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VOLUME 41, NUMBER 13

JUNE 25, 1976

Facile Skeletal Rearrangement by Reaction of Polycyclic Olefins with Lead(IV) and Thallium(III) Salts[1]

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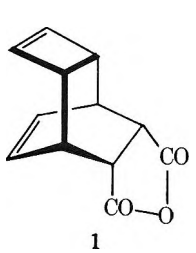
Received November 13, 1975

Reaction of tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives with lead tetraacetate, thallium triacetate, and thallium trinitrate has been studied. The structures of the products were determined by spectral means and chemical transformations. Skeletal rearrangement of the polycyclic hydrocarbons was examined. Some mechanisms for the formation of the products are discussed.

Rigid molecules such as the norbornadiene skeleton containing two isolated double bonds in spatial proximity are known to undergo facile chemical reactions involving π-participation between two double bonds.[2,3] The transannular reactions of these molecules have provided a simple synthetic route to new highly strained polycyclic hydrocarbons and information about the participation between two double bonds. Little is known concerning the relationship among the reactivity, regioselectivity, and stereoselectivity of the transannular reaction, and the nature of the double bond participation.

We have previously reported the reaction of tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives **1** and **2** with electrophiles.[3-6] These results are summarized on the basis of common intermediate **3** which divided into two groups ac-



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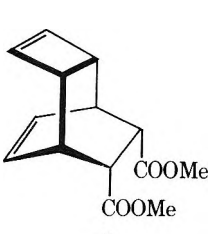

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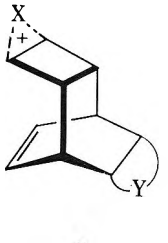

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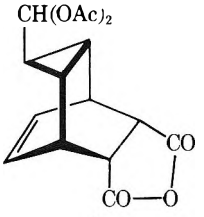
cording to the nature of the bridged ion atom "X": (1) transannular cross cyclization via the intermediacy of a bridged cation with more electronegative atoms such as oxygen, chlorine, and bromine;[3,5] (2) syn addition via an organomercuric intermediate to the strained double bond.[4] An iodine cation intermediate is situated in the intermediate position.[6]

Oxidation of **1** and **2** with mercury(II) acetate has revealed the exo-cis addition to a strained double bond controlled by the twist strain of the transition state.[4] In this connection, it is well known that mercury(II), thallium(III), and lead(IV) salts are isoelectronic and the oxidation potentials of the ions are in the order Hg < Tl < Pb.[7]

In the hope of providing some additional data for understanding the reaction of type 2, we have investigated the reactions of **1** and **2** with lead tetraacetate, thallium triacetate, and thallium trinitrate, respectively, and have also examined the skeletal rearrangement of the related compounds leading to novel strained bridged polycyclic hydrocarbons.

Results

Reaction of Lead Tetraacetate with 1 and 2. The reaction of **1** with equimolar lead tetraacetate in acetic acid at 70 °C gave product **4** in about 10% yield with recovery of the



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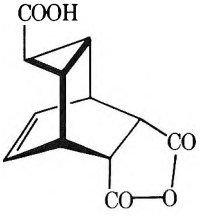

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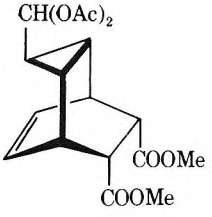

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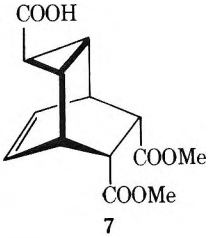

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starting material (90%). Similar reaction at 100 °C gave a complex mixture as evidenced by TLC inspection, but compounds **4** and **5** were obtained in 25 and 3% yields, respectively. On the other hand, the reaction of **2** with lead tetraacetate gave **6** in a moderate yield. The reaction of **2** with lead tetraacetate in the presence of boron trifluoride–acetic acid complex at 70 °C gave **7** in 67% yield, but at 100 °C the yield of **7** decreased considerably.

Table I. Reactions of 1 and 2 with Lead Tetraacetate under Various Conditions

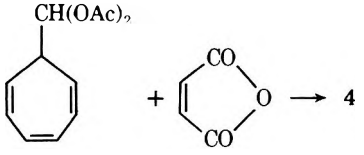
Compd	Reaction conditions: Solvent	Temp, °C	Products (%)	
1	AcOH	70	4 (10)	
	AcOH	100	4 (25)	5 (3)
2	AcOH	70	6 (67)	
		100	6 (63)	
	$AcOH-BF_3$	70	7 (67)	
	$AcOH-BF_3$	100	7 (20)	

These results are summarized in Table I.

Structural elucidation of 4 and 5 was accomplished on the basis of spectral data and chemical transformations.

The ir spectrum of 4 shows carbonyl absorption at 1860, 1840, 1790 (anhydride), and 1770 cm^{-1} (acetoxy). The NMR spectrum of 4 exhibits two characteristic olefinic proton signals at δ 5.93 (t), three methine proton signals of the cyclopropane at δ 1.47–0.84 (m), two methyl groups at δ 2.05 (6 H, s, 2 OAc), a methine proton signal at δ 6.39 (d), and four methine proton signals at δ 3.2–3.5 (m). Furthermore, the structure 4 was established by unequivocal independent synthesis; the Diels–Alder reaction of the diacetoxy acetal of 2,4,6-cycloheptatriene-1-carboxaldehyde[8] with maleic anhydride gave compound 4 as shown in Scheme I.

Scheme I



Compound 5 shows carbonyl absorption at 1860 and 1800 (anhydride) and 1690 cm^{-1} (carboxylic acid) by ir. Moreover, compound 5 was derived from compound 4; heating of 4 with acetic acid in the presence of boron trifluoride in a sealed tube gave a formyl compound 9, which was oxidized to 5 spontaneously at room temperature as shown in Scheme II.

Compound 6 was easily assigned as a ring contracted product, since the NMR spectrum is grossly similar to that of 4 except for the signal of two methoxy groups at δ 3.52 (6 H, s). This assignment was supported by the fact that both 4 and 6 gave 8 by treatment with methanol in the presence of sulfuric acid.

Table II. Reaction of 2 with Thallium Salts under Various Conditions

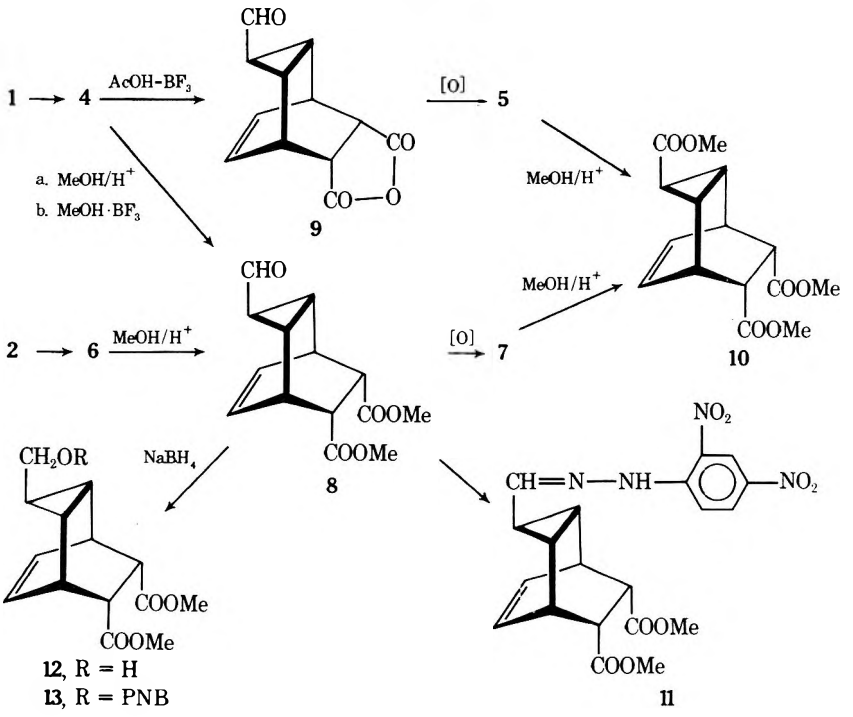
Compd	Reagent	Reaction conditions: Solvent	Temp, °C	Products (%)	
2	$Tl(OAc)_3$	AcOH	25	6 (61)	14 (5)
2	$Tl(OAc)_3$	AcOH	118	8 (59)	7 (31)
2	$Tl(NO_3)_3$	MeOH	25	8 (8)	15 (11)
2	$Tl(NO_3)_3$	MeOH	65	8 (24)	15 (10)

Compound 8, which contains a cyclopropyl aldehyde moiety, was gradually oxidized to give 7, and treated with 2,4-dinitrophenylhydrazine to afford red crystals of 11. Reduction of 8 by sodium borohydride gave 12, which reacted with *p*-nitrobenzoyl chloride in the presence of pyridine to give 13. Further treatment of 5 or 7 with methanol in sulfuric acid gave a trimethyl ester 10. Heating of 6 in acetic acid in the presence of boron trifluoride at 80 °C gave 7. These results indicate that the formyl compound 8 is too labile to exist and readily autoxidized to 7 under these conditions. Thus, it is concluded that the reaction of 2 with lead tetraacetate in the presence of boron trifluoride gave compound 6 as the primary product. These reactions are summarized in Scheme II.

Reaction of 2 with Thallium(III) Salts. The reaction of 2 with equimolar thallium triacetate in acetic acid at room temperature gave 6 (61%) together with 14 (5%). However, similar reaction at reflux temperature gave 8 (59%) and 7 (31%), and compound 14 could not be detected. Compound 7 was also derived from 6 in acetic acid at reflux temperature in almost quantitative yield.

On the other hand, the reaction of 2 with equimolar thallium trinitrate in methanol at room temperature afforded a mixture of 8 and 15. These results are summarized in Table II.

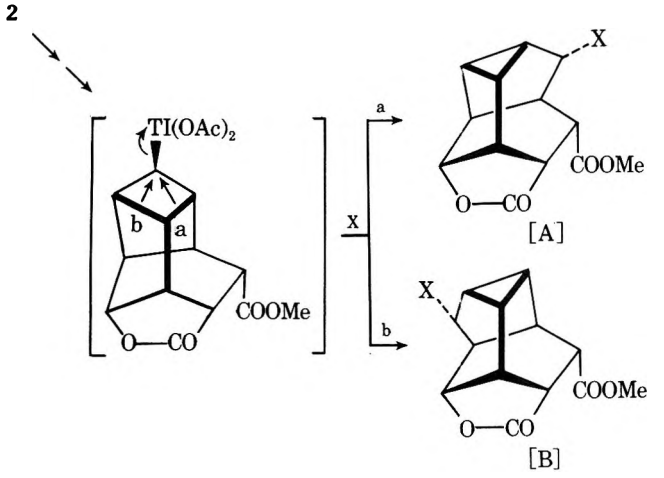
Scheme II



The ir spectrum of **14** shows carbonyl absorption at 1790 and 1730 cm^{-1} suggesting the presence of a five-membered lactone moiety, and acetoxy and ester groups. The NMR spectrum of **14** exhibits a methine proton signal adjacent to an acetoxy group at δ 5.00 (s), a methine proton signal adjacent to a lactone moiety at δ 4.20 (d), one methoxy group at δ 3.57 (3 H, s), one methyl group at δ 2.07 (3 H, s) and three methine proton signals of a cyclopropane ring at δ 1.1–1.7 (m), but no olefinic proton signals were observed.

On the basis of the above data, the structure of the product **14** is assumed to be either A or B via a plausible pathway as shown in Scheme III.

Scheme III



In order to obtain additional information about the structure of **14**, we have attempted the skeletal rearrangement of **16**[3] and **17**.[5] The reaction of **16** with equimolar silver acetate in acetic acid at reflux temperature gave **18** and **19** in a 1:1 ratio. In addition, acetolysis of **17** gave a mixture of **18** and **19** having the same composition. On the other hand, the reaction of **16** with silver acetate in water–acetone gave **20** and **21**, which were converted into the corresponding acetylated compounds **18** and **19** by acetic anhydride in pyridine, respectively. Compound **20** was oxidized by chromic anhydride–acetic acid to give **22**, which was also given from **23** using the same reagent. Compound **25** was derived from **21** by chromic anhydride–pyridine oxidation. These reactions are summarized in Scheme IV.

The NMR spectra of **20** and **18** resemble those of **23** and **24** except for the appearance of a triplet signal instead of a singlet signal of a methine proton adjacent to a hydroxy and an acetoxy moiety, respectively. From these data, the structures of **18, 20,** and **22** were established as depicted in Scheme IV.

The NMR spectrum of **19** exhibits a methine proton signal adjacent to a lactone moiety at δ 4.42 (d), one methoxy group at δ 3.73, one methyl group at δ 2.07, and methine proton signals of a cyclopropane ring at δ 1.5–1.8 (2 H, m) and 1.9–2.0 (1 H, m). Elemental analysis shows the product **19** to be the isomer of **14**. Thus, compound **19** must be either A or B as shown in Scheme III (X = OAc). However, the differences in the chemical shifts of the methine proton signals (H_b) adjacent to the lactone moiety between **19** (δ 4.70) and **25** (δ 4.42) can be accounted for by the carbonyl anisotropy. On the basis of the above results, the structure of **19** was established as B. Consequently, the structure of **14** was assigned as A (X = OAc).

Scheme IV

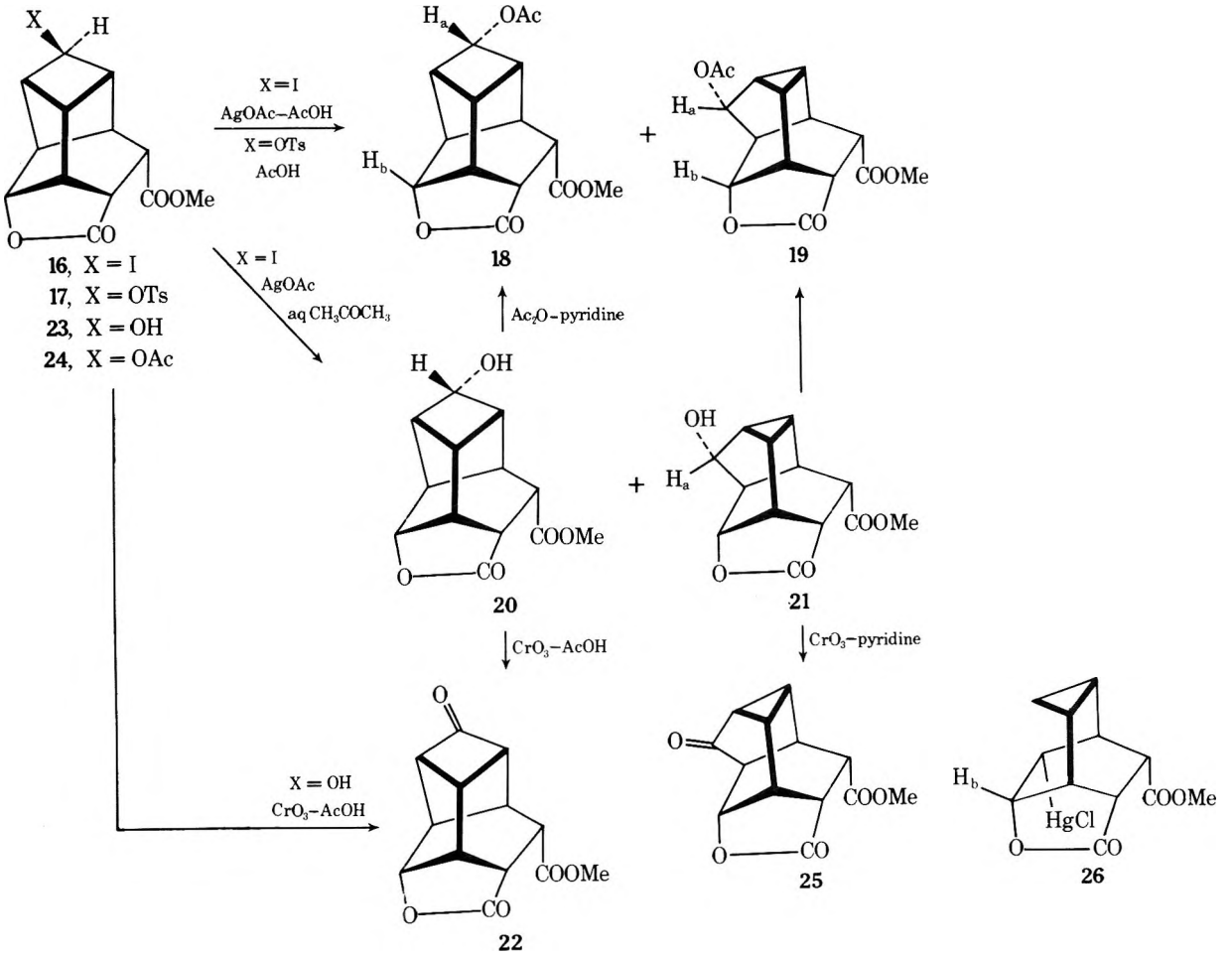
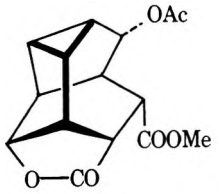


Table III. NMR Data

Compd	Chemical shift (H_b), δ
24[a]	4.77
26[b]	4.47
19	4.42
14	4.20

[a] Reference 5. [b] Reference 4.



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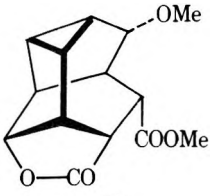

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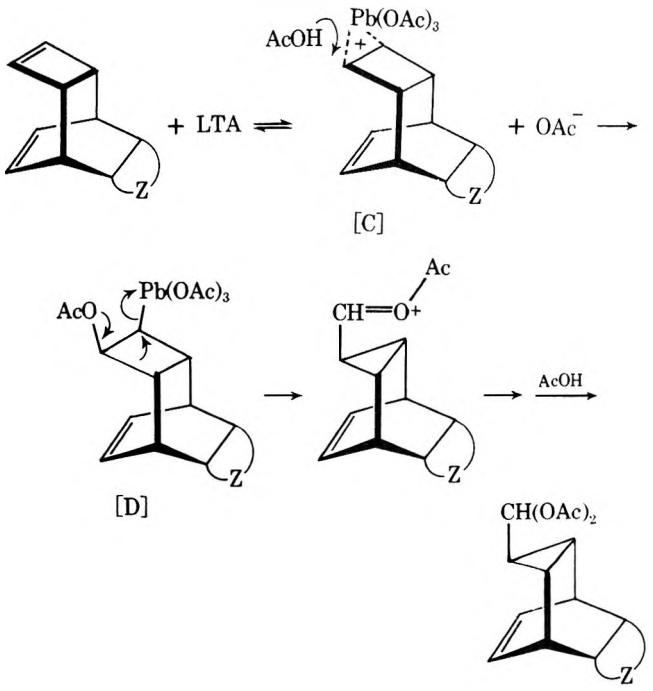
These assignments were also supported by the comparison of the chemical shifts (H_b) of a series of compounds **24**[5] and **26**,[4] which were summarized in Table III. It is also pointed out that the differences in the chemical shifts are dependent on the shielding effect of the cyclopropane ring;[9] the cyclopropyl anisotropy is influenced by the distance between H_b and the cyclopropane ring. The similarity of the value of **26** to that of **19** suggests the similar environment of H_b in both compounds. With respect to **14**, the most upper field displacement of the signal supports the determined structure in which the distance between H_b and the cyclopropane moiety is shorter than that of **19** and **26**.

Compound **15** was easily assigned as type A (X = OMe), since the NMR spectrum of **15** is similar to that of **14**.

Discussion

As described above in the oxyplumbation, the ring-contracted products **4** and **6** are the primary products. They might form via the addition of lead tetraacetate to the strained cyclobutene moiety to form the bridged organolead compound (C) followed by the attack by an acetoxy anion to give an intermediate (D). This intermediate may be a precursor of the ring-contracted products which can be considered to arise from a pinacolic-type reaction as shown in Scheme V.

Scheme V

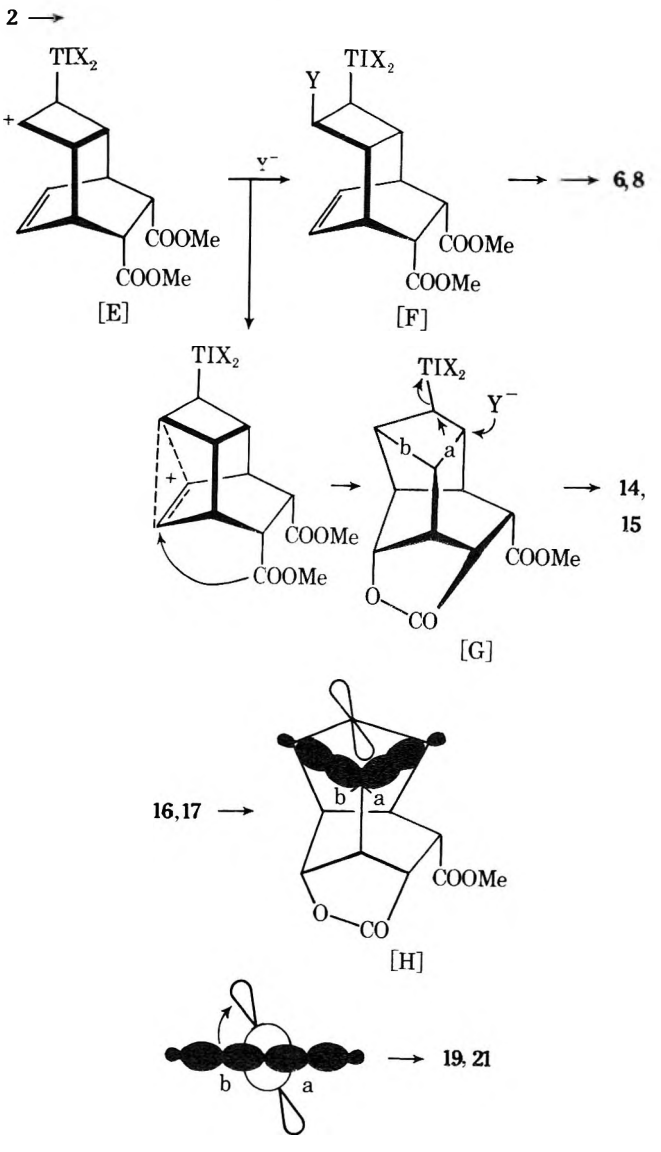


From the results, it is to be noted that Hg(II) affords an isolable organometallic adduct,[4] whereas none is obtained with lead. This may be due in part to the greater electron affinity of Pb(IV).

Oxidation of olefins with Hg(II), Tl(III), or Pb(IV) salts can lead to a variety of products depending on the nature of the metal cation, the anion, the solvent, and the conformation of the cyclic olefins. Previous studies of oxymetallation of olefins with acetate of the three metals have established the intermediate position of the thallium salt.[10]

In view of oxymercuration and oxyplumbation of **1** and **2**, the results of oxythallation are of particular interest; it is quite unexpected that the oxythallation of **2** gave the transannular products **14** and **15**. They might form via the unsymmetrical intermediate (E) followed by competitive attacks by an acetoxy anion and a double bond to give F and G. The experimental data show that at elevated reaction temperature the attack by an acetoxy anion is superior to that of a double bond. Intermediate F may lead to the ring contracted products, **6** and **8**, while intermediate G may give the rearrangement product **14** (or **15**) as shown in Scheme VI. It is pointed out that alkylthallium(III) compounds such as F and G are extremely unstable, and C–Tl bond heterolysis might proceed via a transition state approaching carbonium ion character. On the other hand, rearrangements of polycyclic hydrocarbon skeletons via carbonium ion are well documented. It is as-

Scheme VI



sumed that some of the stability of the new skeleton is felt at the transition state.[11] The transition state energy for a Wagner–Meerwein shift can also be influenced by the effectiveness of orbital overlap dependent on the initial alignment of relevant bonds; for a rearrangement that is concerted with ionization, the migrating group should ideally be antiplanar to the leaving group (sp^3-alignment factor), and for rearrangement to a carbocation site, the migrating group and the p orbital should ideally be in one plane (sp^2-alignment factor).

An examination of stereomodels shows that the sp^3-alignment factor would favor migration of a over b to give A. The sp^2-alignment factor or product stability factor would favor migration of b over a to give B.

According to the above arguments, the reaction of alkylthallium compound such as the intermediate G is assumed to be a concerted process. On the other hand, the solvolysis of **16** or **17** might proceed via an intermediacy of carbonium ion H as shown in Scheme VI.

Taylor reported that thallium nitrate, which is almost ionic, is more effective for ring contraction of cyclic olefins.[12] In this connection, our present results show that the transannular reaction product **15** was obtained in a moderate yield in the reaction of **2** with thallium nitrate in methanol, although the reaction rate was slow as evidenced by TLC inspection.

Experimental Section

The melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. The NMR spectra were taken with a JEOL C-60-XL spectrometer with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The ir spectra were taken with a Jasco Model IRA-1 grating infrared spectrophotometer. The HLC was done on a Shimazu-Du Pont LC 830 high-speed liquid chromatography using a column ODS (7.9 × 1.0 m).

General Procedure for the Oxidations of 1 and 2 with LTA. The diene was added to acetic acid (40 ml) in a three-necked flask (100 ml) equipped with a stirrer and a thermometer. To the solution was added equimolar lead tetraacetate (LTA) in one portion and the temperature of the bath was maintained at 70 or 100 °C. After stirring for 15 h, the bath was removed and the solution was allowed to cool to room temperature. The resulting solution was then added to water and extracted with chloroform. The extract was washed with aqueous sodium chloride, and then dried over sodium sulfate. After the solvent was evaporated by reduced pressure, the residue was subjected to silica gel chromatography (SGC) and recrystallized.

A. A solution of **1** (0.5 g) and LTA (lead tetraacetate) (2.25 g) in acetic acid was stirred at 70 °C. Workup gave **1** (0.45 g) and **4** (0.08 g).

4: mp 249–250 °C dec; ir (KBr) 1860, 1840, 1790, 1770 cm^{-1}; NMR ($CDCl_3$) δ 6.39 (d, J = 6.75 Hz), 5.93 (2 H, t, J = 4.5 Hz), 3.2–3.5 (4 H, m), 2.05 (6 H, s, 2 OAc), 1.47–0.84 (3 H, m).

Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 59.94; H, 5.10.

B. A solution of **1** (0.5 g) and LTA (2.25 g) in acetic acid was stirred for 15 h at 100 °C. Workup gave **1** (0.235 g), **4** (0.21 g), and **5** (0.02 g).

5: mp 284 °C dec; ir (KBr) 1860, 1800, 1690 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.24; H, 4.40.

C. A solution of **2** (0.5 g) and LTA (1.8 g) in acetic acid was stirred at 70 °C. Workup gave **2** (0.12 g) and **6** (0.49 g).

6: mp 167–169 °C; ir (KBr) 1770, 1745 cm^{-1}; NMR ($CDCl_3$) δ 6.32 (1 H, d, J = 6.75 Hz), 5.88 (2 H, t, J = 3.75 Hz), 3.52 (g H, s, COOMe 2), 2.90–3.30 (4 H, m), 2.01 (6 H s, OAc 2), 1.47–0.84 (3 H, m).

Anal. Calcd for $C_{18}H_{22}O_8$: 59.01; H, 6.05. Found: C, 58.95; H, 6.01.

D. A solution of **2** (0.5 g) and LTA (1.8 g) in acetic acid was stirred at 100 °C. Workup gave **6** (0.46 g).

E. A solution of **2** (0.5 g), LTA (1.8 g), and BF_3·2AcOH (0.38 g) in acetic acid was stirred at 70 °C. Workup gave **2** (0.06 g) and **7** (0.372 g).

7: mp 149–151 °C; ir (KBr) 1735, 1675 cm^{-1}; NMR ($CDCl_3$) δ 9.67 (broad s, 1 H, D_2O exchangeable), 6.00 (2 H, t, J = 4.0 Hz), 3.63 (6 H, s, COOMe 2), 3.0–3.2 (4 H, m), 1.73 (2 H, m), 1.38 (1 H, t, J = 2.0 Hz).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.72; H, 5.71.

F. A solution of **2** (0.5 g), LTA (1.8 g), and BF_3·2AcOH (0.38 g) in acetic acid was stirred at 100 °C. Workup gave **7** (0.114 g).

Reaction of Diacetoxy Acetal of 2,4,6-Cycloheptatriene and Maleic Anhydride. A solution of the acetal (0.3 g) and maleic anhydride (0.14 g) in benzene (20 ml) was refluxed for 30 h. The precipitated solids was filtered to give **4** (0.18 g).

Reaction of 4 with Methanol–Sulfuric Acid. A solution of **4** (0.15 g) in methanol (10 ml) and sulfuric acid (1 ml) was refluxed for 4 h. The mixture was cooled and then diluted with water.

The solution was extracted with chloroform and the extract was evaporated by reduced pressure. The residue was subjected to SGC using chloroform to give **8** (0.115 g): mp 87–88 °C; ir (KBr) 2850, 2750, 1750, 1700 cm^{-1}; NMR ($CDCl_3$) δ 9.35 (1 H, d, J = 3.0 Hz), 6.00 (2 H, t, J = 4.0 Hz), 3.63 (6 H, s, COOMe 2), 3.1–3.5 (4 H, m), 1.77 (3 H, m).

2,4-Dinitrophenylhydrazone of **4** (**11**), mp 228–229 °C.

Anal. Calcd for $C_{20}H_{20}O_8N_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.04; H, 4.48; N, 12.67.

Reaction of 4 with Methanol–Boron Trifluoride Etherate. A solution of **4** (0.15 g) and BF_3·Et_2O (0.02 g) in methanol (20 ml) was refluxed for 8 h. Workup gave **8** (0.136 g).

Reaction of 6 with Methanol–Sulfuric Acid. A solution of **6** (0.3 g) in methanol (20 ml) and sulfuric acid (2 ml) was refluxed for 4 h. Workup gave **8** (0.25 g).

Reaction of 6 with Acetic Acid–Boron Trifluoride Acetic Acid Complex. A solution of **6** (0.2 g) and boron trifluoride acetic acid complex (0.02 g) in acetic acid (20 ml) was heated at 80 °C for 4 h. The mixture was diluted with water and extracted with chloroform. The solvent was evaporated by reduced pressure and the residue was subjected to SGC using chloroform to give **7** (0.15 g): mp 149–151 °C; ir (KBr) 1735, 1675 cm^{-1}; NMR ($CDCl_3$) δ 9.67 (1 H, exchangeable by D_2O), 6.00 (2 H, t, J = 4.0 Hz), 3.63 (6 H, s, COOMe 2), 3.43–3.00 (4 H, m), 1.73 (2 H, m), 1.38 (1 H, m).

Reaction of 4 with Acetic Acid–Boron Trifluoride Acetic Acid Complex. A solution of **4** (0.15 g) and boron trifluoride acetic acid complex (0.1 g) in acetic acid (20 ml) was heated at 80 °C in a sealed tube for 8 h. After removal of the solvent, the residue was recrystallized from benzene to give **9** (0.087 g): mp 169–170.5 °C; ir (KBr) 1840, 1785, 1705 cm^{-1}; NMR ($CDCl_3$) δ 9.50 (1 H, d, J = 3.25 Hz), 5.96 (2 H, t, J = 3.75 Hz), 3.60 (2 H, m), 3.30 (2 H, t, J = 1.5 Hz), 1.6–2.0 (3 H, m).

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.17; H, 4.72.

Reaction of 8 with Sodium Borohydride. To a solution of **8** (0.3 g) in methanol (20 ml), sodium borohydride (0.04 g) was added. After stirring for 2 h, the solution was diluted with water and extracted with chloroform. After evaporation of the solvent, the residue was subjected to SGC using chloroform to give **12:** mp 81–82 °C; ir (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) δ 5.87 (2 H, t, J = 4.0 Hz), 3.57 (6 H, s, COOMe 2), 3.4–2.8 (7 H, m, 1 H exchangeable by D_2O), 0.9 (3 H, m).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.26; H, 6.61.

Reaction of 12 with *p*-Nitrobenzoyl Chloride. A solution of **12** (0.4 g) and *p*-nitrobenzoyl chloride (0.36 g) in pyridine (10 ml) was stirred for 6 h at room temperature. The reaction mixture was added with water and then extracted with chloroform. Evaporation of the solvent gave **13** (0.65 g), mp 161–162 °C.

Anal. Calcd for $C_{21}H_{21}O_8N$: C, 60.72; H, 5.10; N; 3.37. Found: C, 60.96; H, 5.02; N, 3.64.

Reaction of 5 with Methanol–Sulfuric Acid. A solution of **5** (0.2 g) in methanol (10 ml) and sulfuric acid (1 ml) was refluxed for 2 h. Workup gave **10** (0.21 g): mp 59–60 °C; ir (KBr) 1750, 1730 cm^{-1}; NMR ($CDCl_3$) δ 5.95 (2 H, t, J = 4.0 Hz), 3.55 (9 H, s, COOMe 3), 3.50–2.95 (4 H, m), 1.80–1.50 (2 H, m), 1.50–1.30 (1 H, m).

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.30; H, 6.10.

Reaction of 7 with Methanol–Sulfuric Acid. A solution of **7** (0.15 g) in methanol (10 ml) and sulfuric acid (1 ml) was refluxed for 2 h. Workup gave **10** (0.15 g).

Reaction of 2 with TTA. A. A mixture of **2** (1.5 g) and thallium triacetate (TTA, 2.3 g) in acetic acid (30 ml) was stirred for 96 h at room temperature. The mixture was diluted with water and extracted with chloroform. The extract was washed with saturated sodium chloride and then water, and dried over sodium sulfate. After the solvent was evaporated by reduced pressure, the residue was subjected to SGC using benzene–chloroform to give **6** (1.28 g) and **14** (0.09 g).

14: mp 181–183 °C; ir (KBr) 1790, 1730 cm^{-1}; NMR ($CDCl_3$) δ 5.0 (1 H, s), 4.20 (1 H, d, J = 7.0 Hz), 3.57 (3 H, s, COOMe), 3.3–2.5 (5 H, m), 3.07 (3 H, s, OAc), 1.7–1.1 (3 H, m).

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.79; H, 5.62.

B. A mixture of **2** (2.0 g) and TTA (3.0 g) in acetic acid (30 ml) was refluxed for 8 h. Workup gave **8** (1.55 g) and **7** (0.697 g).

Reaction of 2 with TTN. A. A solution of **2** (1.7 g) and thallium trinitrate (2.65 g) in methanol (30 ml) was stirred for 5 days at room temperature. After separation of thallium(I) nitrate, the solution was diluted with water and extracted with chloroform. The solvent was evaporated by reduced pressure, and the residue was subjected to SGC

using benzene–chloroform to give 8 (0.15 g), **2** (1.24 g), and **15** (0.187 g).

15: mp 131–132 °C; ir (KBr) 1785, 1720 cm^{-1}; NMR ($CDCl_3$) δ 4.07 (1 H, d, J = 6.0 Hz), 3.70 (4 H, s, COOMe and 1 H), 3.37 (3 H, s, OMe), 3.2–2.6 (5 H, m), 1.2–1.83 (3 H, m).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 67.73; H, 6.50. Found: C, 67.76; H, 6.47.

B. A solution of **2** (2.0 g) and TTN (3.1 g) in methanol (30 ml) was refluxed for 24 h. Workup gave **2** (0.925 g), 8 (0.505 g), and **15** (0.22 g).

Reaction of 16 with Silver Acetate. A. A mixture of **16** (0.4 g) and silver acetate (0.2 g) in acetic acid (20 ml) was refluxed for 2 h. The reaction mixture was filtered for precipitated silver salts, and the solvent was evaporated by reduced pressure. The residue was subjected to SGC using chloroform–benzene to give a mixture of **18** and **19** (0.31 g), which could not be separated by SGC. The mixture consisted of a 1:1 ratio as evidenced by HLC analysis, which was recrystallized from benzene–*n*-hexane to give **18** and **19**.

18: mp 120–120.5 °C; ir (KBr) 1760, 1740 cm^{-1}; NMR ($CDCl_3$) δ 4.80 (1 H, dd, J = 2.0 and 8.0 Hz), 4.65 (1 H, t, J = 2.0 Hz), 3.70 (3 H, s, COOMe), 3.20 (1 H, m), 2.3–2.9 (7 H, m), 2.00 (3 H, s, OAc).

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.57; H, 5.70.

19: mp 138–139 °C ir (KBr) 1770, 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 5.00 (1 H, s), 4.42 (1 H, d, J = 7.0 Hz), 3.37 (3 H, s, COOMe), 3.4–2.7 (4 H, m), 2.3–1.8 (2 H, m), 2.06 (3 H, s, OAc), 1.68 (2 H, m).

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.54; H, 5.70.

B. A mixture of **16** (1.92 g) and silver acetate (0.96 g) in acetone (20 ml) and water (20 ml) was refluxed for 30 h. Workup gave **16** (0.34 g) and a mixture of **20** and **21** 0.7 g). The mixture consisted of a 1:1 ratio as evidenced by HLC analysis, which could not be separated.

Acetolysis of 17. A solution of **17** (0.44 g) and sodium acetate (0.09 g) in acetic acid (20 ml) was heated at 170 °C in a sealed tube for 36 h. Workup gave a mixture of **18** and **19** (0.25 g).

Reaction of 20 and 21 with Chromic Anhydride. To a mixture of chromic anhydride (0.5 g) and pyridine (5 g) a mixture of **20** and **21** (0.7 g) was added. After stirring for 24 h, the mixture was diluted with water and extracted with chloroform. The organic solvent was dried over sodium sulfate and then evaporated by reduced pressure. The residue was subjected to SGC using chloroform to give **25** (0.18 g). Compound **20** was recovered from the reaction mixture, which was treated with chromic anhydride in acetic acid; to a solution of **20** (0.1 g) in acetic acid (20 ml) chromic anhydride (0.03 g) was added. The mixture was stirred for 4 h. After dilution with water, the reaction mixture was extracted with chloroform. Evaporation of the solvent gave **22** (0.03 g).

20: mp 140–141 °C; ir (KBr) 3420, 1730 cm^{-1}; NMR ($CDCl_3$) δ 4.83 (1 H, dd, J = 8.0 and 2.0 Hz), 4.07 (1 H, m, changed to triple by D_2O, J = 3.0 Hz), 3.73 (3 H, s, COOMe), 3.20 (1 H, m), 2.9–2.5 (7 H, m, 1 H exchangeable by D_2O), 2.2 (1 H, m).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.04. Found: C, 62.49; H, 5.78.

22: mp 203–205 °C; ir (KBr) 1805, 1770, 1740 cm^{-1}; NMR (Me_2SO-d_6) δ 4.98 (1 H, dd, J = 9.0 and 2.0 Hz), 3.63 (3 H, s, COOMe), 3.5–2.5 (8 H, m). Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.80; H, 4.82.

25: mp 187–189 °C; ir (KBr) 1770, 1720 cm^{-1}; NMR ($CDCl_3$) δ 4.70 (1 H, d, J = 6.5 Hz), 3.73 (3 H, s, COOMe), 3.6–2.8 (4 H, m), 2.5–2.0 (4 H, m).

Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.98; H, 5.02.

Reaction of 20 and 21 with Acetic Anhydride. A solution of a mixture of **20** and **21** (1:1 ratio) (0.1 g) in acetic anhydride (1 ml) and pyridine (5 ml) was stirred for 24 h at room temperature. The solution was diluted with water and then extracted with chloroform. The extract was washed with 2 N hydrochloric acid and then with water. The organic solvent was dried over sodium sulfate and evaporated by reduced pressure to give **18** and **19** (total 0.15 g).

Reaction of 23 with Chromic Anhydride. To a solution of **23** (0.5 g) in acetic acid (20 ml), chromic anhydride (0.15 g) was added. Workup as described above gave **22** (0.374 g).

Registry No.—**1**, 51447-09-7; **2**, 35211-83-7; **4**, 58832-37-4; **5**, 58865-34-2; **6**, 58832-38-5; **7**, 58832-39-6; **8**, 58832-40-9; **9**, 58832-41-0; **10**, 58832-42-1; **11**, 58832-43-2; **12**, 58832-44-3; **13**, 58832-45-4; **14**, 58832-46-5; **15**, 58832-47-6; **16**, 58832-48-7; **18**, 58865-35-3; **19**, 58832-49-8; **20**, 58865-36-4; **21**, 58832-50-1; **22**, 58832-51-2; **25**, 58832-52-3; LTA, 546-67-8; *p*-nitrobenzoyl chloride, 122-04-3; TTA, 2570-63-0; TTN, 13746-98-0; silver acetate, 563-63-3; diacetoxy acetal of 2,4,6-cycloheptatriene, 58832-53-4; maleic anhydride, 108-31-6.

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Annulated Cyclopentadienone Ketals. A Route to 1,2-Bridged Norbornenes

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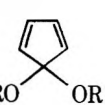
The preparation and properties of a new set of cyclopentadienone ketals are described. These annulated cyclopentadienone ketals are interesting theoretically and are useful in the synthesis of new types of polycyclic systems.

The ketals of cyclopentadienone (**1a–c**) are exceedingly reactive substances; Diels–Alder dimerization occurs very rapidly.[1] The dimethyl ketal **1a**, the least reactive of the set, dimerizes about 270 times faster than cyclopentadiene; the ethylene ketal **1c** dimerizes more than another 1000 times faster. A significant bathochromic shift in the ultraviolet absorption maximum of these dienes has been noted [cyclopentadiene, λ_{max}(pentane) 239 nm; **1a**, 270 nm; **1b**, 272 nm; **1c**, 280 nm] and is most probably related to these large changes in reactivity. The interactions of the cyclopentadiene π system with the nonbonding electrons of the ketal oxygens

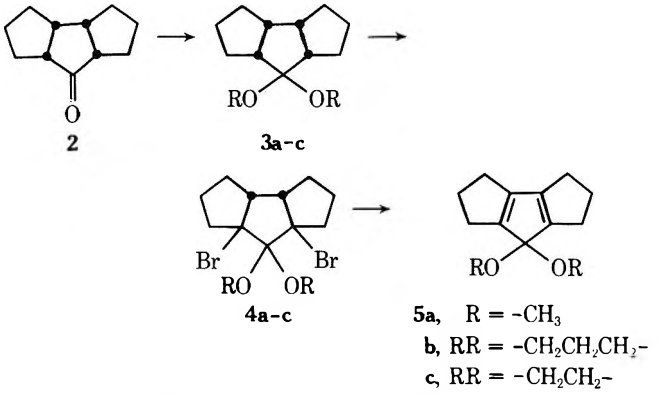


1a, R = $-CH_3$
b, RR = $-CH_2CH_2CH_2-$
c, RR = $-CH_2CH_2-$

are presumably the cause of these effects.[1,2] Unfortunately, the reactivity of these cyclopentadienone ketals has precluded the collection of other data (e.g., photoelectron spectra) important to understanding these interactions.

We wish to report now the preparation and isolation of a set of annulated cyclopentadienone ketals sufficiently stable to permit accumulation of the needed information and sufficiently symmetric and free of extraneous electronic effects to make this effort worthwhile. In addition, these new dienes offer interesting synthetic possibilities.

The tricyclic ketone **2** is readily available, as we describe elsewhere.[3] The ketals of this saturated ketone are preparable by standard acid-catalyzed reactions: the dimethyl ketal (**3a**) by reaction of **2** with excess trimethyl orthoformate; the propylene ketal (**3b**) and the ethylene ketal (**3c**) by reaction of **2** with the appropriate glycols. Each ketal reacts with 2 equiv of pyridinium hydrobromide perbromide (**3a** in methanol; **3b,c** in THF) at 5–15 °C to give the corresponding α,α'-dibromo ketal (**4a–c**). Dehydrobromination is effected directly by reaction under nitrogen with potassium *tert*-butoxide in Me_2SO at room temperature. The desired products are obtainable pure by repeated chromatography on silica gel and/or low-temperature crystallization. The propylene ketal **5b** melts at 79–80 °C; the ethylene ketal **5c**, at 78–80 °C. The dimethyl ketal **5a** has not been obtained crystalline.



