6.00. Found: C, 67.07; H, 6.61; N, 5.60.

Photo Product 11 from 2-Acetyl-3,6-di-*N*-pyrrolidino-5-methyl-1,4-benzoquinone. A stirred solution of 0.070 g (0.232 mmol) of red bispyrrolidinoquinone **9** in 100 mL of distilled benzene purged with nitrogen was irradiated for 40 min with a GE 250-W sunlamp. Silica preparative plate chromatography ($CHCl_3$–EtOAc, 20:80) yielded 0.051 g (72.9%) of a single yellow phenol **11** as an oil: IR ($CHCl_3$) 2.70 br, 3.24, 3.49, 6.00, 7.00, 7.40, 8.58 9.25 μm; NMR ($CDCl_3$) δ 1.73–2.36 (br, m, 8 H), 2.28 (s, 3 H), 2.61 (s, 3 H), 2.92–3.26 (br, m, 5 M, 1 ex), 3.26–4.26 (br, m, 2 H), 5.83–5.99 (br, t, 1 H).

Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.70; H, 7.20; N, 9.27. Found: C, 67.20; H, 7.03; N, 8.90.

Oxidation of Photoproduct 10. A mixture of 0.083 g (0.36 mmol) of phenol **10**, 25 mL of benzene, 5 mL of water, 0.267 g (1.11 mmol) of Ag_2O, and 5 mg of K_2CO_3 was warmed at 45 °C for 3 h. The reaction mixture was worked up by filtration of the silver and silver oxide. That some organic material was adsorbed on the solid was revealed by the recovery of 73% of the organic product. Preparative TLC using 90:10 $CHCl_3$–EtOAc gave a major red band which was characterized as follows: IR ($CHCl_3$) 2.70, 3.42, 6.50 μm; NMR ($CDCl_3$) δ 1.78 (s, CH_3), 1.89 (m, CH_2CH_2), 2.02 (d, J = 1.5 Hz, CH_3), 3.67–4.33 (br m, NCH_2 and OH, exchangeable), 5.15 (m, OCHN), 6.52 (g, J = 1.5 Hz, vinyl H). We were not able to obtain a satisfactory combustion analysis, but its conversion back to **10** as described below allows us to assign its structure as **12.**

Conversion of 12 to 10. A sample of **12** (0.069 g, 0.277 mmol) was hydrogenated in EtOAc using 0.01 g of 10% Pd/C catalyst. Upon removal of the catalyst (again some organic material was adsorbed) and the solvent, 0.050 g (79% yield) of phenol **10** was isolated.

2-Acetyl-5-methyl-3-(1*H*-pyrrol-1-yl)benzoquinone (16). To a stirred solution of excess 3-pyrroline and 0.300 g (1.5 mmol) of cupric acetate in 40 mL of methanol was added 0.130 g (0.793 mmol) of quinone **7** in 15 mL of methanol. After 25 min the reaction was complete and silica chromatography on a preparative plate ($CHCl_3$) yielded 0.048 g (26.4%) of **16** from an orange-yellow band, R_f 0.06, as a paste: IR ($CHCl_3$) 5.81, 5.93, 6.02, 6.21, 6.83, 7.31, 7.53, 7.62, 8.82, 9.14, 9.95, 10.70, 11.23 μm; NMR ($CDCl_3$) δ 2.03 (s, 3 H), 2.14 (d, 3 H, J = 1.5 Hz), 6.38 (t, 2 H, J = 2.5 Hz), 6.67 (q, 1 H, J = 1.Hz), 6.77 (t, 2 H, J = 2.5 Hz).

Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.20; H, 4.80; N, 6.12. Found: C, 68.30; H, 4.96; N, 5.82.

Registry No.—**4**, 63076,91-5; **5**, 63076-92-6; **6**, 63076-93-7; **7**, 63076-94-8; **8**, 63076-95-9; **9**, 43140-86-9; **10**, 63076-96-0; **11**, 63076-97-1; **12**, 63076-98-2; **16**, 63076-99-3; xyloquinone, 137-18-8; pyrrolidine, 123-75-1; 3-pyrroline, 109-96-6.

References and Notes

(1) (a) For a survey of synthetic routes through June 1974, see: G. J. Siuta, R. W. Franck, and R. J. Kempton, *J. Org. Chem.*, **39**, 3739 (1974). (b) A transannular 4,9a closure to a tricyclic has been reported: J. W. Lown and T. Itoh, *Can. J. Chem.*, **53**, 960 (1975); T. Itoh, T. Hata, and J. W. Lown, *Heterocycles*, **4**, 47 (1976). (c) A variant of a Claisen condensation with an imino ether followed by an S_NAr reaction has been used to form the 9,9a and 4,4a bonds: T. Kametani and K. Fukimoto, *ibid.*, **3**, 691 (1975). (d) The one example to date of a mitosene with an angular oxygen: T. Kametani, T. Ohsawa, K. Takahashi, M. Ihara, and K. Fumumcto, *ibid.*, **4**, 1637 (1976). (e) **Note Added in Proof:** Deiminomitomycin A has been synthesized: F. Nakatsubo, A. J. Cocuzza, D. E. Keeley, and Y. Kishi, *J. Am. Chem. Soc.*, **99**, 4835 (1977).