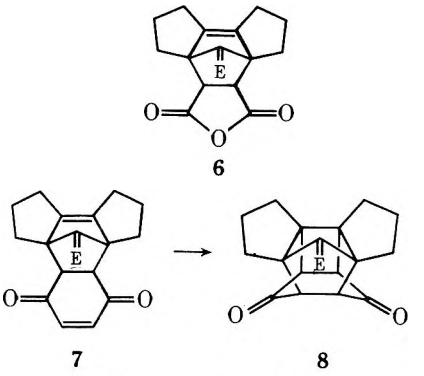
2 **3a-c** **4a-c**

5a, R = $-CH_3$
b, RR = $-CH_2CH_2CH_2-$
c, RR = $-CH_2CH_2-$

It is necessary to note that the dehydrobromination reactions **4** → **5** are not clean. Materials containing vinyl hydrogen, presumably formed by base-catalyzed double bond migrations, contaminate the crude reaction products. In the case of the ethylene ketal **5c**, on which we have concentrated our efforts, only a 25% yield of pure material could be obtained from the dehydrobromination mixture. This was sufficient for our purposes. No doubt, a better dehydrobromination procedure could be developed.

The ultraviolet absorption maximum of the carefully purified dimethyl (**5a**), propylene (**5b**), and ethylene (**5c**) ketals shifts from 294 to 297 to 304 nm with the change in ketal group. This parallels the shift noted for the unsubstituted ketals **1a–c**. The long-term stability of **5a–c** allows measurement of the ^{13}C NMR spectra. The chemical shifts of the olefinic carbon atoms do not change much from ketal to ketal: **5a**, δ 146.8, 150.7; **5b**, 146.4, 151.1; **5c**, 147.4, 150.6 ppm relative to internal Me_4Si.[4] This was unexpected and still seems odd. We had thought that the electronic perturbation of the diene system evident in the ultraviolet shift would also be apparent in the NMR.[6] The photoelectron spectral behavior of these new ketals is under study.

As we hoped, the reactivity of the diene ketals **5a–c** is substantially reduced from that of the parent system **1a–c** by the steric effects of the fused rings. However, these dienes are still quite reactive toward good dienophiles. For example, the ethylene ketal **5c** reacts quickly with maleic anhydride or with *p*-benzoquinone in boiling benzene to give the corresponding Diels–Alder adducts **6** and **7**. Interestingly, intramolecular photocyclization by irradiation of **7** in benzene produces the winged cage **8** in good yield. Compounds **6**, **7**, and **8** are the first



6 **7** **8**

(E = ethylene ketal)

examples of materials with such carbon skeletons. Attention is called in particular to the substantial strain introduced at the norbornene double bond in **6** and in **7** by the fused rings with termini at the vinyl and bridgehead carbon atoms.

Experimental Section

Proton magnetic resonance spectra were taken at 270 MHz on solutions in deuteriochloroform and are referenced to internal Me_4Si. Spectra were recorded for convenience on compressed scale (3 Hz/mm); therefore, quoted shifts are no better than ±0.02 ppm and coupling constants are ±1 Hz, sufficient accuracy for the purpose. Carbon magnetic resonance spectra were run at 22.63 MHz on solutions in deuteriochloroform using standard pulse techniques and white-noise decoupling. These spectra are also referenced to internal Me_4Si; chemical shifts are ±0.1 ppm. Infrared spectra were taken using Nujol mulls; positions of interesting absorptions are quoted ±5 cm^{-1}. The high-resolution mass spectrum of each characterized compound was recorded on an MS-9 spectrometer operating at 50 eV ionization voltage. Each compound exhibited a proper parent peak at *m/e* within 30 ppm of the expected value. Ultraviolet spectra were taken on solutions made up in carefully purified cyclohexane.

Ketals of *cis,syn,cis*-Tricyclo[6.3.0.0^{3,7}]undecan-2-one. Dimethyl Ketal (3a). A mixture of **2**[3] (3 g), trimethyl orthoformate (6 g), and *p*-toluenesulfonic acid (170 mg) was kept at room temperature for 14 h. Gas chromatographic analysis indicated complete disappearance of the ketone. Sodium methoxide (500 mg) was added to the reaction mixture. The suspension was added dropwise to well-stirred, 10% aqueous sodium carbonate (200 ml). This mixture was extracted with light petroleum ether (2 × 150 ml). The organic layer was washed with 10% aqueous sodium carbonate (3 × 100 ml) and dried over sodium carbonate. Removal of solvent in vacuo left an oil (2.8 g). In general, this crude ketal was used directly. The material is thermally labile. A small sample was purified by molecular distillation (~25 °C, 0.01 mm): ^{13}C NMR δ 112.4 (ketal carbon), 52.6 (junction), 50.6 ($-OCH_3$), 48.0 ($-OCH_3$), 44.3 (junction), 28.9 (two signals <2 Hz apart), and 27.3 ppm.

Propylene Ketal (3b). The ketone **2** (4 g), propylene glycol (8 g), and methanesulfonic acid (8 drops) were combined together in benzene (200 ml) and heated under reflux beneath a Dean-Stark trap for 3 days. The mixture was cooled, and sodium methoxide (3 g) was added with stirring. The reaction mixture was added dropwise to stirred, 10% aqueous sodium carbonate, and this mixture was extracted with hexane (2 × 200 ml). The extract was washed with 3% aqueous sodium carbonate and dried over sodium carbonate. The solution was concentrated under vacuum. Distillation of the residue gave a fraction (3.2 g), bp 102–105 °C (0.5 mm), better than 95% pure by GLC analysis on OV-225: ^{13}C NMR δ 109.6 (ketal carbon), 62.4 ($-OCH_2-$), 60.3 ($-OCH_2-$), 53.3, 43.9, 29.0, 28.5, 27.2, 25.8 ppm (the last is probably $-OCH_2CH_2CH_2O-$ based on its relative intensity).

Ethylene Ketal (3c). The ketone **2** (14.0 g), 28.0 g of ethylene glycol, and 4 drops of methanesulfonic acid were combined together in 200 ml of benzene and stirred under reflux beneath a Dean-Stark trap for 4 days. The mixture was cooled, and then added dropwise with rapid stirring to 10% aqueous sodium carbonate. The basic mixture was extracted with hexane (3 × 50 ml). The combined extract was washed with 3% aqueous sodium carbonate and dried over sodium carbonate. Removal of the solvent in vacuo left 15.7 g (88%) of **3c** which was used directly in the next step. A small sample was purified by molecular distillation under high vacuum at room temperature:

^{13}C NMR δ 119.1 (ketal carbon), 66.5 ($-OCH_2-$), 64.2 ($-OCH_2-$), 55.2, 44.9, 28.9, 28.4, and 27.1 ppm.

Bromination of the Ketals 3a–c (→ 4a–c). Pyridinium hydrobromide perbromide (50 g, 93% titre, 145 mmol) was added in small portions to a stirred solution of the ethylene ketal **3c** (15 g, 72 mmol) in 250 ml of dry THF at 5 °C. The reaction mixture was stirred at 5–10° for 1 h; the original orange color of the brominating agent discharged to yellow. After this time, pyridine (12 g) was added with vigorous stirring. The reaction mixture was then added slowly from a dropping funnel into 250 ml of 10% aqueous sodium carbonate solution stirred rapidly. This mixture was extracted with hexane (3 × 150 ml) The extract was washed with 3% aqueous sodium carbonate and dried over Na_2SO_4. Removal of solvent in vacuo gave 29 g of a brown oil containing traces of pyridine. The oil was kept under high vacuum for 24 h to remove most of the pyridine. Crude **4c** was then used directly in the next step.

Similar procedures were followed for the hromination of **3a** and **3b**. For **3a** → **4a**, methanol was substituted for THF; this is essential.

Tricyclo[6.3.0.0^{3,7}]undeca-1(8),3(7)-dien-2-one Ketals (5a–c). Ethylene Ketal (5c). The crude dibromo ketal **4c** (18.5 g) was dissolved in 50 ml of dry Me_2SO. This mixture was stirred rapidly under nitrogen at 15–20 °C as a solution of potassium *tert*-butoxide (22 g) in 200 ml of dry Me_2SO was added dropwise. Stirring at 15–20 °C was continued for 4 h. After this time, the mixture was poured into stirred, 10% aqueous sodium carbonate solution (200 ml). This mixture was extracted with ether (3 × 150 ml). The ether extract was washed with 3% aqueous sodium carbonate (3 × 50 ml), dried over sodium sulfate, and decolorized with Norit. Removal of the solvent in vacuo left 10 g of yellow oil. Crystallization from light petroleum ether at 0–10 °C gave 2.7 g of good **5c** (25%). Recrystallization from petroleum ether gave a pure product: mp 79–80 °C; ^1H NMR δ 4.10 (4 H, s) and 2.1–2.5 ppm (12 H); ^{13}C NMR δ 150.6 and 147.3 (vinyl carbons), 108.2 (ketal carbon), 65.2 ($-OCH_2-$), 27.6, 27.5, and 27.0 ppm; uv λ 304 nm (ε 1700).

Dimethyl (5a) and Propylene Ketal (5b). Similar procedures were followed for the dehydrobromination of **4a** and **4b**. The unsaturated ketals **5a** and **5b** were purified by column chromatography on silica gel using light petroleum ether/ethyl ether (85:15) as eluent. The propylene ketal **5b** could be purified to mp 78–80 °C by crystallization from mixed hexanes at −20 °C. Compound **5a:** ^{13}C NMR δ 150.7 and 146.8 (vinyl carbons), 104.7 (ketal carbon), 51.9 ($-OCH_3$), 29.7, 27.7, and 27.2 ppm; uv λ 294 nm (ε 1120). Compound **5b:** ^{13}C NMR δ 151.1 and 146.4 (vinyl carbons), 102.1 (ketal carbon), 63.1 ($-OCH_2-$), 30.7, 27.7, 26.9, and 25.7 ppm; uv λ 297 nm (ε 1800).

Diels–Alder Adducts from Ethylene Ketal 5c. Adduct 6 from Maleic Anhydride. A solution of maleic anhydride (50 mg, 0.51 mmol) and ketal **5c** (102 mg, 0.50 mmol) in 4 ml of benzene was refluxed for 4 h. The solvent was removed under vacuum, and the residue triturated with ether. The solid residue (110 mg, 73%) was reasonably pure adduct **6**, mp 234–237 °C. A purer sample was obtained by crystallization from acetonitrile: mp 238–240 °C; ^1H NMR δ 3.9 (4 H, center of symmetrical multiplet, ketal), 3.46 (2 H, s, ring junction), 2.2 (2 H, m), and 2.1–1.6 ppm (10 H); ^{13}C NMR δ 171.9 (anhydride carbonyl), 141.2 (vinyl), 69.5 (bridgehead?), 65.9 and 65.7 ($-OCH_2-$), 49.0 (junction), 28.5, 26.0, and 23.7 ppm (cyclopentane CH_2). The quaternary ketal carbon was not found in the ^{13}C NMR spectrum; its relaxation time is probably very long, a result of its isolation from CH units.

Adduct 7 from *p*-Benzoquinone. A solution of ketal **5c** (306 mg, 1.5 mmol) and *p*-benzoquinone (162 mg, 1.5 mmol) in 15 ml of benzene was refluxed for 21 h. The solvent was removed, and the residue chromatographed on silica gel. The 1:1 petroleum ether/ether eluate gave 260 mg (55%) of the desired adduct, which could be further purified by crystallization from mixed hexanes: mp 143–144 °C; ir 1672 cm^{-1}; ^1H NMR δ 6.61 (2 H, s), 3.95 (4 H, center of symmetrical ketal multiplet), 3.27 (2 H, s, junction), 2.2 (2 H, m), 2.1–1.6 ppm (10 H).

Photochemical Closure of 7 to 8. A solution of **7** (40 mg) in 0.5 ml of benzene was exposed to the output from a Hanovia 450-W mercury arc lamp filtered through Pyrex glass. The closure was followed by NMR. When nearly all of the vinyl hydrogen resonance signal of the starting material had disappeared, the irradiation was stopped. The solvent was removed under vacuum. The product was crystallized from benzene to give 30 mg (75%) of **8**: mp 153–155 °C; ir 1742 and 1765 cm^{-1}; ^1H NMR (C_6D_6) δ 3.39 (4 H, s), 2.84 (2 H, s), 2.26 (2 H, s), 1.84 (2 H, m), 1.67 (2 H, m), 1.44 (4 H, m), and 1.17 ppm (4 H, m).

Acknowledgments. We are grateful to the National Science Foundation (GP-30568X) and the National Institutes of Health (CA-12961) for grants in support of our work. Funds for the purchase of the NMR instruments essential to this research were provided, in part, by the National Cancer Institute (CA-14599) via The University of Chicago Cancer Research Center, and by the National Science Foundation. C. G. thanks Montedison S.p.A., Centro Ricerche di Chimica Organica, for a leave of absence.

Registry No. —**2**, 58866-18-5; **3a**, 58881-35-9; **3b**, 58866-62-9; **3c**, 58866-63-0; **4a**, 58881-36-0; **4b**, 58866-64-1; **4c**, 58866-65-2; **5a**, 58866-66-3; **5b**, 58866-67-4; **5c**, 58866-68-5; **6**, 58866-69-6; **7**, 58866-70-9; **8**, 5866-71-0; trimethyl orthoformate, 149-73-5; propylene glycol, 504-63-2; ethylene glycol, 107-21-1; pyridinium hydrobromide perbromide, 39416-48-3; maleic anhydride, 108-31-6; *p*-benzoquinone, 106-51-4.

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(4) We find that the same is true for the dimethyl and ethylene ketals of tetrachlorocyclopentadienone for which there is also a significant red shift and increase in reactivity with change in ketal group.[5] The vinyl carbon resonance positions are 128.7, 129.2 and 128.7, 129.8 ppm, respectively.
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cis,syn,cis-Tricyclo[6.3.0.0^{3,7}]undecane Ketones

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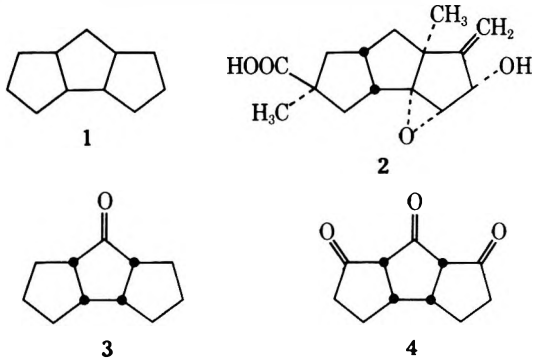
The synthesis of the first examples of compounds in the *cis,syn,cis*-tricyclo[6.3.0.0^{3,7}]undecane series is described. A preparatively useful synthesis of 1,1′-dicyclopentenyl ketone is given.

For our work on the synthesis of peristylane and dodecahedrane[1] we wanted to have available model systems containing three five-membered rings fused serially; that is, compounds in the tricyclo[6.3.0.0^{3,7}]undecane series (**1**). Examples with this carbon skeleton are rare; most that are known are derivatives of the natural product hirustic acid C (**2**)[2] or have been made along the way in the synthesis of that compound.[3] Hirustic acid has cis,anti,cis stereochemistry at the ring fusions. We required compounds in the more hindered cis,syn,cis series. To our knowledge, no preparations of such

materials have appeared previously. We report now the synthesis of two simple members of the series, **3** and **4**, both particularly well suited for further elaboration.

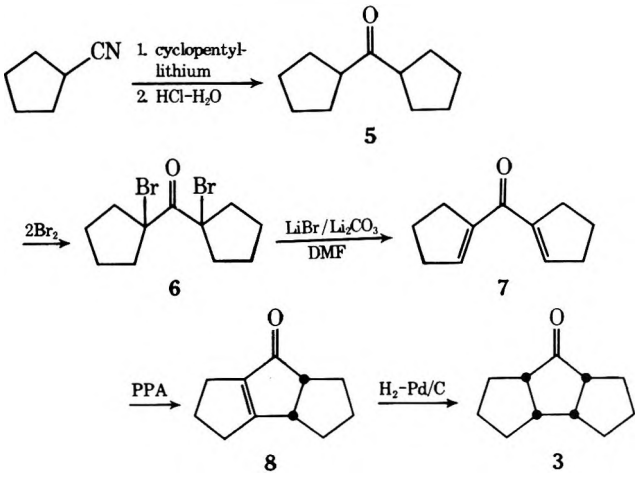


1 2

3 4

Dicyclopentyl ketone (**5**) is available by a variety of published methods.[4] However, we found it easier to make this material by addition of commercial cyclopentyllithium to cyclopentyl nitrile, followed by hydrolysis of the imine salt. As shown in Chart I, direct bromination of dicyclopentyl ketone with 2 equiv of bromine gives **6**, which is readily dehydrobrominated with a mixture of lithium bromide and lithium carbonate in DMF. The overall yield of 1,1′-dicyclopentenyl ketone (**7**) is excellent. This method provides ready access to large quantities of this interesting cross-conjugated ketone.[5] Acid-catalyzed cyclization[6] of **7** leads into the desired tricyclic series. Acids like methanesulfonic acid or phosphorus pentoxide in methanesulfonic acid[7] give mixtures of **8** and double bond isomers. Acids with nucleophilic counterions (X^-) lead to derivatives of **3** with an X substituent α (most probably) to the carbonyl group. Fortunately, cyclization of **7** with polyphosphoric acid gives **8** cleanly and in good yield.

Chart I

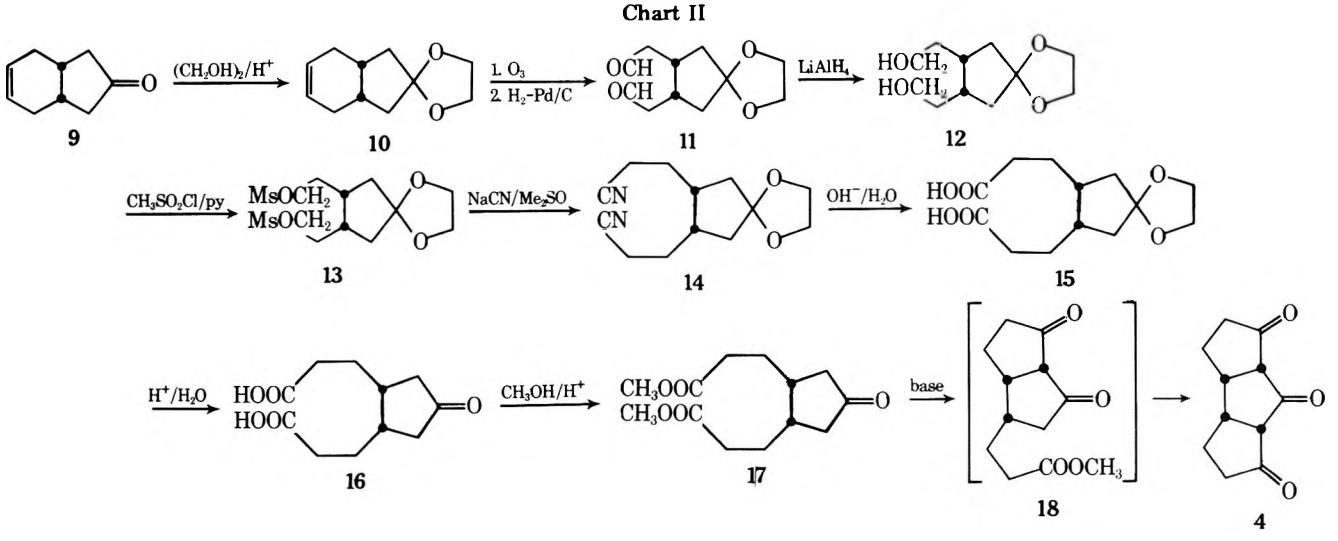


The saturated ring junction in **8** is assigned cis stereochemistry. In simpler but related systems it is clear that this arrangement is much favored over the alternate trans fusion; *cis*-bicyclo[3.3.0]octan-2-one is 6 kcal/mol more stable than the trans isomer.[8] Catalytic hydrogenation of **8** over palladium on carbon gives stereospecifically *cis,syn,cis*-tricyclo[6.3.0.0^{3,7}]undecan-2-one (**3**). The assignment of this stereochemistry follows reasonably from the synthesis and, a fortiori, from ^{13}C NMR spectral data. The proton-decoupled, ^{13}C spectrum of **3** shows only six resonance lines for the 11 carbon atoms. Given the general form of the ring skeleton and assuming, quite reasonably, complete spectral resolution, this requires that **3** have C_2 or C_s symmetry; that is, both ring fusions must be cis or both must be trans. This eliminates two of the six stereochemical relationships possible in the ring system. The ^{13}C NMR spectrum of the ethylene ketal of **3** shows that the two ketal carbons see nonequivalent environments.[9] This eliminates the two isomers of C_2 symmetry, leaving only the cis,syn,cis and the trans,syn,trans possibilities. As the latter is the least favorable sterically of all the isomers, the cis,syn,cis assignment given is quite secure.

The trione **4**, functional in all three rings, can be approached in a variety of ways. We report here "the classic approach", which has the distinct advantage for the first synthesis of **4** of establishing the relative stereochemistry of the nonepimerizable centers without question. We shall present other methods in later papers. The scheme, given in Chart II, is straightforward and requires little annotation. The starting material, *cis*-bicyclo[4.3.0]non-3-en-8-one (**9**), is available easily by elaboration of *cis*-Δ^4-tetrahydrophthalic anhydride as described by Banerjee and Ram in 1972.[10] For our purposes, there was no need to purify or characterize completely any of the intermediate compounds. Indeed, we ran the synthesis using only crude intermediates and obtained, after ten steps, 6% yield overall (not optimized).

The last step in this synthesis of **4**, the base-induced cyclization of **17**, is worthy of brief comment. Many conditions were tried without success; most led only to the bicyclic ester **18**, which resists further closure. No doubt, **18** in basic media is present as its anion, the salt of a β diketone. Formation of the dianion necessary for the second cyclization is difficult. After much frustrating work, we found that potassium *tert*-butoxide

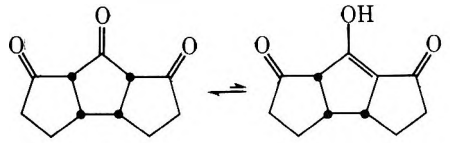
Chart II



in the aprotic, polar solvent THF is sufficiently powerful to overcome this problem without doing damage to the system.

The relative stereochemistry of the hydrogens on the tertiary carbons in **9** is not perturbed in the elaboration to **4**. The original cis configuration of adjacent centers in **9** translates to a syn relationship in the final product. The proton-decoupled ^{13}C NMR spectrum of **4** shows only six resonances for the 11 carbon atoms. These points, in combination, require that **4** be either the cis,syn,cis compound illustrated or its trans,syn,trans isomer. As we have already noted, the latter stereochemistry is very unfavorable; as such, it is most improbable for the product of the synthesis in Chart II.

Compound **4**, although a β triketone, exists predominantly in the unenolized form (eq 1). This is not unexpected. Its close



4 (1)

cousin, *cis*-bicyclo[3.3.0]octane-2,8-dione, behaves similarly.[11] Apparently, it is difficult for a three-carbon chain to bridge an sp^2 carbon to an adjacent sp^3 carbon if both are already in another five-membered ring. Still, alkali metal salts of **4** can be prepared easily.

Experimental Section

Proton magnetic resonance spectra were taken at 270 MHz on solutions in deuteriochloroform and are referenced to internal Me_4Si. Spectra were recorded for convenience on compressed scale (3 Hz/mm); therefore, quoted shifts are no better than ±0.02 ppm and coupling constants are ±1 Hz, sufficient accuracy for the purpose. Carbon magnetic resonance spectra were run at 22.63 MHz on solutions in deuteriochloroform using standard pulse techniques and white-noise decoupling. These spectra are also referenced to internal Me_4Si; chemical shifts are ±0.1 ppm. Infrared spectra were taken using Nujol mulls; positions of interesting absorptions are quoted ±5 cm^{-1}. The high-resolution mass spectrum of each characterized compound was recorded on an MS-9 spectrometer operating at 50 eV ionization voltage. Each compound exhibited a proper parent peak at *m/e* within 30 ppm of the expected value. Ultraviolet spectra were run on solutions in 95% ethanol.

Standard workup refers to extraction with the stated solvent, drying with brine washes followed by treatment with sodium sulfate, and evaporation of the solvent under vacuum on a rotary evaporator.

Dicyclopentyl Ketone (5). One mole of cyclopentyllithium in cyclohexane (Foote Mineral) in 500 ml of additional cyclohexane was placed into a water-jacketed, 2-l. kettle under an atmosphere of nitrogen. Cyclopentyl nitrile[12] (90 g, 0.95 mol) in 50 ml of cyclohexane was added dropwise over 30 min. The temperature of the reaction was kept below 20 °C. The mixture turned bright yellow. It was stirred at room temperature for 1 h. Hydrolysis was then effected by adding 50 ml of 10% HCl—slowly at first, keeping the temperature below 20 °C—and then 200 ml of 30% HCl. The two-phase mixture was stirred rapidly overnight. The cyclohexane layer was separated and washed twice with 100 ml of water. The solution was dried over Na_2SO_4 and evaporated; 118 g (78%) of yellow oil was left. Distillation gave 105 g of dicyclopentyl ketone: bp 70 °C (11 mm) [lit.[4a] 113–116 °C (14 mm)]; ^1H NMR δ 2.98 (2 H, p, J = 7 Hz) and 1.3–2 ppm (16 H).

1,1′-Dibromodicyclopentyl Ketone (6). Bromine (177 g, 1.11 mol) was added dropwise to a stirred solution of dicyclopentyl ketone (92 g, 0.55 mol) in 1500 ml of carbon tetrachloride. The liberated HBr was removed by passing a stream of nitrogen over the solution. The reaction mixture was stirred at room temperature for 1 h after the addition was complete. The volatiles were removed under vacuum to leave 179 g of a yellow oil which crystallized quickly into white needles, mp 40–43 °C. This was used directly in the next step. The dibromo compound could be crystallized from CH_3OH to give material of mp 42–43 °C.

1,1′-Dicyclopentenyl Ketone (7). A uniform mixture of 80 g of lithium bromide and 80 g of lithium carbonate was added portionwise to a cold (10 °C), stirred solution of 1,1′-dibromodicyclopentyl ketone (100 g) in 700 ml of dry DMF under nitrogen. (Note well: do not add the salts separately.) The reaction mixture was warmed to 80 °C and stirred at this temperature for 4 h. The brown mixture was cooled to room temperature and poured into 1000 ml of iced water. The solution was filtered; standard workup (hexane) gave 47.4 g (95%) of yellow solid. The solid was dissolved in hexane; the solution was treated with Norit, filtered, and cooled to 0–10 °C. 1,1′-Dicyclopentenyl ketone, 35 g (70%), was obtained as pale yellow crystals: mp 61–62 °C (lit.[5] 59 °C); ir ν 1610 and 1632 cm^{-1}; uv λ 246 nm (ϵ 3950), 259 (sh, 3120), and 328 (78); ^1H NMR δ 6.56 (2 H), 1.9–2.2 (8 H), 1.32 ppm (4 H, p, $J \sim$ 7 Hz).

***cis*-Tricyclo[6.3.0.0^{3,7}]undec-1(8)-en-2-one (8).** 1,1′-Dicyclopentenyl ketone (19 g) was added with good stirring to hot (100 °C) polyphosphoric acid (100 g) under nitrogen. The colorless PPA immediately turned dark brown. The reaction mixture was stirred for 30 min at 100 °C. After this time, the oil bath was replaced with an ice bath, and ice (100 g) was added immediately to the hot acid. The mixture was stirred for 5 min. A dark precipitate formed during the addition of ice, but dissolved on addition of ether. Standard workup (ether) gave a brown oil (19 g) which was distilled carefully to give the tricyclic enone **8**, better than 95% isomerically pure by GLC on OV-225, as a colorless oil (11.9 g, 62%): bp 60–63 °C (0.05 mm); ir ν 1690 and 1630 cm^{-1}; uv λ 244 nm (ϵ 3700) and 308 (72); ^1H NMR, multiplets centered at ca. δ 3.2 (1 H), 3.1 (1 H), 2.5 (2 H), 2.4 (4 H), 1.9 (1 H), 1.6 (4 H), and 1.3 ppm (1 H); 2,4-DNP, mp 201–202 °C (from $CHCl_3$/CH_3CH_2OH).

***cis,syn,cis*-Tricyclo[6.3.0.0^{3,7}]undecan-2-one (3).** Palladium on carbon (10%, 0.8 g) was added to a solution of the enone **8** (18 g) in 360 ml of ethyl acetate. The suspension was stirred at room temperature under 1 atm of H_2 until absorption was complete. The solution was filtered, and the solvent was removed under vacuum. The residue was distilled to yield 15.2 g (84%) of **3**, pure by GLC on OV-225: bp 82–84 °C (0.3 mm); ir ν 1730 cm^{-1}; ^1H NMR δ 2.9 (4 H, envelope, $W_{1/2} \sim$ 12 Hz), 1.82 (2 H, m), 1.72 (4 H, m), 1.53 (4 H, p, $J \sim$ 7 Hz), and 1.38 ppm (2 H, m); 2,4-DNP, mp 169–170 °C (from ethanol).

***cis,syn,cis*-Tricyclo[6.3.0.0^{3,7}]undeca-2,4,11-trione (4).** *cis*-Bicyclo[4.3.0]non-3-en-8-one (**9**, 20 g), prepared as described in the literature,[10] was combined with excess ethylene glycol (30 g) and methanesulfonic acid (1 g) in 500 ml of benzene. The mixture was stirred and heated to reflux for 24 h beneath a Dean-Stark trap. Afterwards, it was cooled and added dropwise to a well-stirred, 10% aqueous sodium carbonate solution. Standard workup (hexane) gave 23.2 g of crude, oily ketal **10**.

The majority of the crude ketal (19 g) was dissolved in 800 ml of dry ethyl acetate. The solution was cooled to about −70 °C and treated with ozone until its blue color persisted. The excess ozone was flushed out with nitrogen as the solution was warmed to 0 °C. Hydrogenation catalyst (10% Pd/C, 1.5 g) was added, and the mixture at 0–5 °C was exposed with good agitation to hydrogen at 1 atm until hydrogen absorption was complete. The catalyst was removed and the solvent evaporated in vacuo. The residue, the crude aldehyde **11**, was dissolved in 100 ml of ethyl ether, and this solution was added slowly to a suspension of lithium aluminum hydride (10 g) in a mixture of 500 ml of tetrahydrofuran and 250 ml of ether. The reaction was exothermic; the solution came to reflux. The mixture was stirred vigorously for 14 h, and then the excess hydride was destroyed with base according to the standard recipe.[13] The precipitated alumina was removed and washed with tetrahydrofuran. The organics were combined and the solvents removed in vacuo. The residue was dissolved in ether, and the solution put on a column of 200 g of silica gel. Elution with 4:1 ether/acetone gave 17 g of crude diol **12**.

The diol was dissolved in 140 ml of pyridine at 10 °C. Methanesulfonyl chloride (34 g) was added. The temperature rose to 45 °C. The solution was cooled back to 10 °C and held there for 75 min. The reaction mixture was then quenched in 500 ml of 10% aqueous sodium carbonate solution. Standard workup (methylene chloride) followed by removal of the pyridine under high vacuum gave 28 g of crude bismethanesulfonate **13**.

The crude product was dissolved in 80 ml of dry Me_2SO. This solution was added over 20 min to a well-stirred mixture under nitrogen of sodium cyanide (14 g) in 100 ml of Me_2SO at 90 °C, and the whole was maintained at this temperature for 7 h. The dark brown solution was then cooled to room temperature and poured into 600 ml of 5% aqueous sodium carbonate solution. Standard workup (ether) gave 11g of crude bisnitrile **14**.

A solution of the bisnitrile and 22 g of sodium hydroxide in 220 ml of 50% aqueous ethanol was refluxed for 7 h (→ **15** as the salt). The mixture was cooled, diluted with 200 ml of water, and extracted with methylene chloride. This extract was discarded. The aqueous phase was acidified with concentrated hydrochloric acid (→ **16**) and then taken to dryness under vacuum. The solid residue was triturated with

acetone, and the extract was evaporated under vacuum. The oily residue was taken up in 300 ml of methanol containing 0.5 ml of concentrated sulfuric acid. This solution was refluxed for 12 h, then diluted with water and extracted thoroughly with methylene chloride. The extract was concentrated under vacuum, and the residue stirred for 10 min with 50 ml of 5% hydrochloric acid. Standard workup (methylene chloride) gave 11g of crude keto ester **17**, whose quality was improved by quick passage of the material in ether through a small column of silica gel. The keto ester (10 g) showed a major ir absorption at 1740 cm^{-1}; ^1H NMR δ 3.67 (6 H), 2.2–2.4 (8 H), 1.8–2.1 (4 H), and 1.4–1.6 ppm (2 H).

A solution of **17** in 400 ml of dry tetrahydrofuran under nitrogen was mixed with 17 g of potassium *tert*-butoxide at room temperature. The suspension was stirred for 26 h. The mixture was quenched in an equal volume of saturated, aqueous potassium dihydrogen phosphate solution. Standard workup (methylene chloride) gave a solid residue which was purified by chromatography on silica gel using ether followed by 4:1 ether/acetone as eluent. Crystallization from methanol of the residue from evaporation of the ether/acetone eluate gave 1.5 g (6% overall) of pure triketone: mp 120–121 °C; ir ν 1776, 1742, and 1718 cm^{-1}; ^1H NMR δ 3.2–3.5 (4 H), 2.2–2.5 (6 H), and 1.6–1.8 ppm (2 H); ^{13}C NMR δ 208.4, 199.1 (approximate ratio 2:1), and 63.3, 40.8, 38.5, and 22.4 ppm (each of approximately equal intensity).

Acknowledgment. We are grateful to the National Institutes of Health (CA-12,961) and the National Science Foundation (GP-30568X) for financial support and to John Ivy for assistance. Funds for the purchase of the NMR instruments essential to this work were provided, in part, by the National Cancer Institute (CA-14599) via The University of Chicago Cancer Research Center, and by the National Science Foundation. C.G. thanks Montedison S.p.A., Centro Ricerche di Chimica Organica, for a leave of absence.

Registry No.—**3**, 58866-18-5; **3** 2,4-DNP, 58866-19-6; **4**, 58866-20-9; **5**, 17610-48-9; **6**, 58866-21-0; **7**, 58866-22-1; **8**, 58866-23-2; **8** 2,4-DNP, 58866-24-3; **9**, 25886-63-9; **10**, 41065-49-0; **11**, 58866-25-4; **12**, 58866-26-5; **13**, 58866-27-6; **14**, 58866-28-7; **17**, 58866-29-8; cyclopentyllithium, 23473-12-3; cyclopentylnitrile, 4254-02-8.

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Mercury in Organic Chemistry. 7.[1] A Convenient Synthesis of Symmetrical Conjugated Dienes and Polyenes

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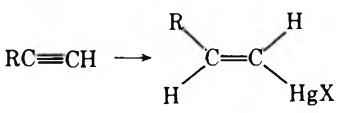
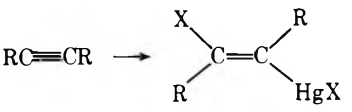
Vinylmercuric chlorides undergo reaction with palladium chloride and lithium chloride in hexamethylphosphoramide at 0 °C to provide essentially quantitative yields of the corresponding symmetrical conjugated dienes. This reaction is especially valuable for the synthesis of functionally substituted dienes and symmetrical polyenes. Divinylpalladium species are presumed to be intermediates in these reactions.

Conjugated dienes are of considerable importance in organic chemistry in themselves,[2] as well as for their utilization in the Diels–Alder reaction. Recently a number of new methods for the preparation of conjugated dienes have appeared utilizing organoaluminum,[3] -boron,[3b,4] -cobalt,[5] -copper,[6] -lithium,[5,6a–d,f,7] -magnesium,[6e] -nickel,[8] and -silver[6b,7] reagents. The scope of many of these reactions is limited by the nature of the organometallic involved or the procedure employed. Very few functional groups have been incorporated in these reactions. We wish to report a convenient new stereospecific coupling procedure utilizing vinylmercurials which both tolerates functionality and produces symmetrical dienes in near-quantitative yield. Furthermore, the reaction appears widely applicable to the preparation of symmetrical polyenes.

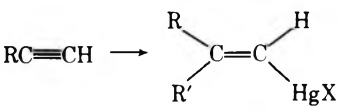
We previously reported convenient procedures for the stereospecific conversion of acetylenes into vinylmercuric halides in high yields (eq 1).[9] Other vinylmercurials are now available through the mercuration of acetylenes (eq 2, 3).[10,11]



(1)



(2)[10]

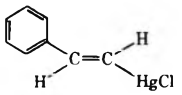
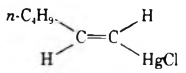
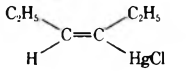


(3)[11]

Vinylmercurials possess a number of features making them attractive as synthetic intermediates. They are remarkably thermally and chemically stable organometallics. They are generally high melting, easily recrystallized solids, stable to air, water, bases, and dilute acids. These features allow one to run synthetic reactions employing these compounds under a wide variety of reaction conditions.

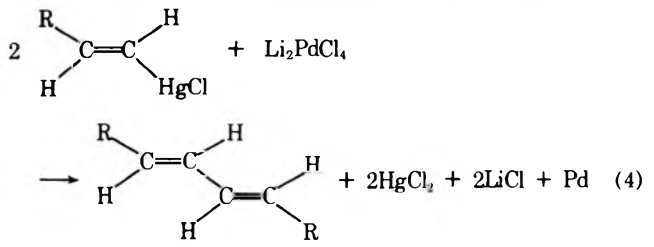
Recently vinylmercurials have proven valuable in the synthesis of α,β-unsaturated ketones,[12] acids,[1] and esters.[1] During the course of this latter study we observed that vinylmercuric chlorides when treated with palladium chloride and lithium chloride rapidly undergo dimerization to the

Table I. Reaction Conditions for Vinylmercuric Chloride Dimerization

Entry	Vinylmercuric chloride[a]	$PdCl_2$, mmol	LiCl, mmol	Solvent[b]	Temp, °C	Diene yield, %[c] trans, trans	cis, trans	cis, cis
1		1		HMPA	25	<5		
2			2			99		
3			4			100		
4		2				94	6	
5		1		C_6H_6		3		
6				Et_2O		4		
7				THF		29		
8				CH_3CN		50		
9				Pyridine		54		
10				Acetone		57		
11				CH_3OH		64		
12				DMF		82		
13				Me_2SO		82		
14				HMPA		68	15	
15					0	100		
16					25		5	75
17					0			75
18		2					7	33

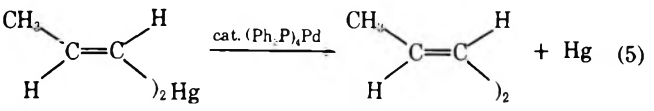
[a] 2 mmol. [b] 10 ml. [c] GLC analysis using an internal standard.

corresponding symmetrical conjugated dienes (eq 4). By the



proper choice of solvent and temperature we have been able to achieve an almost quantitative, highly stereospecific synthesis.

Near the completion of our work, Vedejs and Weeks reported a closely related dimerization of *cis*- and *trans*-dipropenylmercury using catalytic amounts of tetrakis(triphenylphosphine)palladium (eq 5).[13] While the catalytic as-



pect of this reaction is attractive, the increased volatility (and presumably toxicity) of liquid divinylmercurials over the high-melting solid vinylmercuric chlorides is a definite disadvantage. Furthermore, a 4–8% loss of stereospecificity was observed using the palladium(0) reagent. It was also reported that the use of palladium(II) reagents results in variable yields, low stereoselectivity, and in general a more complex reaction. Quite to the contrary, we have found conditions using palladium chloride under which the symmetrical dienes can be obtained in excellent yield and high stereospecificity.

Results and Discussion

Reaction Conditions. During the course of our earlier work on the palladium-promoted carbonylation of vinylmercurials,[1] we observed the appearance of minor amounts of conjugated dienes. In a subsequent effort to improve the yields of dienes obtained from this reaction, we have more carefully studied the effect of reagent, stoichiometry, solvent, and temperature. The results are reported in Table I.

A number of interesting observations can be drawn from the results. Styrylmercuric chloride reacts rapidly with palladium chloride with or without added lithium chloride, but only in its presence is the symmetrical diene obtained in good yield. Excess lithium chloride has no effect. On the other hand, excess palladium chloride decreases the stereospecificity of the reaction as well as the yield of diene (entries 4 and 18). The solvent also plays a critical role in these reactions. The yield of symmetrical diene increases steadily with the polarity of the solvent, hexamethylphosphoramide (HMPA) being the solvent of choice. Better yields and higher stereospecificity are also observed at lower temperatures.

Organophosphorus compounds often play a critical role in transition metal promoted reactions. In view of the importance of HMPA in the dimerization reaction, we chose to briefly examine the effect of other phosphorus compounds on the yield and stereochemistry of the reaction (Table II). No other phosphorus compound proved as effective as HMPA in promoting stereospecific dimerization. Even with only 4 equiv of HMPA in THF an excellent 95% yield of 1,4-diphenylbutadiene is obtained. Unfortunately, some loss of stereospecificity is observed. With tributyl phosphite a new reaction apparently ensues as metallic mercury, not mercuric chloride, is produced in high yield.

Synthesis of Dienes and Polyenes. The generality of the diene synthesis has been examined on a wide variety of vinylmercuric chlorides (Table III). Twenty millimoles of organomercurial was added to 10 mmol of palladium chloride and 40 mmol of lithium chloride in HMPA (100 ml) at 0 °C under nitrogen. The reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The product is obtained by simply extracting with pentane, drying, and removing the solvent. Trans-monosubstituted vinylmercuric chlorides give excellent yields. *cis*-Stilbenylmercuric chloride dimerizes in quantitative yield, but *cis*-3-hexenylmercuric chloride gives a significantly lower yield. We presume that this is due to the presence of a neighboring allylic hydrogen which might undergo β-hydride elimination. A slightly reduced yield (82%) is also observed with the *trans*-β-acetoxymercurial. This might be due to either β-hydride or β-acetoxy elimination reactions. This type of dimerization should prove highly useful for the preparation of functionally, highly substituted dienes

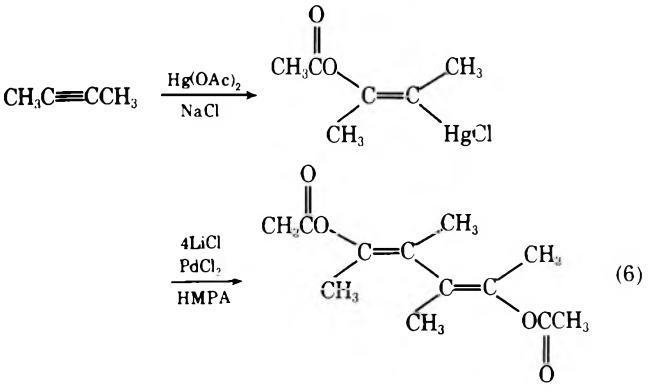
Table II. Effect of Phosphorus Compounds

$$2C_6H_5CH{=}CHHgCl + PdCl_2 \xrightarrow[THF]{0\ ^\circ C} (C_6H_5CH{=}CH)_2$$

Phosphorus compound[a]	Lithium chloride[b]	Diene yield, %[c] trans, trans	cis, trans	Total
Hexamethylphosphoramide	+	82	13	95
	–	0	0	0
Tributylphosphate	+	69	21	90
	–	~10	~5	~15
Tributylphosphine	+	45	2	47
	–	40	3	43
Triphenylphosphine[d]	–	36	22	58
Tributylphosphite	+	17	0	17[e]
	–	7	1	8[e]

[a] 4 equiv per palladium chloride. [b] Either ≤ equiv or none. [c] GLC analysis using a hydrocarbon internal standard. [d] Bis(triphenylphosphine)palladium chloride used. [e] Metallic mercury formed.

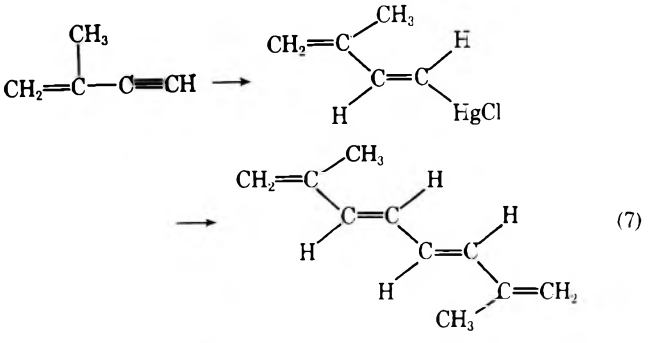
in view of the ready accessibility of such organomercurials (eq 6). The facile dimerization of two functionally substituted



(6)

organomercurials in this study offers promise that this approach to dienes and polyenes might prove general for a wide variety of functionally substituted compounds. Both organomercury and -palladium compounds appear to tolerate a considerable range of functionality.

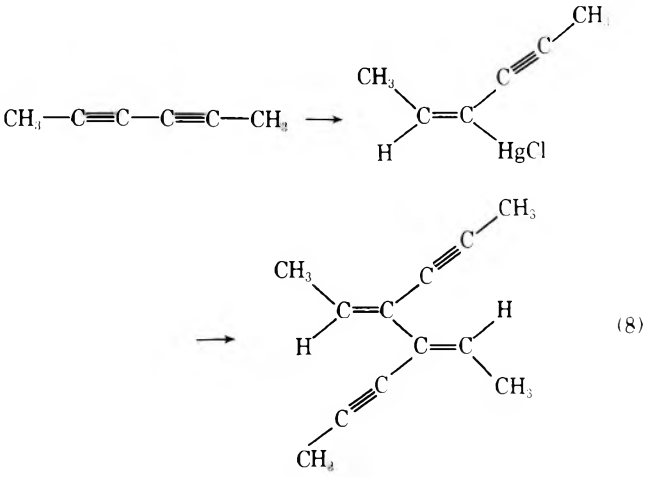
Especially noteworthy among the examples presented in Table III are the last two. Isopropenylacetylene can be selectively hydroborated on the triple bond by dicyclohexylborane. Mercuration gives a good yield of the corresponding dienylmercuric chloride.[9a] Dimerization and workup allow the preparation of the highly sensitive tetraene *trans,trans*-2,7-dimethyl-1,3,5,7-octatetraene in 95% yield (eq 7). All



(7)

spectral data (NMR, uv, ir) are consistent with the assigned structure.

An equally interesting conversion is represented by the hydroboration–mercuration of 2,4-hexadiyne and subsequent dimerization of the resulting vinylmercuric chloride (eq 8). Hydroboration with disiamylborane produces the internally substituted vinylborane. The usual mercuration procedure[9a] gives a good yield of the acetylenic vinylmercuric chloride.



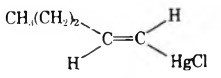
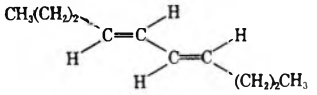
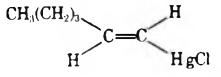
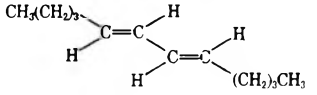
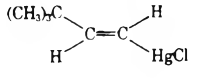
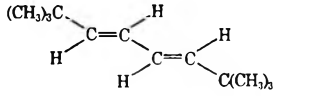
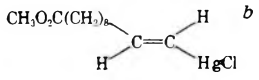
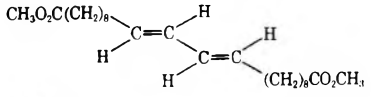
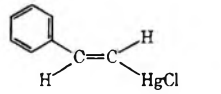
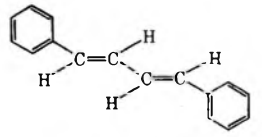
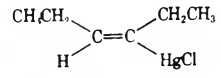
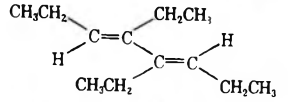
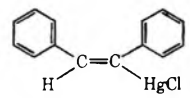
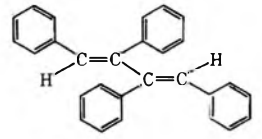
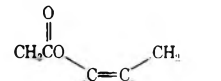
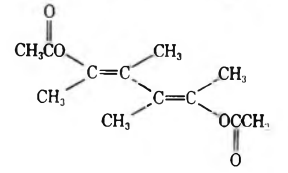
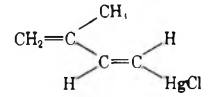
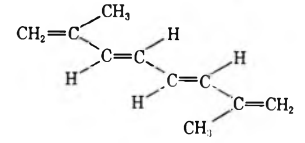
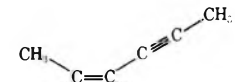
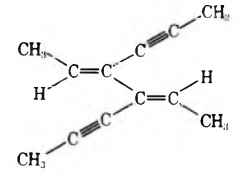
(8)

Dimerization provides a 92% yield of the pale yellow dienediyne readily recrystallized from pentane. Spectral data (NMR, ir, uv) are consistent with the assigned structure.

The above reactions appear to be highly stereospecific. All the simple 1,3-dienes whose yields were determined by gas chromatography were greater than 97% pure as determined by gas chromatographic comparison with authentic samples of all three possible stereoisomers. Crude *trans,trans*-2,2,7,7-tetramethyl-3,5-octadiene and (*Z,Z*)-1,2,3,4-tetraphenyl-1,3-butadiene gave NMR data consistent with the assigned structures and identical with the recrystallized compounds, which in turn had melting points identical with those of authentic samples prepared by alternate procedures. The stereochemistry of the *trans*-β-acetoxymercurial has been assigned from infrared data[14] and dimerization appears to give only one product as determined by NMR. *trans,trans*-2,7-Dimethyl-1,3,5,7-octatetraene exhibits a clean NMR spectra consistent with the assigned structure, as well as ir and uv data almost identical with those of *trans,trans*-1,3,5,7-octatetraene.[15] NMR examination of the dienediyne showed a very clean spectra consistent with the assigned structure and suggestive of only one product. Since hydroboration of 2,4-hexadiyne gives the cis vinylborane, the mercurial dimerization product is presumably (*E,E*)-4,5-diethylidene-2,6-octadiyne. The vinylmercurial derived from methyl 11-undecynoate was not obtained in isomerically pure form; so the resulting diene was a mixture.[1]

The accessibility of a variety of interesting functionally substituted vinylmercurials, the extreme ease with which dimerization occurs, and the ease with which dienes and polyenes can be isolated make this procedure particularly attractive for the synthesis of a number of otherwise difficultly accessible dienes and polyenes. This procedure should also

Table III. Synthesis of Dienes and Polyenes

Organomercurial	Registry no.	Dimer	Registry no.	Yield, %
	36525-00-5		53721-79-2	98[a]
	58873-33-9		30651-68-4	100[a]
	36525-02-7		22430-49-5	96
 [b]	56453-79-3		58873-35-1	94[b]
	36525-03-8		533-81-8	100[a]
	36525-04-9		30651-70-8	75[a]
	16188-35-5		1608-10-2	100
	16187-30-7		58873-36-2	82
	56453-81-7		58873-37-3	95
	58873-34-0		58873-38-4	92

[a] GLC analysis using an internal standard. [b] This organomercurial was not obtained in isomerically pure form via hydroboration–mercuration.

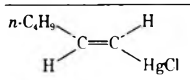
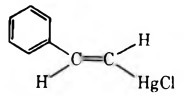
prove valuable for the synthesis of some of the naturally occurring symmetrical carotenoid polyenes.

Alkyl- and Arylmercurial Dimerization Reactions. The ease with which vinylmercurials undergo dimerization encouraged us to study the analogous reaction of alkyl- and arylmercurials. *n*-Hexylmercuric chloride reacts under our standard conditions as judged by a rapid color change from rust red to black. However, no dodecane was observed by GLC analysis. It is likely that palladium hydride elimination occurs to give a mixture of hexenes. To avoid this complication we have examined the dimerization of neopentyl-, allyl- and benzylmercuric halides. Neopentylmercuric chloride reacts only very slowly and no yield was determined. Allylmercuric iodide gave a ~70% yield of 1,5-hexadiene and benzylmercuric chloride dimerized to give a 56% yield of bibenzyl. This latter yield was improved to 70% by allowing the reaction to proceed for 10 days.

We have also examined the analogous coupling reactions of arylmercurials. Phenylmercuric chloride gave a rapid reaction and an 87% yield of biphenyl. However, perfluorophenylmercuric chloride reacts only very slowly and no yield was determined. Diphenylmercury gives a 95% yield of biphenyl based on utilization of both phenyl groups. These results are consistent with previous results on the dimerization of arylmercurials by palladium salts.[16]

Attempted Catalysis. Palladium catalysis of these dimerization reactions would substantially improve the synthetic utility of these reactions. We have previously achieved considerable success in using palladium chloride as a catalyst when cupric chloride is added as a reoxidant.[1] Unfortunately,

Table IV. Tetrakis(triphenylphosphine)palladium(0) Catalysis[a]

Vinylmercuric chloride[b]	Lithium chloride[c]	Diene yield, %[d] trans, trans	cis, trans	Total
	–	42	2	44
	+	59	2	61
	–	46	2	48
	+	80		80

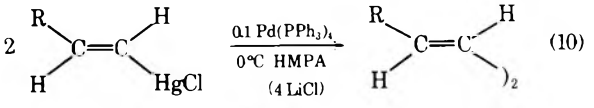
[a] 0.1 mmol catalyst. [b] 2.0 mmol. [c] Either 0 or 4 mmol. [d] GLC analysis using a hydrocarbon internal standard.

this approach failed in our present diene synthesis (eq 9).

$$2C_6H_5CH{=}CHHgCl + 2LiCl + 4CuCl_2 \xrightarrow[25\ ^\circ C,\ HMPA]{0.1\ PdCl_2} (C_6H_5CH{=}CH)_2 \quad (9)$$

15%

Palladium(0) reagents should serve as catalysts without the need for additional reoxidants. Tetrakis(triphenylphosphine)palladium (10%), with and without added lithium chloride, has been added to both *trans*-1-hexenylmercuric chloride and styrylmercuric chloride in HMPA at 0 °C (eq 10).



(10)

R = *n*-C_4H_9, C_6H_5

An immediate darkening and deposition of metallic mercury occurs. Although the corresponding dienes are obtained in good yield when lithium chloride is present, the yields and stereospecificity are not as good as those of the stoichiometric palladium chloride reactions (Table IV).

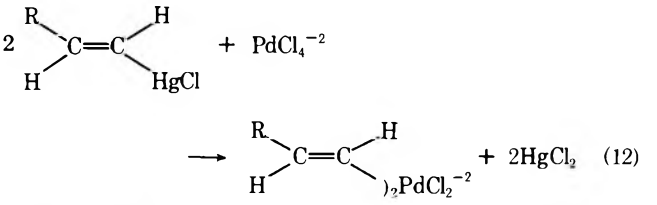
Mechanism. The direct coupling of aromatic compounds by palladium salts is a well-known reaction (eq 11).[16,17] Al-

$$2Ar{-}H + PdX_2 \longrightarrow Ar{-}Ar + Pd + 2HX \quad (11)$$

though intermediate arylpalladium compounds are undoubtedly involved, the precise manner by which coupling occurs is still unclear. Arylmercurials are also reportedly very readily coupled in the presence of palladium salts.[16] For example, Unger and Fouty report the rapid dimerization of tolylmercuric acetate in the presence of palladium acetate and perchloric acid. Bitolylmercury also rapidly couples when treated with "palladium salts" in acetic acid. Unfortunately, none of these experiments appear to have been done starting with the actual organomercurials indicated. Instead the mercurials were apparently prepared in situ and then treated with the palladium salts. Experimental details are lacking. In view of this previous report on arylmercurial dimerizations, it is not surprising that we also observe coupling products from both phenylmercuric chloride and diphenylmercury.

Vinylmercury or -palladium dimerization reactions have until recently been totally neglected. There are, however, several reports of the formation of dienes upon heating olefins and palladium acetate.[18-20] Vinylpalladium species may be involved in these reactions. Vedejs and Weeks have recently reported the smooth catalytic dimerization of *cis*- and *trans*-dipropenylmercury by tetrakis(triphenylphosphine)-palladium.[13] Although they suggest no mechanism for this reaction, some of the side products observed clearly point to vinylpalladium intermediates.

Our palladium chloride–lithium chloride induced coupling of vinylmercuric chlorides also undoubtedly proceeds via intermediate vinylpalladium species. The facile carbonylation of these compounds by carbon monoxide is clear proof of their existence.[1] We suggest that these coupling reactions proceed through initial exchange to form a dichlorodivinylpalladium dianion (eq 12) which then reductively eliminates the diene, chloride anion, and palladium metal (eq 13). While palladium



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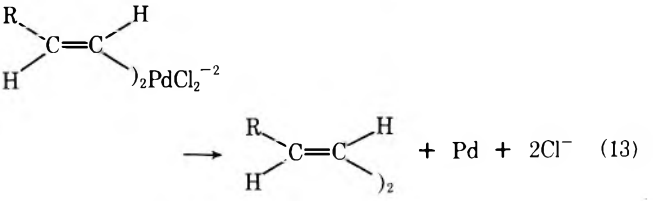

(13)

chloride also rapidly reacts with vinylmercurials, it presumably only forms a neutral divinylpalladium compound which apparently decomposes in a different manner. The chloride ligands presumably facilitate reductive elimination of the diene. The loss of stereospecificity and reduction in yield in the reaction employing excess palladium chloride most likely arises from formation of a monovinylpalladium anionic species which is no longer able to reductively eliminate the diene. Side reactions such as cis–trans isomerization then become increasingly important. The highly polar HMPA presumably promotes the formation of ionic species by solvation. It may also play a role in the stabilization of intermediate vinylpalladium species.

Conclusion

Vinylmercuric chlorides, readily available via acetylene addition reactions, undergo a rapid, stereospecific dimerization reaction with lithium chloride and palladium chloride in HMPA at 0 °C to provide excellent yields of the corresponding symmetrical 1,3-dienes. The reaction is applicable to the synthesis of functionally substituted dienes as well as polyenes. In attempting to extend these palladium-promoted reactions to the synthesis of unsymmetrical dienes we have recently uncovered a novel new route to π-allylpalladium compounds which we hope to report on shortly. Vinylmercury and -palladium reactions also provide a convenient new route to 1,4-dienes which we are presently studying.

Experimental Section

Reagents. All chemicals were used directly as obtained commercially unless indicated otherwise. Diethyl ether, THF, and HMPA were distilled from lithium aluminum hydride prior to use.

Phenylmercuric chloride (Aldrich) and diphenylmercury (Eastman Kodak) were used directly as obtained. Allylmercuric iodide,[21] benzylmercuric chloride,[22] *n*-hexylmercuric chloride,[23] neopentylmercuric chloride,[24] and *trans*-3-acetoxy-2-butenylmercuric chloride[14] were prepared according to literature procedures.

All other vinylmercuric chlorides were prepared using our standard hydroboration–mercuration sequence.[9] All vinylmercurials except that derived from 2,4-hexadiyne have been described before.[1,9] (*E*)-3-Chloromercuri-2-hexen-4-yne was prepared by hydroboration–mercuration of 2,4-hexadiyne using disiamylborane instead of dicyclohexylborane:[9a] mp 136–137 °C dec; ^1H NMR ($DCCl_3$) δ ~1.99 (d, 3, J = 7 Hz, allyl), 2.01 (s, 3, propargyl) (overlapping peaks at 1.99 and 2.01), and 5.81 ppm (q, 1, J = 7 Hz, vinyl). Anal. Calcd for C_6H_7ClHg: C, 22.87; H, 2.24; Hg, 63.65. Found: C, 22.94; H, 2.32; Hg, 63.56.

Tetrakis(triphenylphosphine)palladium was prepared according to the literature procedure.[25] The palladium chloride was generously provided by Matthey Bishop, Inc.

Reaction Conditions. The best reaction conditions for the formation of symmetrical 1,3-dienes were determined by employing the following general procedure. The appropriate amounts of palladium chloride (1 or 2 mmol) and anhydrous lithium chloride (2 or 4 mmol) were placed in a flask containing a nitrogen inlet tube and septum outlet. The flask was flushed with nitrogen and filled with 10 ml of the appropriate solvent and an appropriate hydrocarbon internal standard. After the reaction temperature (0 or 25 °C) was adjusted, 2 mmol of either styrylmercuric chloride or *trans*-1-hexenylmercuric chloride was added by means of a funnel through the top of the reaction flask while backflushing with nitrogen. The flask was then allowed to slowly warm to room temperature and stirred overnight. Ether (5 ml) was added and the reaction mixture was analyzed directly by GLC analysis on an SE-30 column. Product determinations were made by comparison with authentic samples. The exact amount of each reagent and the results are presented in Table I.

Effect of Phosphorus Compounds. The following standard procedure was employed. Palladium chloride (1 mmol) and either 0 or 4 mmol of anhydrous lithium chloride were placed in a flask under nitrogen. THF (10 ml), 4 mmol of the appropriate phosphorus compound, and approximately 0.1 g of octadecane as an internal standard were added and the flask cooled to 0 °C. Styrylmercuric chloride (2 mmol) was added with nitrogen backflushing. The flask was allowed to slowly warm to room temperature and stirred overnight. GLC analysis on an SE-30 column gave the results indicated in Table II.

Standard Procedure for the Synthesis of Dienes and Polyenes. The following procedure for the preparation of *trans,trans*-2,2,7,7-tetramethyl-3,5-octadiene is representative. To a well-dried nitrogen-filled flask with septum inlet were added 100 ml of HMPA, 40 mmol of anhydrous lithium chloride, and 10 mmol of palladium chloride. The flask was thoroughly cooled in an ice bath and 20 mmol of *trans*-3,3-dimethyl-1-butenylmercuric chloride was added rapidly while backflushing with nitrogen. The reaction mixture immediately turned black and was allowed to slowly warm to room temperature and then stirred overnight, at which time activated carbon, water, and pentane were added. After filtration the organic layer was separated and the aqueous layer repeatedly extracted with pentane. The combined extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated, leaving 1.60 g (96%) of a very pale yellow solid which was analytically pure by GLC and NMR analysis: mp 78–79 °C (EtOH); ^{1}H NMR (CCl_4) δ 1.02 (s, 18, CH_3) and 5.3–6.0 ppm (m, 4, vinyl). This compound was identical with an authentic sample.[3c]

The following compounds were prepared in a similar fashion. Dimethyl *cis,trans*- and *trans,trans*-10,12-docosadienedioate: mp ~40 °C (mixture of isomers by ^{1}H NMR and GLPC); ir (max) (neat) 2910, 2840, 1740, 1435, 1170, and 980 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.31 (m, 24, CH_2), 1.8–2.4 (m, 8, $CH_2C{=}O$ and $CH_2CH{=}$), 3.58 (s, 6, CH_3O), and 5.0–6.3 ppm (m, 4, vinyl); *m/e* 394.3079 ± 0.0020 (calcd for $C_{24}H_{42}O_4$, 394.3083). *cis,cis*-1,2,3,4-Tetraphenylbutadiene (use a benzene extraction): mp 182–184 °C (hexane–benzene) (lit.[26] mp 183 °C). (*E,E*)-2,5-Diacetoxy-3,4-dimethyl-2,4-hexadiene: mp 32.5–33.0 °C; ir (max) (neat) 2920, 1755, 1685, 1435, 1375, 1235, 1180, 1070, and 1015 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.57 (m, 6, allyl), 1.78 (m, 6, allyl), and 2.08 ppm (s, 6, $CH_3C{=}O$); *m/e* 226.1204 ± 0.0012 (calcd for $C_{12}H_{18}O_4$, 226.1205). *trans,trans*-2,7-Dimethyl-1,3,5,7-octatetraene: yellow oil; ir (max) (CCl_4) 3080, 3020, 2970, 2915, 1770, 1620, 1578, 1263, 1100, 985, and 885 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.73 (m, 6, CH_3), 4.84 (m, 4, vinyl), and 6.14 ppm (m, 4, vinyl) (each peak closely approaches a singlet but has some very slight splitting); λ_{max} (cyclohexane) 270, 281, 293, and 307 nm (same relative extinction coefficients as 1,3,5,7-octatetraene[15]); *m/e* 134.1094 ± 0.0007 (calcd for $C_{10}H_{14}$, 134.1096). (*E,E*)-4,5-Diethylidene-2,6-octadiyne: mp 95–96 °C; ir (max) (KBr) 3020, 2950, 2890, 2830, 2225, 1675, 1600, 1435, 1325, 935, 830, and 785 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.90 (d, 3, J = 7 Hz, allyl), 2.04 (s, 3, propargyl), and 6.28 ppm (q, 1, J = 7 Hz, vinyl); λ_{max} (hexane) 239 nm (ϵ 16 600), 246 (20 800), and 255 (17 600); *m/e* 158.1098 ± 0.0008 (calcd for $C_{12}H_{14}$, 158.1096). All reactions appear to proceed with very high stereospecificity as indicated by NMR and GLC analysis and described in the text. All other dienes were identified by comparison with authentic samples of all three possible stereoisomers prepared by alternate methods.

All GLC yields were determined on reactions run on one-tenth the above scale following a GLC analysis procedure identical with that outlined in the section entitled "Reaction Conditions". Internal standard correction factors were determined using authentic diene samples.

Alkyl- and Arylmercurial Dimerization Reactions. These reactions were run exactly as the above GLC diene reactions. Internal standard correction factors were determined using authentic hydrocarbon samples.

Attempted Catalysis. All attempted catalytic reactions were run according to our above GLC diene procedure. The cupric chloride reaction was run using the following reagents: styrylmercuric chloride (2 mmol), lithium chloride (2 mmol), anhydrous cupric chloride (4 mmol), palladium chloride (0.1 mmol), and HMPA (10 ml). The tetrakis(triphenylphosphine)palladium reactions were run using *trans*-1-hexenylmercuric chloride or styrylmercuric chloride (2 mmol), lithium chloride (0 or 4 mmol), tetrakis(triphenylphosphine)palladium (0.1 mmol), and HMPA (10 ml). All yields were determined using an appropriate hydrocarbon internal standard.

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Registry No.—Dimethyl *cis,trans*-10,12-docosadienedioate, 58873-39-5.

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Mercuration of Naphthalene—Salient Features[1]

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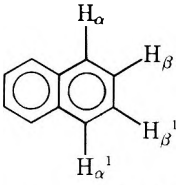
The mercuration of naphthalene by mercuric acetate in acetic acid (uncatalyzed) and under conditions of perchloric acid catalysis has been studied. Kinetically the reactions are first order in Hg(II) and in naphthalene, although under catalytic conditions some deviations from second-order behavior occur as the Hg(II) concentration is varied. The effects of added water, sodium perchlorate, and perchloric acid on the rates have been studied, and the results rationalized on the basis of certain acid–base reactions that are possible under these conditions, and delineated previously by Kresge and Brown. Naphthalene is mercurated very predominantly at the α position, based on a technique of accumulation of ^{199}Hg–^{1}H satellite intensity in the ^{1}H NMR spectra of the total product. The mercuration of naphthalene exhibits substantial isotope effects (k_H/k_D = 3.6 for uncatalyzed and 7.2 for $HClO_4$-catalyzed) and coupled with the kinetics, implicates a mechanism whereby the σ intermediate, in low concentration, is formed rapidly and reversibly from the Hg(II) electrophile and naphthalene, followed by rate-determining proton loss. Naphthalene, on a site for site basis, is more reactive at the α position than is benzene by factors of 11.7 (uncatalyzed) and 18.4 (catalyzed), in line with the low selectivity of this reaction. Some comments on the apparently high (α,β) positional selectivity but low substrate selectivity are made.

The mercuration reaction has been of considerable value in providing kinetic and isomer distribution data to test certain quantitative approaches to aromatic reactivity.[3,4] Considerable understanding of the mechanisms of aromatic mercuration has been achieved,[5-9] but very little information is available on even qualitative aspects of mercuration of aromatic systems other than benzene and substituted benzenes. Some years ago we conducted a thorough study of the mercuration of naphthalene by mercuric acetate in acetic acid, both "neutral" and catalyzed by perchloric acid,[1] at about the time Kresge and Brown[7-9] published their definitive mechanistic analyses of the mercuration of benzene. Consequently, we deferred publication of our results, but in view of recent interest in aromatic metalation reactions generally, and private requests for aspects of our data, we have decided to publish the salient features of the mercuration of naphthalene under various conditions, but to restrict mechanistic discussion, in view of Kresge and Brown's impressive previous reports.[7-9]

Results and Discussion

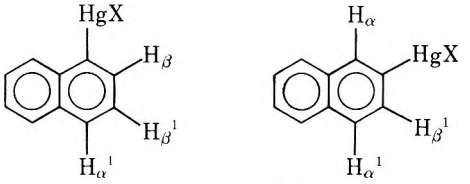
A. Isomer Distributions. We were stimulated by the reports[10,11] that mercuration of naphthalene under some conditions yielded substantial amounts of β isomer, and thallation of naphthalene with thallium(III) isobutyrate has been considered to be almost exclusively β, since only β-naphthylmercuric chloride was obtained by treatment of the naphthylthallium compound with mercuric chloride.[12] If these reactions were authentic electrophilic substitution, the above isomer distributions seemed odd for conditions of kinetic control, and prompted careful assessment of the isomer distribution in mercuration.

For isomer determinations, a number of approaches, including polarography, bromodemercuration, etc., were tried, but eventually we developed a new method based on computer accumulation of ^{199}Hg–^{1}H satellites (^{199}Hg is 16.8% naturally abundant; I = ½) which allows direct observation of reaction products, and the method has general applicability to reactions of the present type where metal–^{1}H coupling occurs. The ^{1}H NMR spectrum of naphthalene has been analyzed as an A_2B_2 system,[13] which is valid if the A_4B_4 system is regarded as the superposition of two A_2B_2 sets, with inter-ring coupling ignored. In α-deuterionaphthalene it is the lower half of the initial mirror-image pattern that is of reduced intensity, so that H_α resonates at lower field. This spectrum closely resembles that of α-naphthylmercuric acetate or chloride (mercuric substituents exert feeble substituent effects)[14] so that the coupling constants found for naphthalene apply, for the present level of precision, to the naphthylmercurials. Thus it is possible to predict the effects of substituting HgX for H_α or H_β lead-



$J_{H_\alpha-H_\beta} = 8.6$ Hz
$J_{H_\alpha-H_{\beta'}} = 1.4$ Hz
$J_{H_\beta-H_{\beta'}} = 6$ Hz

ing to α-$C_{10}H_7HgX$ or β-$C_{10}H_7HgX$, and in particular, the multiplicities of the ^{199}Hg satellites. In α-$C_{10}H_7HgX$, the satellites of H_β should appear basically as a broadened dou-



blet since $J_{H_\beta-H_{\beta'}} \sim 6$ and $J_{H_\beta-H_{\alpha'}} \sim 1.4$ Hz, and in the spectrum of α-$C_{10}H_7HgCl$ (Me_2SO solvent) signals of appropriate intensity and multiplicity are located 112 Hz to the low- and high-field sides of the higher field component of the aromatic resonance. Thus $J_{Hg-H_\beta} \sim 224$ Hz. In β-$C_{10}H_7HgX$, the situation is simpler since now H_α is feebly coupled to $H_{\beta'}$ ($J \sim 1.4$ Hz) so that H_α protrudes from the α portion of the aromatic resonance as a broadened singlet. Consequently, the ^{199}Hg satellites appear essentially as singlets and again $J_{Hg-H_\alpha} \sim 224$ Hz. Coupling to $H_{\beta'}$ would also occur, and the satellites would each appear as broadened doublets as $J_{H_{\beta'}-H_{\alpha'}} \sim 6$ and $J_{H_{\beta'}-H_\alpha} \sim 1.4$ Hz. There is some evidence for this on the downfield side of the main β resonance but distribution of intensity among four lines (or two broadened signals) makes it far less obvious than the H_α satellite. These situations are summarized in Figure 1 in a schematic fashion since the details of the main aromatic resonance pattern are not important to the argument.

Thus the low-field satellite pattern for a mixture of α- and β-$C_{10}H_7HgX$ would consist of a singlet (J_{Hg-H_α}) separated by ca. 15 Hz from two overlapping broadened dou-

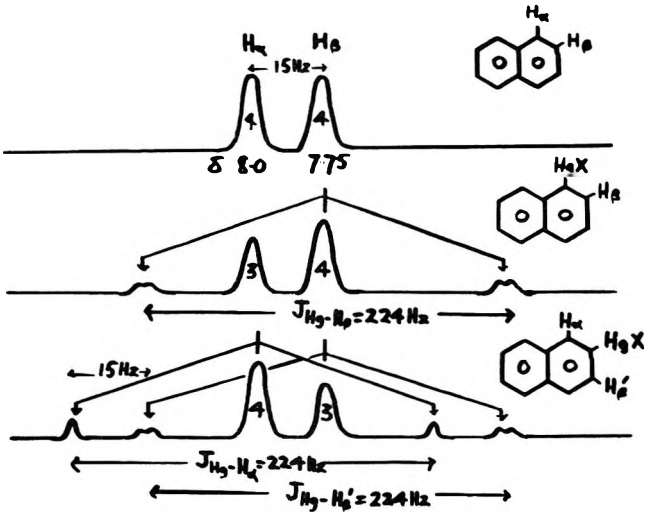
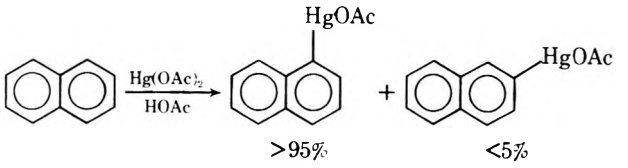


Figure 1. Schematic representation of ^1H spectral traces associated with naphthalene and the α- and β-naphthylmercury halides. The relative intensities of the main H_α and H_β resonances are indicated, and the flanking ^{199}Hg-H satellites shown for the two situations.

blets (J_{Hg-H_β} and $J_{Hg-H_{\beta'}}$). Presence of substantial amounts of β isomer, therefore, would be indicated by the presence of both satellite regions while predominating α isomers would lack the characteristic satellite singlet (J_{Hg-H_α}). As described in the Experimental Section, the product acetates were precipitated as the chlorides and their ^1H NMR spectra in the low-field satellite region were continually scanned with the Varian computer of average transients (CAT) until a high satellite intensity was accumulated. The computer readouts are shown in Figure 2 and in a and b are the readouts for the uncatalyzed and $HClO_4$-catalyzed reactions. The large peak (now a broadened singlet in the readout) on the right hand side of each diagram is due to the α isomer, and indicated with a double asterisk. c and d are the readouts from reaction mixtures identical in composition and conditions of study, except for the addition of ~5% of β-naphthylmercuric acetate, after the completion of the reaction but prior to the precipitation as the chloride. The response due to the added β isomer is clearly seen as a pronounced peak downfield from the α resonance. The presence of β isomer is more noticeable as the amplitude is increased (upper trace), but clearly less than 5% of β-mercuration occurs in both the neutral and acid-catalyzed reactions. Intensity comparisons would suggest not less than 95% α-mercuration. This conclusion is also in har-



mony with kinetic isotope effects for naphthalene-d_8 and specifically deuterated naphthalenes (vide infra).

Under other conditions it does appear that substantial postkinetic $\alpha \gtrsim \beta$ equilibration occurs. For example, Verwey and Kooyman report[10,11] that the reaction of $C_{10}H_8$ (1.23 mol) with $Hg(OAc)_2$ (0.005 mol) at 96 °C for 3 h leads to 65% α and 35% β substitution. It is of interest that we could not detect equilibration of the α isomer with the β after several half-lives of the substitution reaction at 70 °C. However, the different solvent system and temperature could account for this. The predominant formation of α product is in line with other authentic electrophilic substi-

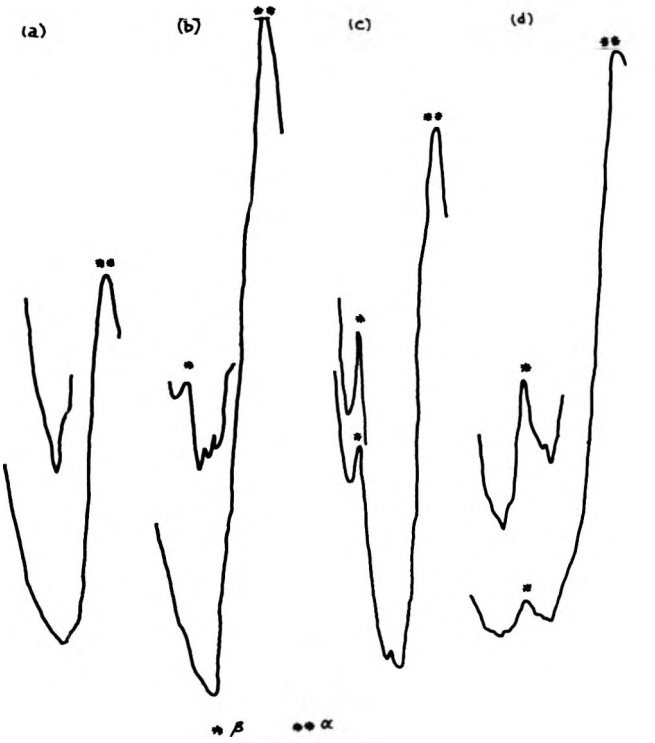
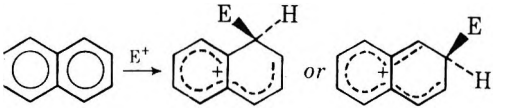


Figure 2. (a) Computer readout of low-field satellites region of product naphthylmercuric chlorides from the uncatalyzed reaction. (b) Similarly for $HClO_4$-catalyzed reaction. The large peak (**) is due to the α isomer, while that for the β isomer (*) is barely perceptible. (c) and (d) are the readouts corresponding to (a) and (b), respectively, except that 5% of β-acetomercurinaphthalene has been added after completion of reaction but prior to precipitation as the chloride. The response due to the β isomer is clearly seen (marked *) downfield from the α resonance, and indicates that less than 5% of β isomer was formed in direct mercuration.

tutions in naphthalene, as bromination,[15] chlorination,[16] and nitration[17] yield α isomers to the extents of 99, 97, and 90%, respectively. These results are rationalized by rudimentary MO theory,[18] as L^+, the cationic localization energy, is related to the loss of π-election stabilization on forming the Wheland-type intermediate $C_{10}H_8E^+$. For β-substitution, $L^+ = 2.48\beta$, but 2.29β for α-substitution, thus favor-



ing the latter. It may have been thought that the supposed "bulky" nature of metal electrophiles would be a factor operating against α-substitution, but the evidence is[19,20] that the steric requirements of HgOAc would be inconsequential.

Kinetics of Mercuration. A. $Hg(OAc)_2$ in Acetic Acid. The reactions were followed by the well-established thiocyanate titration technique[21] for unreacted Hg(II) and product RHg(II) species. The stoichiometry was established as $C_{10}H_8$:$Hg(OAc)_2$:1-acetatomercurinaphthalene = 1:1:1 on the basis of "infinity" titres after ca. 6 half-lives, under conditions with naphthalene in excess by at least a factor of 6 to avoid complicating polymercuration.[21] Under these conditions, plots of log $(2T_t - T_0)$ vs. time were satisfactorily linear, and pseudo-first-order rate constants were determined graphically (T_t = titre after time "t"; T_0 = titre at time zero). For varying concentrations of $Hg(OAc)_2$ and $C_{10}H_8$, division of the pseudo-first-order constant by $[C_{10}H_8]$ yielded acceptably invariant second-order rate

Table I. Results of Kinetic Studies of the Reaction of Naphthalene and Mercuric Acetate in Glacial Acetic Acid (Uncatalyzed)

I	II	III	IV	V	VI	VIII
No.	Temp, °C	[Naph], mol/l.	[$Hg(OAc)_2$], mol/l.	[H_2O], %	[NaOAc], mol/l.	$k_2 \times 10^3$, mol^{-1} min^{-1}
1	70	0.97	0.0919			2.67
2	70	0.97	0.092			2.67
3	70	0.98	0.1195			2.74
4	70	0.98	0.1190			2.74
5	70	0.928	0.089			2.78
6	70	0.928	0.0875			2.78
7	70	1.875	0.12			2.70
8	70	1.875	0.125			2.70
9	70	1.5	0.1035			2.725
10	70	1.5	0.1025			2.725
11	70	0.588	0.0950			3.02
12	70	0.588	0.0966			3.02
13	70	0.997	0.113	5.75		3.14
14	70	0.997	0.113	5.75		3.14
15	70	0.996	0.113	5.75	0.114	2.91
16	70	0.997	0.113	5.75	0.114	2.91
17	60	0.871	0.108			1.132
18	60	0.871	0.0995			1.132
19	80	0.838	0.1009			6.07
20	80	0.838	0.1005			6.07

constants. Thus the reaction is first order in both $C_{10}H_8$ and Hg(II). The details are assembled in Table I.

A very slight acceleration accompanies an increase in the water content (run 13), while addition of NaOAc under these conditions causes a slight retardation (run 15). A number of factors may be associated with these altered conditions, but the effects are so small that meaningful analysis is not possible. There seems no reason to doubt that the electrophile under these conditions is very largely un-ionized mercuric acetate.

The temperature variation of k_2 is also shown in Table I and in standard fashion, a plot of log k_2 vs. $1/T$ yielded a value of the energy of activation, E_a, of 17.8 kcal/mol with $\Delta H^{\ddagger} = 17.2$ kcal/mol at 25 °C.

The rate data in Table I may be compared with those available for benzene,[21] and α-mercuration is ca. 11.7 times as fast as mercuration at a single benzene position. This is remarkably low, when compared with nitration and chlorination, where reactivity ratios of ca. 470 and 10^5 are observed,[22] demonstrating the low selectivity[3] of uncatalyzed mercuration.

B. $Hg(OAc)_2$ in Acetic Acid Catalyzed by Perchloric Acid. As noted by Westheimer[6] and investigated in great detail by Kresge and Brown,[7-9] $HClO_4$ strongly catalyzes the mercuration of benzene. In the case of naphthalene, accelerations of comparable magnitude are observed, and, for example, at 70 °C (extrapolated from data at lower temperatures) mercuration in the presence of 0.115 M $HClO_4$ and 0.55 M H_2O proceeds ca. 1440 times faster than the uncatalyzed reaction. The essential aspects of our kinetic data are shown in Table II. The stoichiometry of the catalyzed reaction was established as outlined earlier. A comparison of entries 8, 9, 12, 13, 14, and 15 in Table II in which the only variable is [$C_{10}H_8$] shows that the k_2 values, calculated as before, are essentially invariant over the range studied. Thus first-order dependence in $C_{10}H_8$ is again established. Deviation from strict first-order behavior was observed when the initial [$Hg(OAc)_2$] was altered, with other conditions constant. This follows from runs 1, 14, and 15 where a significant increase in k_2 is observed when [$Hg(OAc)_2$] is halved.

Runs 1–6 in Table II show a definite positive linear dependence on perchloric acid concentration, as has been observed previously for the benzene system. The equilibrium

$$HClO_4 + Hg(OAc)_2 \rightleftharpoons {}^{+}HgOAc\ ClO_4^{-} + HOAc \quad (A)$$

has been regarded[7] as responsible, producing a more potent mercurating agent. Dampening this effect somewhat is the presence of water, since its weakly basic nature in acetic acid allows interaction with and competition for the available $HClO_4$.

$$H_2O + HClO_4 \rightleftharpoons H_3{}^{+}O\ ClO_4^{-}$$

It is clear from the work of Brown and Kresge[7] that under these conditions ${}^{+}HgOAc\ ClO_4^{-}$ is the major mercurating agent, with perhaps small contributions from mercuric perchlorate ion triplets $Hg^{2+}(ClO_4^{-})_2$, and un-ionized-$Hg(OAc)_2$. However it can be calculated that at 20 °C, the rate constant for substitution by $Hg(OAc)_2$ is ca. 2×10^{-5} mol^{-1} min^{-1}, and therefore the observed rate of $(3\text{–}28) \times 10^{-3}$ must arise predominantly from a reaction between acetatomercuric perchlorate ion pairs and naphthalene.

The positive deviation from second-order behavior mentioned above has been noted by Kresge, Dubeck, and Brown[7] and explained in terms of the consequence of lowering [$Hg(OAc)_2$] on the equilibrium A above.

Runs 20–25 indicate an approximate linear relation between k_2 and [$NaClO_4$], and this is associated with the solvolysis of $NaClO_4$, to produce a significant concentration of $HClO_4$.

$$NaClO_4 + HOAc \rightleftharpoons NaOAc + HClO_4\ (K \sim 6 \times 10^{-5}\ M \text{ for } 0.1\ M \text{ salt})$$

This acid then converts enough $Hg(OAc)_2$ to ${}^{+}HgOAc\ ClO_4^{-}$ to provide the observed rate accelerations.

Under standard conditions[9] at 25 °C where $[HClO_4]_{anal} = 0.50$ M and $[H_2O]_{anal} = 0.20$ M, naphthalene is 12.3 times as reactive as benzene. As $HClO_4$-catalyzed mercuration is essentially exclusively α, this α-substitution is ca. 18.4 times as facile as at a single benzene position. The catalyzed reaction has been shown to be more discriminating,[9] and discussion[9] of this unusual phenomenon is available.