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(6) Analyses were performed by Spang Laboratories, Ann Arbor, Mich. NMR spectra were determined with Varian A-60A, XL 100, and Perkin-Elmer R12B spectrometers with chemical shifts expressed in δ units. For funds used to purchase the Perkin-Elmer R12B, we acknowledge Biomedical Sciences Support Grant RR 07150 from DHEW. Further we acknowledge the National Cancer Institute for grant CA 11421. We thank Dr. Ian Baxter for pertinent suggestions concerning quinone chemistry.

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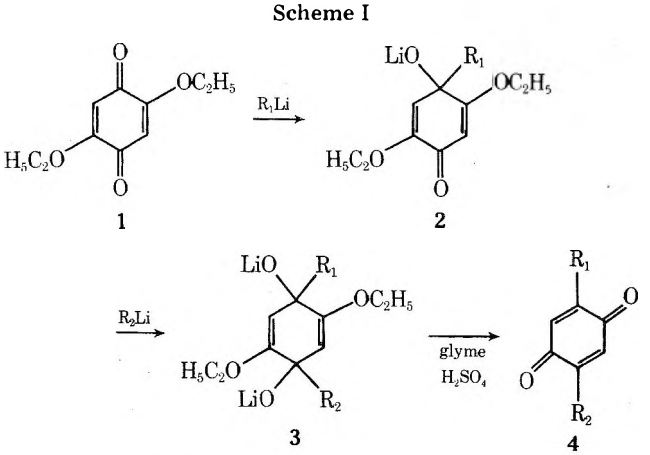
A Simple Synthetic Route to 2,5-Disubstituted 1,4-Benzoquinones

Summary: For the first time synthetic methodology is presented which allows the facile construction of 1,4-benzoquinones which are alkylated, alkynylated, or arylated at the 2,5 positions. Specifically, 2,5-diethoxy- and 2,5-dichloro-3,6-dimethoxy-1,4-benzoquinone react with organolithium reagents via 1,2 addition to the carbonyl groups. The enol ether linkages in the resulting adducts undergo acid hydrolysis to give the 2,5-disubstituted 1,4-benzoquinones.

Sir: A wide variety of naturally occurring quinones exist in which the nucleus is functionalized at the 2 and 5 positions.[1] However, no synthetic methodology currently exists which allows the facile construction of such structural features. Described here is a method which provides a simple, "one pot" solution to this problem. Specifically, we have observed that organolithium reagents undergo 1,2 addition to the carbonyl groups of 2,5-diethoxy-1,4-benzoquinone[2] (**1**). Acid hydrolysis of the resulting adducts, **3a–d,** gives the corresponding 2,5-disubstituted 1,4-benzoquinones (**4a–d**) in respectible yields. This total transformation can be accomplished without isolation of the intermediate products. It is also noteworthy that this technique can be employed to make unsymmetrically substituted quinones by utilizing two different organolithium reagents. This methodology for the synthesis of unsymmetrical quinones is particularly good when lithium alkynylide is employed as the first reagent. Attempts to make unsymmetrical alkyl, aryl, or alkylaryl 1,4-benzoquinones generally gave an appreciable amount of the symmetrical quinone. However, since the alkynyl group possesses significant synthetic versatility, one can envisage its utility for the construction of a large variety of unsymmetrically substituted quinones.

The general procedure involves treatment of a diethyl ether/THF (1:1) solution of the quinone with the organolithium reagents (Scheme I). The reaction is accomplished at −22 to 0 °C depending upon the specific example. After approximately 8 h the reaction mixture is quenched with ammonium chloride and a few drops of 2 N H_2SO_4 are added, which accomplishes the hydrolysis of one of the enol ether linkages. The solvent is then removed in vacuo and the residue dissolved in a mixture of glyme and concentrated H_2SO_4, which accomplishes the final hydrolysis. The quinone products were then isolated by column chromatography on silica gel. The structures of the new products were assigned on the basis of the following data. 2,5-Di(3-benzyloxy-1-propynyl)-1,4-benzoquinone (**4c**); mp 70–72 °C; ^1H NMR ($CDCl_3$, δ) 4.33 (s, 2 H), 4.53 (s, 2 H), 6.97 (s, 1 H), 7.40 (s, 5 H); IR (Nujol, cm^{-1}) 2215, 1650, 1570. Anal. C, 78.82; H, 5.20. 2-(3-Benzyloxy-1-propynyl)-5-phenyl-1,4-benzoquinone (**4d**); mp 96–97 °C; ^1H NMR ($CDCl_3$, δ) 4.37 (s, 2 H), 4.70 (s, 2 H), 6.97 (s, 1 H), 7.03 (s, 1 H), 7.43 (s, 5 H), 7.50 (s, 5 H); IR (Nujol, cm^{-1}) 2210, 1657, 1645, 1597, 1585. Anal. C, 80.73; H, 4.95.

Scheme I



	R_1	R_2	Yield, %
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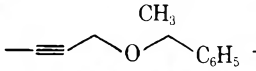
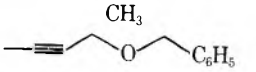
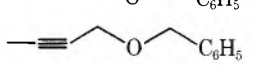
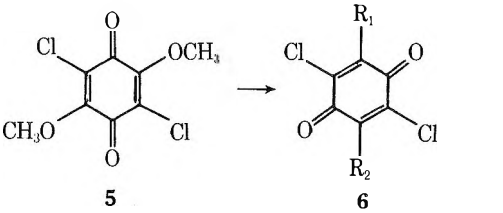
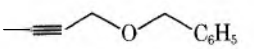
b	CH_3	CH_3	52[3b]
c			56
d		C_6H_5	60

It was of interest to extend the scope of this reaction to include more highly substituted quinones, particularly those having halogens at the 3 and 6 positions. In certain situations quinones such as these provide a synthetic advantage, since the halogen substituents are easily replaced by a variety of nucleophiles. For example, hydroxyquinones can be obtained from the corresponding chloroquinones under hydrolytic conditions, and a number of natural products contain the 2,5-dialkyl- (or aryl-) 3,6-dihydroxy-1,4-benzoquinone moiety.[1] A specific example is polyporic acid, 2,5-dihydroxy-3,6-diphenyl-1,4-benzoquinone, which has been obtained by hydrolysis of the corresponding 2,5-dichloroquinone **6a**.[4] It was, in fact, found that when 2,5-dichloro-3,6-dimethoxy-1,4-benzoquinone (**5**)[5] was subjected to the methodology outlined here, the corresponding 2,5-disubstituted-3,6-dichloro-1,4-benzoquinones **6a–d** were realized.



5 **6**

	R_1	R_2	Yield, %
a	C_6H_5	C_6H_5	50
b	C_6H_4-*p*-OCH_3	C_6H_4-*p*-OCH_3	50[6b]
c	CH_3	CH_3	64[7]
d		CH_3	55

Structural data for the previously unknown 2-(3-benzyloxy-1-propynyl)-3,6-dichloro-5-methyl-1,4-benzoquinone (**6d**) follows: mp 99–100 °C; ^1H NMR ($CDCl_3$, δ) 2.18 (s, 3 H), 4.40 (s, 2 H), 4.60 (s, 2 H), 7.45 (s, 3 H); IR (Nujol, cm^{-1}) 2270, 1680, 1670, 1570. Anal. C, 60.95; H, 3.74; Cl, 21.10.

Although a systematic study of the reactions of quinones with organometallic reagents has never appeared, one thinks of such reactions as being fraught with difficulties due to electron-transfer processes. Indeed it has been observed that Grignard reagents react with simple quinones to give very complex reaction mixtures.[8] In the work described here, one is presumably circumventing such complex reaction pathways by utilizing the alkoxy-substituted quinones. The reduction

potential of such quinones would be lowered and electron transfer reduced.[9]

The synthetic methodology outlined in this manuscript provides potentially the simplest route to 2,5-disubstituted 1,4-benzoquinones and complements recent advances directed toward the monoalkylation or arylation of the quinone nucleus. Particularly noteworthy in this regard are the utilization of trimethylsilyl cyanide (TMSCN) protected quinones,[10] the use of lithium salts of 1-bromo-3,3,6,6-tetramethoxy-1,4-cyclohexadiene (a latent quinone carbanion),[11] the reactions of quinones or protected bromoquinols with π-allyl-nickel complexes,[12] the utilization of monoketals of quinones,[13] and the use of 1,4-dimethoxynaphthyllithium.[14]

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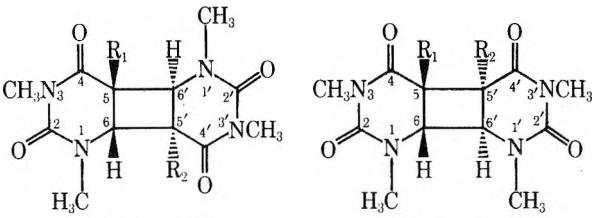
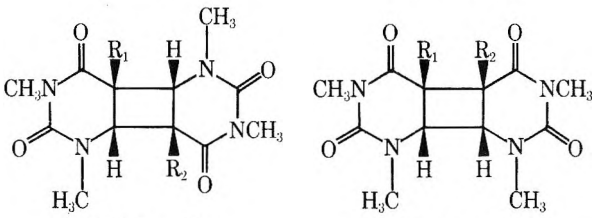
C-Alkylation and Deuterium Exchange of Cyclobutane–Dipyrimidines

Summary: A novel method for C-alkylation and deuteration of pyrimidine dimers with retention of configuration is described.