Kinetic Isotope Effects. Large primary isotope effects

Table II. Results of the Kinetic Study of the Reaction between Naphthalene and Mercuric Acetate in Acetic Acid (ca. 99%) Catalyzed by Perchloric Acid

I	II	III	IV	V	VI	VII	VIII
No.	Temp, °C	[Naph], mol/l.	$[Hg(OAc)_2]$, mol/l.	$[H_2O]$, mol/l.	$[HClO_4]$, mol/l.	$[NaClO_4] \times 10^2$, mol/l.	$k \times 10^2$, mol^{-1} min^{-1}
1	20	0.532	0.116	0.554	0.1129		2.31
2	20	0.532	0.116	0.561	0.0921		2.115
3	20	0.532	0.116	0.55	0.0922		2.19
4	20	0.532	0.116	0.56	0.069		1.225
5	20	0.532	0.116	0.546	0.0502		0.93
6	20	0.532	0.116	0.604	0.0247		0.242
7	20	0.532	0.116	0.548	0.0215		0.32
8	20	0.274	0.0508	0.55	0.11		2.76
9	20	0.281	0.0508	0.55	0.11		2.79
10	20	0.399	0.0508	0.567	0.0467		0.794
11	20	0.397	0.051	0.556	0.0461		0.798
12	20	0.399	0.051	0.55	0.11		2.78
13	20	0.398	0.051	0.55	0.11		2.72
14	20	0.532	0.051	0.55	0.115		2.81
15	20	0.532	0.051	0.55	0.115		2.81
16	24	0.532	0.0508	0.55	0.115		4.30
17	24	0.532	0.051	0.55	0.115		4.39
18	28	0.532	0.0508	0.55	0.115		6.90
19	28	0.532	0.0509	0.55	0.115		6.95
20	70	1.00	0.101			0.1	4.11
21	70	1.00	0.101			0.1	4.12
22	70	1.00	0.101			0.2	5.50
23	70	1.00	0.101			0.2	5.52
24	70	1.00	0.101			0.3	6.81
25	70	1.00	0.101			0.3	6.78

Table III. Results of Kinetic Studies of Deuterium-Labeled Naphthalenes with Mercuric Acetate in Glacial Acetic Acid at 70 ± 0.05 °C

No.	Substrate	[Substrate], mol/l.	$k_2 \times 10^4$, mol^{-1} min^{-1}	Kinetic isotope effect
1a	Naphthalene-h_8	0.867	29.3	
b	Naphthalene-d_8	0.867	8.4	3.49
2a	Naphthalene-h_8	0.854	28.0	
b	Naphthalene-d_8	0.854	7.6	3.68
3a	Naphthalene-h_8	0.854	28.8	
b	Naphthalene-1-d_1	0.856	22.1	1.305 (1.21)
c	Naphthalene-1,4-d_2	0.854	20.7	1.39 (1.56)
4a	Naphthalene-h_8	0.89	27.4	
b	Naphthalene-1-d_1	0.875	21.5	1.272 (1.22)
c	Naphthalene-1,4-d_2	0.889	16.5	1.66 (1.56)

Table IV. Results of Kinetic Studies of Deuterium-Labeled Naphthalenes with Mercuric Acetate in 99% Acetic Acid at 20 ± 0.01 °C, Catalyzed by Perchloric Acid [a]

No.	Substrate	[Substrate], mol/l.	$k_2 \times 10^3$, mol^{-1} min^{-1}	Kinetic isotope effect
1a	Naphthalene-h_8	0.425	21.75	
b	Naphthalene-d_8	0.425	2.95	7.35
2a	Naphthalene-h_8	0.425	21.75	
b	Naphthalene-d_8	0.425	3.02	7.2
3a	Naphthalene-h_8	0.425	21.75	
b	Naphthalene-1-d_1	0.425	18.4	1.17 (1.27)
c	Naphthalene-1,4-d_2	0.425	12.6	1.725 (1.75)
4a	Naphthalene-h_8	0.425	21.75	
b	Naphthalene-1-d_1	0.425	19.35	1.12 (1.27)
c	Naphthalene-1,4-d_2	0.425	15.32	1.44 (1.75)

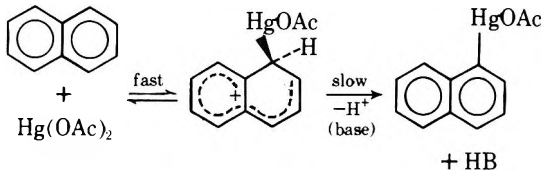
[a] Perchloric acid concentration 0.0995 M; water concentration 0.553 M.

have been recorded for uncatalyzed mercuration of benzene by $Hg(OAc)_2$ ($k_H/k_D \sim 3.2$)[23] and under $HClO_4$ catalysis[8] ($k_H/k_D = 6.0$) at 25 °C. In the latter situation reaction occurs via $^+HgOAc\ ClO_4^-$ (90%) and $Hg^{2+}\ (ClO_4^-)_2$ (10%). In our work, mercurations of 1-deuterionaphthalene, 1,4-dideuterionaphthalene, and naphthalene-d_8 were studied under both catalyzed and uncatalyzed conditions. In Table III the results for uncatalyzed mercuration are listed.

From 1a, 1b and 2a, 2b a primary isotope effect of 3.6 ± 0.1 is associated with the substitution, if secondary effects are neglected. Placing reliance in this data, it is possible to calculate what the observed ratio of rate constants for ($C_{10}H_8$, 1-D-$C_{10}H_7$) and ($C_{10}H_8$, 1,4-D_2-$C_{10}H_6$) should be if α-substitution is as exclusive as we concluded earlier. The calculated values are shown in parentheses and the agreement is very reassuring indeed.

Under conditions of $HClO_4$ catalysis, the kinetic isotope effects are substantially larger (7.3 ± 0.1) and the data are assembled in Table IV. Again calculated ratios for the 1-D and 1,4-D_2 systems are shown in parentheses and the agreement is not as impressive as for the uncatalyzed cases.

The mechanistic significance of these large kinetic isotope effects in mercuration has been discussed in detail by Kresge and Brennan[8] and as the mercuration is first order in $C_{10}H_8$ under our conditions, the transition state of the slowest step contains a molecule of $C_{10}H_8$. These results together are consistent with rapid and reversible combination of electrophile and naphthalene to form a σ complex in low concentration from which proton loss is rate determining. For uncatalyzed mercuration, the electrophile has been



demonstrated[7] to be predominantly un-ionized $Hg(OAc)_2$ while the base is probably acetic acid solvent. For the catalyzed reaction a more complex mechanistic situation would exist, as delineated by Kresge and Brown,[7-9] but again proton loss from a σ complex, present in low concentration, would be rate determining. The larger k_H/k_D values for the naphthalene system may be associated with greater stabilization of the naphthalene σ intermediate.

Positional and Substrate Selectivity. Aromatic mercuration[3,7-9] is known to be a reaction of low selectivity compared with, for example, chlorination,[22] and the rather small rate differential between benzene and naphthalene is therefore not surprising. However, on this basis, it may have been anticipated that significant amounts of both α and β isomers would have been formed, but determinations indicate not less than 95% α product. Comparison of positional and substrate selectivities (benzene vs. α, and β in naphthalene) for mercuration and, for example, chlorination is difficult, because aromatic mercuration is located toward the other end of the mechanistic spectrum usually considered to describe aromatic electrophilic substitution,[9] i.e., proton removal, is largely, if not completely, rate determining. Therefore, both the ratio (k_1/k_{-1}), regulating the concentration of σ intermediate, and k_2, describing proton loss, are important ($k_{-1} \gg k_1 > k_2$) and act in antagonistic fashion. That is, the α σ intermediate, presumably more stable, will be less prone to deprotonate compared with the β σ intermediate. Other factors, such as accessibility of base for deprotonation, differing degrees of C–Hg hyperconjugative stabilization for the two σ intermediates, etc., are likely to be important in a subtle and finely balanced situation. It requires only a relatively small energy difference to change the relative (α,β) rates so that the isomer distribution is substantially altered. (The evidence is that the α mercurial is less stable thermodynamically than β.)[10]

Conclusions

The mercuration of naphthalene by mercuric acetate in acetic acid with and without $HClO_4$ catalysis provides predominantly α-naphthylmercury product. The general features of the reactions parallel those reported for mercuration of benzene, and in particular pronounced $HClO_4$ catalysis and kinetic (hydrogen) isotope effects are observed. Naphthalene is more reactive (on a site for site basis) at the α position by factors of 11.7 (uncatalyzed) and 18.4 (catalyzed). These results confirm the generally low selectivity of the mercuration reaction.

Experimental Section

Reagents. Acetic acid was purified by refluxing with chromium trioxide until the solution remained permanently orange, indicating the removal of all oxidizable material. The acid was then distilled through glass halices in a glass-walled, vacuum-jacketed column (42 × 1 in.) using a reflux ratio of 8:1. Precautions were taken to exclude atmospheric moisture, and the acid was redistilled from mercuric acetate just prior to the kinetic runs.

Mercuric acetate (May and Baker Ltd.) was used without further purification (Found: C, 15.05; H, 1.88. Calcd for $C_4H_6HgO_4$: C, 15.09; H, 1.89). Perchloric acid [70%, specific gravity 1.70 (BDH Ltd.), Analytical Reagent Grade] was used as supplied. Sodium perchlorate (Ajax Chemicals Ltd., Univar, AR Grade) was dried at 110 °C for 4 h. Naphthalene (BDH) was refluxed for 72 h under N_2 over molten sodium. The naphthalene was then distilled and twice recrystallized from absolute ethanol and finally dried in a current of nitrogen, mp 80.5 °C (lit. 80.8 °C). Naphthalene-d_8 (Merck Sharp and Dohme of Canada Ltd.) was used as supplied. Naphthalene-*1*-d_1 and naphthalene-*1,4*-d_2 were synthesized according to Renaud and Leitch.[24] Mass spectral analysis provided the following.

		$C_{10}H_6D_2$, %	$C_{10}H_7D$, %	$C_{10}H_8$, %
Naphthalene-*1*-d_1	(a)		100	
	(b)		97	3
Naphthalene-*1,4*-d_2	(a)	99.5	0.5	
	(b)	95.5	4.5	

1-Chloromercurinaphthalene was made by the method of Blicke and Smith[25] and had mp 190–192 °C (lit. 188–190 °C). 2-Chloromercurinaphthalene was made by treatment of the double salt 2-diazonaphthylmercuric chloride with copper powder in a modified Sandmeyer reaction.[26] The acetatomercurinaphthalenes were made by treatment of the bis(naphthyl)mercury compounds with an equimolar amount of mercuric acetate in THF. The acetates were recrystallized from methanol to yield fine needles of 1-acetatomercurinaphthalene, mp 156–159 ° (lit. 154 °C),[27] and 2-acetatomercurinaphthalene, mp 148–150 °C (Found: C, 37.18; H, 2.57. Calcd for $C_{12}H_{10}HgO_2$: C, 37.25; H, 2.68). The ^1H NMR spectra (CH_2Cl_2 solvent δ 5.32) confirm the structures. The α isomer exhibits signals at δ 2.17 (3 H) $OCOCH_3$; 7.32–7.65 (4 H, complex) β protons; 7.70–8.22 (3 H, complex) α protons. For the β isomer signals are observed at δ 2.17 (3 H) $OCOCH_3$; 7.32–7.72 (complex, 3 H) β protons; 7.75–8.05 (complex, 4 H) α protons. A prominent "broad" singlet at δ 7.82 is assigned to H_1 in this β compound, since it experiences no ortho coupling. These spectra are consistent with the facts that (a) β protons resonate at higher field than α protons in naphthalene[13] and (b) the –HgOAc group has a feeble electronic effect.[14]

The bis(naphthyl)mercury compounds used in the above syntheses were made from the corresponding chloromercurinaphthalenes by symmetrization with an eight molar ratio of sodium iodide in acetone.[28]

Kinetics. The thiocyanate titration technique[21] was employed for following the reactions, and is based on the fact that Hg(II) consumes 2 equiv of SCN^-, whereas the product RHg(II) consumes but one. It is easy to demonstrate that, under conditions with $C_{10}H_8$ in large excess (>6 molar ratio) log $(2T_t - T_0)$ vs. time should be linear for a first-order dependence on Hg(II). T_t is the KSCN titre at time t, and T_0 at time zero. The large excess of $C_{10}H_8$ avoided the significant onset of complicating polymercuration. The pseudo-first-order rate constants were obtained graphically and converted to second-order constants by dividing by the essentially invariant $[C_{10}H_8]$. Rate constants are considered accurate to 5%. The procedure used in a typical run, regarding preparation of kinetic solution, titration technique, etc., have been described in detail by Brown and Kresge.[7-9] The reactions were generally followed for at least 2 half-lives, and at least duplicated. For determination of the kinetic isotope effect, simultaneous runs involving deuterated and regular substrate were conducted. Water concentrations were estimated by the Karl Fischer technique.

The products from the reaction were identified by ^1H NMR spectroscopy and comparisons with authentic samples of the α- and β-naphthylmercuric chlorides and acetates, as described below.

Isomer Distributions. Mixtures of naphthalene and $Hg(OAc)_2$ were allowed to react under the conditions employed in the kinetic studies. After ca. 90% reaction had occurred, the reaction mixture was quenched by pouring into aqueous sodium chloride. The precipitate was filtered and dried, and the dried precipitate evacuated at 100 °C and 10^{-1} mmHg for 3 h to remove the majority of the unreacted naphthalene. The mixture of product halides and residual naphthalene was dissolved in dimethyl sulfoxide in which the arylmercuric chlorides are extremely soluble. (~5 M). The ^1H NMR spectra were then analyzed in the region 100–130 H downfield from the aryl resonance, using a Varian A-60 spectrometer and a Varian CAT. Analysis of isomer distribution for the $HClO_4$-catalyzed reaction was estimated similarly. It was found by treatment of standard mixtures in exactly the same manner, the method was sensitive to less than 3% of β isomer.

Registry No.—Naphthalene, 91-20-3; mercuric acetate, 1600-27-7; 1-acetatomercurinaphthalene, 32049-36-8; 2-acetatomercurinaphthalene, 38487-16-0.

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Coupling of Nonequivalent Aromatic Rings by Soluble Nickel Catalysts. A General Route to the 1,8-Diarylnaphthalenes[1a]

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A facile route to the 1,8-diarylnaphthalene derivatives is described. The parent compound, 1,8-diphenylnaphthalene, can be prepared in two steps with 35% overall yield from the commercial 1,8-diaminonaphthalene. The key step in these preparations is the direct joining of two nonequivalent aromatic molecules by an organonickel-catalyzed Grignard–aryl halide coupling reaction at −15 °C. The coupling reaction is regiospecific with respect to the position of substitution of both aromatic halves. The yields of this coupling reaction are high, even though the 1,8-diarylnaphthalenes are sterically crowded. The efficiency of the reaction under a variety of conditions is evaluated. The order of reactivity of aryl halides is found to be I > Br > Cl, and it is possible to effect coupling preferentially at an iodo group in the presence of a chloro group, the latter being available for further synthetic functionalization.

The 1,8-diarylnaphthalenes are of interest because of their unusual geometry and their inherent strain due to steric overcrowding. The crowded peri-aryl rings are constrained to face each other.[2] Adjacent parallel π systems are also a feature of the extensively studied[3a] paracyclophanes, though the phenyl rings of the latter are substantially warped from planarity,[3b] while the aryl rings of the diarylnaphthalenes, which are not bound together at both ends, retain their planarity.[2] Many unusual properties have been observed with the paracyclophanes and these have been related to the closely held parallel aromatic ring geometries.[3a]

The 1,8-diarylnaphthalenes have, at the same time, π systems which are nearly perpendicular, because the naphthyl and peri-aryl ring planes are restricted from approaching coplanarity. The barrier to a 180° rotation about a naphthyl–aryl bond has been measured[4] as ~15 kcal which seems surprisingly low judging from examination of molecular models. The distance between atoms 1 and 8 in naphthalene is 2.44 Å, while the van der Waals separation between parallel π systems is 3.4 Å.[5] Thus, substantial repulsive interactions must exist between the peri-aryl substituents.[2]

We have undertaken a series of investigations of the conformational, thermodynamic, spectroscopic, and chemical properties of 1,8-diarylnaphthalene derivatives, which necessitated development of a convenient and efficient general synthesis for this class of compounds.[2b,6-9] The most straightforward approach envisioned was a direct joining of aryl and naphthyl groups, but preparative techniques for effecting carbon–carbon bond formation between two aromatic rings are notably lacking. Major classical methods for aromatic arylation are outlined below.

I Ullman reaction[2a,10] $2ArI \xrightarrow{Cu} Ar—Ar$

II Scholl reaction[11] $2ArH \xrightarrow[H^+]{AlCl_3} Ar—Ar$

III Radical-mediated coupling[12]

$[Ar—N_2]^+$
$Ar—N{=}N—Ar$
$[Ar—CO_2]_2$
$Ar—I, h\nu$
or other radical source
$\Big\}$ + $Ar'H \longrightarrow Ar—Ar'$

IV Benzyne-mediated coupling[13]

$Ar—X$ + $Ar'—Li \longrightarrow$ benzyne (from $Ar—X$) $\xrightarrow{Ar'Li}$ $Ar—Ar'$

V Grignard homo coupling and aryllithium homo coupling[14]

$$2ArMgX \xrightarrow{\text{catalyst}} Ar—Ar$$

$$2ArLi \xrightarrow{\text{catalyst}} Ar—Ar$$

(catalysts include TlBr, $CoBr_2$, $CrCl_3$, $CuCl_2$)

VI Lithium diarylcuprate and aryl iodides[9,15]

$$Ar—X + LiAr_2Cu \longrightarrow Ar—Ar$$

These techniques suffer from various problems, including primary limitation to preparation of symmetric biphenyls (I, II, and V), lack of regiospecificity with respect to both reactants resulting in mixtures of isomeric products (II, III, and IV), rather severe reaction conditions, and often low yields. The investigation described here had two parallel goals, establishment of a convenient general synthesis for 1,8-diarylnaphthalenes and development of an efficient technique for the direct coupling of nonequivalent aromatic systems.

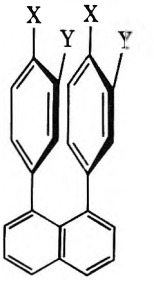
Results and Discussion

It has long been known that reaction of aryl halides with magnesium to form Grignard reagents is often accompanied by formation of a small amount of diaryl compound. The coupling of Grignards with activated alkyl halides is also well known.[16] We have observed that under forcing conditions, some mixed aryl coupling may be effected, though this reaction probably has little preparative value. Thus, on refluxing phenylmagnesium bromide with 1-iodonaphthalene for 48 h in toluene, a yield of about 45% of 1-phenylnaphthalene was obtained. Naphthalene and biphenyl were also identified in the product mixture, along with unreacted 1-iodonaphthalene. An attempt to prepare the internally crowded 1,8-diphenylnaphthalene by this technique was completely unsuccessful.

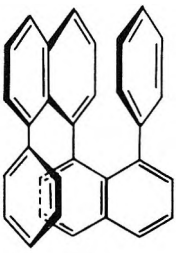
It has been reported that some transition-metal compounds, especially of copper, iron, nickel, and silver, may catalyze the reaction between certain Grignard reagents and organohalides, though reports have concentrated almost exclusively on cross-couplings of the type alkyl–alkyl, alkyl–vinyl, alkyl–aryl, and vinyl–aryl.[17] We have employed catalytic amounts of soluble organonickel complexes to effect aryl Grignard–aryl halide coupling in high yield under very mild conditions, to provide a direct route to the 1,8-diarylnaphthalenes. Experiments with two organonickel compounds, nickel(II) acetylacetonate [$Ni(acac)_2$] and dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II),[18] indicated that both complexes were highly active in inducing heteroaryl coupling, and that the relative effectiveness of the two was essentially the same. The former, a readily available commercial compound, was selected for use in further experiments. Reactions were found to proceed smoothly with a molar ratio of nickel catalyst:aryl halide of 1:100 (ratio of catalyst molecule:halide substituent 1:200).

1,8-Dihalonaphthalenes were prepared for use in the coupling reaction from the commercial 1,8-diaminonaphthalene using the Sandmeyer technique. The best success was obtained when the reactions were run at −30 °C.[2b] The yields follow: 1,8-diiodonaphthalene, 49%; 1,8-dibromonaphthalene, 17%; 1,8-dichloronaphthalene, 15%. A description of a preparation of 1,8-diphenylnaphthalene is given below, followed by a discussion of results obtained under other conditions.

An eightfold excess of phenylmagnesium iodide in ether was slowly added to a solution of 1,8-diiodonaphthalene and a catalytic amount of nickel acetylacetonate in ether–benzene at −15 to −10 °C. The solution turned to a bright red which faded to brown during the course of the reaction. Pure 1,8-diphenylnaphthalene (1a) was obtained in a yield of 70% based on diiodonaphthalene; the reaction was repeated several times to give yields reproducible to within several percent.



1a, X = Y = H
b, X = CH_3, Y = H
c, X = H, Y = OCH_3
d. X = H, Y = Cl



2

Biphenyl and 1-phenylnaphthalene were also isolated, and gas chromatography–mass spectral analysis provided evidence for the presence of small amounts of 2.

When the reaction was followed by gas chromatography, a transient peak was observed having a retention time between that of the starting diiodo compound and 1,8-diphenylnaphthalene, and for this, mass spectroscopy gave a molecular weight of 330, as expected for the monophenylmonoiodonaphthalene.[2b] The rates of coupling of the first and second phenyl groups were of similar magnitude, the first step being slightly more rapid. Interruption of the reaction and use of monoarylmonoiodonaphthalene as an intermediate in preparation of 1,8-diarylnaphthalenes having different aryl groups should be possible, as has been done with the lithium diarylcuprate couplings,[2b] though low overall yields would be anticipated. The reaction was seen to be essentially complete 4 h after Grignard addition was begun, when the reaction temperature was −15 to −10 °C. Use of a higher temperature gave enhanced reaction rate but decreased yields. The gradual color change during the course of the reaction suggested the possibility that the catalyst was slowly destroyed, and that the yield might be improved by periodic addition of catalyst. However, addition of catalyst at 45-min intervals, beginning at the start of the Grignard addition, resulted in no change in yield.

The use of excess Grignard reagent is necessary to give good results. Use of 7:1 Grignard:diiodonaphthalene (3.5 mol Grignard/mol iodo substituent) was found to be an ample excess. Higher Grignard:halide ratios did not improve matters, while use of only 3:1 Grignard:diiodonaphthalene resulted in incomplete conversion of the diiodonaphthalene. The product was then largely the 1-phenyl-8-iodonaphthalene intermediate.

The $Ni(acac)_2$ catalyst was found to cause some homo-Grignard coupling. When two portions of phenylmagnesium iodide, one of which contained added $Ni(acac)_2$, were stirred overnight at 0 °C, the solution containing the catalyst was found to contain a significantly larger amount of biphenyl. Analysis of the freshly prepared Grignard solution showed that it contained some biphenyl but no iodobenzene.

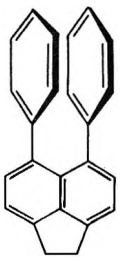
Approximately 20% of the initial 1,8-diiodonaphthalene was converted to 1-phenylnaphthalene under the conditions of the coupling reaction. It seemed possible that this unwanted side reaction might have proceeded by Grignard exchange between the phenylmagnesium iodide and the iodo compound. This would also cause some loss of phenylmagnesium iodide. For each molecule exchanged, two molecules of phenylmagnesium iodide would be converted to one molecule of biphenyl. That such an exchange is in fact facile was demonstrated when 1,8-diiodonaphthalene was combined with excess phenylmagnesium iodide at 0 °C and kept overnight in the absence of catalyst. After hydrolysis, the reaction mixture was found to contain large quantities of 1-iodonaphthalene and iodobenzene in equimolar amounts, along with some remaining

1,8-diiodonaphthalene. This exchange between an aryl Grignard reagent and an aryl halide is quite unusual. Earlier attempts at effecting such exchanges have been unsuccessful.[19] It seems likely that the driving force for the reaction in this system may stem from the high overcrowding of the peri-iodo substituents. Consistent with the observed Grignard–halide exchange, it was found that the yield of 1,8-diphenylnaphthalene was critically dependent on the rate of Grignard addition. Thus, when the phenylmagnesium iodide was added all at once, a substantial increase in 1-phenylnaphthalene was found in the product mixture. Apparently the nickel catalyst becomes saturated, and Grignard exchange is enhanced more than coupling by the presence of a large amount of Grignard reagent.

The reactivities of aryl halides in this system toward-$Ni(acac)_2$-catalyzed coupling with Grignard reagent was found to be I > Br ≫ Cl. Thus, when a 7-molar excess of phenylmagnesium iodide was added all at once to $Ni(acac)_2$-containing solutions of 1,8-diiodonaphthalene, 1,8-dibromonaphthalene, and 1,8-dichloronaphthalene at 0 °C after 30 min the diiodo compound had completely reacted, while the dibromo compound reacted only to the extent of 50%. With 1,8-dichloronaphthalene, the reaction was 30% complete after 4 h. Dibromonaphthalene gave a yield of diphenylnaphthalene equivalent to that obtained with the diiodo compound. The yield was lower with dichloronaphthalene.

Interestingly, the Grignard reagents of iodobenzene and bromobenzene were found to give pronounced differences in the coupling reaction. Substitution of phenylmagnesium bromide decreased the yield of 1,8-diphenylnaphthalene by more than half. The major product of the reaction was 1-phenylnaphthalene. Apparently, the rate of coupling is relatively less rapid compared with Grignard exchange in the case of the bromo Grignard. It was expected that for reactions with noncrowded halides where Grignard exchange would not be a problem, good yields would be obtained with a bromo Grignard. Consistent with this, it was found that reaction of phenylmagnesium bromide with 1-iodonaphthalene gives 1-phenylnaphthalene in a yield of >85%.

We have prepared *peri*-diphenylacenaphthene (**3**) from *peri*-diiodoacenaphthene and phenylmagnesium iodide at



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−15 °C with $Ni(acac)_2$ in 78% yield using the procedure described for 1,8-diphenylnaphthalene. 1,8-Bis(*p*-tolyl)naphthalene (**1b**) and 1,8-bis(3-methoxyphenyl)naphthalene (**1c**) were also prepared by this method from 1,8-diiodonaphthalene in yields of 53 and 49% by use of the respective Grignard reagents, *p*-tolylmagnesium iodide and *m*-methoxyphenylmagnesium iodide.

The differences in reactivities of halides toward coupling with Grignard reagent suggested the possibility of coupling with an iodide in the presence of a chloro substituent. The substituent could serve as a site for further chemical functionalization of the aromatic product. This possibility has been realized. Thus, when a 5-molar excess of *m*-chlorophenylmagnesium iodide was added to 1,8-diiodonaphthalene and $Ni(acac)_2$ at −20 °C and the reaction mixture hydrolyzed immediately after it was judged to be complete by gas chromatography, 1,8-bis(3-chlorophenyl)naphthalene (**1d**) was obtained in 52% yield, based on diiodonaphthalene. Use of higher temperature or larger excess of Grignard gave lower yields. When the reaction was allowed to continue for a longer time, the yield of the product decreased, presumably because of a slow reaction of the chloro substituent.

Experimental Section

^1H NMR spectra were taken with a Varian Associates A-60 or T-60 spectrometer. All spectra were obtained using deuteriochloroform as a solvent, with Me_4Si as an internal standard. Infrared absorption spectra were obtained on a Perkin-Elmer Model 257 infrared spectrometer. Mass spectra were run on an EAI Quad 300 quadrupolar mass spectrometer under the control of an SCC 4700 computer. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. GLC separations were carried out on a Hewlett-Packard Model 5750 gas chromatograph with a flame ionization detection system, utilizing a 6 ft × 0.125 in. column packed with 3% SE-30 on 40–60 mesh Chromasorb P. Injections were made at an oven temperature of 90 °C, and the instrument was programmed to raise the column temperature to 300 °C at 20 °C per minute. The observed peaks were catalogued in accord with the oven temperature at which they began to appear.

Uncatalyzed Grignard–Halide Coupling. A solution of 0.01 mol of phenylmagnesium iodide from 2.04 g of iodobenzene and 0.24 g of magnesium in 20 ml of ether was added to 2.54 g (0.01 mol) of 1-iodonaphthalene in 15 ml of toluene. The excess ether was distilled and the mixture was allowed to reflux for 48 h. After hydrolysis with 10% HCl, gas chromatographic analysis showed 45% conversion of iodonaphthalene to 1-phenylnaphthalene. Biphenyl and naphthalene were also present. The products were identified by retention times in the gas chromatograph. The 1-phenylnaphthalene was isolated by chromatography on silica gel with hexane eluent and its identity confirmed by comparison of the infrared spectrum with that of a commercial sample. When phenylmagnesium bromide was substituted for phenylmagnesium iodide in the above procedure, the gas chromatogram showed that, after 69 h at reflux, the conversion was only 25% complete. When 0.02 mol of phenylmagnesium iodide was heated to reflux with 0.01 mol of 1,8-diiodonaphthalene for 96 h, no 1,8-diphenylnaphthalene was formed.

1,8-Diphenylnaphthalene (1a). Magnesium turnings (0.59 g, 24 mmol) were placed in a three-necked round-bottomed flask equipped with a reflux condenser, and the system purged with nitrogen for 5 min while the flask and metal turnings were heated with a heat gun. To the cooled flask was added 3 ml of ether. Approximately 10% of a solution of iodobenzene (4.9 g, 24 mmol) in 20 ml of ether was drawn off from an addition funnel, and the mixture was heated to initiate the reaction. The remaining iodobenzene solution was added just rapidly enough to maintain a gentle reflux (about 45 min). The resulting Grignard reagent was pipetted through glass wool (to prevent contamination with small, unreacted slivers of magnesium) into an addition funnel and then added slowly (during 2 h) to a solution of 1.14 g (3 mmol) of 1,8-diiodonaphthalene and 0.005 g (0.027 mmol) of nickel(II) acetylacetonate[20] in 25 ml of a 1:1 mixture of ether and benzene, which was kept stirring in a dry ice–acetone bath at −15 to −10 °C. The mixture was stirred for an additional 2 h at this temperature, at which time gas chromatographic analysis showed that all starting diiodo compound had reacted. The flask was left stirring overnight at room temperature, the mixture hydrolyzed with concentrated NH_4Cl solution, the aqueous layer extracted once with ether, and the combined organic fractions dried over Na_2SO_4. The 2.4 g of crude mixture remaining after evaporation of the solvent was subjected to chromatography on silica gel with hexane as eluent to yield 0.59 g (70% based on diiodonaphthalene) of pure 1,8-diphenylnaphthalene (mp 147–148 °C, lit.[7] mp 149–150 °C). The ^1H NMR spectrum showed a singlet at δ 6.9 (10 H) and a multiplet at δ 7.2–7.9 (6 H) at 60 MHz. The early chromatographic fractions contained 0.8 g of a white, crystalline solid which was identified as biphenyl by its melting point (69 °C) and by comparison of its infrared spectrum with that of an authentic sample. Several fractions collected between those containing biphenyl and those containing the diphenylnaphthalene were found to contain 0.14 g of a clear, viscous liquid which was identified as 1-phenylnaphthalene by comparison of its infrared spectrum with that of an authentic sample.

A series of reactions analogous to the above was performed with one or more reaction conditions varied as described in the Discussion. Other parameters were held constant during these runs. Results were

evaluated using gas chromatography retention times, and by isolation of products using column chromatography.

1,8-Bis(*p*-tolyl)naphthalene (1b) was prepared as described for 1,8-diphenylnaphthalene. From 3 mmol of 1,8-diiodonaphthalene and 25 mmol of *p*-tolylmagnesium iodide, 1.59 mmol (53% based on diiodonaphthalene) of **1b** was obtained, following column chromatography with hexane as eluent (mp 175–177.5 °C): ^{1}H NMR δ 2.17 (s, 6 H), 6.77 (m, 8 H), 7.2–8.0 (m, 6 H); mass spectrum *m/e* 308.

Anal. Calcd for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 93.36; H, 6.59.

The early chromatographic fractions were found to contain naphthalene and *p,p'*-bitolyl, identified by comparison of the NMR spectra with those of commercial samples.

1,8-Bis(3-methoxyphenyl)naphthalene (1c) was prepared similarly to 1,8-diphenylnaphthalene, employing 3 mmol of 1,8-diiodonaphthalene and 26 mmol of 3-methoxyphenylmagnesium iodide. Column chromatography with 5% ether in hexane as eluent gave 1.46 mmol of **1c** (49% based on diiodonaphthalene) as a viscous liquid: ^{1}H NMR δ 3.62 (s, 6 H), 6.2–7.2 (m, 8 H), 7.2–8.1 (m, 6 H).

Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.78; H, 6.00.

Early chromatographic fractions contained naphthalene and 3,3'-dimethoxybiphenyl, identified by comparison of the NMR spectra with those of commercial samples.

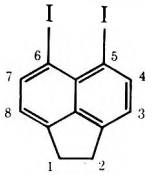
1,8-Bis(3-chlorophenyl)naphthalene (1d). The best yield of 1,8-bis(3-chlorophenyl)naphthalene was obtained when a smaller excess (~5:1) of Grignard reagent and somewhat lower temperature than that used for the 1,8-diphenylnaphthalene synthesis was employed, with the reaction carefully monitored by gas chromatography and stopped immediately at completion. Thus, 15 mmol of *m*-chlorophenylmagnesium iodide, which formed readily on addition of 3.6 g (15 mmol) of *m*-chloroiodobenzene in 18 ml of ether to 0.36 g (15 mmol) of magnesium turnings, was added dropwise to a stirred solution of 1.14 g (3 mmol) of 1,8-diiodonaphthalene and 0.02 g (0.1 mmol) of nickel acetylacetonate in 15 ml of benzene and 12 ml of ether.

The reaction vessel was held in a −15 to −20 °C bath during the 2-h Grignard addition. This temperature was maintained and the mixture stirred as the reaction was allowed to continue. During this time, the gas chromatograms of successive aliquots showed disappearance of the diiodo compound (210 °C peak) while a new peak (240 °C) grew and then disappeared at the expense of a higher peak (260 °C). At the end of 4 h, the reaction was seen to be essentially complete. Hydrolysis with saturated ammonium chloride solution followed by column chromatography on silica gel with pentane as the eluent gave 0.53 g (52%) of 1,8-bis(3-chlorophenyl)naphthalene (mp 95–97 °C, lit.[21] mp 97–98.5 °C): mass spectrum parent peaks *m/e* 248, 250, 252, with expected ratio for two chlorine atoms.

Anal. Calcd for $C_{22}H_{14}Cl_2$: C, 75.66; H, 4.04; Cl, 20.30. Found: C, 75.57; H, 4.14; Cl, 19.93.

When the reaction was run with a 10-molar excess of Grignard reagent at −10 to −5 °C for 6 h, or at −4 °C for 12 h, the gas chromatograms showed that the 1,8-bis(3-chlorophenyl)naphthalene peak reached a maximum and then slowly decreased.

***peri*-Diiodoacenaphthene (7)** was prepared in four steps from acenaphthene by a sequence essentially in accord with that described



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previously.[22,23] The reaction of 40 g (0.24 mol) of acenaphthene with 62 g of iodine and 90 g of mercuric iodide in refluxing ethanol gave 50.1 g (46%) of 5-iodoacenaphthene (**4**), which crystallized as white needles from methanol (mp 62–64 °C, lit.[22] mp 65 °C; picrate mp 97–99 °C, lit.[22] mp 100 °C). In the nitration of **4** (13.5 g, 0.48 mol) with 5 ml of fuming HNO_3 in 140 ml of glacial acid at room temperature, gas chromatography showed that the reaction was complete after 4 days. The 10 g of crude product which had precipitated was a mixture of isomers. Nine successive recrystallizations from glacial acetic acid gave 2.5 g (16%) of 5-iodo-6-nitroacenaphthene (**5**) as yellow needles (mp 175–178 °C, lit.[22] mp 179–180 °C). Reduction of 10 g (31 mmol) of **5** by refluxing with 80 g of $SnCl_2$ in a solution containing 800 ml of concentrated HCl and 140 ml of ethanol gave 2.6 g (28%) of light yellow 5-iodo-6-aminoacenaphthene, **6** (mp 104–107 °C, lit.[22] mp 107–108 °C). Diazotization of **6** (2.6 g, 8.8 mmol) was accomplished by treatment with 0.75 g of $NaNO_2$ in 55 ml of 10% H_2SO_4 at −4 °C for 40 min. Addition of a solution of 2.5 g of KI in 10 ml of water precipitated the diazonium iodide, which was decomposed by refluxing in acetone for 1 h. The black solid product was treated with $Na_2S_2O_3$ and subjected to chromatography on silica gel with ligroin as eluent to give 1.7 g (48%) of white crystalline 5,6-diiodoacenaphthene (*peri*-diiodoacenaphthene, **7**) (mp 156–158 °C, lit.[22] mp 159–160°C): NMR ($CDCl_3$) δ 3.30 (s,4H), (ABq,4H).

***peri*-Diphenylacenaphthene (3)** was prepared using the same conditions described earlier for preparation of 1,8-diphenylnaphthalene. Addition of 8 mmol of phenylmagnesium iodide to 0.41 g (1 mmol) of **6** at −14 to −10 °C during a 2-h period, followed by a 2.5-h period at −10 °C and 1 h of slow warming to room temperature, afforded, after column chromatography on silica gel with ligroin as eluent, 0.24 g (78% based on diiodoacenaphthene) of pure **3** (mp 156–157 °C): NMR δ 3.43 (s, 4 H), 6.87 (s, 10 H), 7.30 (s, 4 H); mass spectrum 306.1410 (calcd for $C_{24}H_{18}$, 306.1408).

Registry No.—**1a**, 1038-67-1; **1b**, 58541-18-7; **1c**, 58541-19-8; **1d**, 7731-47-7; **3**, 57620-87-8; **6**, 58541-20-1; **7**, 55143-88-9; nickel(II) acetylacetonate, 18918-08-6; acenaphthene, 83-32-9.

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Reduction of Perfluoroacyl Halides with Organosilicon Hydrides. A Direct Synthesis of Fluorine Containing Esters and Lactones

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A method is described for the synthesis of fluorine containing esters of 1,1-dihydroperfluoroalkyl alcohols by a catalyzed organosilicon hydride reduction of perfluoroacyl halides. Using this technique, $CF_3CF_2OCF_2CF_2$-$CO_2CH_2CF_2CF_2OCF_2CF_3$ (1) and $C_6F_{11}CO_2CH_2C_6F_{11}$ (2) were produced directly from perfluoroethoxypropionyl fluoride and perfluorocyclohexyl carbonyl fluoride, respectively. In addition, five- and six-membered lactones of hydroxy fluorocarbon carboxylic acids, compounds **3–5**, were obtained from the perfluorodiacyl halides: perfluorosuccinyl fluoride, perfluoroglutaryl fluoride, and perfluorooxydiacetyl chloride.

Synthesis of esters from highly fluorinated alcohols normally involves a number of synthetic steps,[1] including production of the necessary 1,1-dihydroperfluoroalkyl alcohols by reduction of a perfluoroalkyl carbonyl compound. A more convenient technique was sought for this transformation, based on the synthetic potential of organosilicon hydrides which have been exploited in the past to convert hydrocarbon acyl chlorides to aldehydes[2] and acyl fluorides to esters,[3] both conversions utilizing palladium on carbon as a catalyst. This paper describes the use of a catalyzed organosilicon hydride reduction to produce esters of 1,1-dihydroperfluoroalkyl alcohols, $R_FCO_2CH_2R_F$, and lactones of fluorine containing hydroxy acids in one step from perfluoroacyl halides and perfluorodiacyl halides, respectively.

The results of the organosilicon hydride reductions of various perfluoroacyl halides are summarized in Table I. In each case, trimethylsilane was heated with the perfluoroacyl halide to 160–210 °C in a Hoke stainless steel reactor in the presence of platinum on carbon, zinc chloride, and potassium fluoride. Thus, a mixture of trimethylsilane and perfluoroethoxypropionyl fluoride[4] was heated at 180 °C with platinum on charcoal, zinc chloride, and potassium fluoride to yield the ester, $CF_3CF_2OCF_2CF_2CO_2CH_2CF_2CF_2OCF_2CF_3$. A similar reaction with perfluorocyclohexyl carbonyl fluoride[5] also gave the corresponding ester **2**. In general, the product yields ranged from 10 to 30%.

With perfluorodiacyl halides, which are capable of ring closure to a five- or six-membered ring, lactones of the corresponding hydroxy fluorocarbon carboxylic acids were formed. Upon reaction with trimethylsilane, perfluorosuccinyl fluoride, perfluoroglutaryl fluoride, and perfluorooxydiacetyl chloride[6] gave the lactones, compounds **3–5**. The only reference to this type of fluorocarbon lactone is a patent[7] on the preparation of 5-hydroxy-2,2,3,3,4,4-hexafluorovaleric acid which suggested that the hydroxy acid may exist in equilibrium with its lactone but offered no confirming data.

All products were characterized on the basis of their elemental analyses and infrared and NMR spectra, with the results being summarized in the Experimental Section. The more complicated products gave NMR resonances which were broad or, at best, complex under high resolution. In these cases, the center of the resonance was taken as the chemical shift. However, the NMR pattern for compound **5a** could be analyzed by a first-order treatment owing to its asymmetrical nature. Results obtained for this compound are given in Table II.

In order to gain some insight into the reaction sequence, the following experiments were carried out. Excluding only the potassium fluoride from the reaction, perfluorocyclohexyl carbonyl fluoride was heated with trimethylsilane to yield [(perfluorocyclohexyl)methoxy]trimethylsilane (**6**). In addition, a sample of tetra(2,2,2-trifluoroethoxy)silane[8] and perfluorocyclohexyl carbonyl fluoride, heated in the presence of potassium fluoride, led to the isolation of trifluoroethyl perfluorocyclohexyl carboxylate (**7**). Citron[9] has also reported the formation of esters by reaction of acyl fluorides with alkoxy silanes. Finally, perfluorocyclohexyl carbonyl chloride (**8**) was characterized from a heated reaction of zinc chloride with perfluorocyclohexyl carbonyl fluoride.

No evidence was found for the presence of perfluoro-β-oxa-δ-valerolactone which was previously isolated from perfluorooxydiacetyl halide and potassium fluoride.[10] Formation of this lactone was rationalized by postulating a cyclization of a fluoroformyl-substituted perfluoroalkoxide formed by addition of a fluoride ion to one of the acyl fluoride end groups. A similar addition of fluoride ion to the aldehydic carbonyl of the $OHCCF_2OCF_2CFO$ intermediate thought to be present from the initial reaction of trimethylsilane and perfluorooxydiacetyl chloride could also be involved in the formation of compound **5a**. In accordance with the documented reduction by organosilicon hydrides of hydrocarbon acyl halides to the corresponding aldehyde,[2] an initial reduction of the perfluoroacyl halide to the aldehyde would be very likely here.

In summary, the use of catalyzed organosilicon hydride reactions with perfluoroacyl halides provides a convenient method for the synthesis of fluorine containing esters. In addition, certain lactones of fluorine containing hydroxy acids can be produced in a single synthetic step from perfluorodiacyl halides.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer using NaCl plates. The ^{19}F nuclear magnetic resonance measurements, made with a Varian V-4300-2 spectrometer operating at 40.0 MHz and utilizing an internal standard of $CFCl_3$ for the determination of chemical shifts, are reported as ϕ^* values.[11] ^1H NMR values were obtained from a Varian Model A-60 instrument with $CFCl_3$ as solvent and reported as τ values with tetramethylsilane as reference.[12] Finally, the GC unit used to trap analytical samples was a Perkin-Elmer Model 154 gas chromatograph employing 12 ft × 0.375 in. columns packed with either 33% FS-1265 or 25% SE-52 on Chromosorb P.

The 1% platinum on 28–150 mesh charcoal was purchased from Matheson Coleman and Bell. Perfluoroglutaryl chloride and perfluorosuccinic acid, both converted to the acyl fluorides by standard techniques, as well as trimethylsilane, were obtained from PCR, Inc.

Reaction of Perfluoroethoxypropionyl Fluoride with Trimethylsilane. A 150-ml Hoke stainless steel pressure reactor was loaded with 2.9 g of KF and evacuated, and 2.8 g of $C_2F_5OC_2F_4COF$[4] and 1.5 g of $(CH_3)_3SiH$ added. After the reactor was heated to 130 °C for 6 h, an ir spectrum indicated only starting materials. The reactor was cooled with liquid nitrogen, 1 g of 1% Pt/C and 0.2 g of $ZnCl_2$ added, the cooled reactor reevacuated, and the mixture reheated to 180 °C for 18 h. The products were allowed to vaporize into two evacuated traps connected in series, cooled to −40 and −196 °C, respectively, as the temperature of the reactor rose from −196 to 180 °C. This vacline separation led to the isolation of 1.8 g of $(CH_3)_3SiF$

Table I. Products from Acyl Halides and Silicon Hydrides

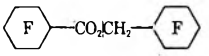
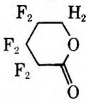
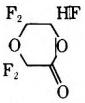
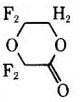
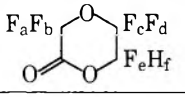
Registry no.	Acyl halide	Ester or lactone product	Compd	Registry no.
377-75-3	$CF_3CF_2OCF_2CF_2COF$	$CF_3CF_2OCF_2CF_2CO_2CH_2CF_2CF_2OCF_2CF_3$	1	58816-72-1
6588-63-2			2	58816-73-2
679-13-0	$FOC(CF_2)_2COF$		3	58816-74-3
678-78-4	$FOC(CF_2)_3COF$		4	58816-75-4
21297-62-1	$O(CF_2COCl)_2$		5a	58816-76-5
			5b	58816-77-6

Table II. Chemical Shift and Coupling Constants of 5a[a]



δ_a, δ_b 69.62, 70.54 ϕ*		J_{ab} = 177.6 Hz
δ_c, δ_d 78.26, 89.51 ϕ*		J_{cd} = 165.1 Hz
δ_e 135.58 ϕ*	δ_f 3.95 τ	J_{ef} = 51.25 Hz
J_{ac} = 4.34 Hz	J_{bc} = 8.88 Hz	J_{ce} = 9.34 Hz
J_{ad} = 2.16 Hz	J_{bd} = 2.15 Hz	J_{cf} = 1.44 Hz
J_{ae} = 3.23 Hz	J_{be} = 8.02 Hz	J_{de} = 12.94 Hz
J_{af} = 0.50 Hz	J_{bf} = 0.15 Hz	J_{df} = 1.64 Hz

[a] The NMR spectrum was obtained using a Varian XL-100 spectrometer and the coupling constants given represent the average of two measured values.

and 0.5 g of $CF_3CF_2OCF_2CF_2CO_2CH_2CF_2CF_2OCF_2CF_3$ (1): ir (neat, 5.55 μ (C=O); NMR ($CFCl_3$) τ 5.25 (t, J = 12.0 Hz, CH_2), ϕ* 87.3 (CF_3), 89.0 (CF_3CF_2), 86.6 (CF_2CF_2CO), 121.7 (CF_2CO), 124.0 (t, J = 12.0 Hz, CH_2CF_2), 85.8 ($CH_2CF_2CF_2$).