Sir: Generally, it is agreed[1–5] that the most significant breakthrough in nucleic acid photochemistry was the isolation and identification of the thymine dimer (Thy<>Thy)[6] by Beukers and Berends[7] and by Wang.[8] As pyrimidine (Pyr) photodimerization has gained significance in biological systems,[9,10] it has become one of the most intensively studied topics.[11] However, reports concerning studies of the chemistry of Pyr dimers are infrequent.[2,12]

N-Methylation of uracil dimer (Ura<>Ura) was first found[13] to give primarily Me^3Ura<>Me^3Ura. With dimethyl sulfate and diazomethane, Ura<>Ura yielded a mixture of di- and trimethyl derivatives.[2] However, complete methylation was obtained when *cis,syn-* and *cis,anti-*Ura<>Ura were treated with methyl iodide and silver oxide in dimethylformamide.[14] Finally, the complete methylation of





a, $R_1 = R_2 = H$ — Me_2Ura<>Me_2Ura
b, $R_1 = CH_3$; $R_2 = H$ — Me_2Thy<>Me_2Ura
c, $R_1 = CH_3$; $R_2 = CH_3$ — Me_2Thy<>Me_2Thy
d, $R_1 = CH_2CH_3$; $R_2 = H$ — Me_2EtUra<>Me_2Ura
e, $R_1 = R_2 = CH_2CH_3$ — Me_2EtUra<>Me_2EtUra
f, $R_1 = R_2 = C_6H_5CH_2$ — Me_2BzUra<>Me_2BzUra
g, $R_1 = R_2 = D$ — Me_2d_1Ura<>Me_2d_1Ura

the four isomeric Ura<>Ura to their corresponding Me_2Ura<>Me_2Ura was found to be feasible in dimethyl sulfoxide.[15]

Unexpectedly, we discovered that subsequent to complete N-methylation, C-methylation occurred when *trans,syn-* and *trans,anti-*Ura<>Ura were treated under similar conditions. This finding prompted us to investigate further the C-alkylation of cyclobutane derivatives.

The general procedure for C-alkylation was as follows. First, silver oxide (2 mmol, 460 mg) was added to a solution of Me_2Ura<>Me_2Ura (0.2 mmol, 56 mg) in $HCON(CH_3)_2$ (2 mL). To this mixture, 12 mmol of an alkyl halide was added; this was stirred for an appropriate period at ambient temperature. This reaction mixture was then poured into 200 mL of 5% NaCN solution to decompose the "silver complex".[16] The product was extracted three times with 200 mL of chloroform. Chloroform was evaporated from the combined extracts, and the residue was applied on silica gel thin-layer plates for chromatography with an eluent of chloroform/acetone (2:1). We found that the R_f values for dialkylated compounds are greater than the value of the monoalkylated products which, in turn, are greater than those of the starting materials. For this reason, these product mixtures were easily separated. The product was then eluted with methanol and recrystallized. The reaction conditions and the properties of the alkylation products are summarized in Table I.

We found that C-methylation of cis isomers is slower than for trans isomers (see Table I). This appears to correlate with our observation in deuterium exchange of the dimers. In this process, a solution of a dimer in D_2O was treated with 2 molar equiv. of silver oxide at ambient temperature with stirring for 24 h, and the insoluble material was removed by filtration. The deuterated product was then extracted from the filtrate with chloroform. After being dried over anhydrous Na_2SO_4, chloroform was evaporated. The residue was dissolved in $CDCl_3$ for the NMR analysis of the extents of deuteration. As can be seen from Table II, deuterated Ia and IIa both showed only three singlets, with the disappearance of the signal corresponding to C(5)H. This clearly indicates that "complete"deuteration at C(5) to C(5)D occurred. However, after similar deuterium exchange, IIIa and IVa gave quite complex spectra showing a pair of "pseudo" triplets for C(5)H and C(6)H. This evidence suggests that cis dimers were only par-

Table I. Alkylation of $Me_2Ura<>Me_2Ura$ at Room Temperature in Dimethylformamide

$Me_2Ura<>Me_2Ura$	RI	Reaction time, h	Product	Yield, %	Solvent for crystallization	Mp, °C
trans,anti (Ia)	CH_3	24	Ic	92	CH_3OH	259–260[e]
	C_2H_5	96	Id	24	AcOEt[d]	180
			Ie	31	CH_3OH	sublime
	$C_6H_5CH_2$[a]	24	If[c]	34	CH_3OH	>270
trans,syn (IIa)	CH_3	24	IIc	86	CH_3OH	253–254[e]
	C_2H_5	96	IId	42	AcOEt	182–183
			IIe	13	C_2H_5OH	sublime
	$C_6H_5CH_2$[a]	24	IIf[c]	39	CH_3OH	273
cis,anti (IIIa)	CH_3	48[b]	IIIb	27	AcOEt	208–209
			IIIc	4	CH_3OH	226–227[e]
cis,syn (IVa)	CH_3	48[b]	IVb	32	AcOEt	206–207
			IVc	<2	CH_3OH	252–253[e]

[a] Benzyl bromide was used instead of iodide. [b] Equal portions of the reagents were added at 6-, 18-, and 24-h intervals. [c] Mother liquors after recrystallization were not studied. [d] Petroleum ether was added for recrystallization. [e] These melting points are comparable to those reported by Kleopfer and Morrison.[19]

Table II. NMR Spectra of $Me_2Ura<>Me_2Ura$ [220 MHz, 25 °C, $CDCl_3$ solvent, $Si(CH_3)_4$ internal standard]

	Chemical shift, δ, ppm					
	Nondeuterated			Deuterated		
$Me_2Ura<>Me_2Ura$	$N(CH_3)$[6 H, s]	C(5)H[2 H, s]	C(6)H[2 H, s]	$N(CH_3)$	C(5)H	C(6)H
trans,anti	3.16	3.56	4.14	3.11 (6 H, s)	No	4.11 (2 H, s)
Ia → Ig	3.31	(3.43)[a]	(4.18)[a]	3.27 (6 H, s)		
	(3.13)[a]	(3.52)[b]	(4.10)[b]			
	(3.3)[a]					
trans,syn	3.09	3.73	3.88	3.09 (6 H, s)	No	3.89 (2 H, s)
IIa → IIg	3.27	(3.72)[a]	(3.92)[a]	3.27 (6 H, s)		
	(3.12)[a]	(3.63)[b]	(3.90)[b]			
	(3.3)[a]					
cis,anti	3.14	3.77	4.11	3.14 (s)	3.79 (t)[d]	4.12 (t)[d]
IIa → IIIg	3.16	(3.79)[b]	(4.12)[b]	3.16 (s)		
	(3.17)[a]	(3.98)[a,c]	(3.98)[a,c]			
cis,syn	3.02	3.78	4.08	3.02 (s)	3.79 (t)[d]	4.08(t)[d]
IVa → IVg, IVa	3.19	(3.80)[b]	(4.08)[b]	3.18		
	(3.1)[a]	(3.72,	(4.06,			
	(3.22)[a]	3.80,	4.14,			
		3.88)[a]	(4.22)[a]			

[a] Values reported by Elad et al.[14] [b] Values given were calculated from those reported by Fahr et al.,[20] and the NMR spectra were measured with a 90-MHz spectrometer. [c] These signals appeared as a multiple centered at δ 3.98. The correlation between the NMR patterns of C(5)H and C(6)H of $Me_2Ura<>Me_2Ura$, $Me_2Thy<>Me_2Ura$, and $Me_2Thy<>Me_2Thy$ are quite interesting. Their interpretations and possible importance in the assignments of various stereoisomers of homo and hetero dimers have been reported.[21] [d] These signals are due to a combination of doublet and singlet of un- and dideuterated species.

tially deuterated because these triplet signals can be assigned to both the deuterated and the nondeuterated starting materials (see Table II). This difference between cis and trans isomers can be attributed to the variance in anion formation at the exchange sites, i.e., the sites of alkylation. Thus, it is reasonable to suggest that the ease of anion formation at methylation sites is responsible for the difference in C-methylation of cis and trans dimers.

Under the condition of complete C-methylation of these dimers, only partial ethylation and benzylation were obtained, even for trans isomers. These results are also presented in Table I. However, attempts to introduce isopropyl or *tert*-butyl groups have been unsuccessful so far.

Although alkylation and deuteration have not been detected previously for Pyr dimers, our finding that these processes occur with ease was not entirely unexpected. An earlier study[17] of the effects of ring size on the rates of base-catalyzed enolization of cycloalkanones showed that the reactivity is 4 > 5 > 6 > 7 in $HCON(CH_2)_2$–D_2O. Indeed, we find that neither methylation nor deuteration takes place when 5,6-dihydro derivatives of the six-membered ring compounds Me_2Ura and Me_2Thy are subjected to the same conditions. However, the possibility that the *trans*-dihydropyrimidine ring, which is on the same side as the proton being removed, may help form a complex with the Ag_2O that may facilitate this reaction should also be considered.[18]

Since the stereochemistry of various isomers of $Me_2Ura<>Me_2Ura$ and $Me_2Thy<>Me_2Thy$ has been well established[19] and, as we have shown, C-methylation of $Me_2Ura<>Me_2Ura$ isomers resulted in the respective $Me_2Thy<>Me_2Thy$ isomer with the same configuration, this methylation process must take place with the retention of configurations.

The importance of the above findings may be indicated by several reasons. Obviously, they furnish information enabling a better understanding of the correlation of Pyr<>Pyr. This approach of C-alkylation provides a convenient method for the preparation of various isomers of Thy<>Ura derivatives,[21] one of which has been implicated as a product isolable from the acid hydrolysates of UV-irradiated DNA *in vivo* and *in vitro*.[22] In addition, the susceptibility of deuterium exchange is being developed as a sensitive method for assaying various uracil homo and hetero dimers in the presence of Thy<>Thy by tritium labeling of photoproducts of UV-irradiated DNA and RNA. Although all of the above specifies aspects that have direct relevance to the studies of photobiology of nucleic acids, this reaction may be pertinent with regard to alkylation of cyclobutane derivatives in general. The latter study has much current interest.[23]