Anal. Calcd for $C_{10}H_2F_{18}O_4$: C, 22.7; F, 64.8. Found: C, 22.9; F, 65.0.

Reaction of Perfluorocyclohexyl Carbonyl Fluoride[5] with Trimethylsilane. Trimethylsilane (3.3 g), perfluorocyclohexyl carbonyl fluoride (6.6 g), 1% Pt/C (1 g), KF (3 g), and $ZnCl_2$ (100 mg) were heated together in a Hoke reactor to 160 °C for 18 h. The workup procedure consisted of a filtration, using $CHCl_3$ as a solvent, and a short-path distillation. Isolated was 1 g of [(perfluorocyclohexyl)-methyl]perfluorocyclohexyl carboxylate (2): mp 86.5–88 °C; ir (neat) 5.58 μ (C=O); NMR ($CFCl_3$) τ 4.92 (d, J = 17.2 Hz, CH_2), ϕ* 189.2 (complex, $CFCH_2$), 180.2 (complex, CFCO) plus complex absorptions between 115 and 150 (six AB quartets, J_{AB} 290 Hz, ring CF_2 groups).

Anal. Calcd for $C_{14}H_2F_{22}O_2$: C, 27.1; F, 67.4. Found: C, 26.8; F, 67.0.

Reaction of Perfluorosuccinyl Fluoride with Trimethylsilane. A Hoke reactor containing 2.9 g of KF, 1 g of 1% Pt/C, 0.2 g of $ZnCl_2$, 1.0 g of $FOC(CF_2)_2COF$, and 0.7 g of $(CH_3)_3SiH$ was heated at 170 °C for 15 h at 210 °C for 2 h. A vacline separation gave 0.2 g of the lactone of 4-hydroxy-2,2,3,3-tetrafluorobutyric acid (3): ir (gas) 5.40 μ (C=O); NMR ($CFCl_3$) τ 5.43 (t, J = 11.6 Hz, CH_2), ϕ* 131.1 (t, J = 6.2 Hz, CF_2CO), 127.1 (t, t, CH_2CF_2).

Anal. Calcd for $C_4H_2F_4O_2$: C, 30.4; F, 48.1. Found: C, 30.2; F, 48.3.

Reaction of Perfluoroglutaryl Fluoride with Trimethylsilane. After a Hoke reactor containing 2.9 g of KF, 1 g of 1% Pt/C, 0.2 g of $ZnCl_2$, 2.4 g of $FOC(CF_2)_3COF$, and 1.5 g of $(CH_3)_3SiH$ was heated to 170 °C for 75 h, a vacline separation was carried out. Recovered was 0.4 g of starting material. Also isolated was 0.2 g of the lactone of 5-hydroxy-2,2,3,3,4,4-hexafluorovaleric acid (4): ir (neat, 5.54 μ (C=O); NMR ($CFCl_3$) τ 5.44 (t,t, J = 11.0 and 2.0 Hz, CH_2), ϕ* 125.0 (complex, CF_2CH_2), 135.7 (complex, $CF_2CF_2CH_2$), 121.2 (complex, CF_2CO).

Anal. Calcd for $C_5H_2F_6O_2$: C, 28.9; F, 54.8. Found: C, 28.6; F, 54.4.

Reaction of Perfluorooxydiacetyl Chloride[6] with Trimethylsilane. A Hoke reactor was charged with 2.9 g of KF, 1 g of 1% Pt/C, 0.2 g of $ZnCl_2$, 3.6 g of $O(CF_2COCl)_2$, and 2.2 g of $(CH_3)_3SiH$ and heated to 160 °C for 48 h and 210 °C for 2 h. Two products were isolated from the −40 °C trap after a vacline separation. Found was 0.35 g of the lactone of 5-hydroxy-3-oxa-2,2,4,4,5-pentafluorovaleric acid (5a), ir (neat) 5.47 μ (C=O).

Anal. Calcd for $C_4HF_5O_3$: C, 25.0; F, 49.5. Found: C, 25.1, F, 50.1.

Also collected was 0.5 g of the lactone of 5-hydroxy-3-oxa-2,2,4,4-tetrafluorovaleric acid (5b): ir (neat) 5.50 μ (C=O); NMR ($CFCl_3$) τ 5.26 (complex, CH_2), ϕ* 75.8 (complex, CF_2CH_2) and 76.3 (complex, CF_2CO).

Anal. Calcd for $C_4H_2F_4O_3$: C, 27.6; F, 43.7. Found: C, 27.4; F, 43.8.

Reaction of Perfluorocyclohexyl Carbonyl Fluoride with Trimethylsilane. A mixture of 1 g of 1% Pt/C, 0.2 g of $ZnCl_2$, 1.5 g of $(CH_3)_3SiH$, and 3.3 g of perfluorocyclohexyl carbonyl fluoride was heated in a Hoke reactor to 140 °C for 89 h. A vacline separation led to the recovery of 1.2 g of starting material. Pumping on the hot reactor gave 0.4 g of [(perfluorocyclohexyl)methoxy]trimethylsilane: NMR ($CFCl_3$) τ 9.84 (CH_3), 5.70 (d, J = 19.3 Hz, CH_2), ϕ* 190.3 (complex, CF), 119.9 and 133.0, 123.5 and 140.4, 124.8 and 142.4 (three AB quartet patterns, J_{AB} = 290, 286, and 280 Hz, respectively, ring CF_2 groups).

Anal. Calcd for $C_{10}H_{11}F_{11}OSi$: C, 31.2; F, 54.4; H, 2.9. Found: C, 30.9; F, 55.0; H, 3.1.

This material was also prepared in much higher yield by the reaction of (perfluorocyclohexyl)methanol[13] and chlorotrimethylsilane.

Reaction of Perfluorocyclohexyl Carbonyl Fluoride with Tetra(2,2,2-trifluoroethoxy)silane.[8] A Hoke reactor was charged with 5.8 g of KF, 2.2 g of $Si(OCH_2CF_3)_4$, and 6.6 g of perfluorocyclohexyl carbonyl fluoride. After the reactor was heated to 160 °C for 18 h and 210 °C for 2 h, a vacline separation gave 8.5 g of 2,2,2-trifluoroethylperfluorocyclohexyl carboxylate (7): ir (neat) 5.58 μ (C=O); NMR ($CFCl_3$) τ 5.28 (q, J = 7.8 Hz, CH_2), ϕ* 75.0 (t, J = 7.8 Hz, CF_3), 180.4 (complex, CF), 118.3 and 131.6, 123.4 and 139.2, 122.6 and 141.8 (three AB quartet patterns, J_{AB} quartet patterns, J_{AB} = 294, 283, and 286 Hz, respectively, ring CF_2 groups).

Anal. Calcd for $C_9H_2F_{14}O_2$: C, 26.5; F, 65.2. Found: C, 26.6; F, 65.4.

Reaction of Perfluorocyclohexyl Carbonyl Fluoride with Zinc Chloride. Isolated by a short-path distillation was 9.5 g of perfluorocyclohexyl carbonyl chloride after a Hoke reactor containing 6.6 g of perfluorocyclohexyl carbonyl fluoride and 2.7 g of $ZnCl_2$ was heated to 185 °C for 20 h. Perfluorocyclohexyl carbonyl chloride (8): ir (neat) 5.55 μ (C=O); NMR ($CFCl_3$) ϕ* 167.0 (CF), 119.0 and 131.0, 123.5 and 138.9, 122.9 and 141.6 (three AB quartet patterns, J_{AB} = 294, 292, and 291 Hz, respectively, ring CF_2 groups).

Anal. Calcd for $C_7ClF_{11}O$: C, 24.4; F, 60.7. Found: C, 24.4; F, 61.1.

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Registry No.—7, 58816-78-7; 8, 58816-79-8; trimethylsilane, 993-07-7; [(perfluorocyclohexyl)methoxy]trimethylsilane, 58816-80-1; tetra(2,2,2-trifluoroethoxy)silane, 338-39-6; zinc chloride, 7646-85-7.

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Controlled Substituent Exchange in Cyclopropenium Ions. Role of Counterion in Friedel–Crafts Reactions of the Trichlorocyclopropenium Ion

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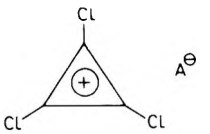
Friedel–Crafts reactions of the trichlorocyclopropenium cation ($C_3Cl_3^+$) with unsaturated substrates are very sensitive to the nature of its counterion. The triflate salt is ideal in Friedel–Crafts reactions with *nonactivated* aromatic substrates and permits facile synthesis of the corresponding triarylcyclopropenium systems. $SbCl_6^-$ is the counterion of choice in reactions of $C_3Cl_3^+$ with *olefinic and acetylenic bonds*. Thus usage of $C_3Cl_3^-SbCl_6^-$ opens up a synthetic pathway to representatives of the hitherto unknown di- and trivinylcyclopropenium salts. A mechanistic model is offered which accounts for the observed anion effects.

Owing to their multifunctional character and high internal energy[1] cyclopropenium ions (and derived cyclopropenes) should possess considerable potential as synthons. With this final aim in mind it is of interest to attach diverse structural units to the cyclopropenium system as a template and thus create molecular frameworks which are both synthetically useful and theoretically interesting.

Trichlorocyclopropenium salts 1 offer a good starting point for such an exercise because they are highly reactive and easily



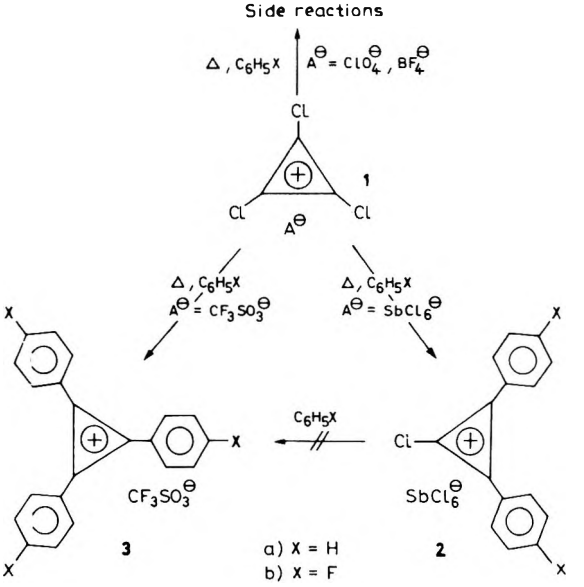
1

accessible on the basis of cheap starting materials.[2] Consequently, since the pioneering work of West[3] considerable efforts have been spent on replacing the chlorine atoms in 1 by various other substituents.[4] As a rule it was not generally possible to control the extent of substituent exchange and, in a number of cases, to avoid destruction of the highly strained cyclopropenium system. We now report that the course of such reactions can be controlled by two important independent factors: (a) selection of an appropriate counterion A^- in 1 and (b) choice of a selective exchange reagent. In this paper we focus on a, looking at Friedel–Crafts reactions of 1, while in subsequent papers[5] we shall deal with b.

Results and Discussion

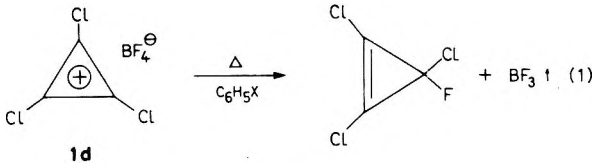
A. Reactions with Aromatic Substrates. Friedel–Crafts reactions of 1 with aromatic substrates were among the first things studied when this highly reactive species became known. Selective temperature-controlled mono- and disubstitutions of Cl atoms in 1 by phenyl and its weakly activated (*p*-alkyl-substituted) or deactivated (*p*-halo-substituted) derivatives were reported by West.[2,6] However, attempts to synthesize *triaryl*cyclopropenium systems via this route met with failure unless strongly activated substrates like phenols were used.[7] In this section we discuss reasons for this restriction and show how it can be relieved. It had occurred to us that in the earlier work one potentially important structural parameter had been neglected, namely the nature of counterion A^- in 1. For it is highly unlikely that the trichlorocyclopropenium ion and its partially arylated successor ions will exist in "free" form in the essentially nonpolar media (benzene and its derivatives) used.[2,6] Rather, these cations will be more or less tightly bound to their counterions A^-. Consequently, we tested the substitution behavior of various trichlorocyclopropenium salts in benzene and fluorobenzene as solvent and substrate, respectively, and indeed found a very pronounced counterion dependence of product distributions. Results are summarized in Scheme I.

Scheme I



First, in order to reduce the danger of counterion association via, e.g., halide bridging, we replaced $AlCl_4^-$ in 1 (West's compound,[6,7] **1a**) by the coordinatively much more stable $SbCl_6^-$ (**1b**). This, however, proved to be of no advantage as

the exchange reaction stopped after disubstitution to give **2** just as with **1a**. When **1c** (**1**, A^- = ClO_4^-) and **1d** (**1**, A^- = BF_4^-) generated in situ from tetrachlorocyclopropene and the corresponding silver salts were used, no arylcyclopropenium salts were formed. Instead, side reactions set in which resulted in irreversible consumption of the anions (no ir bands attributable to ClO_4^- or BF_4^- could be observed in the ether-soluble product mixture which remained after removal of benzene or fluorobenzene). In **1d** a Schiemann-type reaction (1) probably accounts for the disappearance of BF_4^-:

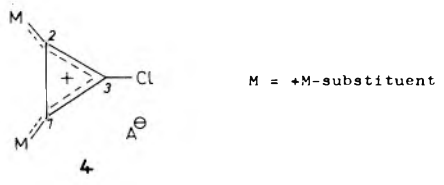


1d

As for the fate of **1c** the appearance of intense C=O vibrations at 1700 cm^{-1} in the ir spectrum of the product mixture points to an oxidizing effect of ClO_4^-, most likely involving a covalent cyclopropenyl perchlorate. Although of interest in themselves neither reaction was investigated in detail.

Finally the triflate **1e** (**1**, A^- = $CF_3SO_3^-$) was generated in situ from C_3Cl_4 and $AgCF_2SO_3$. Using the same reaction conditions as before (several days reflux in benzene or fluorobenzene) *we were thus for the first time able to reach the trisubstitution stage of* **1** *with nonactivated aromatic substrates.* After appropriate workup (cf. Experimental Section) cyclopropenium salts **3** (cf. Scheme I) could be isolated in yields >70%. **3a** was identical with an independently synthesized sample. The structure of hitherto unknown **3b** follows from elemental analysis and spectroscopic data (see Experimental Section). Both **3a** and **3b** show intense broad ir bands in the 1400-cm^{-1} region which are diagnostic of aryl-substituted cyclopropenium ions. *p*-Fluorine substitution in **3b** is evidenced by a symmetrical A_2X_2 pattern for the aromatic protons in NMR.[8]

Viewing our results together with those of West we thus arrive at the conclusion that at the disubstitution stage the role of the counterion may become critical (depending on the nature of the nucleophilic substrate). The following arguments may serve to explain this situation: from application of elementary perturbation theory it can easily be derived that replacement of two Cl atoms in the trichlorocyclopropenium system by stronger +M substituents must lead to a first-order bond fixation.[9] This bond fixation tends to distort the cyclopropenium system toward a trimethine cyanine system of type **4**.



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The stronger the electron-donating character of M the more pronounced this distortion and concomitant delocalization of positive charge onto substituents M. As a consequence counterion A^- gets less and less tightly bound to the three-membered ring, and, with strong donors M, the unperturbed cation is open to attack by the substrate MH (SN1 limit). Whether or not trisubstitution occurs should then only depend on the electronic properties of MH and the di-M-substituted cyclopropenium system and could be theoretically decided upon by looking at one of the various reactivity parameters of aromatic substitution.

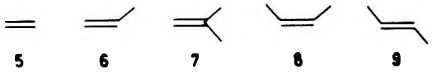
This situation is probably met with MH = anisole or phenol which according to West[7] give trisubstitution of **1** under mild conditions. The situation may change, however, if the donor capacity of M and, as a directly related phenomenon, the nucleophilicity of MH is diminished, e.g., in going over to **4** with M = C_6H_5. This manipulation leads to an increased concentration of positive charge on ring positions 1,2 and in particular 3, which still carries the least stabilizing substituent. As a consequence A^- should become more tightly bound to the cyclopropenium core in general and somewhat asymmetrically to position 3 in particular. The experimental facts that (a) **4** (M = C_6H_5) undergoes further Friedel–Crafts substitution with anisole[7] but not with less nucleophilic benzene for A^- = $AlCl_4^-$, $SbCl_6^-$ while (b) benzene can be brought to reaction with **4** (M = C_6H_5) if A^- = $CF_3SO_3^-$ (the best leaving group known) clearly show that the reaction has now largely adopted SN2 character with its characteristic dependence upon both entering and leaving group.

As a practical consequence of these considerations it can be safely predicted that a large number of new tris aryl-substituted cyclopropenium salts will become accessible via Friedel–Crafts reactions of **1e**.

B. Reactions with Olefins and Acetylenes. The classical synthetic approach toward the cyclopropenium system involves as the key step a carbene addition to an acetylene. This step is bound to meet with considerable difficulties if the substrate contains additional olefinic moieties.[10] It is, therefore, not surprising that to date no simple alkenylcyclopropenium salts have been reported in the literature.

There have been two attempts to bypass this synthetic route by allowing **1a** to react with olefins in a Friedel–Crafts sense.[11,12] However, success in these reactions was restricted to highly chlorinated ethylenes which are not prone to polymerize. Several chloro-substituted divinylcyclopropenones became thus accessible in modest yields (intermediate chlorodivinylcyclopropenium salts were not isolated).[11,12]

We have investigated the behavior of the following simple monoolefins in attempted Friedel–Crafts reactions with **1**:

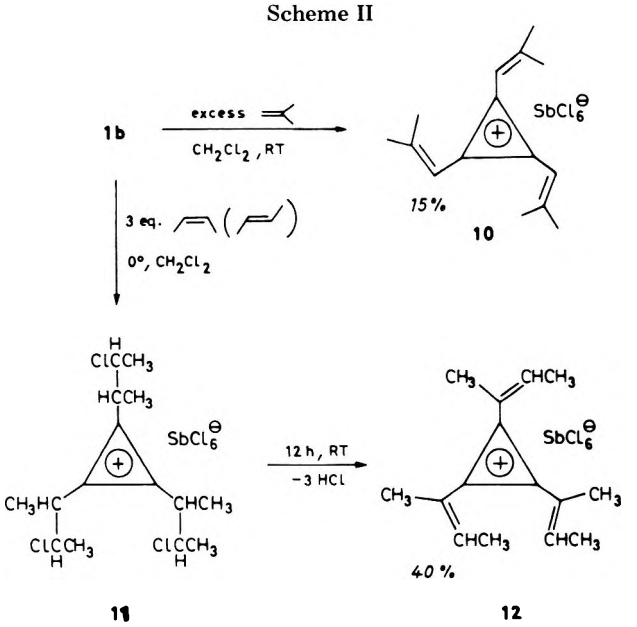


5 **6** **7** **8** **9**

Although all of these nucleophilic substrates readily reacted with **1a** (as a suspension in CH_2Cl_2) at room temperature we were unable to isolate vinylcyclopropenium salts (or, after aqueous workup, vinylcyclopropenones) from the resulting dark solutions. If **1e** was used in reactions with **5**–**9** the picture was similar. However, when we tested **1b** we were again confronted with a striking counterion influence upon the reactivity of the trichlorocyclopropenium system. While **5** and **6** were too unreactive toward **1b** under the reaction conditions used (0–20 °C, CH_2Cl_2 suspension of **1b**) the more nucleophilic olefins **7**–**9** gave the desired reaction which proceeded directly to trisubstitution according to Scheme II. Thus the first trivinylcyclopropenium salts **10** and **12** could be isolated in moderate to fair yield after addition of ether to the reaction mixture. These salts are perfectly stable compounds and were fully characterized (cf. Experimental Section). In particular both compounds exhibit a characteristic broad ir band at approximately 1400 cm^{-1}, just as does the corresponding triphenyl species.

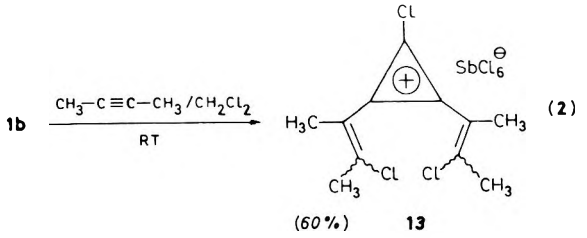
Important conclusions concerning the mechanism of these new reactions can be drawn from our observation that after addition of 3 equiv of *cis*- (or *trans*-) 2-butene to a CH_2Cl_2 suspension of **1b** a primary product can be precipitated as an oil from the dark green reaction mixture. The NMR spectrum of this impure intermediate is consistent with structure **11**; during standing at room temperature in $CDCl_3$ solution the primary NMR signals gradually disappear in favor of the signals of the end product **12** (cf. Experimental Section). This process is accompanied by HCl evolution. These observations

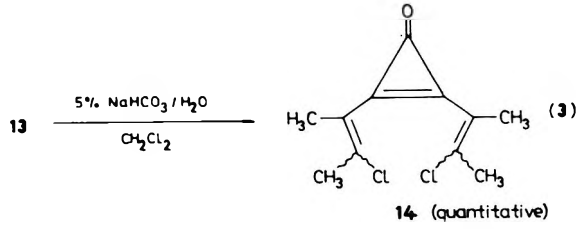
Scheme II



strongly suggest that **12** is formed in an addition–elimination sequence (cf. discussion below). The same should hold for the formation of **10** where no search for intermediates was undertaken. Remarkably, *both cis-* and *trans*-2-butene react with **1b** to give **12.** Presently, we do not know in which reaction step stereospecificity is lost, nor do we know the stereochemical configuration of the end product.

Finally we tested simple alkynes as substrates. Just as with monoolefins (same reaction conditions) **1a** and **1c** gave a complex product mixture with 2-butyne from which no substituted cyclopropenium salts could be isolated. However, again a dramatic effect was observed when the hexachloroantimonate **1b** was allowed to react with the same substrate. Under these conditions a very clean and efficient reaction was observed which proceeded according to eq 2.



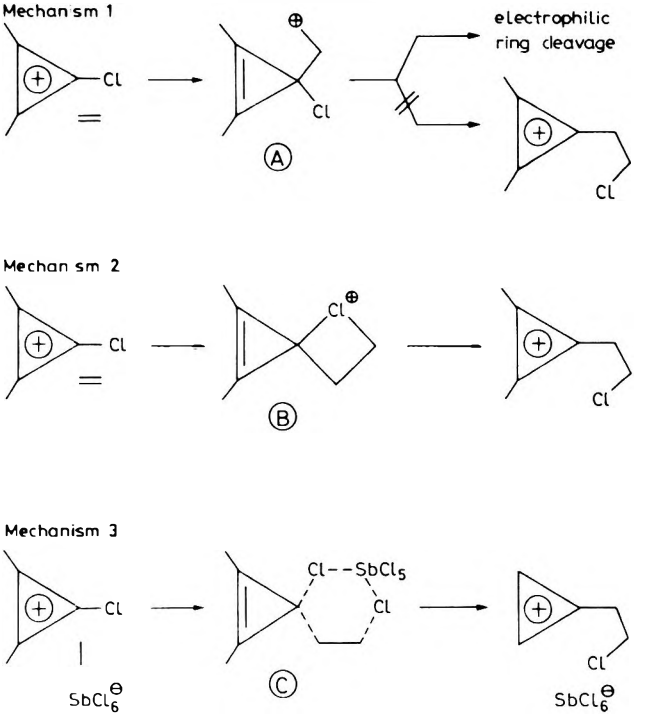


Reaction 2 was almost instantaneously complete with analytically pure **13** precipitating directly from the CH_2Cl_2 solution. Structural identification of **13** rests on its elemental analysis, its characteristic ring vibration at 1420 cm^{-1} in the infrared, and its facile and quantitative conversion into the divinylcyclopropenone **14** according to eq 3. The reaction sequence leading to **14** represents the most convenient and efficient synthesis of a divinylcyclopropenone so far available. Excess of 2-butyne does not lead to formation of the corresponding trivinylcyclopropenium system. It thus seems that the situation is similar as with aromatic substrates. No attempt was made to stop the reaction before the disubstitution stage, however.

The net result of eq 2 is the unprecedented *insertion* of an acetylene into C–Cl bonds of an aromatic halocarbenium ion. The stereochemistry of this process is unknown at present (the NMR spectrum of **13** suggests that one is dealing with a 4:1 mixture of two isomers). The question of cis vs. trans addition could in principle be easily resolved by NMR analysis of the corresponding *acetylene* adduct. Unfortunately the latter could not be obtained as acetylene was not attacked by **1b.** *Mono*alkylacetylenes have not been tested so far.

The specific success of the hexachloroantimonate **1b** and the complete failure of the corresponding triflate in Friedel–Crafts reactions with olefins and acetylenes is in marked contrast to the performance of these salts with aromatic substrates. To account for this situation it is useful to realize that the highly strained cyclopropene system will have very little chance of survival in any process which creates a free carbonium ion in its neighborhood. *Stepwise* addition of the aromatic halocarbenium moiety to an unsaturated substrate (Scheme III, mechanism 1) has to go through such an inter-

Scheme III



mediate A. At this point electrophilic attack at the cyclopropene σ or δ bonds with concomitant release of ring strain should be thermodynamically strongly favored over attack at the Cl atom and formation of the addition product.[13] In principle a concerted four-center process (Scheme III, mechanism 2) would remove the danger of irreversible ring destruction but would be energetically very costly both because of orbital symmetry restrictions and involvement of a highly strained intermediate (or transition state) B.

These difficulties can be avoided by counterion participation as shown in mechanism 3 (cf. Scheme III). In this case empty 5d orbitals on antimony would allow the intimate ion pair to react synchronously with a double (triple) bond via a *six-center* transition state C. This pathway lacks all of the negative features of mechanisms 1 and 2 and should be theoretically open to the corresponding tetrachloroaluminate **1a** as well, *not,* however, to the triflate **1e,** where A hardly can be avoided.

The failure of the latter salt to give vinylcyclopropenium salts with olefins and acetylenes can thus be satisfactorily accounted for. Although the negative role of **1a** in these reactions is not so readily understandable it is clear that one

contributing factor is the polymerizing effect of free $AlCl_3$ generated in the equilibrium of $AlCl_4^-$ with $C_3Cl_3^+$. This may explain why only highly chlorinated olefinic substrates could be induced to react with **1a**.[11,12]

In summary it can be said that Friedel–Crafts reactions of the trichlorocyclopropenium cation with unsaturated substrates are very sensitive to the nature of the counterion. The triflate ion has emerged as an ideal counterion for Friedel–Crafts reactions with aromatics (electrophilic substitution) while $SbCl_6^-$ acts as a specific catalyst in such reactions with double and triple bonds (addition, or addition–elimination).

Work is in process to further extend the scope of the reactions described in this paper with particular emphasis on synthesis and reactions of alkenylpropenium ions.

Experimental Section

General. Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 125 and are reported in units of cm^{-1}. Nuclear magnetic resonance spectra were determined using Models A-60 and EM-360 of Varian Associates, using tetramethylsilane as an internal standard. Chemical shifts are reported in the τ scale. Uv spectra were run on Zeiss Models RPQ 20 and DMR 10. Mass spectra were determined using an AEI MS 902 instrument of Associated Electrical Industries with an ionizing voltage of 70 eV.

Triphenylcyclopropenium Trifluoromethanesulfonate (3a). To a solution of 1.76 g (10.0 mmol) of tetrachlorocyclopropene in 30 ml of dry benzene was added 1 equiv of $AgCF_3SO_3$ (2.57 g). The reaction mixture was refluxed until HCl development ceased (~4 days). After this period the mixture had become dark and a voluminous precipitate of AgCl and **3a** had formed. This precipitate was filtered off and **3a** was extracted with CH_3CN and precipitated with ether as colorless crystals, yield 3.1 g (75%), mp 250 °C dec. Uv, NMR, and ir spectra (apart from absorptions due to the triflate ion at 1140 and 1270 cm^{-1}) were identical with the corresponding spectra of authentic triphenylcyclopropenium bromide.[14] As further structural proof **3a** was reductively dimerized to hexaphenylbicyclopropenyl-3,3′ according to a published procedure.[15]

Anal. Calcd for $C_{22}F_3H_{15}O_3S$: C, 63.46; H, 3.63. Found: C, 63.50; H, 3.55.

Tri-*p*-fluorophenylcyclopropenium Trifluoromethanesulfonate (3b) was prepared analoguously to the procedure described above. Starting from 1.76 g (10.0 mmol) of tetrachlorocyclopropene 3.53 g (75%) of **3b** was obtained as colorless crystals: mp 210 °C dec; ir (KBr) 1600 (m), 1410 (s, broad), 1260 (s, broad) 1150 (m), 1030 (m), 840 cm^{-1} (w); uv (CH_3CN) 322 nm (ϵ 4000), 307 (45 200), 255 (13 800); NMR (CD_3CN) τ 1.47 (center of m, 6 H), 1.73 (center of m, 6 H); mass spectrum *m/e* (rel intensity) 642 (75), 321 (100).

Anal. Calcd for $C_{22}F_6H_{12}O_3S$: C, 56.18; H, 2.57. Found: C, 56.86; H, 2.50.

Tri[(2-methyl)-1-propenyl]cyclopropenium Hexachloroantimonate (10). Isobutylene was bubbled through a suspension of 2.40 g (5.07 mmol) of **1b** in 25 ml of dry CH_2Cl_2 until the reaction mixture became homogeneous (~20 min). Subsequently 100 ml of dry ether was added. After 1 week standing in the refrigerator 0.41 g (15%) of salt **11** had crystallized. Reprecipitation from CH_2Cl_2/ether yielded **10** as yellowish needles: mp 141 °C dec; ir (KBr) 1580 (s), 1420 (s, broad), 1330 (s), 1220 (w), 1070 (w), 940 (w), 830 cm^{-1} (m); uv (CH_2Cl_2) 315 nm (ϵ 36 000), 306 (36 500), 248 (18 200); NMR ($CDCl_3$) τ 3.31 (s, broad, 3 H), 7.52 (s, 9 H), 7.64 (s, 9 H).

Anal. Calcd for $C_{15}Cl_6H_{21}Sb$: C, 33.61; H, 3.94. Found: C, 33.90; H, 3.95.

Tri[(1-methyl)-1-propenyl]cyclopropenium Hexachloroantimonate (12). **1b** (9.60 g, 20.3 mmol) was suspended in 50 ml of dry CH_2Cl_2 and the suspension cooled down to 5 °C. Within 30 min 15 ml of *cis*-2-butene (cooled down to 0 °C) was added dropwise under vigorous stirring. While **1b** gradually dissolved the reaction mixture took on a dark green color. Dry ether (1 l.) was added. Crystallization of **12** started after several hours standing at 0 °C and went to completion after several days standing at −30 °C. Thus was obtained 4.35 g (40%) of slightly greenish needles. After reprecipitation from CH_2Cl_2/Et_2O the compound was colorless: mp 149 °C dec; ir (KBr) 1840 (w), 1630 (s), 1430 (s, broad), 1380 (m), 1330 (m), 1170 (w), 1100 (w), 1070 (w), 1010 (w), 825 (m), 720 cm^{-1} (m). The general appearance of this spectrum is very similar to the ir spectrum of the isomer **10**. However, the occurrence of some additional adsorptions points to a symmetry lower than D_{3h}, caused by substitution patterns around the double bonds and/or nonplanarity (see below). Particularly illustrative is the observation of the A_1' vibration at 1840 cm^{-1} which is ir inactive in D_{3h}[4a] and is not observed with **10**.

Uv (CH_2Cl_2) 283 nm (ϵ 2900), 263 (25 060). In comparison with the isomer **10** there is a pronounced blue shift of the longest wavelength absorption which points to serious deviation of the vinyl substituents from coplanarity. NMR ($CDCl_3$) τ 2.40 (center of m, 3 H), 7.81 (center of m, 18 H).

Anal. Calcd for $C_{15}Cl_6H_{21}Sb$: C, 33.58; H, 4.10. Found: C, 33.59; H, 3.82.

In one run *n*-hexane was added to the reaction mixture about 30 min after addition of *cis*-2-butene. A dark green oil deposited which was collected and freed of volatile components in vacuo at room temperature. The NMR spectrum ($CDCl_3$) of this product was essentially compatible with intermediate **11**. It consisted of two complex multiplets centered at τ 5.80 and 8.30 in an approximate ratio 1:3. These signals can be reasonably attributed to the single protons α and β to the cyclopropenium ring and the methyl groups of **13**, respectively. Furthermore, during standing in $CDCl_3$ at room temperature both groups of signals gradually disappeared in favor of the spectrum of **12**. The latter salt could be isolated in pure form after 12 h standing of the $CDCl_3$ solution by addition of ether. With *trans*-2-butene as starting olefin the observed sequence of events was entirely analogous. However, isolated yields of **12** were much lower (20%).

1,2-Di[(1-methyl-2-chloro)-1-propenyl]-3-chlorocyclopropenium Hexachloroantimonate (13). To a suspension of 2.36 g (5 mmol) of **1b** in 50 ml of dry CH_2Cl_2 was dropped within 5 min at room temperature 0.9 g (16 mmol) of 2-butyne dissolved in 20 ml of dry CH_2Cl_2. During this operation **1b** was consumed and replaced by a voluminous precipitate of **13**. After filtration and three washings with CH_2Cl_2 1.53 g (60%) of **13** was obtained as almost colorless, analytically pure microcrystals: mp 137 °C dec; ir (KBr) 1600 (s), 1450 (s, broad), 1300 (m), 1100 (w), 960 (w), 830 (w), 695 cm^{-1} (w); uv (CH_2Cl_2) 292 nm (ϵ 30 300). NMR (CD_3CN) indicates a 82/18 mixture of two stereoisomers. Component I (82%) has signals at τ 7.33 [q, J = 1 Hz (long-range coupling), 3 H] and 7.69 [q, J = 1 Hz (long-range coupling), 3 H]. Component II (18%) has signals at τ 7.47 (s, broad) and 7.69 (hidden under the high-field peak of component I) in a 1:1 ratio. The low-field signals of both components are assigned to the terminal methyls both because of allylic resonance involving and Cl substitution of the carbon atom to which they are attached.

Anal. Calcd for $C_{11}Cl_9H_{12}Sb$: C, 22.65; H, 2.05. Found: C, 22.85; H, 2.31.

Di[(1-methyl-2-chloro)-1-propenyl]cyclopropenone (14). A suspension of 2.0 g (3.42 mmol) of **13** in 50 ml of CH_2Cl_2 was vigorously stirred together with 100 ml of 5% aqueous $NaHCO_3$ solution. After 2 h the organic phase was separated and dried over $MgSO_4$. After evaporation of the solvent there remained 0.78 g (99%) of pure **14**: mp 102 °C; ir (KBr) 1850 (s, broad), 1590, 1620 (s, intensity 1:1), 1440 (m), 1360, 1380 (s, intensity 1:1), 1210 (w), 1080, 1105 (s, intensity 1:1), 950 (m), 820 (w), 725 cm^{-1} (m); uv (CH_2Cl_2) 293 nm (ϵ 26 800). NMR ($CDCl_3$) indicates two isomers: I (82%) τ 7.29 [q, J = 1 Hz (long range), 3 H], 7.81 [q, J = 1 Hz (long range), 3 H]; 7.63 (s, broad), 7.86 (partly hidden under the 7.81 signal of I) with ratio 1:1; mass spectrum *m/e* (assignment, rel intensity) 230 (M^+, 3), 202 ($M^+ - CO$, 100).

Anal. Calcd for $C_{11}Cl_2H_{12}O$: C, 57.25; H, 5.22. Found: C, 57.01; H, 5.35.

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Registry No.—**1b**, 10421-73-5; **3a**, 58815-76-2; **3b**, 58815-78-4; **10**, 58815-80-8; **12**, 58815-82-0; **13**, 58815-84-2; **14**, 58815-89-4; tetrachlorocyclopropene, 56-23-5; $AgCF_3SO_3$, 2923-28-6; isobutylene, 115-11-7; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; 2-butyne, 503-17-3.

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Substituent Effects in the Homolytic Brominolysis of Substituted Phenylcyclopropanes

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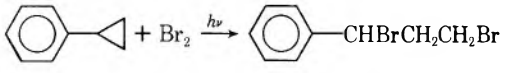
Competitive photochemical brominolyses of substituted phenylcyclopropanes in carbon disulfide at 20 °C gave linear Hammett plots with σ^+ ($\rho = -1.84$, correlation coefficient −0.996) or with σ ($\rho = -2.16$, correlation coefficient −0.982). The substituent effect is similar to that found in homolytic bromination of toluenes, and is similarly interpreted in terms of a polar transition state for the displacement reaction.

Bimolecular homolytic substitutions at carbon (SH2 reactions) are seldom encountered. The best known examples are cleavages of cyclopropane rings by halogen atoms.[1] Although this process has been investigated with respect to its kinetic order,[2] stereochemistry,[1,3,4] and regiospecificity,[3,5] it has not been studied with respect to the electron demands at the involved carbon atoms in the transition state, except for one preliminary study[2b] which gave some gross (not site-specific) substituent effects. The present study provides this information for the leaving carbon radical by a Hammett study of brominolysis of substituted phenylcyclopropanes.

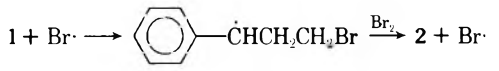
The bromination of phenylcyclopropane (1) under a variety of conditions has been studied by LaLonde, Ferrara, and Debboli,[6] who found a light-induced bromination in carbon tetrachloride at 25 °C to give exclusively 1,3-dibromo-1-phenylpropane (2). Although the simplest and most obvious



1 2

mechanism for this process is a conventional free-radical chain (Scheme I), those authors were unwilling to endorse that

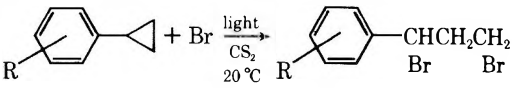
Scheme I



mechanism, partly because they could not demonstrate inhibition with nitrobenzene or trinitrobenzene and partly because of the general unreactivity of cyclopropanes toward free-radical ring opening. Our preference was to accept Scheme I as the mechanism in view of the abundant evidence cited above for homolytic halogenolysis of cyclopropanes, and we have in fact found that although the reaction of 1 with bromine is not retarded by nitrobenzene (in agreement with LaLonde), it is strongly inhibited by isoamyl nitrite. Without isoamyl nitrite, a solution of 1 and bromine decolorized fully in 7 min of illumination. With added isoamyl nitrite, an identical mixture showed no visible decoloration after 1 h of illumination.

A series of substituted phenylcyclopropanes were prepared by conventional methods, some by way of electrophilic substitutions on 1 and some from substituted acetophenones through a Mannich condensation and subsequent pyrazoline formation and thermolysis.[7] Details are in the Experimental Section. Substituents were chosen to avoid reactions of the substituent with bromine, to avoid activation of the aromatic ring toward electrophilic substitution, and to avoid charged groups which might reduce solubility in nonpolar solvents.

All of the phenylcyclopropanes (3) reported here underwent light-induced addition of bromine in carbon disulfide at 20



3 4

a, R = *p*-phenyl
b, R = *p*-Cl
c, R = *p*-Br
d, R = *m*-Br
e, R = *p*-I
f, R = *p*-CN
g, R = *p*-NO_2

°C to give the 1,3-dibromo-1-arylpropanes (4). The NMR spectra of the 1,3-dibromides were very similar, all showing the benzylic doublet of doublets at δ 4.93–5.10, the central methylene multiplet at δ 2.1–3.0, and the terminal methylene multiplet at δ 3.0–3.6. Control reactions in the absence of light showed no significant reaction for any of the compounds **3** in 30 min or longer, except that **3a** gave a 22.5% yield of **4a** in 1 h in the dark. All but **3f** and **3g** gave 100% yields of **4** in 18 min or less when illuminated with a sunlamp. The reaction of **3a** in the light was complete in 2 min. **3f** and **3g** gave reactions only 70% (1 h) and 19% (2 h) complete, respectively, under illumination, but no products other than **4f** and **4g** were detected. It is important that no exchange of aryl halogen for bromine was observed in recovered **3b** and **3e** (dark reactions) or **4b** and **4e** (from photoreactions).

To obtain relative rate constants for the brominolyses of compounds **3**, it was found necessary for practical reasons to measure each in competition with *p*-chlorotoluene (which gives α-bromination) rather than in competition with one another. The mixtures obtained from more than one of the phenylcyclopropanes were not easily analyzed by NMR or gas chromatography, whereas the NMR signals from *p*-chlorobenzyl bromide (δ 4.27) and *p*-chlorobenzal bromide (δ 6.52) were cleanly resolved with respect to the spectra of compounds **3** and **4**, and permitted accurate quantitative analysis. It was shown that the hydrogen bromide formed in bromination of the *p*-chlorotoluene does not react with either **1** or **3f** under the conditions used in the competitive reactions.

Table I lists the results of competitive brominations of the phenylcyclopropanes against *p*-chlorotoluene, with k_2 being the rate constant for brominolysis of the cyclopropane and k_1

Table I. Competitive Rates of Bromination Relative to *p*-Chlorotoluene in Carbon Disulfide at 20 °C under Illumination

Substrate	Log (k_2/k_1)	Substrate	Log (k_2/k_1)
3a	+0.95 ± 0.07	**3c**	+0.20 ± 0.04
1	+0.62 ± 0.04	**3d**	−0.13 ± 0.02
3e	+0.32 ± 0.05	**3f**	−0.66 ± 0.02
3b	+0.28 ± 0.04	**3g**	−0.87 ± 0.03

Table II. Competitive Rates of Bromination Relative to *p*-Cyanophenylcyclopropane in Carbon Disulfide at 20 °C under Illumination

Substituted toluene	Log (k_1/k_2)
p-Cl	+0.66 ± 0.02
p-Br	+0.60 ± 0.03
m-Br	+0.072 ± 0.03
m-NO_2	−0.86 ± 0.06

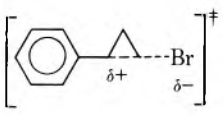
being the rate constant for bromination of the toluene. The errors shown are combined statistical errors from the average deviations of successive NMR integrations in each run and from average deviations of three separate determinations of log k_2/k_1 for each compound.

The data from Table I are plotted against σ^+ values[8] in Figure 1. The least-squares slope (ρ^+) is −1.85 and the correlation coefficient is −0.996. A similar plot (not shown) using ordinary Hammett σ values gives a slope of −2.16 and a correlation coefficient of −0.982. This plot is less satisfactory than the σ^+ plot, but not sufficiently inferior to conclude with certainty that the rates correlate with σ^+.

The data for the ring-opening brominolyses are strikingly similar to those for abstraction of benzylic hydrogens from substituted toluenes by bromine atoms. Thus at 19 °C in benzene the benzylic bromination follows σ^+ with a ρ of −1.76.[9] In view of the expected sensitivity of this process to solvent changes,[10] it was decided to investigate the substituent effect briefly in CS_2 solvent to make certain that the apparent similarity to the cyclopropane cleavages was not the result of a cancellation of opposite effects. Data for relative rates of four toluenes (k_1) vs. *p*-cyanophenylcyclopropane (k_2) in CS_2 at 20 °C are shown in Table II.