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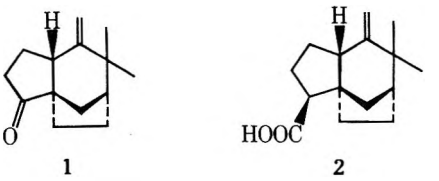
The Synthesis of Khusimone

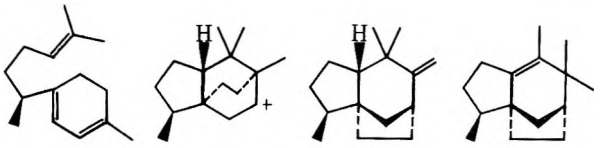
Summary: A biogenetically patterned synthesis of khusimone (1), a norsesquiterpene with zizaene skeleton, proceeds through the two epimeric tricyclic ketones 14 and 15, prepared by intramolecular Diels–Alder cyclization of the trienone ketal 13. Acid-catalyzed isomerization of 15 gives exclusively isokhusimone (17), while isomerization of epimer 14 yields norcedrenone (16) and isokhusimone (17) in a ratio of 2:1. To convert isokhusimone (17) to the less stable racemic khusimone (1), the allylic alcohol 21 produced on photooxygenation of 17 is reduced with zinc and hydrogen chloride in ether.

Sir: Vetiver oil [*Vetiveria zizanioides* (L.) Nash] is one of the important raw materials for the composition of refined fragrances. The characteristic scent of the essence is partly due to khusimone (1), a tricyclic norsesquiterpene ketone.[1] Oxidative decarboxylation of *natural* zizanoic acid (2) with lead tetraacetate, followed by oxidation of the resulting secondary alcohol, has been utilized[2] to produce quantities of khusimone (1), but the two published *total* syntheses[3] of zizanoic acid (2) are unfortunately not practicable.

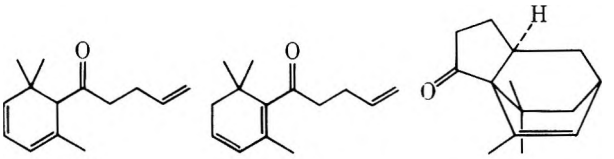
We describe a total synthesis of khusimone (1), which in its critical stages mimics the most likely biogenetic pathway.


1 2

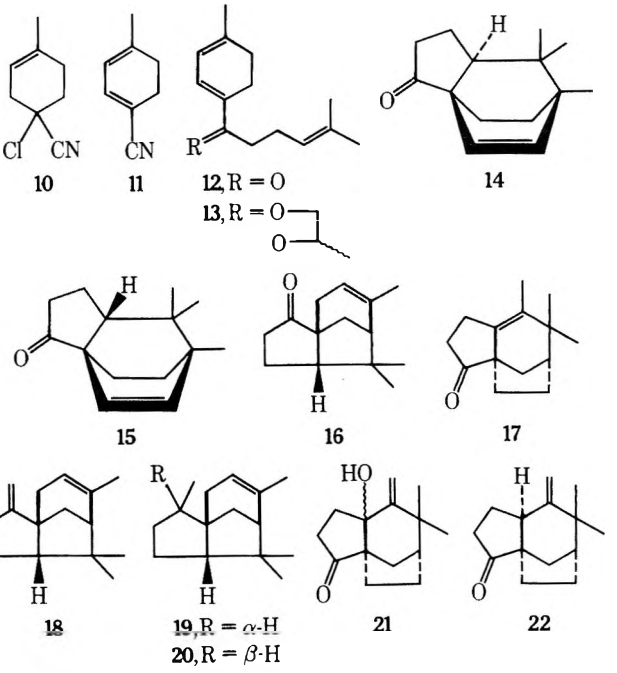
Yoshikoshi[4] was the first to suggest that zizaenes might biogenetically be derived from γ-curcumene (3) via the ion 4, followed by two Wagner–Meerwein rearrangements. The subsequent discovery of prezizaene (5),[5] its acid-catalyzed isomerization to, among other products, isozizaene (6), and the very inefficient dehydration of allocedrol (secondary alcohol derived from 4) to *enantio*-prezizaene[6] provided indirect evidence in support of this biogenetic scheme.


3 4 5 6

Our plan to construct the critical tricyclic olefin 14 or 15 by an intramolecular Diels–Alder reaction was based on the previously observed thermal cyclization of 7 to 9 (70% yield), which seems to proceed via the hypothetical intermediate 8, the product resulting from a 1,5-hydride shift.[7]


7 8 9

Addition of isoprene to α-chloroacrylonitrile[8] in the presence of some 2,5-di-*tert*-butylhydroquinone (15 h, 100 °C) gave the adduct 10 accompanied by 30% of its isomer. In preparative runs these were not separated, and the mixture was treated with 1,5-diazabicyclo[3.4.0]non-5-ene in tetrahydrofuran at 0–5 °C. Fractional distillation afforded the pure nitrile 11, UV max (95% EtOH) 295 nm (ε 9950), in 55% overall yield. Condensation of 11 with 5-lithio-2-methylpent-2-ene, prepared from the corresponding bromide[9] and lithium con-


10 11 12, R = O 13, R = O 14
15 16 17
18 19, R = α-H 20, R = β-H 21 22

taining 1% sodium in ether at −10 °C, followed by hydrolysis of the ketimine with 1 N aqueous hydrochloric acid–ether, gave the trienone **12**, bp 94–95 °C (0.02 mm), UV max (95% EtOH) 315 nm (ε 11 700) (75%). Experiments to effect the Diels–Alder condensation within this intermediate were discouraging and produced mainly the aromatic ketone derived from **12**. Ketal **13**, prepared with 1,2-propanediol (91% yield) in benzene with a trace of 85% phosphoric acid (Dean–Stark trap, 60 h), when heated in a sealed tube in mesitylene solution at 250 °C for 24 h, followed by hydrolysis of the crude product with perchloric acid in aqueous tetrahydrofuran, furnished a mixture of two epimeric ketones, **14** and **15**, in 55% yield. Chromatography of the ketals on silica gel and hydrolysis afforded pure isomers **14** [75%; mp 64–65 °C; IR ($CHCl_3$) 1735 cm^{-1}; NMR (CCl_4) δ 6.04 (1 H, d, J = 8 Hz)] and **15** [25%, mp 38–39 °C; IR ($CHCl_3$) 1735 cm^{-1}; NMR (CCl_4) δ 6.28 (1 H, d, J = 8 Hz). The configurations already assigned are based on the relative chemical shifts of the vinyl protons in the β position to the carbonyl group.

Heating epimer **15** with *p*-toluenesulfonic acid in benzene caused isomerization to racemic isokhusimone (**17**) (80%), identical with (−)-isokhusimone prepared by acid-catalyzed isomerization of (−)-khusimone (**1**).[11] The selectivity observed in this isomerization came as no surprise. Protonation of the double bond in **15** could lead to two carbonium ions. That located β to the carbonyl group is not likely to rearrange because 1,2-alkyl shifts would lead to either an electron deficiency α to the carbonyl group or a bridgehead carbonium ion. Methyl migration within the other cation would again create a forbidden carbonium ion, while migration of the most substituted carbon atom would give a strained *trans*-bicyclo[3.3.0]octane. Of the six possible 1,2-migrations, five are thus highly unlikely and were in fact not observed.

Isomerization of epimer **14** gave two products separable, as of now, only with loss of material. Isokhusimone (**17**) (15% of pure material) is now the minor and norcedrenone (**16**) [40% of pure material; mp 57–59 °C; IR ($CHCl_3$) 1730 cm^{-1}], a substituted *cis*-bicyclo[3.3.0]octane, the major product. Condensation of the new ketone **16** with methylenetriphenylphosphorane produced the liquid diene **18**, which on reduction with diimide (N_2H_4, H_2O_2) gave a mixture of α-cedrene (**19**) and *epi*-2α-cedrene (**20**).[12]

The contrathermodynamic isomerization of isokhusimone (**17**) to khusimone (**1**) caused difficulties, but was eventually accomplished as follows. Photosensitized oxygenation (Rose Bengal, EtOH–H_2O, 90 min, 25 °C), followed by workup with triethyl phosphite (20 °C, 8 h), yielded the allylic alcohols **21**, mp 107–110 °C (77%), which could be reduced with zinc and hydrogen chloride[13] in 75% yield to a mixture of epikhusimone (**22**) (30%) and racemic khusimone (**1**), mp 72–72.5 °C (70%). Identity with natural material was established by comparison of IR and NMR spectra, as well as chromatographic behavior.

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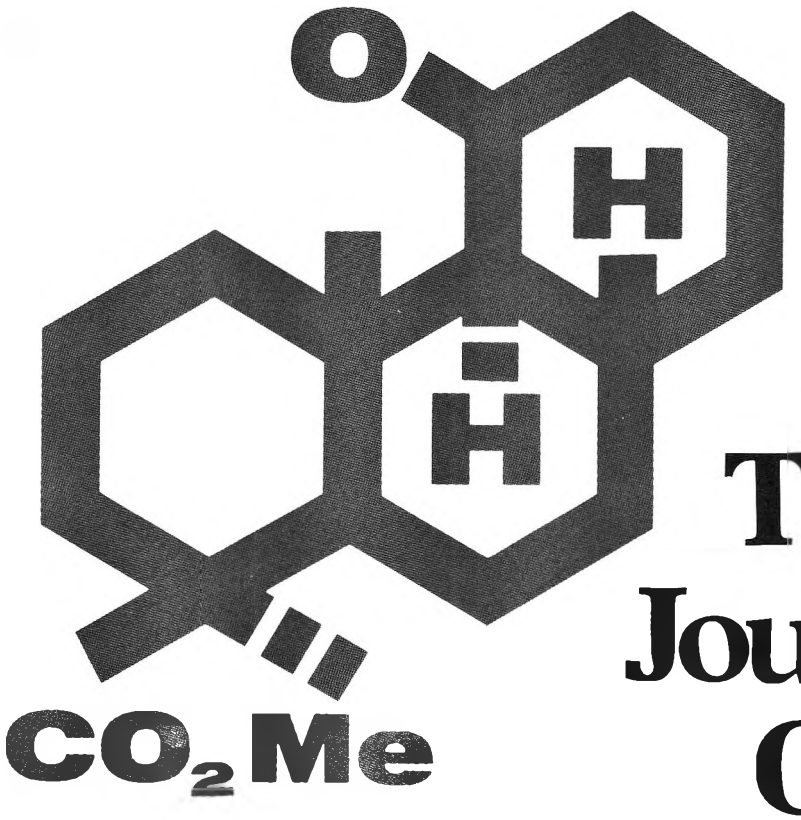