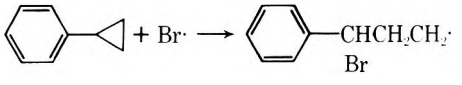
The data in Table II correlate with σ^+ to give ρ −2.67 and correlation coefficient −0.988. The correlation with σ gives ρ −3.26 and correlation coefficient −0.996. The slight superiority of the σ correlation with these few data must be considered insignificant in view of the established superiority of σ^+ correlations in more extensive studies.[9,11]

The most acceptable interpretation of the present data is that the transition state for cyclopropane brominolysis has some charge separation like that (but perhaps smaller in magnitude) postulated to account for the negative ρ and correlation with σ^+ in the hydrogen abstractions:



Cognizance must be taken of recent criticisms by Zavitsas of this kind of interpretation,[12] but satisfying counterarguments are also now on hand.[13]

It must be noted that the site of attack on the cyclopropane ring could be at the benzylic carbon:



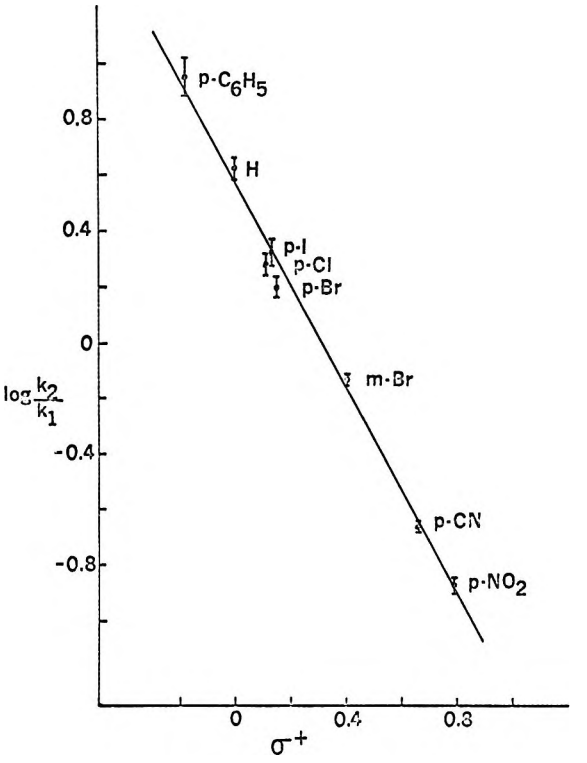


Figure 1.

Such benzylic attack has been proposed by Shea and Skell[3] to account for the regiospecificity in additions of bromine to 1-alkyl-2-phenylcyclopropanes, where the leaving-group radical would be secondary. The substituent effects observed in the present work seem most easily accommodated with the β-attack as proposed, but further experiments are needed to exclude benzylic attack rigorously.

The significance of the present results with respect to the fundamental nature of the SH2 reaction at carbon is not yet clear. It is interesting that the only cases of such reactions are those in which polarized transition states are possible and, as shown here, occur. The generality of the finding will be evident after the completion of the future experiments which it suggests.

Experimental Section[14]

Phenylcyclopropane (1) was prepared in 50% yield by the method of Peterson and Skell.[15] It had bp 57.5 °C (9 mm) [lit.[15] bp 60 °C (13 mm)] and had infrared[16] and NMR[17] spectra identical with those reported.

ω-Dimethylamino-*p*-chloropropiophenone Hydrochloride. Following a similar procedure by Maxwell,[18] dimethylamine hydrochloride (126 g, 1.54 mol), paraformaldehyde (51.0 g, 0.57 mol) and *p*-chloroacetophenone (208 g, 1.35 mol) were mixed and then dissolved in 500 ml of 95% ethanol. Concentrated HCl (5 ml) was added to ensure that all dimethylamine was in its hydrochloride form. The mixture was refluxed on a steam bath for 30 h. The hot solution was then poured into a large Erlenmeyer flask with 200 ml of 95% ethanol. Crystals formed as the solution cooled. These crystals along with a second crop from the mother liquor were recrystallized from a mixture of absolute ethanol and acetone. The material was then dried under vacuum for 20 h to give 208.9 g (62%) of white crystals, mp 174 °C (lit.[7] mp 174 °C).

Anal. Calcd for $C_{11}H_{15}Cl_2NO$: C, 53.24; H, 6.09; Cl, 28.58; N, 5.65. Found: C, 53.48; H, 6.18; Cl, 28.91; N, 5.75.

***p*-Chlorophenylcyclopropane (3b).** ω-Dimethylamino-*p*-chloropropiophenone hydrochloride (169.8 g, 0.686 mol) was dissolved in 500 ml of hot methanol and added slowly to a solution of 82.3 g (1.4 mol) of 85% hydrazine hydrate and 28.0 g (0.70 mol) of sodium hydroxide in 600 ml of absolute methanol. The mixture was stirred and refluxed. After 4.5 h the flask was fitted with a distillation head and the methanol was removed by distillation. The residue was partitioned between ether and water. The ether layer was dried over anhydrous

magnesium sulfate. The ether was removed by means of a Rotavap. The remaining material was distilled slowly from a 300-ml Pyrex flask using a Woods Metal bath. Most of the product was collected with a pot temperature of 230–260 °C and a head temperature of 180–200 °C. The distillate was diluted with diethyl ether and extracted successively with 3% aqueous hydrochloric acid and saturated aqueous sodium bicarbonate. The ether layer was dried over anhydrous sodium sulfate. The solvent was removed by means of a Rotavap leaving 37.6 g of a clear liquid (36% yield of crude product). Further purification of the material was accomplished by distillation at reduced pressure through a 20-cm column of glass helices. The clear liquid product (bp 59 °C, 0.1 mm) [lit.[7] bp 110–115 °C (15 mm)] was found to be homogeneous on VPC with a 10 ft × 0.25 in. o.d. column of 25% SE-30 on Firebrick at 200 °C with a flow rate of 60 ml/min. The infrared spectrum corresponded peak for peak with that of *p*-chlorophenylcyclopropane as reported by Levina and co-workers.[16] The NMR spectrum (CCl_4) showed absorptions at δ 7.10 (d, 2 H, J = 9 Hz), 6.83 (d, 2 H, J = 9 Hz), 1.98–1.50 (m, 1 H), and 1.10–0.37 (m, 4 H).

ω-Dimethylamino-*p*-phenylpropiophenone Hydrochloride. Dimethylamine hydrochloride (49.2 g, 0.60 mol), paraformaldehyde (19.8 g, 0.22 mol), and *p*-phenylacetophenone (84.0 g, 0.50 mol) were mixed in their solid forms and dissolved in 700 ml of hot 95% ethanol. Concentrated hydrochloric acid (5 ml) was added to ensure that all dimethylamine was in its hydrochloride form. The solution was refluxed for 48 h over a steam bath and was then poured into an Erlenmeyer flask. White crystals formed as the solution slowly cooled. Two crops of crystals were collected. After recrystallization from absolute ethanol, the crystals were dried under vacuum to yield 85.3 g (59%) of product (mp 185–186 °C). An analytical sample was recrystallized three times from absolute ethanol and dried under vacuum.

Anal. Calcd for $C_{17}H_{20}ClNO$: C, 70, 47; H, 6.91; Cl, 12.26; N, 4.84; O, 5.52. Found: C, 70.62; H, 6.66; Cl, 12.37; N, 4.58.

***p*-Phenylphenylcyclopropane (3a).** ω-Dimethylamino-*p*-phenylpropiophenone hydrochloride (85.3 g, 0.294 mol) was dissolved in 500 ml of absolute methanol and the solution was added dropwise to a second solution of 0.30 mol of sodium hydroxide and 0.60 mol of 85% hydrazine hydrate in 1000 ml of refluxing methanol. Refluxing was continued for 24 h. Methanol solvent was removed by distillation, and the remaining white residue was partitioned between diethyl ether and water. The ether layer was separated, dried over anhydrous magnesium sulfate, and filtered. The ether was removed on a Rotavap to leave a residue which was then heated to 240–300 °C at 43 mm pressure while a white-yellow solid distillate (45.3 g, 79%) was collected, bp 210–215 °C (43 mm). The solid was purified by eluting it through an 18-in. column of silica gel with chloroform as the solvent. The first elutions were placed on a Rotavap to remove the solvent. The white solid material thus obtained had mp 69–71 °C. After the material was zone refined, mp 71–72 °C was obtained. The infrared spectrum showed bands at 3100–3300 (m), a series of weak bands 1950–1560, 1445 (m), 1410 (m), 1120 (m), 1080 (m), 1050 (m), 1020 (m), 908 (m), 893 (m), 830 (s), 813 (s), 762 (s), 721 (s), and 690 cm^{-1} (s). The NMR spectrum (CCl_4) showed absorptions at δ 7.55–7.07 (m, 7 H), 6.93 (d, 2 H, J = 8 Hz), 2.07–1.57 (m, 1 H), 1.10–0.50 (m, 4 H).

Anal. Calcd for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.28; H, 7.30.

ω-Dimethylamino-*m*-bromopropiophenone hydrochloride was prepared by a procedure closely similar to that shown above for the *p*-chloro compound, but with the reflux period extended to 3 days. The yield of white crystals from methanol was 118.1 g (73%), mp 202.5–203.5 °C (lit.[7] mp 205 °C).

***m*-Bromophenylcyclopropane (3d).** ω-Dimethylamino-*m*-bromopropiophenone hydrochloride (118.1 g, 0.405 mol) was allowed to react with 18.0 g (0.45 mol) of sodium hydroxide in 700 ml of 95% ethanol. The precipitated sodium chloride was removed by filtration, and the filtrate was added dropwise during 1 h to a refluxing solution of 47.0 g (0.8 mol) of 85% hydrazine hydrate in 300 ml of 95% ethanol. Refluxing was continued for another 0.5 h, after which time ethanol was removed slowly by distillation. After most of the ethanol had been removed, the remaining mixture was filtered to remove undissolved salts. The filtrate was heated to temperatures of 200–300 °C with a Woods Metal bath while a distillation head and condenser were used to collect the product. The collection of product was begun at the approximate boiling point of hydrazine (120 °C). The material which was collected was partitioned between ether and water. The ether layer was dried over anhydrous sodium sulfate, subsequently filtered and concentrated by means of a Rotavap. A total of 50.6 g of crude product was obtained. The crude product was distilled at reduced pressure with collection of the product (35.6 g, 32.5%) at 87–88 °C (3 mm) [lit.[7] bp 98–100 °C (14 mm)]. The material appeared homogeneous by GC analysis on a 10 ft column of 20% SE-30 on Chromosorb P at 225 °C. The infrared spectrum showed bands at 3070 (m), 3000 (m), 1600 (s), 1570 (s), 1475 (s), 1455 (m), 1420 (m), 1225 (w), 1170 (w), 1095 (w), 1078 (m), 1053 (m), 1023 (m), 998 (m), 910 (s), 865 (w), 810 (m), 778 (s), and 687 cm^{-1} (s). The NMR spectrum (CCl_4) showed absorptions at δ 7.25–6.70 (m, 4 H), 2.05–1.58 (m, 1 H), 1.13–0.43 (m, 4 H).

Anal. Calcd for C_9H_9Br: C, 54.85; H, 4.60; Br, 40.55. Found: C, 54.65; H, 4.48; Br, 40.39.

***p*-Bromophenylcyclopropane (3c)** was prepared by the method of Levina.[19] To a stirred solution of 12.0 g (0.104 mol) of phenylcyclopropane in 200 ml of chloroform at −75 °C was added over 5 min 19.2 g (0.12 mol) of bromine. After 4 h, the mixture was washed with 200 ml of 10% aqueous sodium sulfite. The organic layer was added slowly (caution!) to a cooled solution of 0.2 mol of sodium ethoxide in absolute ethanol. The resulting solution was refluxed for 1.5 h, and the solvent was removed by a Rotavap. The residue was partitioned between ether and water. The ether layer was dried over anhydrous magnesium sulfate and distilled at reduced pressure to yield 17.1 g (83%) of a colorless liquid (bp 102–106 °C, 9 mm; mp 14 °C) [lit.[19] bp 116 °C (15 mm); mp 15 °C)]. The product was subjected to VPC on a 15 ft × 0.25 in. o.d. column of 5% SE-30 on Chromosorb P at 200 °C with a flow rate of 50 ml/min. Under these conditions only one peak was observed. The infrared spectrum showed bands at 3070 (w), 3000 (w), 1485 (s), 1454 (w), 1403 (w), 1225 (w), 1173 (w), 1100 (m), 1073 (s), 1045 (m), 1008 (s), 900 (m), 815 (s), 744 (m), and 707 cm^{-1} (w). The NMR spectrum (no solvent, only Me_4Si added) showed absorptions at δ 7.18 (d, 2 H, J = 8.3 Hz), 6.67 (d, 2 H, J = 8.3 Hz), 1.88–1.39 (m, 1 H), 1.03–0.31 (m, 4 H).

***p*-Iodophenylcyclopropane (3e).** A solution of 40.0 g (0.202 mol) of *p*-bromophenylcyclopropane in 100 ml of dry tetrahydrofuran was added dropwise to a refluxing, stirred suspension of 9.8 g (0.4 g-atom) of magnesium turnings in 200 ml of dry tetrahydrofuran under a nitrogen atmosphere. The mixture was allowed to cool and stirred for 2.5 h, after which a solution of 51 g (0.2 mol) of iodine in 100 ml of tetrahydrofuran was added slowly. The addition was terminated when an iodine color persisted. The mixture was filtered to remove precipitated salts and unreacted magnesium. The filtrate was then extracted with 10% aqueous sodium thiosulfate to remove unreacted iodine. The organic layer was dried over anhydrous magnesium sulfate and filtered. Most of the solvent was removed on a Rotavap. GC analysis of the remaining material was done using a 6 ft × 0.25 in. o.d. column of 25% SE-30 on 60/80 Firebrick at 200 °C and a flow rate of 60 ml/min. A ratio of *p*-bromophenylcyclopropane to some higher boiling component was found to be 14:154. Thus, 92% conversion of *p*-bromophenylcyclopropane was obtained. The product was purified by distillation at reduced pressure, followed by zone refining. A white, crystalline solid (bp 99 °C, 2.4 mm; mp 46–47 °C) was obtained. The infrared spectrum showed bands at 3030 (w), 2970 (m), 1895 (w), 1640 (w), 1480 (m), 1445 (m), 1418 (m), 1395 (s), 1360 (m), 1340 (m), 1220 (w), 1170 (w), 1115 (m), 1098 (s), 1045 (s), 1018 (s), 1003 (m), 900 (s), 812 (s), 738 (w), and 705 cm^{-1} (m). The NMR spectrum (CCl_4) showed absorptions at δ 7.40 (d, 2 H, J = 8.3 Hz), 6.66 (d, 2 H, J = 8.3 Hz), 2.00–1.48 (m, 1 H), 1.10–0.37 (m, 4 H).

Anal. Calcd for C_9H_9I: C, 44.28; H, 3.72; I, 51.99. Found: C, 44.16; H, 3.70; I, 51.57.

***p*-Cyanophenylcyclopropane (3f).** To a stirred suspension of 10.6 g (0.118 mol) of cuprous cyanide in 35 ml of pyridine at 165 °C was added dropwise 16.0 g (0.0812 mol) of *p*-bromophenylcyclopropane. After 48 h at 165 °C the reaction mixture was distilled directly from the flask at reduced pressure. The crude product mixture was analyzed by VPC on a 3 ft × 0.25 in. o.d. column of 25% SE-30 on 60/80 Firebrick at 230 °C with a flow of 50 ml/min. Three components were observed to be present. The two peaks with lowest retention times had retention times the same as those of pyridine and *p*-bromophenylcyclopropane. A careful distillation of the mixture yielded 6.6 g (56%) of a clear liquid (bp 118 °C, 5 mm) [lit.[7] bp 150 °C (14 mm)] [lit.[20] bp 84 °C (1–2 mm)]. This material was found to be homogeneous by VPC analysis under the conditions mentioned above. The infrared spectrum (NaCl plates) showed bands at 3070 (w), 3000 (m), 2225 (s), 1610 (s), 1510 (m), 1460 (m), 1415 (m), 1225 (m), 1185 (m), 1175 (m), 1115 (m), 1048 (s), 1022 (m), 900 (s), and 828 cm^{-1} (s). The NMR spectrum (CCl_4) showed absorptions at δ 7.42 (d, 2 H, J = 8.3 Hz), 7.07 (d, 2 H, J = 8.3 Hz), 2.15–1.67 (m, 1 H), 1.25–0.53 (m, 4 H).

Anal. Calcd for $C_{10}H_9N$: C, 83.88; H, 6.33; N, 9.78. Found: C, 83.65; H, 6.34; N, 9.67.

***p*-Nitrophenylcyclopropane (3g).** *p*-Nitrophenylcyclopropane was obtained from the nitration of phenylcyclopropane.[20,21] Phenylcyclopropane (35 g, 0.23 mol) was dissolved in 150 ml of acetic anhydride. The temperature was lowered to −40 °C, and 40 ml of nitric

acid was added in a dropwise manner. The mixture was stirred for 0.5 h at −40 °C and poured into hot water (Caution—do not allow the temperature of the reaction mixture to rise above −20 °C until it is added to water!). The resulting mixture was extracted with ether, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed by means of a Rotavap. VPC analysis on a 3 ft × 0.25 in. o.d. column of 25% SE-30 on 60/80 Firebrick at 200 °C with a flow rate of 85 ml/min showed two major components with retention times of 2.45 and 3.65 min. The peak integrations were 4.1 and 1.0, respectively. Phenylcyclopropane had a retention time of 0.65 min. The two components were separated by preparative VPC under conditions similar to those listed above. The component with a retention time of 2.45 min was identified as o-nitrophenylcyclopropane. The compound with a retention time of 3.65 min was identified as the para isomer. The ortho–para isomer mixture was distilled carefully at reduced pressure through a 20-in. column of glass helices. A total of 19 separate fractions were taken. The separation of the two isomers was not entirely clean. o-Nitrophenylcyclopropane (with less than 3% of the para isomer as an impurity) had a boiling point of 105 °C, 1.7 mm [lit.[20] bp 99–100 °C (3 mm)]. The infrared spectrum of o-nitrophenylcyclopropane (NaCl plates) showed bands at 3070 (m), 2990 (m), 1680 (m), 1610 (m), 1520 (s), 1345 (s), 1280 (m), 1030 (m), 903 (m), 852 (s), 784 (s), 744 (s), and 704 cm^{-1} (m). The NMR spectrum of o-nitrophenylcyclopropane (CCl_4) showed absorptions at δ 7.81–7.05 (m, 4 H), 2.60–2.08 (m, 1 H), 1.20–0.50 (m, 4 H).

p-Nitrophenylcyclopropane (with less than 3% of the ortho isomer as an impurity) had a boiling point of 123 °C 1.5 mm [lit.[20] bp 100–115 °C (3 mm)]. The p-nitrophenylcyclopropane thus obtained was zone refined continuously for 1 week. A melting point of 31 °C (lit.[20] mp 30–31 °C) was obtained. The infrared spectrum (NaCl plates) showed bands at 3060 (m), 2990 (m), 1600 (s), 1510 (s), 1435 (m), 1340 (s), 1267 (m), 1230 (m), 1185 (m), 1104 (s), 1050 (s), 897 (s), 857 (s), 823 (m), 783 (m), 745 (s), and 694 cm^{-1} (m). The NMR spectrum (CCl_4) showed absorptions at δ 7.97 (d, 2 H, J = 9 Hz), 7.08 (d, 2 H, J = 9 Hz), 2.21–1.72 (m, 1 H), 1.33–0.60 (m, 4 H).

Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.97; H, 5.64; N, 8.43.

Bromination of Substituted Phenylcyclopropanes at 20 °C in the Dark. To a solution of 2.5 mmol of a substituted phenylcyclopropane in 40 ml of carbon disulfide at 20 °C in the dark was added 2.5 mmol of bromine in 10 ml of carbon disulfide. After the desired reaction time, 7.5×10^{-3} mol of sodium thiosulfate dissolved in 20 ml of water was added. The reaction mixture was maintained in the dark until all bromine color had disappeared. Carbon tetrachloride (30–40 ml) was added to the mixture, and the organic layer was removed and dried over anhydrous $MgSO_4$. The solution was then filtered and solvent removed on a Rotavap. NMR spectra of the residues were taken using CCl_4 as a solvent and Me_4Si as a reference. The phenylcyclopropanes used and the lengths of the bromination reactions were **1** (60 min), **3a** (60 min), **3b** (120 min), **3c** (120 min), **3d** (30 min), **3e** (120 min), **3f** (180 min), and **3g** (180 min). Only **3a** and **3b** produced detectable amounts of **4**, in 22.5 and 3.3% yields, respectively. The ^1H NMR spectrum of **4a** showed signals at δ 5.10 (doublet of doublets, 1 H), 3.5–3.15 (m, 2 H), and 2.75–2.25 (m, 2 H). The spectrum of **4b** showed similar multiplets at δ 5.05, 3.45–3.1, and 2.7–2.25.

NMR Spectra of the Photochemical Bromine Adducts of Phenylcyclopropanes. A substituted phenylcyclopropane was dissolved in carbon disulfide. The solution was stirred and was maintained at 20 ± 2 °C by means of a cold water bath. The solution was irradiated by means of a 275-W GE sunlamp through a glass wall of the water bath. A solution of bromine in carbon disulfide was added, and the reaction was allowed to proceed until the solution decolorized or until the desired time interval had elapsed. The solvent was then removed by means of a Rotavap. In those cases where the solution was not fully decolorized, the remaining bromine was removed with the solvent on the Rotavap. The rate of solvent removal on the Rotavap was regulated so that the flask remained cold. NMR spectra were taken of the residues.

NMR spectrum of the alkyl protons in 1-(4-biphenyl)-1,3-dibromopropane (**4a**) (CS_2): δ 4.98 (doublet of doublets, 1 H), 3.45–3.00 (m, 2 H), 2.7–2.1 (m, 2 H). 1,3-Dibromo-1-phenylpropane (**2**) (CS_2): δ 7.17 (s, 5 H), 5.05 (doublet of doublets, 1 H), 3.65–3.00 (m, 2 H), 3.00–1.80 (m, 2 H). 1-(p-Chlorophenyl)-1,3-dibromopropane (**4b**) (CS_2): δ 7.17 (s, 4 H), 5.05 (doublet of doublets, 1 H), 3.65–3.10 (m, 2 H), 3.00–1.80 (m, 2 H). 1-(p-Bromophenyl)-1,3-dibromopropane (**4c**) (CS_2): δ 7.30 (d, 2 H, J = 8.5 Hz), 7.15 (d, 2 H, J = 8.5 Hz), 5.03 (doublet of doublets, 1 H), 3.75–3.00 (m, 2 H), 3.00–1.80 (m, 2 H). 1,3-Dibromo-1-(p-iodophenyl)propane (**4e**) (CCl_4): δ 7.70 (d, 2 H, J = 8.5 Hz), 7.17 (d, 2 H, J = 8.5 Hz), 5.15 (doublet of doublets, 1 H), 3.85–3.25 (m, 2 H), 2.90–2.20 (m, 2 H). Alkyl protons in 1-(m-bromophenyl)-1,3-dibromopropane (4d) (CS_2): δ 4.96 (doublet of doublets, 1 H), 3.65–3.00 (m, 2 H), 2.95–2.10 (m, 2 H). 1-(p-Cyanophenyl)-1,3-dibromopropane (**4f**) (CS_2): δ 7.58 (s, 4 H), 5.23 (doublet of doublets, 1 H), 3.70–3.30 (m, 2 H), 2.85–2.35 (m, 2 H). Alkyl protons on 1,3-dibromo-1-(p-nitrophenyl)propane (**4g**) (CCl_4): δ 5.28 (doublet of doublets, 1 H), 3.75–3.40 (m, 2 H), 2.95–2.45 (m, 2 H).

Inhibition of the Photobromination of Phenylcyclopropane. Three simultaneous photobrominations were carried out. Flask A contained a carbon disulfide solution which was 0.05 M in phenylcyclopropane. Flask B contained a carbon disulfide solution which was 0.05 M in phenylcyclopropane and 0.025 M in nitrobenzene. Flask C contained a carbon disulfide solution which was 0.05 M in phenylcyclopropane and 0.025 M in isoamyl nitrite. All three flasks were the same size and contained the same volume of solution. The flasks were immersed in a bath at 20 ± 2 °C. The bath contained water and had Pyrex glass walls. Bromine (0.54 equiv for each equivalent of phenylcyclopropane) was quickly added to each flask in the dark. A 275-W GE sunlamp was positioned such that the distance to each flask was the same. Both flask A and flask B decolorized in less than 7 min of irradiation. Flask C did not decolorize after 1 h of irradiation with the sunlamp.

Bromination of p-Chlorotoluene in the Dark at 20 °C in Carbon Disulfide. A carbon disulfide solution of p-chlorotoluene was treated with bromine in the dark for 1 h. The reaction procedure was the same as that for the bromination of substituted phenylcyclopropanes in the dark (above). A 60-MHz NMR spectrum of the product was identical with that of starting material.

Photobromination of p-Chlorotoluene in Carbon Disulfide at 20 °C. A carbon disulfide solution which was 0.05 M in p-chlorotoluene and 0.04 M in bromine was stirred and maintained at 20 ± 2 °C. The solution was illuminated with a sunlamp through the Pyrex flask. After 30 min of illumination the bromine color had disappeared. The carbon disulfide solvent was removed by means of a Rotavap, and a 60-MHz NMR spectrum of the product mixture was taken (CS_2 solvent). The methyl group of the unreacted p-chlorotoluene appeared at δ 2.27, the methylene group of p-chlorobenzyl bromide appeared at δ 4.32, and the methine proton of p-chlorobenzal bromide appeared at δ 6.45.

Control Study of Possible HBr–Bromine Reaction of Phenylcyclopropane at 20 °C in the Dark. To a solution of 81 ml of 0.157 M hydrogen bromide in carbon disulfide (12.7 mmol HBr in solution) at 20 °C was added 5.0 mmol of bromine in 14 ml of carbon disulfide. The mixture was stirred and 0.59 g (5.0 mmol) of phenylcyclopropane was added in the dark. After 1 h, 15 mmol of sodium thiosulfate dissolved in 40 ml of water was added. The reaction mixture was maintained in the dark until the bromine color was discharged. Carbon tetrachloride (70 ml) was added and the organic phase was removed and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent removed on a Rotavap. The NMR of the crude product in carbon disulfide showed resonances for phenylcyclopropane only. None of the ring-opened product was observed. Some sulfur was formed in the dark reaction.

Control Study of Possible Reactions of Phenylcyclopropanes with Hydrogen Bromide. Phenylcyclopropane (0.295 g, 2.5×10^{-3} mol) was dissolved in 49 ml of 0.128 N hydrogen bromide in carbon disulfide (a total of 6.3×10^{-3} mol of HBr in solution). The solution was irradiated for 10 min at 20 °C with a 275-W GE sunlamp. The carbon disulfide solvent was removed by means of a Rotavap, and an NMR spectrum was taken of the residue. The NMR spectrum was identical with that of phenylcyclopropane, and no other peaks were observed.

p-Cyanophenylcyclopropane (1.25×10^{-3} mol) was dissolved in 24.0 ml of 0.057 M HBr in CS_2. The solution was maintained at 20 °C and illuminated with a sunlamp for 20 min. After removal of the solvent on a Rotavap, an NMR spectrum showed the residue to be p-cyanophenylcyclopropane.

Competitive Brominations of Substituted Phenylcyclopropanes. Approximately 2.5×10^{-3} mol of p-chlorotoluene and 2.5×10^{-3} mol of the desired substituted phenylcyclopropane were weighed into a 100-ml Pyrex round-bottom flask. In the bromination of p-nitrophenylcyclopropane, 5.0×10^{-3} mol of p-nitrophenylcyclopropane and 2.5×10^{-3} mol of p-chlorotoluene were used. In the bromination of p-phenylphenylcyclopropane, 1.25×10^{-3} mol of p-phenylphenylcyclopropane and 2.5×10^{-3} mol of p-chlorotoluene were used. A Teflon coated stirring bar was placed in the flask along with 47 ml of carbon disulfide. The flask was immersed in a water bath at 20 ± 2 °C, and the solution was stirred by means of a magnetic stirrer. The flask was illuminated through the water bath with a 275-W GE sunlamp. A 1.0 M solution of bromine in carbon disulfide (2.0 ml) was added. For the bromination of p-phenylphenylcyclopropane, only

1.0 ml of the bromine solution was added. Illumination and stirring were continued until the bromine color disappeared. The lengths of time required to decolorize bromine in the competitive brominations p-C_6H_5, H, p-Cl, p-Br, p-I, m-Br, p-CN, and p-NO_2 were approximately 3, 4, 5, 9, 7, 10, 20, and 30 min, respectively.

The Teflon stirring bar was removed, and the flask was placed on a Rotavap to remove excess carbon disulfide solvent. The rate of solvent removal was regulated such that the flask remained cold to the touch throughout the removal of solvent. Solvent removal was terminated when 2–5 ml of the solvent remained in the flask. A sample of the reaction mixture was added to an NMR tube along with 2 drops of 50% tetramethylsilane. A 60-MHz NMR spectrum of the product mixture was taken. All peaks except those in the aromatic region were integrated three times. The integral amplitude was adjusted so that the largest peak grouping integrated nearly full scale on the chart paper.

Each NMR spectrum consisted of the following groupings of peaks: aromatic absorptions δ 8.2–6.8 (A_1); the benzylic proton of the ring-opened dibromide, doublet of doublets, δ 4.9–5.2 (A_2); the methylene protons of p-chlorobenzyl bromide, singlet, δ 4.3–4.4 (A_3); the terminal methylene group of the ring-opened dibromide, δ 3.0–3.7 (A_4); the central methylene protons of the ring-opened dibromide plus a methyl absorption for unreacted p-chlorotoluene plus the benzylic proton of unreacted substituted phenylcyclopropane, δ 3.1–1.4 (A_5); the methylene protons of unreacted substituted phenylcyclopropane, δ 1.3–0.4 (A_6). In the competitive brominations of p-nitrophenylcyclopropane vs. p-chlorotoluene, small amounts of p-chlorobenzal bromide were produced with singlet absorption at δ 6.5–6.6 (A_7).

Values of log (k_2/k_1) were calculated from the relationship

$$\log k_2/k_1 = \log\left[\log\frac{(y-B)}{y} \Big/ \log\frac{(x-A)}{x}\right]$$

where k_2 is the rate constant for bromination of the phenylcyclopropane (y) and k_1 is the rate constant for bromination of p-chlorotoluene (x). B and A are the respective amounts of y and x consumed in the reaction. The relative values of the quantities in the equation are related to the NMR integrals by the relations $y - B = A_6/4$; $y = A_6/4 + A_2$:

$$x - A = (A_5 - A_4 - A_6/4)/3$$
$$x = (A_5 - A_4 - A_6/4)/3 + A_7 + A_3/2$$

Five artificial reaction mixtures were prepared using known quantities and subjected to the analysis. In each case, the calculated log k_2/k_1 was well within the statistical error of the theoretical value.

Competitive Brominations of Substituted Toluenes. The same procedure as used for the competitive brominations of phenylcyclopropanes was employed, with p-cyanophenylcyclopropane as the constant competitor.

Registry No.—**1**, 873-49-4; **2**, 17714-42-0; **3a**, 35076-77-8; **3b**, 1798-84-1; **3c**, 1124-14-7; **3d**, 1798-85-2; **3e**, 57807-27-9; **3f**, 1126-27-8; **3g**, 6921-44-4; **4a**, 58873-50-0; **4b**, 19714-76-2; **4c**, 58873-51-1; **4d**, 58873-52-2; **4e**, 58873-53-3; **4f**, 58873-54-4; **4g**, 58678-85-6; ω-dimethylamino-p-chloropropiophenone hydrochloride, 1798-83-0; ω-dimethylamino-p-phenylpropiophenone hydrochloride, 5409-63-2; dimethylamine hydrochloride, 506-59-2; p-phenylacetophenone, 92-91-1; ω-dimethylamino-m-bromopropiophenone hydrochloride, 2192-15-6; m-bromoacetophenone, 2142-63-4; o-nitrophenylcyclopropane, 10292-65-6; p-chlorotoluene, 106-43-4.

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X-Ray Crystal Structure Analysis of Triquinacene at 90 K

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The crystal structure of the $C_{10}H_{10}$ hydrocarbon triquinacene, whose three multiply fused cyclopentene rings adopt an unusual cup-shaped geometry having pπ orbitals projected toward the center of the concave face, has been determined at 90 K from three-dimensional x-ray counter data. A crystal grown in a stream of cold nitrogen gas was found to have space group $R\bar{3}$ and a (hexagonal) unit cell of a = 7.272 (5) Å and c = 23.557 (13) Å, with six molecules per cell. The structure was refined using 484 unique reflections with $I > 3\sigma_I$ to a final conventional R factor of 0.052. The molecule has nearly ideal C_{3v} symmetry but, because of packing considerations, only a threefold axis is utilized in the crystalline state.

Homoaromatic character is thought to be present in several cationic and anionic species having one or two homoconjugate linkages.[2,3] Comparable properties have not been uncovered in neutral molecules, presumably because the driving force underlying charge dissipation is no longer present to encourage electronic delocalization, at least to the same extent. As concerns possible neutral six-electron homoaromatic analogues of benzene, the four hydrocarbons **1**–**4** have commanded recent attention. Two of these, *cis,cis,cis*-1,4,7-cyclononatriene (**2**)[4] and triquinacene (**3**),[5] have three

double bonds properly disposed for possible interaction, and are potential trishomoaromatic systems.

1 2

3 4

In the case of **2**, it was not possible by x-ray crystallography, ^{1}H NMR spectroscopy, or heats of hydrogenation to detect any interaction of the double bonds.[4,6] Several chemical and spectroscopic studies have also failed to uncover interaction between the π bonds in **3**.[5] Recent studies by Heilbronner and co-workers using photoelectron spectroscopy have, however, revealed an appreciable interaction of the π bonds in the cyclononatriene.[7] Other photoelectron spectral studies have demonstrated that there exists a much smaller overall interaction of the π levels in **3** relative to **2**.[8]

The geometry of triquinacene is such that the three double bonds occupy fixed positions having one lobe of their pπ orbitals projected toward the midpoint of the concave surface. Comparable rigidity is not seen in **2** which possesses the ability for facile conformational inversion of its crown-to-crown structure in the liquid phase.[6] Modified through space interaction of the π levels in **3** is therefore expected. Such interaction is related not only to the degree of overlap of the orbitals involved, but also to their energy separation.[9] The observed very small split in the e(π) and $a_1(\pi)$ levels in **3**[8] can be attributed either to decreased through space interaction relative to **2** or to large through bond contributions involving the $a_1(\pi)$ and $a_1(\sigma)$ levels. In an effort to gain additional three-dimensional information about triquinacene, its x-ray crystal structure has now been determined. The molecular structure of **2**, obtained previously,[6] was available for direct comparison.

Experimental Section

Preparation. Triquinacene was prepared by previously described procedures[5d,e] and purified by preparative VPC on a 6 ft × 0.25 in. column packed with 5% SE-30 on Chromosorb P at 130 °C. The ^{1}H NMR spectrum of **3** (in $CDCl_3$) shows two sharp signals at δ 5.63 and 3.71. Its ^{13}C NMR spectrum (in $CDCl_3$) is characterized by peaks at 132.89, ~~47.96~~, and ~~29.24~~ ppm. ✱57.68 ; ✱✱47.96

Crystallographic Data. Because of the low melting point of **3** (18–19 °C), the hydrocarbon was handled as a liquid and a small drop was sealed in a 0.2-mm glass capillary and mounted on a Picker FACS-I automated diffractometer. The crystal was obtained by slowly translating a stream of cold nitrogen gas onto the sample. The cold stream was generated using a modified Enraf Nonius gas flow system. After many attempts, it was possible to grow the entire sample into a single crystal, as confirmed with x-ray oscillation photographs. The temperature of the gas stream was maintained at 90 K within ±2 K as measured with a copper–constantan thermocouple.

Cell dimensions were obtained from least-squares refinement of the setting angles of 17 carefully centered high-order reflections. From searches for reflections using the diffractometer, only systematic absences (hkl: $-h + k + l = 3n$) consistent with space groups $R3$, $R32$, $R\bar{3}$, $R3m$, and $R\bar{3}m$ were observed. The additional observation that $I_{hkl} \neq I_{\bar{h}\bar{k}\bar{l}}$ implies that the space group must be $R3$ or $R\bar{3}$. Crystallographic data for **3** are given in Table I.

X-Ray Data Collection. All reflections in the sphere $2\theta < 55°$ were measured with Nb-filtered Mo Kα radiation using a θ–2θ step scan technique. A total scan range of [2.5° + 0.7° tan θ] was used with a step size of 0.03°2θ and a count time of 1.00 s per step. The intensities of three standard reflections measured after every 50 reflections did not change significantly during data collection. Integrated intensities were obtained from analysis of the step scan profiles[10] and corrected for absorption (μ = 0.63 cm^{-1}) assuming the crystal to be a cylinder of length 0.3 mm and diameter 0.2 mm. Standard deviations were assigned according to the expression

$$\sigma_I = (\sigma^2_{count} + (0.03\,I)^2)^{1/2}$$

where σ_{count} was calculated from counting statistics.

Averaging of the symmetry equivalent forms reduced the total of 2942 measured reflections to 597 independent ones. The average discrepancy between symmetry related forms of the 120 strongest unique reflections was 3.6%. A total of 484 unique reflections with $I > 3\sigma_I$ was used in solution and refinement of the structure.

Solution and Refinement of the Structure. The statistical distribution of normalized structure amplitudes (E's) indicated a centrosymmetric structure. The space group was taken to be $R\bar{3}$. The structure was solved using Long's[11] sign predicting program. The 100 E's above 1.3 were used with a starting set of four permutable signs in addition to one sign determining the origin. The carbon atoms skeleton was easily identified in the E map from the solution set with the highest consistency index (0.59). However, large disagreement between F_o and F_c for low-order 00l reflections in an initial structure factor calculation indicated that the placement of the molecule along the c axis was incorrect. A translation of the molecule by $c/6$ gave the correct solution.

Scattering factors for carbon and for a "spherical bonded" hydrogen atom were taken from Vol. IV of the International Tables.[12] Least-squares refinement with anisotropic temperature factors for the carbon atoms and isotropic temperature factors for the hydrogens gave a final R of 0.052 and R_w of 0.032.[13] The quantity minimized in the refinement was $\Sigma w(|F_o| - |F_c|)^2$ with weights $w = 1/\sigma_F^2$. An isotropic extinction parameter was included as a variable in the refinement. All programs used for data reduction and refinement are part of the Integrated Crystallographic Computing Library at the State University of New York at Buffalo. A table of observed and calculated structure factors is available.[14]

Table I. Crystallographic Data for Triquinacene (3)

Mol wt	130.2	Space group	$R\bar{3}$
a, Å	7.272 (5)	ρ_{calcd}, g/cm^3	1.202 for Z = 6
c, Å	23.557 (13) (hexagonal cell)	Volume, Å^3	1078.8

Table II. Final Fractional Atomic Coordinates and Isotropic Thermal Parameters[a]

Atom	x	y	z	U_{iso},[b] Å^2
C1	0.29350 (23)	0.05699 (23)	0.23908 (7)	
C2	0.21398 (24)	0.17736 (24)	0.27398 (7)	
C3	0.14964 (24)	0.31032 (21)	0.23895 (7)	
C4	0.0	0.0	0.29904 (13)	
H1	0.4221 (25)	0.1266 (25)	0.2180 (7)	0.0361 (42)
H2	0.3164 (22)	0.2685 (24)	0.3029 (7)	0.0315 (38)
H3	0.2470 (22)	0.4293 (24)	0.2176 (7)	0.0329 (42)
H4	0.0	0.0	0.3404 (13)	0.0337 (74)

[a] Standard deviations in parentheses. [b] Isotropic thermal parameters expressed as $\exp(-2\pi^2 U_{iso} \sin^2\theta/\lambda^2)$.

Results and Discussion

The final positional and isotropic thermal parameters are given in Table II. The anisotropic thermal parameters are presented in Table III. Although the molecule has a crystallographically imposed threefold rotation axis parallel to the c axis, the individual units have nearly ideal C_{3v} symmetry. Atoms labeled with ′ and ″ are generated by rotations about the threefold axis of 120 and 240°, respectively (Figure 1). The more important intramolecular bond distances and bond angles are given in Figure 1. Full details are given in the supplementary material. Standard deviations in distances and

Table III. Anisotropic Thermal Parameters[a,b] (Å²)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	0.0236 (8)	0.0321 (8)	0.0322 (9)	0.0146 (7)	0.0004 (7)	0.0024 (7)
C2	0.0244 (8)	0.0271 (8)	0.0316 (9)	0.0097 (7)	−0.0050 (7)	−0.0037 (7)
C3	0.0322 (9)	0.0214 (8)	0.0326 (9)	0.0117 (7)	0.0022 (7)	−0.0006 (7)
C4	0.0298 (9)	0.0298[c]	0.0246 (16)	0.0149[c]	0.0	0.0

[a] Anisotropic thermal parameters expressed as exp $-2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + U_{12}a^*b^*hk + U_{13}a^*c^*hl + U_{23}b^*c^*kl)$. [b] Standard deviations in parentheses. [c] From symmetry $U_{11} = U_{22} = 2U_{12}$.

Table IV. Intermolecular Contacts of <3.0 Å

Atoms		Distance	No.
H3 ... H3′	(1 + X, 1 + Y, Z)	2.62	6
... H3″	(X, 1 + Y, Z)		
H2 ... H2′	(⅓ − X, ⅔ − Y, ⅔ − Z)	2.75	6
... H2″	(⅓ − X, −⅓ − Y, ⅔ − Z)		
H3 ... H3′	(−⅓ − X, ⅓ − Y, ⅓ − Z)	2.84	6
... H3″	(⅔ − X, ⅓ − Y, ⅓ − Z)		
H1 ... H1′	(1 + X, Y, Z)	2.87	6
... H1″	(1 + X, 1 + Y, Z)		
H2 ... H4	(⅓ − X, ⅔ − Y, ⅔ − Z)	2.89	3
H4 ... H2	(⅓ − X, ⅔ − Y, ⅔ − Z)	2.89	3
... H2′	(−⅔ − X, −⅓ − Y, ⅔ − Z)		
... H2″	(⅓ − X, −⅓ − Y, ⅔ − Z)		
H1 ... H3	(⅔ − X, ⅓ − Y, ⅓ − Z)	2.90	6
H1 ... H1	(⅔ − X, ⅓ − Y, ⅓ − Z)	2.93	3
H1 ... H3′	(1 + X, Y, Z)	2.94	6

angles were calculated from the full variance–covariance matrix obtained from the last cycle of refinement.

Corrections to the bond distances due to librational thermal motion were calculated using the rigid-body TLS analysis.[15] The negligible corrections reflect the small degree of thermal motion at 90 K.

The five-membered rings in the molecule are slightly nonplanar. The deviations from the least-squares plane ($4.337x - 2.782y + 18.769z = 5.594$) through atoms C1, C2, C4, C2″, and C3″ are 0.008, −0.017, 0.005, −0.015, and 0.019 Å, respectively. A better least-squares plane ($4.246x - 2.724y + 18.992z = 5.630$) is obtained through atoms C1, C2, C2″, and C3″ giving deviations of 0.002, −0.001, −0.002, and 0.001 Å, respectively, with atom C4 0.049 Å above the plane. Atoms H1 and H3″ are −0.024 and −0.031 Å from the first plane and −0.043 and −0.050 Å from the second plane, respectively.