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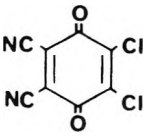
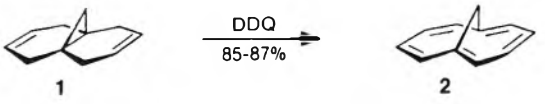
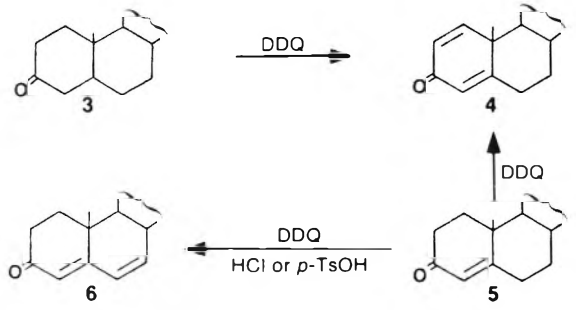


DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), a quinone of high oxidation potential, is a versatile reagent with proven applications in synthesis.[1] It is often the reagent of choice for dehydrogenation and selective oxidation. Thus, **DDQ** effects the dehydrogenation of the methano-bridged hexahydronaphthalene **1** to give the 10-π-electron annulene **2** in excellent yield.[2]

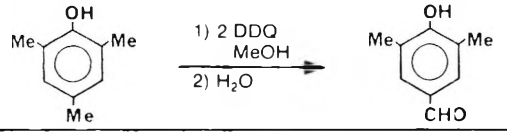


DDQ has recently been employed in the synthesis of diolepoxides of benz[*a*]anthracene, indicating its potential use in the synthesis of diolepoxides of other polynuclear aromatic hydrocarbons. These metabolites are currently of intense interest because of the proven muta- and carcinogenicity of a diolepoxide of benzo[*a*]pyrene.[3]

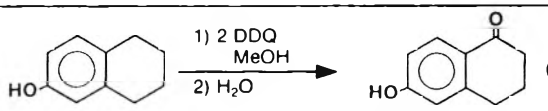
The dehydrogenation of 3-ketosteroids is only one example of the extensive use of **DDQ** in the steroid field.[4] Saturated 3-ketosteroids (**3**) give the corresponding $\Delta^{1,4}$-derivatives (**4**).[5,6] Δ^4-3-Ketosteroids (**5**) yield the same $\Delta^{1,4}$ product under aprotic conditions, but $\Delta^{4,6}$-dienes (**6**) in the presence of hydrogen chloride[7] or *p*-toluenesulfonic acid.[6]



Many of the useful synthetic reactions of suitably substituted phenols with **DDQ** can be rationalized as proceeding through an intermediate quinone methide. Thus, mesitol is oxidized in methanol to the corresponding *p*-carboxaldehyde by two equivalents of **DDQ** (eq 1),[8] and 6-hydroxy-

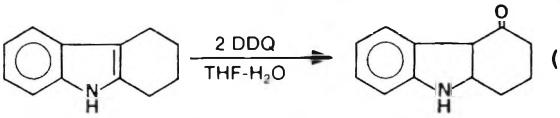


(eq 1)



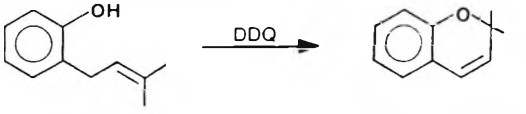
(eq 2)

tetralin gives the tetralone (eq 2).[9] Similarly, 3-alkylindoles are converted to 3-acylindole derivatives (eq 3).[10]



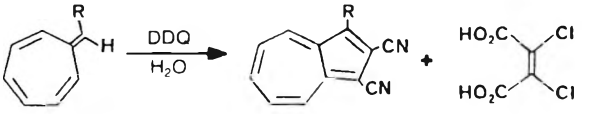
(eq 3)

Upon treatment with **DDQ**, 2-(3,3-dialkylallyl)phenols undergo oxidative cyclization to 2,2-dialkylchromenes (eq 4).[11] Phenols with *o*-allyl groups unsubstituted in the 3-position undergo oxidation to coumarins.[12]



(eq 4)

DDQ also functions as a component in cycloaddition reactions. Thus, **DDQ** and 8-substituted heptafulvenes yield 3-substituted 1,2-dicyanoazulenes, a result which can be rationalized as an ($8\pi + 2\pi$) cycloaddition.[13]



DDQ has also been employed as a spray reagent in the tlc analysis of carbazoles.[14]

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