The molecules in the crystal structure are arranged in layers perpendicular to the c axis. Contacts between molecules are top to top and bottom to bottom in alternate layers (Figure 2). The closest intermolecular contacts are listed in Table IV. Contacts between hydrogens apparently prevent the compound from crystallizing in a structure which utilizes the full C_{3v} symmetry of the molecule. In contrast, the C_{3v} symmetry of **2** is incorporated in its crystal structure.[6]

The nonbonded intraannular methylene hydrogen interactions in **2** have the effect of denying close approach of one CH_2 group to another. Notwithstanding, the degree of pucker in the cyclononatriene (defined as the vertical distance of CH_2 group from the basal plane adopted by the trigonal carbons) is expected to be more accentuated than that in triquinacene, particularly since an apical carbon and multiple cyclopentene ring formation need not be accommodated. In actuality, the angle defined by atoms C3″–C1–C2 in **2** (124°) is approximately 11° wider than the corresponding angle in **3** (112.8°). As a result, the allylic carbons in triquinacene (e.g., C2 and C2″) are separated by 2.497 Å and the C1–C2–C3 angle is enlarged to 113.8°. For **2**, this angle is significantly smaller (108°). It follows that the nonbonded C1 ... C3 distance

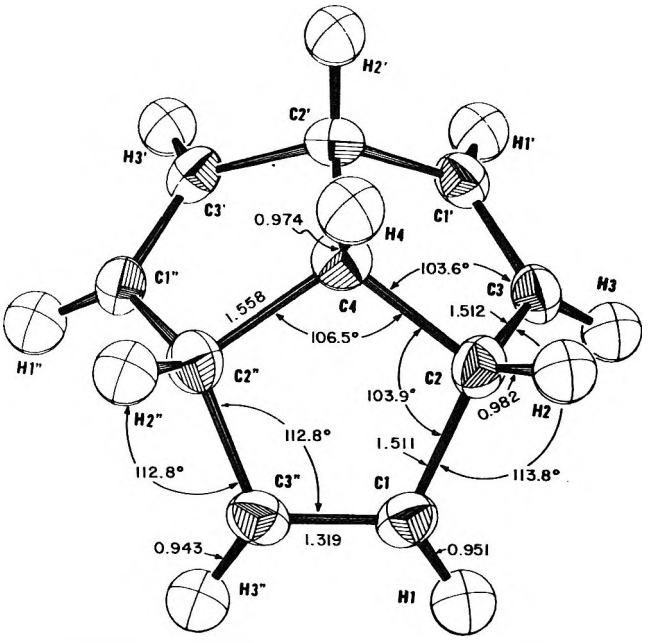

Figure 1. Numbering scheme for the triquinacene molecule. The threefold axis is along the C4–H4 bond. Thermal ellipsoids are drawn at 50% probability.

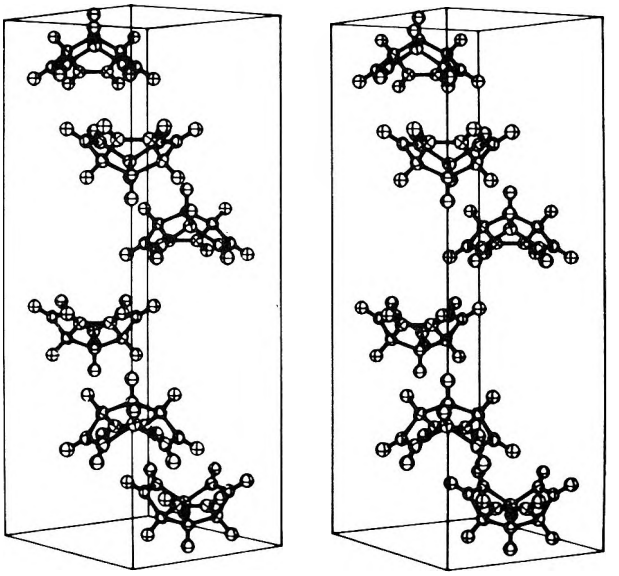

Figure 2. Stereoscopic view of the packing in the hexagonal unit of triquinacene molecules.

adopted by **3** (2.533 Å) is necessarily larger than that in **2** (2.46 Å). Both distances are too long for normal π–π bonding overlap from the convex direction and deny the possibility for conventional peripheral delocalization in both systems.

That neither **2** nor **3** can partake of homoallylic participation on their exo surfaces due to the excessively long gaps

between the individual π bonds is consistent with their chemical reactivity. The answer to the critical question of whether stabilization is made possible from such a π-orbital arrangement on the concave underside is decidely negative. That homoconjugative interaction is entirely prohibited is evidenced further by the complete lack of anchimeric assistance to ionization in *exo*-2,3-dihydrotriquinacen-2-ol tosylate[16] and the electronic properties of 2,3-dihydrotriquinacen-2-one.[17]

The increased nonbonded distance separating the allylic carbons in *cis,cis,cis*-1,4,7-cyclononatriene will result in a somewhat more favorable canting of the π orbitals in the molecular interior. It seems reasonable to assume therefore that **2** will be capable of better through space interaction than **3** and that the photoelectron spectroscopic results[18] provide a quantitative measure of these effects. In other words, through space interaction between the three π-bond segments increases with increased molecular puckering. For bridged bicyclic dienes of the Dewar benzene, norbornadiene, bicyclo[2.2.2]octadiene, etc., type, the same is true. In this series, through space interaction falls off as the length of the saturated bridge increases from 0 to 4.[18] This comparable behavior points up convincingly the somewhat analogous orbital alignments which characterize these two groups of molecules.

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Registry No.—**3**, 6053-74-3.

Supplementary Material Available. A complete listing of intramolecular bond distances and bond angles (4 pages). Ordering information is given on any current masthead page.

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(13) $R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$, $R_w = [\Sigma(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$.
(14) See paragraph at end of paper regarding supplementary material.
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Quantitative Structure–Activity Relationships of D- and L-*N*-Acyl-α-aminoamide Ligands Binding to Chymotrypsin. On the Problem of Combined Treatment of Stereoisomers[1a]

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The binding of D- and L-*N*-acyl-α-aminoamides [RCH(NHCOR')CONH$_2$] to chymotrypsin is correlated with the molar refractivity (MR) of R and NHCOR'. The group with the largest MR value appears to bind in the so-called hydrophobic cleft (ρ_2 area); the smaller group binds in ρ_1 space. Working from this premise, the K_m values for 23 L amides and the K_i values for 22 D amides can be correlated in a single equation. This appears to be the first instance where the structure–activity relationship of optical isomers has been correlated in a single equation.

One of the challenges facing those interested in the formulation of quantitative structure–activity relationships (QSAR) is the problem of including different stereoisomers in a single equation. Sometimes there is little difference in the biological activity of, say, D and L isomers and sometimes there is vast difference between high activity and complete inactivity. An excellent system with which this problem can be explored is α-chymotrypsin and the various ligands with which it interacts. The structure and mechanism of action of this enzyme are probably better understood than those of any other enzyme.

Over the years many studies of substituent effects on ligand interactions with enzymes have been made but attempts to formulate linear free-energy relationships of the Hammett type correlating structure with activity have been limited to sets with small numbers of congeners. Until recently, these correlation studies have tried to rationalize substituent effects using a single electronic parameter such as σ or σ$^-$. With the development[2] of the hydrophobic parameter π, analogous to σ, it has been shown that taking hydrophobic effects as well as steric effects (E_s) of substituents into account enables one to formulate much more comprehensive QSAR for chymotrypsin.[3] Various groups have begun to test the use of hydrophobic parameters in the formulation of structure–activity relationships with chymotrypsin.[4–10]

The parameter π is defined as $\pi_X = \log P_X - \log P_H$ where P_X is the octanol/water partition coefficient of a derivative and P_H that of the parent compound. Considerable evidence has accumulated to indicate that π models the hydrophobic interaction of substituents with lipophilic portions of enzymes[11] as well as other macromolecules.[12]

While much attention has been focused on the interaction

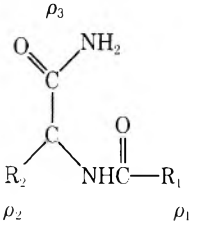
of ligands with the hydrophobic portions of enzymes, little discussion has developed about how ligands might interact with the nonhydrophobic parts of enzymes; that is, in terms of substituent constants one should a priori expect two types of constants to be necessary to describe the interaction of ligand substituents with biomacromolecules. π would be expected to model cases where desolvation is the main driving force. We have found[3,13-15] that molar refractivity (MR) appears to account for a second type of nonspecific interaction where desolvation does not play the dominant role.

Pauling and Pressman appear to have been the first to suggest[17] the use of MR for the correlation of substituent effects on the binding of haptens by antibodies. More recently Agin et al.[18] have discussed the theory behind the use of this parameter in correlating ligand interaction. Both groups started with the London equation and the idea that dispersion forces are most important in the attachment of enzyme and ligand. They have shown, with certain assumptions, that MR of the substituent should be correlated with the logarithm of the binding constant. Agin et al. believe that one should not neglect the ionization potential of the ligand, while Pauling and Pressman neglect this quantity. Because ionization potentials of organic molecules have a small range for compounds consisting mainly of second-row elements, we have followed the lead of Pauling and Pressman.

Franks[19] has recently presented evidence for a second type of "hydrophobic bonding" in which groups with their surrounding flickering clusters of water are held together in solution without desolvation playing the major role. It may be that high correlation with MR reflects this type of interaction. It should be mentioned that Franks restricts his second type of hydrophobic interaction to apolar groups. We are employing MR to model substituent effects of polar as well as apolar groups. With apolar substituents such as halogens and alkyl groups, π and MR are so collinear that, in an operational sense, they yield the same information in correlation analysis. When π and MR are orthogonal and the QSAR is related to MR, all that can be said at present is that the interaction does not depend primarily on desolvation.

In the present report we are concerned with obtaining a better general understanding of the forces which bind enzyme and substrate or inhibitor. We have employed data from Niemann's extensive studies on D and L amides of the type

Chart I



The L form of the amide binding to ρ_1, ρ_2, and ρ_3 space of the enzyme is shown in Chart I. This use of ρ corresponds to that proposed by Hein and Niemann.[20] The H on the α carbon in Chart I is projecting below the plane of the page. In general, L amides function as substrates, while D amides act as inhibitors of chymotrypsin hydrolysis. We have formulated eq 1-3 from Niemann's data and the physicochemical constants of Table I to correlate the binding of inhibitors (K_i) and substrates (K_m) to chymotrypsin.

Experimental Section

The constants π and MR of Table I are from our recent compilation.[21] In order to test the characteristics of our correlation equations, three new amides were synthesized and their K_m values determined under the conditions employed by Niemann by means of a Radiometer titration.

α-*N*-Nicotinyl-L-4-nitrophenylalanine Ethyl Ester. To a mixture of L-4-nitrophenylalanine (5.6 g, 27 mmol) and 100% ethanol (100 ml), hydrogen chloride gas was introduced until solution resulted (20 min) and a precipitate occurred (1 h). The mixture was then refluxed for 2 h, after which the alcohol was evaporated under reduced pressure. The residue was washed with ether to give crude nitrophenylalanine ethyl ester hydrochloride (5.9 g, 21 mmol) of mp 212-214 °C. Careful treatment of the hydrochloride with potassium carbonate solution converted it to the oily free base. To this material was added nicotinyl azide (3.7 g, 25 mmol) and ethyl acetate (20 ml) and the mixture was allowed to stand overnight. This solution was extracted with 5% HCl. This phase was neutralized with $NaHCO_3$ and extracted with ethyl acetate. After drying the extract over $MgSO_4$, the solvent was removed under reduced pressure. The residue was washed with ether and recrystallized from acetone–ether to give needles (3.8 g), mp 135-137 °C.

Anal. Calcd for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99. Found: C, 59.83; H, 5.04.

α-*N*-Nicotinyl-L-4-nitrophenylalaninamide. The above ester (3 g) was dissolved in methanol (15 ml) and liquid ammonia (15 ml). This solution was allowed to stand at room temperature for 2 days after which the solvent was evaporated. The solid residue was recrystallized from ethanol to give fine needles (2.4 g), mp 200-201 °C.

Anal. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49. Found: C, 57.93; H, 4.03.

α-*N*-Nicotinyl-L-alanine Ethyl Ester. A mixture of ethyl alaninate (from 3.07 g of the hydrochloride) and nicotinyl azide (3.70 g) in ethyl acetate (20 ml) was allowed to stand overnight and then extracted with 5% HCl. The aqueous phase was neutralized with $NaHCO_3$ and extracted with ethyl acetate. The extracts were dried and solvent removed under reduced pressure. The solid residue was washed with hexane and recrystallized from acetone–pentane to afford needles (3.55 g), mp 92-93 °C.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35. Found: C, 60.11; H, 6.01.

α-*N*-Nicotinyl Alaninamide. The above ethyl ester (0.75 g) was dissolved in 15 ml of methanol and 15 ml of liquid ammonia. After standing overnight, the solvent was removed under reduced pressure and the solid residue recrystallized from ethanol–acetone to give needles (0.50 g), mp 230-232 °C.

Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74. Found: C, 56.20; H, 5.71.

α-*N*-Benzoyl-4-nitrophenylalanine Ethyl Ester. To a mixture of benzoic acid (12.2 g) and pyridine (30 ml) was added benzenesulfonyl chloride (6.4 ml) and then L-4-nitrophenylalanine ethyl ester (13.7 g). After standing for 1 day, the excess pyridine was vacuum evaporated and the residue was partitioned between water and ethyl acetate. The water phase was extracted with ethyl acetate and the combined extracts were washed with 5% HCl, NaCl solution, $NaHCO_3$ solution, and again with NaCl solution. The ethyl acetate solution was dried over potassium carbonate and evaporated to dryness. Three recrystallizations of the residue from aqueous ethanol gave needles (10 g), mp 117-119 °C.

Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30. Found: C, 63.93; H, 5.67.

α-*N*-Benzoyl-4-aminophenylalanine Ethyl Ester. α-*N*-Benzoyl-4-nitrophenylalanine ethyl ester (2.5 g) was dissolved in 60 ml of ethanol and hydrogenated in the presence of PtO_2 at 33-52 psi for 25 min. The catalyst was removed by filtration and the solvent evaporated. Recrystallization of the residue from aqueous ethanol gave colorless needles (2.0 g), mp 140-143 °C.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45. Found: C, 68.92; H, 6.50.

α-*N*-Benzoyl L-4-Methanesulfonylamidophenylalaninamide. α-*N*-Benzoyl L-4-aminophenylalanine ethyl ester (0.5 g) was dissolved in 100 ml of pyridine and placed in an ice bath. To this solution methanesulfonyl chloride (1 ml) was added dropwise. After standing for 1 day, the pyridine was removed by vacuum evaporation and the residue partitioned between ethyl acetate and 5% HCl. The organic phase was washed with NaCl solution, $NaHCO_3$ solution, and then NaCl solution. After drying over K_2CO_3, the solvent was evaporated and the oily residue dissolved in 10 ml of methanol and 15 ml of liquid ammonia. After standing overnight, it was evaporated to dryness and the solid residue recrystallized from aqueous methanol to afford needles (0.5 g), mp 258-260 °C.

Anal. Calcd for $C_{17}H_{19}N_3O_4S$: C, 56.50; H, 5.30; N, 11.63. Found: C, 56.90; H, 5.28; N, 11.24.

Enzyme Experiments. All enzymatic hydrolyses were conducted

Table I. Constants Used for Deriving Equations 1–3

No.	Compd	Log 1/*K* Obsd[a]	Log 1/*K* Calcd[b]	|Δ log 1/*K*|	MR-L	MR-S	I-1	I-2	Ref
1	CH_3CO-Gly-NH_2	0.46	0.35	0.11	1.49	0.10	0.0	1.0	16a
2	C_6H_5CO-Gly-NH_2	1.89	1.77	0.12	3.46	0.10	0.0	1.0	16d
3	D-Tyr-NHOH	1.40	1.67	0.27	3.18	0.54	0.0	1.0	16e
4	D-C_2H_5OCO-Tyr-NH_2	1.68	2.03	0.35	3.18	2.12	0.0	1.0	16a
5	D-CF_3CO-Tyr-NH_2	1.70	1.87	0.17	3.18	1.43	0.0	1.0	16a
6	D-CH_3CO-Tyr-NH_2	1.92	1.88	0.04	3.18	1.49	0.0	1.0	16a
7	D-CH_3CO-Phe-NH_2	2.00	1.75	0.25	3.00	1.49	0.0	1.0	16a
8	D-NiCO-Tyr-NH_2	2.05	2.31	0.25	3.23	3.18	0.0	1.0	16a
9	D-NiCO-Phe-NH_2	2.05	2.27	0.22	3.23	3.00	0.0	1.0	16a
10	D-CH_3CO-Tyr-$NHNH_2$	2.12	2.21	0.09	3.18	1.49	1.0	1.0	16c
11	D-CH_3CO-Tyr-NHOH	2.12	1.88	0.24	3.18	1.49	0.0	1.0	16c
12	D-$ClCH_2CO$-Tyr-NH_2	2.19	2.00	0.19	3.18	1.98	0.0	1.0	16a
13	D-Try-NH_2	2.40	2.42	0.02	4.23	0.54	0.0	1.0	16d
14	D-CF_3CO-Try-NH_2	2.40	2.63	0.23	4.23	1.43	0.0	1.0	16d
15	D-CH_3CO-Try-$NHCH_3$	2.74	2.64	0.10	4.23	1.49	0.0	1.0	16c
16	D-CH_3CO-Try-NH_2	2.77	2.64	0.13	4.23	1.49	0.0	1.0	16a
17	D-NiCO-Try-NH_2	2.80	3.04	0.24	4.23	3.23	0.0	1.0	16a
18	D-CH_3CO-Try-$NHNH_2$	3.10	2.96	0.14	4.23	1.49	1.0	1.0	16d
19	D-C_6H_5CO-Try-NH_2	3.15	3.09	0.06	4.23	3.46	0.0	1.0	16d
20	D-4-$CH_3OC_6H_4CO$-Try-NH_2	3.22	3.24	0.02	4.23	4.10	0.0	1.0	16d
21	D-4-$NO_2C_6H_4CO$-Try-NH_2	3.74	3.24	0.50	4.23	4.10	0.0	1.0	16f
22	L-CH_3CO-Tyr-$NHCH_3$	1.21	1.57	0.36	3.18	1.49	0.0	0.0	16b
23	L-CH_3CO-Tyr-NHOH	1.37	1.57	0.20	3.18	1.49	0.0	0.0	16b
24[c]	L-$(CH_3)_3CCO$-Tyr-$NHNH_2$	1.40	2.22	0.82	3.18	2.89	1.0	0.0	16b
25	L-CH_3CO-Tyr-NH_2	1.41	1.57	0.16	3.18	1.49	0.0	0.0	16a
26	L-CH_3CO-Phe-NH_2	1.51	1.44	0.07	3.00	1.49	0.0	0.0	16a
27	L-CH_3CO-Tyr-$NHNH_2$	1.52	1.90	0.38	3.18	1.49	1.0	0.0	16b
28	L-$ClCH_2CO$-Tyr-NH_2	1.57	1.69	0.12	3.18	1.98	0.0	0.0	16a
29	L-CH_3CO-$C_6H_{11}CH_2$-NH_2	1.57	1.54	0.03	3.13	1.49	0.0	0.0	16b
30	L-CF_3CO-Tyr-NH_2	1.58	1.56	0.02	3.18	1.43	0.0	0.0	16a
31	L-CH_3CO-Tyr-Gly-NH_2	1.64	1.57	0.07	3.18	1.49	0.0	0.0	16b
32	L-NiCO-Phe-NH_2	1.72	1.96	0.24	3.23	3.00	0.0	0.0	16a
33	L-NiCO-Tyr-NH_2	1.80	2.00	0.20	3.23	3.18	0.0	0.0	16a
34	L-HCO-Tyr-NH_2	1.92	1.47	0.45	3.18	1.03	0.0	0.0	16b
35	L-HCO-Tyr-$NHNH_2$	2.01	1.79	0.22	3.18	1.03	1.0	0.0	16b
36	L-PiCO-Tyr-NH_2	2.04	2.00	0.04	3.23	3.18	0.0	0.0	16b
37	L-iso-NiCO-Tyr-NH_2	2.05	2.00	0.05	3.23	3.18	0.0	0.0	16c
38	L-NiCO-Tyr-$NHNH_2$	2.10	2.32	0.22	3.23	3.18	1.0	0.0	16b
39	L-Try-NH_2	2.10	2.11	0.01	4.23	0.54	0.0	0.0	16d
40	L-C_2H_5OCO-Tyr-NH_2	2.19	1.72	0.47	3.18	2.12	0.0	0.0	16a
41	L-CH_3CO-Try-$NHCH_3$	2.19	2.33	0.14	4.23	1.49	0.0	0.0	16b
42	L-Cl_2CHCO-Tyr-$NHNH_2$	2.28	2.12	0.16	3.18	2.48	1.0	0.0	16b
43	L-CH_3CO-Try-NH_2	2.30	2.33	0.03	4.23	1.49	0.0	0.0	16a
44	L-NiCO-Try-NH_2	2.60	2.73	0.13	4.23	3.23	0.0	0.0	16a
45	L-C_6H_5CO-Tyr-NH_2	2.60	2.16	0.44	3.46	3.18	0.0	0.0	16b
46	L-C_6H_5CO-Tyr-$NHNH_2$	2.66	2.49	0.17	3.46	3.18	1.0	0.0	16b
47[d]	L-NiCO-Ala-NH_2	1.40	1.40	0.00	3.23	0.57	0.0	0.0	
48[d]	L-C_6H_5CO-4-CH_3SO_2NHPhe-NH_2	1.78	3.14	1.36	4.72	3.46	0.0	0.0	
49[d]	L-NiCO-4-NO_2Phe-NH_2	2.34	2.30	0.04	3.63	3.23	0.0	0.0	

[a] Calculated from results of Niemann et al. (1–46) and the present authors (see ref 16). [b] Calculated using eq 3. [c] This molecule not used in deriving equations. [d] Compounds made in this work. These points not used in deriving eq 1–3.

at 25 °C, pH 7.9 ± 0.02 with 0.10 M sodium chloride. The rate of hydrolysis was determined by means of a Radiometer pH-stat system. Crystalline chymotrypsin was obtained from Worthington Biochemical Corp. The procedure used was that of Niemann. The value of K_m for α-*N*-nicotinyl-L-tyrosinamide was determined as a standard and found to be identical with that obtained by Kartz and Niemann.[22]

Results and Discussion

Equations 1 and 2 correlate K_m for the L isomers and K_i for D isomers and glycine derivatives of the *N*-acyl-α-aminoamides, respectively. In these equations, *n* is the number of data points, *r* is the correlation coefficient, *s* is the standard deviation, and the figures in parentheses are the 95% confidence intervals. MR-L refers to the molar refractivity of the larger of the two α substituents regardless of its stereochemistry and MR-S refers to the smaller. This approach yields considerably better results than using MR-1 and MR-2 for R_1 and R_2 where

$$\log 1/K_m = 0.666(\pm0.27)\text{MR-L} + 0.227(\pm0.12)\text{MR-S} + 0.300(\pm0.27)\text{I-1} - 0.867(\pm0.99) \quad (1)$$

n	*r*	*s*
24	0.826	0.249

$$\log 1/K_i = 0.744(\pm0.18)\text{MR-L} + 0.225(\pm0.10)\text{MR-S} + 0.344(\pm0.37)\text{I-1} - 0.824 \quad (2)$$

n	*r*	*s*
21	0.955	0.234

MR-1 refers to the acylamino or amino substituent and MR-2 refers to the α-R group. The close correspondence between the coefficients in eq 1 and 2 strongly supports the idea that the larger substituent preferentially attaches the ligand by interactions in ρ_2 space. The correlation with eq 1 is not as good as eq 2 with respect to r; it is also somewhat poorer with respect to s. Part of this apparent poorer correlation is due to the smaller range in the values of log $1/K$ for the L isomers compared to the D isomers. Another possible contribution to the lower correlation of eq 1 may be that since K_m is not a pure constant, it may contain information on the hydrolytic step as well as simple binding.

In eq 1 and 2, I-1 is an indicator variable assigned a value of 1 for hydrazides and a value of 0 for all other cases. Its positive coefficient shows that, on the average, hydrazides bind twice as strongly as amides. Substituted amides such as NHOH and $NHCH_3$ do not need special correction.

The coefficients in eq 1 and 2 are so similar that they at once suggest that, to a first approximation, the intermolecular forces holding substrate and inhibitor to the enzyme are the same.

Equation 3 results from merging the two data sets. I-1 in eq 3

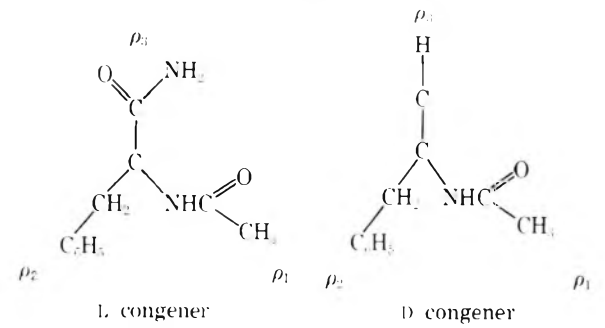
$$\log 1/K = 0.72(\pm0.13)\text{MR-L} + 0.230(\pm0.07)\text{MR-S} + 0.323(\pm0.20)\text{I-1} + 0.311(\pm0.15)\text{I-2} - 1.062(\pm0.45) \quad (3)$$

n	r	s
45	0.928	0.235

is the indicator variable for hydrazides, I-2 takes the value of 1 for D congeners and glycine amides which are inhibitors, while L congeners are assigned a value of 0. The positive coefficient with I-2 reflects the tighter binding of the inhibitors. All of the terms in eq 3 are justified at $\alpha = 0.005$ by the stepwise application of the F test. The overall picture given by eq 3 seems reasonable. Neurath and Hartley[23] first summarized evidence to show that K_m appears to represent a simple binding constant for chymotrypsin. Zerner and Bender[24] have emphasized that K_i and K_m are comparable parameters for the interaction of amides with chymotrypsin. They felt that such an assumption is not justified with esters since they are hydrolyzed so much more rapidly. The good fit of the data to eq 3 supports the idea that K_m and K_i are quite similar equilibrium constants for amides.

Since the D congeners are not hydrolyzed and since the large apolar groups show the same binding characteristics, we can rationalize the results as follows.

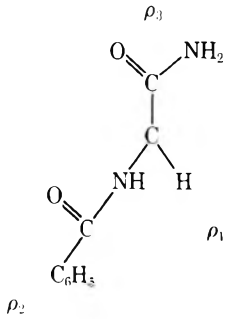
Chart II



If hydrolysis occurs in ρ_3 space, the L congener binds properly as a substrate; however, the D congener binds so that the $CONH_2$ is now in ρ_H space and not well positioned for hydrolysis. Hence these ligands act as inhibitors.

The two glycine derivatives (**1**, **2** in Table I) present a special problem since they act as inhibitors despite the fact that they can, in principle, assume proper binding.

Chart III



It would appear that a group at least as large as NH_2 or CH_3 must bind in ρ_1 space to induce hydrolysis. Such binding may cause a conformational change which places the amide function in proper position for hydrolysis. The glycine derivatives lacking such activating groups act only as inhibitors.

Compound **24** of Table I was not used in formulating eq 3. Its very poor fit to eq 3 is probably the result of the very bulky *tert*-butyl group not fitting into ρ_2 space.

In order to test eq 3 we have synthesized three new acylamides (**47**–**49**) and measured their K_m values under the conditions employed by Niemann. Two of these derivatives (**47** and **49**) are well fit by eq 3 and the third (**48** with 4-$NHSO_2Me$) is poorly fit. The poor fit of **48** is not unexpected since the so-called hydrophobic cleft in chymotrypsin has been shown not to properly accommodate 4-iodophenylalanine; in fact, the size of this pocket has been well established from x-ray crystallographic studies. Steitz et al.[25] state that it is a flattened shape with dimensions of 10–12 Å by 5.5–6.5 Å by 3.5–4.0 Å. They note that 4-iodophenylacetate binds with its I deep in this pocket. Our results with **48** support the limited dimensions of the cleft in chymotrypsin.

The fact that **49** is well fit shows that a substituent as large as 4-NO_2 can be accommodated by this pocket.

The most interesting case is that of **47**. Since the point is well fit by eq 3, "wrong-way binding" is implied with the nicotinyl moiety falling into ρ_2 space. If MR-1 and MR-2 parameters are employed in eq 3, compound **48** is very poorly fit ($\Delta\log 1/C = 0.52$). One of the glycine derivatives is also very poorly fit by MR-1 and MR-2. Because there are only two data points (**47** and **48**) for which MR-1 $\gg$ MR-2, more compounds should be tested to confirm this finding. Since the larger α substituent appears to preempt ρ_2 space, it would appear that **47** undergoes hydrolysis even though "wrong-way binding" takes place. Since compound **47** shows a very slow rate of hydrolysis it appears that both "right" and "wrong-way binding" can occur and that there is enough flexibility in the enzyme to allow some hydrolysis. Somehow the amide group must be reasonably well fit in ρ_3 space.

It was concluded in our earlier survey of the interactions of ligands with chymotrypsin that ρ_1 space was not typically hydrophobic since binding in this area correlated well with MR and not with π for data not highly collinear in MR and π. At that time, ρ_2 space was characterized as hydrophobic although, for the data studied, π and MR were highly collinear. The present study confirms our earlier conclusion that ρ_1 is not hydrophobic. More interesting, however, is the finding that binding in ρ_2 space is not well correlated by π but is well correlated by MR.

If, in eq 3, we substitute the corresponding π constants for MR, a quite poor correlation is obtained ($r = 0.669$). It is evident from the squared correlation matrix of Table II that MR-L and π of MR-L are reasonably noncollinear ($r^2 = 0.29$). Thus it appears that desolvation is not the primary determinate of binding in ρ_2 space.

Our conclusion that the binding pocket around the active

Table II. Squared Correlation Matrix for Variables Pertaining to Equation 3

	MR-L	MR-S	π-MR-L	π-MR-S	I-1	I-2
MR-L	1.00	0.06	0.29	0.04	0.00	0.03
MR-S		1.00	0.07	0.50	0.00	0.01
π-MR-L			1.00	0.48	0.00	0.02
π-MR-S				1.00	0.00	0.02
I-1					1.00	0.02
I-2						1.00

site in chymotrypsin is not typically hydrophobic is supported by the analysis of Dickerson and Geis.[26] The "hydrophobic" pocket in chymotrypsin is circumscribed by the following two peptide sequences:

Gly Ala Ser Gly Val Ser Ser Cys Met
184 185 186 187 188 189 190 191 192

Ilu Val Ser Trp Gly Ser Ser Thr Cys Ser Thr Ser Thr Pro Gly Val
212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227

The vast majority of these residues are hydrophilic, not hydrophobic; thus, correlation with MR can be used to characterize nonhydrophobic enzyme space as π can be used for hydrophobic space.[27]

Equation 3 does establish the fact that it is possible to construct QSAR for stereoisomers by taking into account the type of space into which substituents fall. We believe that the approach used in formulating eq 3 should be generally applicable to problems involving stereoisomers.

Registry No.—α-*N*-Nicotinyl-L-4-nitrophenylalanine ethyl ester, 58816-65-2; L-4-nitrophenylalanine, 949-99-5; L-4-nitrophenylalanine ethyl ester HCl, 58816-66-3; L-4-nitrophenylalanine ethyl ester, 34276-53-4; nicotinyl azide, 4013-72-3; α-*N*-nicotinyl-L-4-nitrophenylalaninamide, 58816-67-4; α-*N*-nicotinyl-L-alanine ethyl ester, 58816-68-5; ethyl alaninate, 3082-75-5; α-*N*-nicotinyl alaninamide, 53503-62-1; α-*N*-benzoyl-4-nitrophenylalanine ethyl ester, 58816-69-6; α-*N*-benzoyl-4-aminophenylalanine ethyl ester, 58816-70-9; α-*N*-benzoyl-L-4-methanesulfonylamidophenylalaninamide, 58816-71-0; methanesulfonyl chloride, 124-63-0.

References and Notes

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Ring Opening of Aziridine Phosphonates. Correlation of Structure, Nuclear Magnetic Resonance Spectra, and Reactivity[1a]

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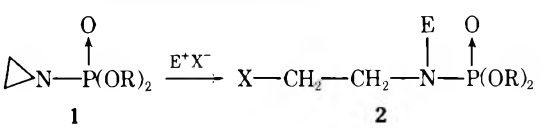
The ring opening of several dimethyl *N*-aziridinylphosphonates **3** with Cl_2 and HCl was studied. The reaction was found to be stereospecific and in most cases regiospecific. Conformational preferences in these compounds could be correlated with 1,3 P-H (PNCCH) coupling constants and with reactivity in ring opening.

The importance of aziridines as well as their N-phosphorylated derivatives in biological systems is well documented.[2] It is generally assumed that the cytotoxic behavior of such compounds is due to their ability to undergo ring opening by nucleophilic sites of enzymes.

The ring opening of unsubstituted aziridine phosphonates of type **1** to **2** with electrophilic reagents (E^+X^-) including

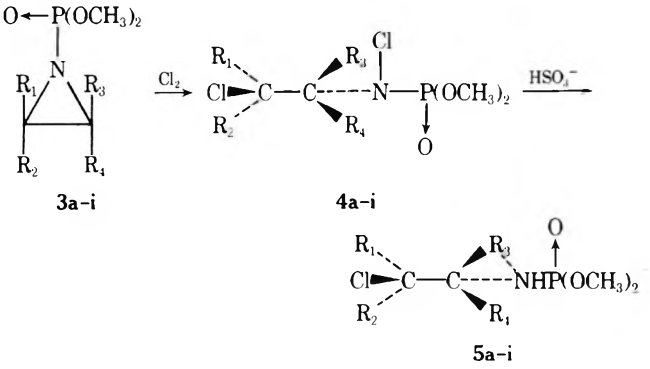


1 **2**

carboxylic acids, chlorine, and alkyl halides has been investigated by Russian chemists.[3a] Related *N,N*-dialkylaminoaziridinyl phosphoric amides react similarly.[3b]

In this study we are reporting on the chlorination of several ring substituted aziridine phosphonates **3** in an effort to determine the factors which influence the stereochemistry, regiochemistry, and the rate of ring opening.

Results and Stereochemistry. The reaction of dimethyl *N*-aziridinylphosphonates **3a–i** with chlorine in CCl_4 solution at 0–5 °C leads to dimethyl *N*-chloro-*N*-(β-chloroethyl)phosphoramidates **4a–i** in high yield. These *N*-chloro compounds cannot be purified effectively, but are reduced

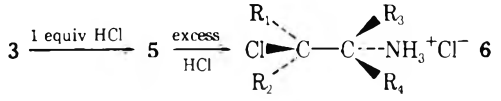


3a-i 4a-i 5a-i

a, $R_1 = C_6H_5$; $R_2 = R_3 = R_4 = H$
b, $R_1 = C_6H_5$; $R_4 = CH_3$; $R_2 = R_3 = H$
c, $R_1 = C_6H_5$; $R_3 = CH_3$; $R_2 = R_4 = H$
d, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
e, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$
f, $R_1 = R_2 = R_3 = H$; $R_4 = C(CH_3)_3$
g, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
h, $R_3 = R_4 = CH_3$; $R_1 = R_2 = H$
i, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$

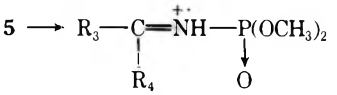
with $NaHSO_3$ in methanol[4] and the dimethyl *N*-(β-chloroethyl)phosphoramidates **5a–i** characterized by elemental analysis, spectra, and chemical conversions.

Ring opening of the aziridine derivatives **3** with 1 equiv of HCl in ether produces the identical phosphoramidates **5**. If an excess of HCl is employed cleavage of **5** takes place and the corresponding β-chloroethylamine hydrochlorides **6** are isolated.[4]

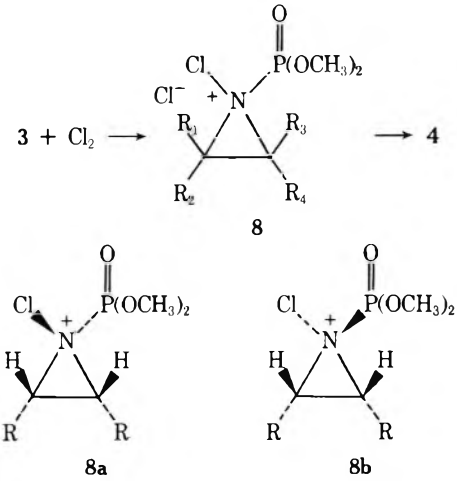


The stereochemical identity of **5** and **6** provides proof that the ring opening of **3** occurred in a stereospecific manner. Thus, **3b** (trans) produces only the erythro diastereomer **5b,** whereas the cis isomer **3c** leads exclusively to the threo product **5c.** Proof of trans ring opening is provided by the hydrolysis of **5d** and **5e** to the known erythro and threo β-chloroethylamine hydrochlorides **6d** and **6e,** respectively.

Regiochemistry. The spectral properties of the products **4** and **5** (Table I) indicate that ring opening of the aziridine phosphonates **3** occurs in a regioselective manner. In most cases attack by the nucleophile takes place at the most highly substituted carbon atom. Exceptions are the aziridines **3g** and **3h,** which give mixtures of products in the reaction with chlorine (**3h** also gives a mixture with HCl), and **3f,** in which ring opening occurred in the opposite regiochemical sense. The mass spectra of **5** showed base peaks resulting from cleavage α to N, confirming the regiochemical assignment.[5]



Mechanism. The following mechanism is most plausible. Attack of electrophilic chlorine on the nitrogen electron pair leads to intermediate **8** which is opened from the back side by chloride ion (stereospecific trans ring opening). For most of the aziridines studied there are two possible configurational intermediates, **8a** and **8b.** Of these, **8b** should be highly favored since chlorine is expected to have a much smaller steric requirement than the phosphonate group. For the same reason the phosphonate is expected to occupy the least hindered configuration in **3.** Since it is reasonable to assume that inversion about the nitrogen is rapid in phosphorylated aziridines **3,**[6] the relative proportion of **8a** and **8b** will depend on the free energies of the transition states leading to their formation. The results indicate that the chlorine molecule prefers



8 8a 8b

to approach the aziridine ring from the most hindered side forming the more stable isomer **8b.** Hence, the aziridine is chlorinated from its most stable conformation. It follows that if the aziridine has bulky cis groups as in **3c** or **3f** it chlorinates more slowly since the chlorine must enter cis to these groups. This was borne out experimentally. The relative rate of chlorination of **3a:3b:3c** was 460:17:1. **3f** was also chlorinated very slowly.

Conformations and Long-Range P–H Coupling. Information on the conformational preferences in simple phosphorylated aziridines **3** may be obtained frrom their NMR spectra[7] (Table II). Their basic NMR features have been discussed elsewhere.[6] In addition, we have noticed for the $C-CH_3$ groups in **3** long-range $^{31}P-^{1}H$ coupling which depends on certain stereochemical features. For instance, J_{PH} values of 0.6 Hz were observed for aziridine phosphonates in which the phosphorus function is expected to be cis or trans to the methyl groups with equal facility (as in **3d, 3h,** and **3j**). These were verified by ^{31}P decoupling.[8] Aziridines which have two cis groups (as in **3c, 3e,** and **3l**) show larger couplings, generally 1.2–1.6 Hz. This may be rationalized in terms of a conformational preference leading to the well-known "W" effect.[7] The phosphorus and one hydrogen on the methyl group can be in a "W" conformation only when they are on opposite sides of the ring as shown in **9.** This prerequisite is met when the methyl is found on the more substituted side of the aziridine ring causing the phosphorus to be trans to it. Attempts to find a correlation for the ring protons failed. A related compound, *N*-azetidinyltriphenylphosphonium iodide (**10**), prepared

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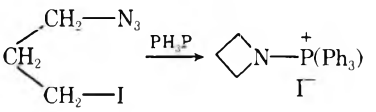

10

from 1-azido-3-iodopropane, also showed an abnormally large four-bond coupling constant (4.5 Hz). This could be a result of a similar conformational bias enhanced by the availability of two σ bond pathways to transmit nuclear spin.

Experimental Section

The aziridine phosphonates, with the exception of **3f** described below, were synthesized from alkenes by IN_3 addition and reaction with trimethyl phosphite, a general method described elsewhere.[9] All compounds (with the exceptions of compound **4** noted in the text and of **5c,** which could not be obtained crystalline) had satisfactory (±0.3%

Table I. Physical Properties of *N*-(β-Chloroethyl) Phosphoramidates 4 and 5

Compd	Yield, %	Mp, °C	NMR spectra, τ (CCl_4)
4a	100		2.63 (m, 5), 4.84 (broad t, J = 7), 4.0–4.4 (m, 2), 6.30 (d, 3, J = 11), 6.63 (d, 3, J = 11)
4b	100		2.6 (m, 5), 5.17 (d, 1, J = 10), 5.3–5.9 (m, 1), 6.39 (d, 3, J = 11), 7.12 (d, 3, J = 11), 8.41 (d, 3, J = 6)
4c	100		2.64 (broad s, 5), 5.09 (d, 1, J = 10), 5.2–5.9 (m, 1), 6.18 (d, 3, J = 11), 6.24 (d, 3, J = 11), 9.00 (d, 3, J = 6)
4d	92		6.22 (d, 6, J = 11), 5.9–6.4 (m, 2), 8.42 (d, 3, J = 6), 8.57 (d, 3, J = 6)
4e	94		6.20 (d, 3, J = 11), 6.22 (d, 3, J = 11), 5.6–6.4 (m? 2), 8.43 (d, 3, J = 6), 8.58 (d, 3, J = 6)
4f	100		6.28 (d, 3, J = 11), 6.29 (d, 3, J = 11), 5.9–6.4 (m, 3), 8.93 (s, 9)
4g	100		5.90 (q, 1, J = 7), 6.23 (d, 3, J = 11), 6.24 (d, 3, J = 11), 8.33 (s, 6), 8.58 (d, 3, J = 7)
4h, 4i	100		6.0–6.5, 8.32, 8.52, 8.80
5a	52[a] 69[b]	67–69	2.67 (m, 5), 5.12 (t, 1, J = 7), 5.3–5.9 (broad, 1, NH), 6.35 (d, 3, J = 11), 6.50 (d, 3, J = 11), 6.6–6.9 (m, 1)
5b	54	95–97	2.7 (m, 5), 5.00 (d, 1, J = 5), 3.8–4.2 (broad, 1, NH), 4.1–4.7 (m, 1, buried), 4.37 (d, 3, J = 11), 4.57 (d, 3, J = 11), 8.82 (d, 3, J = 6)
5d	32	67–68	5.6–6.1 (broad, 1, NH), 6.4–7.0 (m, 1), 6.34 (d, 6, J = 11), 8.48 (d, 3, J = 6), 8.79 (d, 3, J = 6)
5e	55[a] 99[b]	84–86	5.0–5.8 (broad, 1, NH), 5.8–6.2 (m, 1), 6.4–7.0 (m, 1), 6.31 (d, 6, J = 11), 8.44 (d, 3, J = 7), 8.71 (d, 3, J = 7)
5f	40[a] 99[b]	128–129.5	6.23 (d, 6, J = 11), 6.0–7.3 (m, 3), 6.9 (broad, 1, NH), 9.00 (s, 9)
5g	Low[a] 99[b]	58–61	6.27 (d, 3, J = 11), 6.28 (d, 3, J = 11), 6.5–7.3 (m, 2, 1 H exchanges with D_2O), 8.35 (s, 3), 8.45 (s, 3), 8.70 (d, 3, J = 7)
5h	99	71–73	5.0–5.6 (broad, 1, NH), 6.35 (d, 6, J = 11), 4.53 (s, 2), 8.70 (s, 6)
5i			4.8–5.4 (broad, 1, NH), 6.35 (d, 6, J = 11), 6.94 (dd, 2, J = 7, 9, collapses into a doublet, J = 9, upon exchange of NH with D_2O), 8.43 (s, 6)

[a] By Cl_2 addition to **3** followed by $NaHSO_3$ reduction. [b] By HCl addition to **3**.

in C and H) analyses. The following aziridines have not previously been reported and are recorded here. The NMR spectra below were taken on a Varian A-60A spectrometer in CCl_4 solution.

Dimethyl *N*-(*cis*-2-methyl-2-phenylaziridinyl)phosphonate (3c) was obtained from *threo*-1-azido-1-phenyl-2-iodopropane in 83% yield after two distillations: bp 124–128 °C (0.1 mm); NMR τ 2.59 (s, 5), 6.22 (d, 3, J = 11 Hz), 6.26 (d, 3, J = 11 Hz), 6.4 (buried, 1), 6.8–7.7 (m, 1), and 9.03 (dd, 3, J = 5.5, 1.5 Hz).

Dimethyl *N*-(2-*tert*-butylaziridinyl)phosphonate (3f) was obtained by adding trimethyl phosphite (50 g) in 50 ml of cyclohexane to 75.4 g of 1-azido-2-iodo-3,3-dimethylbutane in 150 ml of cyclohexane at such a rate that gentle distillation of the cyclohexane occurred. After 1 day at room temperature the reaction was complete. Removal of the solvent in vacuo followed by distillation through a short path distillation apparatus gave two major fractions, one boiling at about 70 °C and one at about 100 °C (0.1 mm). Redistillation of the lower boiling fraction through a 6-in. column packed with glass helices gave 43 g (68%) of **3f**, bp 69–72 °C (0.1 mm). Redistillation of the higher boiling fractions through a short path distillation apparatus gave 15.5 g (14%) of dimethyl *N*-methyl-*N*-(2-iodo-3,3-dimethyl-1-butyl)phosphoramidate, bp 108–112 °C (0.09 mm). The NMR of **3f** showed τ 6.29 (d, 6, J = 11 Hz), 7.5–8.4 (m, 3), and 9.08 (s, 9).

Dimethyl *N*-(2,2-dimethylaziridinyl)phosphonate (3h) was obtained from 2-azido-1-iodo-2-methylpropane in 95% yield: bp 56–62 °C (0.1 mm); NMR τ 6.27 (d, 6, J = 11 Hz), 7.91 (d, 2, J = 14 Hz), and 8.62 (d, 6, J = 0.6 Hz).

Dimethyl *N*-(2,2,3,3-tetramethylaziridinyl)phosphonate (3j) was obtained from 2-azido-3-iodo-2,3-dimethylbutane on a small scale in 50% yield: approximate bp 70 °C (0.1 mm); NMR τ 4.37 (d, 6, J = 11 Hz) and 8.63 (d, 12, J = 0.7 Hz).

Dimethyl *N*-(*trans*-2-methyl-3-*tert*-butylaziridinyl)phosphonate (3k) was obtained from *erythro*-4-azido-3-iodo-2,2-dimethylpentane in 84% yield: bp 68–70 °C (0.07 mm); NMR τ 6.28 (d, 3, J = 11 Hz), 6.30 (d, 3, J = 11 Hz), 7.3–8.2 (m, 2), 8.58 (dd, 3, J = 5, 0.54 Hz), and 9.10 (s, 9).

Dimethyl *N*-(*cis*-2-methyl-3-*tert*-butylaziridinyl)phosphonate (3l) was obtained as follows. IN_3 addition to *cis*-4,4-dimethyl-2-pentene according to a published[10] procedure gave *threo*-4-azido-3-iodo-2,2-dimethylpentane in 92% yield. An analytical sample was provided by bulb-to-bulb distillation at 85 °C (0.07 mm): NMR τ 6.08 (d, 1, J = 1.5 Hz), 6.78 (dq, 1, J = 1.5, 6 Hz), 8.60 (d, 3, J = 6 Hz), and 8.85 (s, 9). This material was converted to **3k** in 81% yield: bp 72–76 °C (0.1 mm); NMR τ 6.29 (d, 6, J = 11 Hz), 7.2–8.3 (m, 2), 8.76 (dd, 3, J = 6, 1.2 Hz), and 9.0 (s, 9).

General Procedure for Chlorine Ring Opening of Aziridinylphosphonates 3. The aziridines **3** were mixed with a 5–12% solution of chlorine in CCl_4 calculated to contain a 10–20% excess of chlorine. The reaction was allowed to proceed at 5 °C until complete (NMR monitoring). Removal of the remaining chlorine and solvent in vacuo gave the phosphoramidates **4** in the yield indicated in Table I. Generally the product thus obtained was fairly pure (NMR); however, those aziridines requiring long contact times (**3c, 3f,** and **3g**) contained up to about 25% impurities.

Table II. Long-Range P–H Coupling in *N*-Aziridinyl Phosphonates 3

Compd	Chemical shift[a]	J_{CH_3-P} Hz
3b	154.7	0
3c	94.0	1.3
3d	131.0	0
3e	118.2	1.4
3g	120.3	1.2
	120.8	
	140.3	
3h	136.1	0.70
3j, $R_1 = R_2 = R_3 = R_4 = CH_3$	134.0	0.70
3k, $R_1 = CH_3$; $R_4 = C(CH_3)_3$; $R_2 = R_3 = H$	138.9	0.65
3l, $R_1 = CH_3$; $R_3 = C(CH_3)_3$; $R_2 = R_4 = H$	135.0	1.2
3m, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$	128.0	1.15

[a] At 100 MHz.

General Procedure for $NaHSO_3$ Reduction of *N*-Chlorophosphoramidates (4). A mixture of 5 g each of **4** and $NaHSO_3$ was stirred together in 50 ml of methanol (water bath cooling). The methanol was removed in vacuo and the residue extracted with 300 ml of ether. After drying ($MgSO_4$) the ether was removed in vacuo and the residue recrystallized (−30 °C) giving pure product. Repeated recrystallization gave the analytical samples of **5** with the melting points indicated in Table I.

General Procedure for HCl Ring Opening of Aziridinylphosphonates (3). To a 10% solution of **3** in ether in a dry ice–acetone bath was added a 5% solution of anhydrous HCl in ether calculated to contain 5% excess HCl. After the solution was warmed to room temperature the ether was removed in vacuo to give the crude product. In this way **5e** (99% crude yield, crude mp 81–84 °C), **5g** (99% crude yield, crude mp 44–50 °C), **5a** (69% yield of recrystallized product, mp 58–63 °C), and **5f** (99% crude yield, crude mp 128–129 °C) were synthesized. **3h** gave a 46:54 mixture of **5h** and **5i** by NMR analysis.

Determination of the Relative Chlorination Rates of 3a, 3b, and 3c. In a NMR tube at 0 °C were mixed 0.5 ml each of a 0.10 M

solution of Cl_2 and a 0.10 M solution of **3a, 3b,** or **3c** in CCl_4. The tube was placed in the probe of a Varian A-60A spectrometer held at 2 °C. The relative intensities of the aromatic protons vs. the benzylic protons in the products were compared by integration. Under these conditions the time required for 40% reaction was 3, 55, and 1440 min for **3a, 3b,** and **3c,** respectively. This gives a relative rate of chlorination of 460:17:1.

***N*-Azetidinyltriphenylphosphonium iodide (10)** was prepared in several steps from acrolein as follows. A solution of β-azidopropionaldehyde (prepared from 17.2 g of acrolein)[11] in ether was added with ice bath cooling to a stirred solution of 5 g of $NaBH_4$ in 30 ml of H_2O at such a rate that the temperature remained below 20 °C. After 10 min the aqueous phase was saturated with NaCl and the ether separated, dried ($MgSO_4$), and removed in vacuo giving 17.5 g (65% based on acrolein) of 3-azido-1-propanol. This product was added dropwise to 12 g of $SOCl_2$ in 15 ml of pentane. Removal of the solvent and distillation gave 9.25 g (58%) of 1-azido-3-chloropropane: bp 51 °C (15 mm); NMR τ 6.2–6.7 (overlapping triplets, 4, J = 7 Hz) and 8.0 (quintet, 4, J = 7 Hz). Treatment of 23.8 g of this material with 60 g of NaI in 500 ml of 2-butanone at reflux for 15 h gave, after water–pentane workup, 33 g (78%) of 1-azido-3-iodopropane: bp 83–84 °C (15 mm); NMR τ 6.7 (overlapping triplets, J = 7 Hz) and 8.0 (m, 2). When 5.4 g of this material was refluxed with 6.55 g of triphenylphosphine in 150 ml of hexane for 3 h, after cooling and filtration 5.4 g (49%) of **10** was obtained, mp 157–161 °C. The analytical sample was obtained by recrystallization from absolute ethanol/2-propanol and had mp 162–165 °C after drying at 65 °C (20 mm); NMR τ 2.0–2.5 (m, 15), 5.7 (m, 4, J_{P-H} = 4.0. J_{H-H} = 7.5 Hz), and 6.8–7.6 (m, 2, J_{PNCCH} = 4.5, J_{H-H} = 7.5 Hz).

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Registry No.—**3a,** 27356-57-6; **3b,** 27278-93-9; **3c,** 58503-29-0; **3d,** 30271-50-2; **3e,** 27278-92-8; **3f,** 58503-30-3; **3g,** 27356-56-5; **3h,** 58503-31-4; **3j,** 58503-32-5; **3k,** 58503-33-6; **3l,** 58503-34-7; **3m,** 58503-35-8; **4a,** 58503-36-9; **4b,** 58503-37-0; **4c,** 58503-38-1; **4d,** 58503-39-2; **4e,** 58503-40-5; **4f,** 58503-41-6; **4g,** 58503-42-7; **4h,** 58503-43-8; **4i,** 58503-44-9; **5a,** 58503-45-0; **5b,** 58503-46-1; **5d,** 58503-47-2; **5e,** 58503-48-3; **5f,** 58503-49-4; **5g,** 58503-50-7; **5h,** 58503-51-8; **5i,** 58503-52-9; **10,** 58503-53-0; **10** pentavalent form, 58503-54-1; *threo*-1-azido-1-phenyl-2-iodopropone, 58503-55-2; trimethyl phosphite, 121-45-9; 1-azido-2-iodo-3,3-dimethylbutane, 58503-56-3; 2-azido-1-iodo-2-methylpropane, 58503-57-4; 2-azido-3-iodo-2,3-dimethylbutane, 58503-58-5; *erythro*-4-azido-3-iodo-2,2-dimethylpentane, 16717-75-2; *cis*-4,4-dimethyl-2-pentene, 26232-98-4; *threo*-4-azido-3-iodo-2,2-dimethylpentane, 58503-59-6; β-azidopropionaldehyde, 58503-60-9; 1-azido-3-chloropropane, 58503-61-0; 1-azido-3-iodopropane, 58503-62-1.

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Synthesis of 3-Hydroxy-, 3-Chloro-, and 3-Methoxy-3-cephems from Penicillins via 4-Dithio-2-azetidinone Intermediates[1]

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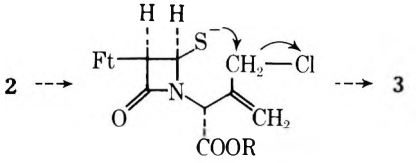
Cyclization of monocyclic dithioazetidinone **2** to 3-methylene cepham **3** with potassium iodide was accomplished. A key intermediate **3** after ozonolysis afforded 3-hydroxy-3-cephem **5,** which in turn was treated with phosphorus trichloride in dimethylformamide to give 3-chloro-3-cephem **6.** From the reaction of the enol **5** with diazomethane the corresponding 3-methoxy-3-cephem **7** was obtained. Preparation of compounds **3, 5, 6,** and **7** from **2** and **4** is significant since it represents the first synthesis of directly 3-substituted cephalosporins from penicillins.

Recently a new series of potent cephalosporin antibiotics having halo and methoxy groups attached directly to the 3 position of the 3-cephem ring system have been discovered.[2] These antibiotics were synthesized from various cephalosporanic acids, in which the 3-acetoxymethyl group was converted to 3-methylene cephams.[3] The latter compounds were ozonized to the 3-hydroxy-3-cephems and converted to 3-methoxy- and 3-chloro-3-cephems by standard methods. While this synthetic scheme led directly to 3-substituted cephalosporins, there still existed a need to prepare these antibiotics more economically from penicillins. For this reason we sought a shorter synthesis from readily available penicillins.

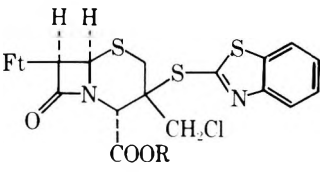
It seemed to us that a key intermediate, 3-methylene cepham **3,** might be synthesized from a monocyclic azetidinone **2.** The desired 4-benzothiazol-2′-yldithio-2-azetidinone (**2**) was prepared from 2β-chloromethylpenam 1-(*R*)-sulfoxide (**1**) by refluxing with 2-mercaptobenzothiazole in benzene for 30–50 min according to the method described by Kamiya and co-workers.[4] The first transformations attempted on compound **2** centered at the allylic halide position. However, **2** did not react with silver nitrate in acetone at room temperature even after prolonged refluxing (24 h) with an excess of silver salt. Nucleophilic displacement of the allylic chloride in **2** with sodium thiocyanate in refluxing acetone for 20 h also did not succeed. This was surprising since we had expected the allyl halide to be very reactive. Our attention was then turned to reduction of the disulfide linkage in **2.** We believed that reduction should give an intermediate having a mercapto group, and hopefully after nucleophilic displacement as depicted by A, the desired 3-methylene cepham **3** would be formed. However, reduction with (a) stannous chloride in THF, (b) sodium cyanoborohydride in methanol/dimethylformamide



A

at pH 4.0, and (c) hydrogen over palladium on carbon in methanol/tetrahydrofuran at room temperature for 1 h resulted only in minor degradation of the starting material. After all these unsuccessful reductions we decided to try oxidation of the disulfide bond. Oxidation with *m*-chloroperbenzoic acid in methylene chloride, even when the reaction was carried out at room temperature for prolonged periods of time, resulted in a complete recovery of the starting material.

In view of the rather peculiar reactivity encountered with this compound, we reexamined the proposed structure for **2**. One possible structure is the following:



B

Therefore, ^{13}C magnetic resonance studies were carried out in order to verify the structure. ^{13}C NMR spectroscopy provided a simple way of choosing between **2** and B. The spectrum of **2a** showed five resonances typical of sp^3 carbons: a methylene resonance (45.6 ppm), an *O*-methyl resonance (52.7 ppm), and three methine resonances (55.1, 59.1, and 76.3 ppm). Clearly such a result is not consistent with B.

The successful ring closure of compound **2** to desired key intermediate **3** was finally achieved with potassium iodide. Refluxing of **2** in acetone in the presence of potassium iodide for 40 h resulted in ring closure to **3** in 30–52% yield. Upon ozonolysis compound **3** was converted to the 3-hydroxy-3-cephem **5**, which was also prepared by cyclization of **4** with potassium iodide. Treatment of **5** with phosphorus trichloride in dimethylformamide for 1 h at room temperature gave the desired 3-chlorocephem **6** in good yield. 3-Methoxycephem **7** was obtained by treating 3-enol cephem **5** with diazomethane in methylene chloride.

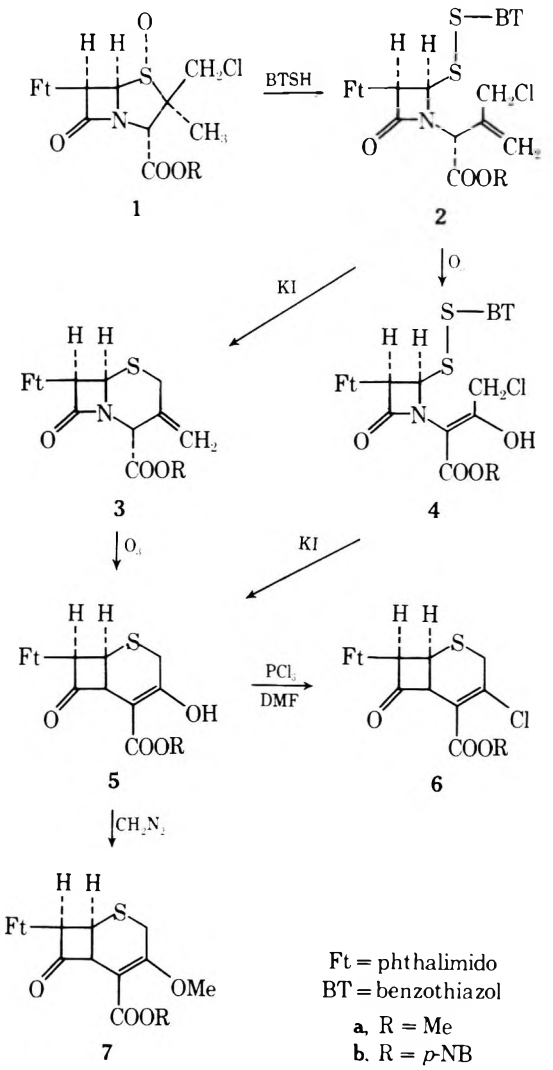
The cyclization of **2** to **3** is significant since it represents the first conversion of penicillins into a key intermediate for the synthesis of 3-substituted cephalosporins.

Experimental Section[5]

4-(2′-Benzothiazolyldithio)-3-phthalimido-1-(1′-methoxycarbonyl-2′-chloromethylprop-2′-enyl)-azetidin-2-one (2a). To 200 ml of methylene chloride was added 11.2 g (28.4 mmol) of methyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate.[6] Methylene chloride (100 ml) containing 5.68 g (28.4 mmol) of *m*-chloroperbenzoic acid was added, and the resulting mixture was stirred for 1 h at ice bath temperature. The reaction mixture was then washed successively with 50 ml of 5% aqueous sodium sulfite, twice with 50 ml of 5% sodium bicarbonate, 100 ml of water, and 100 ml of brine. The mixture was then dried over magnesium sulfate and evaporated to give 11.54 g (28.1mmmol) of methyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate 1α-oxide (**1a**): NMR ($CDCl_3$) δ 1.41 (s, 3, CH_3), 3.81 (s, 3, OCH_3), 4.14 (s, 2, CH_2Cl), 4.92 (s, 1, H3), 4.96 (d, 1, J = 4.5 Hz), 5.93 (d, 1, J = 4.5 Hz), and 7.81 (m, 4 ArH).

To 150 ml of benzene were added 11.54 g (28.1 mmol) of methyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate 1α-oxide and 4.7 g (28.1 mmol) of 2-mercaptobenzothiazole. The mixture was heated to reflux for 30 min, and then evaporated to give the title compound as a light yellow foam: NMR ($CDCl_3$) δ 3.81 (s, 3, OCH_3), 4.3 and 4.5 (AB q, 2, CH_2Cl, J = 12 Hz), 5.43 (s, 1), 5.53 (s, 1), 5.65 (s, 1), 5.98 (s, 2, azetidinone H), and 7.81 (m, 4 ArH).

Chart I



Anal. Calcd for $C_{24}H_{18}ClN_3O_5S_3$: C, 51.47; H, 3.24; N, 7.50; S, 17.18. Found: C, 51.40; H, 3.21; N, 7.55; S, 17.09.

4-(2′-Benzothiazolyldithio)-3-phthalimido-1-[1′-(*p*-nitrobenzyloxycarbonyl)-2′-chloromethylprop-2′-enyl]azetidin-2-one (2b). To 200 ml of methylene chloride was added 6.45 g (12 mmol) of *p*-nitrobenzyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate.[6] An insoluble portion of approximately 100–200 mg was filtered off, and 2.4 g (12 mmol) of *m*-chloroperbenzoic acid was added. The mixture was stirred for about 30 min and then washed successively with aqueous sodium bicarbonate and aqueous sodium chloride. The mixture was dried over magnesium sulfate and evaporated. The residue was dissolved in a mixture of 10 ml of methylene chloride and 3 ml of cyclohexane. The insolubles were filtered off, and the solvent was evaporated to give 5.6 g of *p*-nitrobenzyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate 1α-oxide (**1b**): NMR ($CDCl_3$) δ 1.42 (s, 3, CH_3), 4.38 (s, 2, CH_2Cl), 5.08 (s, 1, C_3 H), 5.1 (d, 1, J = 5 Hz), 5.4 (s, 2, CH_2 of *p*-NB), 6.05 (d, 1, J = 5 Hz), and 7.5–8.4 (m, 8 ArH).

A mixture of 5.32 g (10 mmol) of *p*-nitrobenzyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate 1α-oxide and 1.7 g (10 mmol) of 2-mercaptobenzothiazole in 100 ml of benzene was refluxed for 50 min, and the resulting clear, warm solution was transferred to another flask and allowed to crystallize overnight. Crystals (4.5 g, 66%) of the title compound were collected by filtration and shown by TLC to be one spot material: mp 204–205 °C dec; NMR ($CDCl_3$) δ 4.23 and 4.5 (AB q, 2, CH_2Cl, J = 12 Hz), 5.3 (s, 1), 5.33 (s, 2, CH_2 of *p*-NB), 5.5 (s, 1), 5.6 (s, 1), 5.75 (d, 1, J = 4.5 Hz), 5.85 (d, 1, J = 4.5 Hz), and 7.4–8.3 (m, 8 ArH); ir (KBr) 1790, 1778, 1750, and 1720 cm^{-1}.

Anal. Calcd for $C_{30}H_{21}ClN_4O_7S_3$: C, 52.90; H, 3.11; Cl, 5.20; S, 14.12; O, 16.44. Found: C, 53.11; H, 3.08; Cl, 5.29; S, 14.42; O, 16.11.

Methyl 7-Phthalimido-3-methylenecepham-4-carboxylate (3a). To a solution of 1.12 g (2 mmol) of 4-(2′-benzothiazolyldithio)-3-phthalimido-1-(1′-methoxycarbonyl-2′-chloromethylprop-2′-

enyl)azetidin-2-one in 75 ml of acetone was added 0.50 g (3 mmol) of potassium iodide. The mixture was refluxed for 3 days, after which TLC of the reaction mixture showed a spot indicative of unreacted starting material. An additional 0.5 g of potassium iodide was added and refluxing was continued for an additional 1 day. The mixture was evaporated to dryness, and the residue was taken up in 50 ml of ethyl acetate. The ethyl acetate solution was washed successively with 20 ml of 0.1 N sodium bisulfite solution, 25 ml of water, and 25 ml of brine. The ethyl acetate solution was then dried over sodium sulfate and evaporated to give 1.05 g of the title compound as a tan foam. Recrystallization from ethyl acetate gave colorless crystals: mp 194–196.5 °C dec; $[\alpha]^{25}D$ +179°; NMR ($CDCl_3$) δ 3.38 and 3.63 (AB q, 2, J = 14 Hz), 3.80 (s, 3), 5.32 (m, 3), 5.46 (d, 1, J = 4.5 Hz), 5.67 (d, 1, J = 4.5 Hz), 7.83 (m, 4); mass spectrum m/e 358, 330, 299, 272, 187, 172, ir ($CHCl_3$) 1790, 1775, 1725 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}N_2O_5S$ (358.37): C, 56.98; H, 3.94; N, 7.82; O, 22.32; S, 8.95. Found: C, 56.79; H, 4.04; N, 7.74; O, 22.18; S, 8.95.

***p*-Nitrobenzyl 7-Phthalimido-3-methylenecepham-4-carboxylate (3b).** A mixture of 1.3 g of 4-(2′-benzothiazolyldithio)-3-phthalimido-1-[1′-(*p*-nitrobenzyloxycarbonyl)-2′-chloromethylprop-2′-enyl]azetidin-2-one and 400 mg of potassium iodide in 70 ml of acetone was refluxed, and a TLC of the reaction mixture after 19 h of reflux indicated that approximately one-half of the starting material remained. Refluxing was continued for a total of 44 h, after which time a TLC of the reaction mixture indicated the absence of starting material. The solution was evaporated, and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed successively with aqueous sodium thiosulfate, water aqueous sodium bicarbonate, and aqueous sodium chloride. The ethyl acetate solution then was dried over magnesium sulfate and evaporated to give a solid residue. The residue was dissolved in 5 ml of toluene after which crystallization began to occur, and 200 mg of the title compound was collected by filtration and recrystallized from a mixture of 5 ml of benzene and 2 ml of chloroform. Crystals of the title compound were collected and again were recrystallized from a mixture of 4 ml of benzene and 3 ml of chloroform.

The toluene filtrate was evaporated, and the residue (650 mg) was chromatographed over a silica gel column (1.5 × 30 cm) and eluted with a 9:1 mixture of toluene and ethyl acetate to obtain an additional 300 mg of the title compound, total yield 52%. A sample for analysis was recrystallized from methylene chloride and cyclohexane. Colorless rosettes melted at 194–196 °C; $[\alpha]^{25}D$ +139° (in $CHCl_3$); mass spectrum m/e 479, 451, 433, 293, 187; NMR ($CDCl_3$) δ 3.3 and 3.62 (AB q, 2, CH_2S, J = 14 Hz), 5.37 (s, 5 H), 5.43 (d, 1, J = 4.5 Hz), 5.62 (d, 1, J = 4.5 Hz), and 7.4–8.3 Hz (m, 8 ArH).

Anal. Calcd for $C_{23}H_{17}N_3O_7S$: C, 57.62; H, 3.57; N, 8.76; S, 6.69. Found: C, 57.37; H, 3.72; N, 8.87; S, 6.79.

Methyl 7-Phthalimido-3-chloro-3-cephem-4-carboxylate (6a). Methyl 7-phthalimido-3-methylenecepham-4-carboxylate (7.5 g, 21 mmol) was dissolved in 300 ml of methylene chloride and cooled in a dry ice–acetone bath. A stream of oxygen containing ozone was passed through the cold solution until a light blue color was seen. Oxygen was then passed through to discharge the color followed by sulfur dioxide for 2 min. The solution was then allowed to warm to room temperature and dried ($MgSO_4$). The solvent was removed in vacuo giving 7.68 g of a light yellow foam of methyl 7-phthalimido-3-hydroxy-3-cephem-4-carboxylate (**5a**). This material was then dissolved in 60 ml of dry *N,N*-dimethylformamide and 2.8 ml (1.5 equiv) of phosphorus trichloride was added. After 1 h the crude product was poured onto a mixture of 100 ml of ethyl acetate and 100 ml of water. The layers were then separated and the lower layer washed with 1 N hydrochloric acid (2 × 100 ml), water (2 × 100 ml), and brine (1 × 100 ml) and dried ($MgSO_4$). Evaporation in vacuo gave 4.3 g of a light yellow foam. Chromatography over silica gel gave 1.76 g of methyl 7-phthalimido-3-chloro-3-cephem-4-carboxylate. Recrystallization from acetone gave colorless needles: mp 193–195 °C; NMR ($CDCl_3$) δ 3.47 and 3.96 (AB q, 2, J = 17 Hz), 3.87 (s, 3), 5.20 (d, 1, J = 4.5 Hz), 5.80 (d, 1, J = 4.5 Hz), 7.83 (m, 4); mass spectrum m/e 378, 350, 291, 230, 192, 187.

Anal. Calcd for $C_{16}H_{11}N_2O_5SCl$ (378.78): C, 50.73; H, 2.93; N, 7.40; O, 21.12; S, 8.46; Cl, 9.36. Found: C, 50.99; H, 3.13; N, 7.16; O, 20.91; S, 8.19; Cl, 9.20.

***p*-Nitrobenzyl 3-Chloro-3-cephem-4-carboxylate (6b).** A solution of 350 mg of *p*-nitrobenzyl 7-phthalimido-3-methylenecepham-4-carboxylate in 100 ml of chloroform was prepared and cooled in a dry ice–acetone bath. Ozone was then passed through the mixture for 2–3 min until the color of the mixture turned blue. Sulfur dioxide gas was passed through the solution for about 2 min, and magnesium sulfate was then added to the solution. The solution was brought to room temperature and filtered. The filtrate was evaporated to give 270 mg of *p*-nitrobenzyl 7-phthalimido-3-hydroxy-3-cephem-4-carboxylate (**5b**) as a colorless solid: NMR ($CDCl_3$) δ 2.95 and 4.02 (AB q, 2, CH_2S, J = 15 Hz), 5.25 (d, 1, J = 4.5 Hz), 5.4 (s, 2, CH_2 of *p*-NB), 5.76 (d, 1, J = 4.5 Hz), and 7.6–8.3 Hz (m, 8 ArH).

This material was dissolved in 5 ml of dry DMF and 0.1 ml of phosphorus trichloride was added. After usual workup the crude product was purified by chromatography over silica gel. A sample for analysis was recrystallized from methylene chloride and cyclohexane: NMR ($CDCl_3$) δ 3.5 and 3.9 (AB q, 2, J = 16 Hz, CH_2S), 5.24 (d, 1, J = 5 Hz), 5.47 (s, 2, CH_2 of p = NB), 5.97 (d, 1, J = 5 Hz), 7.5–8.4 Hz (8 ArH).

Anal. Calcd for $C_{22}H_{14}N_3O_7SCl$: C, 52.86; H, 2.82; N, 8.41; S, 6.41; Cl, 7.09. Found: C, 52.60; H, 3.03; N, 8.29; S, 6.14; Cl, 7.26.

Methyl 7-Phthalimido-3-methoxy-3-cephem-4-carboxylate (7a). A solution of 1.12 g (2 mmol) of 4-(2′-benzothiazolyldithio)-3-phthalimido-1-(1′-methoxycarbonyl-2′-chloromethylprop-2′-enyl)-azetidin-2-one in 100 ml of CH_2Cl_2 was cooled in an acetone–dry ice bath and ozone was introduced into this solution from a generator for 5 min. In order to reduce the formed ozonide sulfur dioxide gas was passed through the solution for 2 min. The mixture was then warmed to room temperature and was washed with water and brine. After drying over $MgSO_4$, the solvent was evaporated to give 870 mg of compound **4a**: NMR ($CDCl_3$) δ 3.75 (s, 3, OCH_3), 4.45 and 4.75 (AB q, 2, CH_2Cl, J = 12 Hz), 5.70 (d, 1, J = 5 Hz), and 5.92 (d, 1, J = 5 Hz).

Anal. Calcd for $C_{23}H_{16}ClN_3O_6S_3$: C, 49.15; H, 2.87; N, 7.48; O, 17.08. Found: C, 49.58; H, 3.29; N, 7.21; O, 16.89.

A solution of 870 mg of 4-(2′-benzothiazolyldithio)-3-phthalimido-1-(1′-methoxycarbonyl-2′-oxo-3′-chloropropyl)azetidin-2-one (**4a**) and 500 mg of potassium iodide in 40 ml of acetone was refluxed for 20 h. The solvent was evaporated, and the residue was dissolved in a mixture of 50 ml of ethyl acetate and 10 ml of water. The ethyl acetate extract was washed with 10 ml of brine and dried over $MgSO_4$. The solvent was evaporated to give methyl 7-phthalimido-3-hydroxy-3-cephem-4-carboxylate (**5a**): NMR ($CDCl_3$) δ 2.93 and 4.07 (AB q, 2, CH_2S, J = 15 Hz), 3.8 (s, 3, OCH_3), 5.22 (d, 1, J = 4.5 Hz), 5.75 (d, 1, J = 4.5 Hz), and 7.8 (m, 4, ArH).

To a solution of 460 mg of **5a** in 10 ml of methylene chloride, an ethereal solution of diazomethane (ca. 5 mmol) was added at 0–5 °C and stirred for 35 min. The excess of diazomethane was treated with acetic acid, the solvent evaporated, and the crude product purified by chromatography over silica gel (toluene–ethyl acetate, 9:1). Fractions 78–101 contained 220 mg of **7a**, which was recrystallized from 1.0 ml of methylene chloride and 1.0 ml of cyclohexane, giving needles: mp 236–237 °C; $[\alpha]^{25}D$ −40.3° (Me_2SO); mass spectrum m/e 374, 346, 331, 315, 287, and 255; NMR ($CDCl_3$) δ 3.15 and 3.97 (AB q, 2, J = 15 Hz, C_2 H), 3.8 (s, 3, OMe), 3.95 (s, 3, OMe), 5.18 (d, 1, J = 4.5 Hz, azetidinone H), 5.7 (d, 1, J = 4.5 Hz, azetidinone H), and 7.8 (m, 4, ArH).

Anal. Calcd for $C_{17}H_{14}N_2O_6S$: C, 54.54; H, 3.77; N, 7.48; O, 25.64; S, 8.56. Found: C, 54.35; H, 3.92; N, 7.21; O, 25.42; S, 8.34.

***p*-Nitrobenzyl 7-Phthalimido-3-methoxy-3-cephem-4-carboxylate (7b).** A solution of 650 mg of 4-(2′-benzothiazolyldithio)-3-phthalimido-1-[1′-(*p*-nitrobenzyloxycarbonyl)-2′-chloromethylprop-2′-enyl]azetidin-2-one (**3b**) and 100 ml of CH_2Cl_2 was cooled in an acetone–dry ice bath, and ozone was introduced until a blue color appeared (3–5 min). Sulfur dioxide gas then was passed through the solution for 2 min and the mixture was warmed to room temperature. The mixture was then washed with water and a brine solution. After drying over $MgSO_4$, the solvent was evaporated to yield **4b**.

A mixture of 465 mg of **4b**, 350 mg of potassium iodide, and 30 ml of acetone was refluxed for 21 h. The solvent was evaporated, and the residue dissolved in ethyl acetate and washed with brine. The solution was dried ($MgSO_4$) and the solvent evaporated to give **5b** as a colorless foam: NMR ($CDCl_3$) δ 2.95 and 4.02 (AB q, 2, CH_2S, J = 15 Hz), 5.25 (d, 1, J = 4.5 Hz), 5.4 (s, 2, CH_2 of pNB), 5.76 (d, 1, J = 4.5 Hz), and 7.6–8.3 (m, 8 ArH).

The colorless foam was dissolved in 10 ml of dichloromethane and treated with an excess of an ethereal diazomethane for 30 min at room temperature. The solvent was removed in vacuo and the crude product chromatographed by preparative TLC (silica gel; toluene–ethyl acetate, 7:3). The extracted material (110 mg) was recrystallized from acetone–ether. Colorless crystals of **7b** melted at 205–206 °C dec; NMR ($CDCl_3$) δ 3.3 and 4.0 (AB q, 2, C_2H, J = 15 Hz), 4.0 (s, 3, OCH_3), 5.28 (d, 1, J = 4.5 Hz), 5.78 (d, 1, J = 4.5 Hz), and 7.5–8.35 (m, 9 ArH); $[\alpha]^{25}D$ −18.1°.

Anal. Calcd for $C_{23}H_{17}N_3O_8S$: C, 55.76; H, 3.46; H, 8.48; O, 25.83; S, 6.47. Found: C, 55.51; H, 3.50; N, 8.23; O, 25.61; S, 6.19.

Acknowledgment. We are grateful to Mr. G. M. Maciak and associates for microanalyses, J. L. Occolowitz for mass spectra, and L. A. Spangle and associates for spectral data.

Registry No.—**1a**, 51416-11-6; **1b**, 58735-17-4; **2a**, 58735-18-5; **2b**, 58735-19-6; **3a**, 58735-20-9; **3b**, 58735-21-0; **4a**, 58735-22-1; **4b**, 58735-23-2; **5a**, 58735-24-3; **5b**, 58735-25-4; **6a**, 58735-26-5; **6b**, 58735-27-6; **7a**, 58735-28-7; **7b**, 58735-29-8; methyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate, 51415-59-9; 2-mercaptobenzothiazole, 149-30-4; *p*-nitrobenzyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate, 56446-37-8.

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Photochemical Reaction of 4-Diphenylmethylene-4*H*-thiopyrans

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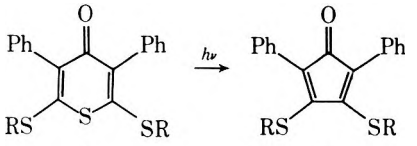
Ultraviolet irradiation of 4-diphenylmethylene-2,6-bis(methylthio)-3,5-diphenyl-4*H*-thiopyran affords 2-diphenylmethylene-4,5-bis(methylthio)-3,6-diphenyl-2*H*-thiopyran via the triplet state of the former. Photolysis of 4-diphenylmethylene-4*H*-thiopyran, 4-diphenylmethylene-2,6-bis(methylthio)-3,5-dimethyl-4*H*-thiopyran, and 4-diphenylmethylene-3,5-diphenyl-4*H*-thiopyran resulted in the recovery of the starting materials. All of these 4-diphenylmethylene-4*H*-thiopyrans fluoresce at room temperature, but do not phosphoresce at 77 K.

The photochemistry of 4-thiopyrones has been the subject of study in this and other laboratories. Under the influence of ultraviolet light, unhindered 4*H*-thiopyran-4-ones undergo dimerization,[2] whereas hindered 4*H*-thiopyran-4-ones lead to elimination of sulfur atom.[3] In this photochemical rearrangement of 2,6-bis(alkylthio)-3,5-diphenyl-4*H*-thiopyran-4-ones (**1**) to 3,4-bis(alkylthio)-2,5-diphenylcyclopentadienones (**2**), evidence in favor of the mechanism

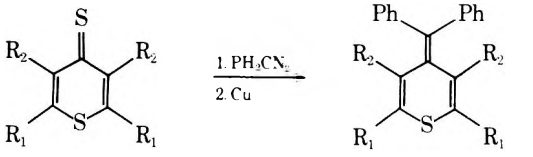


1 **2**

involving its n,π* triplet state was given.[3] It seemed of considerable import to inspect the photochemistry of a system lacking n,π* excitation but having a similar π system. Such a molecule would have available only π,π* excited state and its photochemistry would define the behavior of these states. Accordingly the diphenylmethylene analogues were selected for the present study. Specifically, 4-diphenylmethylene-2,6-bis(methylthio)-3,5-diphenyl-4*H*-thiopyran was chosen for study of the photochemical reaction in detail.[4]

Results and Discussion

4-Diphenylmethylene-4*H*-thiopyrans (**3**–**6**) were most conveniently prepared by the reaction of corresponding 4*H*-thiopyran-4-thiones (**7**–**10**) with diphenyldiazomethane, followed by treatment with copper powder according to the established procedure.[5,6] The structure assigned to 4-diphenylmethylene-4*H*-thiopyrans rests on their elemental analysis and spectral data. Their mass spectra showed an intense peak correspondent with their parent ion. The ir spectra exhibited a stretching vibration of the exocyclic double bond at 1605–1620 cm^{-1}. The NMR spectra of **3** and **4** showed the equivalent thiomethyl protons at δ 2.2–2.3 and those of **5** and



7, R_1 = SMe; R_2 = Ph
8, R_1 = SMe; R_2 = Me
9, R_1 = R_2 = H
10, R_1 = H; R_2 = Ph

3, R_1 = SMe; R_2 = Ph
4, R_1 = SMe; R_2 = Me
5, R_1 = R_2 = H
6, R_1 = H; R_2 = Ph

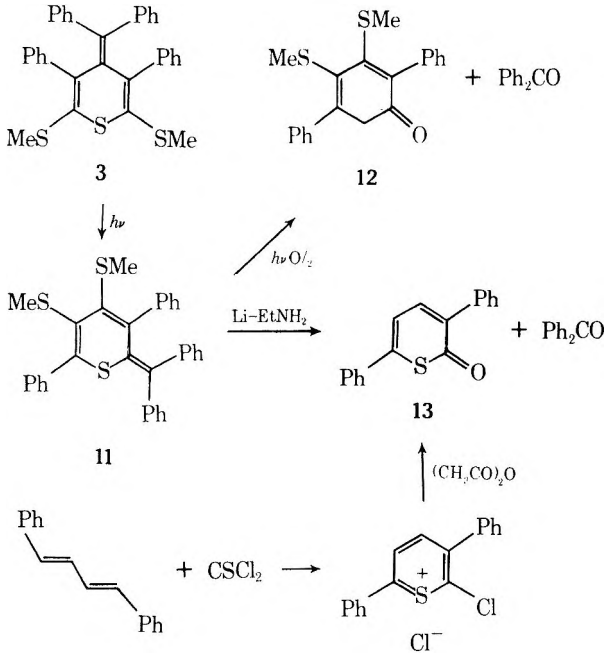
6 displayed the olefinic protons at δ 6.2–6.9. These spectral data were in complete agreement with the structure and are given in the Experimental Section.

Irradiation of 4-diphenylmethylene-2,6-bis(methylthio)-3,5-diphenyl-4*H*-thiopyran (**3**) in benzene with a medium-pressure mercury lamp through a Pyrex filter gave an almost quantitative yield of a product isomeric with the starting material. This is assigned structure **11** on the basis of chemical reaction outlined in Scheme I. Photooxygenation of the photoproduct yielded 4,5-bis(methylthio)-3,6-diphenyl-2*H*-thiopyran-2-one (**12**). Upon addition to Li–$EtNH_2$ the photoproduct was desulfurized[7] to give 3,6-diphenyl-2*H*-thiopyran-2-one (**13**),[8,9] identical with an authentic sample[11,12] in ir and NMR spectra. The irradiation of **3** in methylene chloride under similar conditions also afforded **11** in excellent yield.

Irradiation of **4** or **5** or **6** in benzene with a medium-pressure mercury lamp equipped with a Pyrex filter or a 313–436-nm solution filter[13] produced no reaction. Prolonged irradiation of **4**, **5**, or **6** also resulted in the recovery of the starting materials. When photolysis was sensitized by acetophenone which absorbed more than 95% of the incident light, **5** was also recovered unchanged.

Ultraviolet absorption spectra of the 4-diphenylmethylene-4*H*-thiopyran in ethanol are given in Figure 1, which shows two broad intense bands at 230–240 and 340–380 nm, whereas the corresponding 4*H*-thiopyran-4-ones exhibit two

Scheme I



intense bands at 230–280 and 300–310 nm.[14] Hypsochromic shifts were observed for **3, 4,** and **6** relative to the spectrum of **5,** whereas a bathochromic shift was observed for 4-diphenylmethylene-2,6-diphenyl-4*H*-thiopyran. This hypsochromic shift might be caused by steric factors which significantly reduce electron interaction between the thiopyran ring and the substituents at the C-3 and C-5 positions. This steric hindrance was also reflected into the ultraviolet spectra of the corresponding 4*H*-thiopyran-4-ones.[14]

The 4-diphenylmethylene-4*H*-thiopyrans **3–6** fluoresce in ethanol at room temperature. No evidence of phosphorescence was obtained at least at 77 K. The observed luminescence is diagnosed as fluorescence from the overlap of excitation and emission bands in the 0–0 band region (Figure 1) and from the short luminescence lifetimes which allowed complete suppression of the emission when the phosphoroscope was used. Observation of emission spectra at room temperature also indicates that the obtained emission indeed is fluorescence. It is worthy to note that the 4-diphenylmethylene-4*H*-thiopyrans studied fluoresce in solution at room temperature but do not phosphoresce at 77 K, whereas the corresponding ketone analogues, 4*H*-thiopyran-4-ones,[14] do not fluoresce in solution at both room and low temperature (77 K) but phosphoresce at 77 K.

Quantum yields for appearance of **11** in benzene or methylene chloride were determined using potassium ferrioxalate actinometry.[15] The deaerated samples were irradiated with the 360-nm light.[13] Reactions were carried out in 2–3% conversion and the yield of product was determined by the ultraviolet spectrophotometric method. The results of these run (Table I) showed the average quantum yield to be very high (1.00), as has been obtained in the photorearrangement of 4,4-diphenyl-2,5-cyclohexadienone.[16]

Thioxanthone (E_T = 65.6 kcal/mol) and acridine (E_T = 45.3 kcal/mol) were selected for sensitization studies because of their high molecular extinction coefficients at 360 nm. Quantum efficiency for the formation of **11** on thioxanthone sensitization absorbing over 90% of incident light did not give a reproducible value. This would be due to the self-quenching reaction of thioxanthone[17] at the high concentration used. Under preparative conditions, however, **3** was rearranged to **11** in the thioxanthone-sensitized run as effectively as in the direct run. On the other hand, sensitization by acridine did not lead to the formation of photoproduct. Cyclooctatetraene

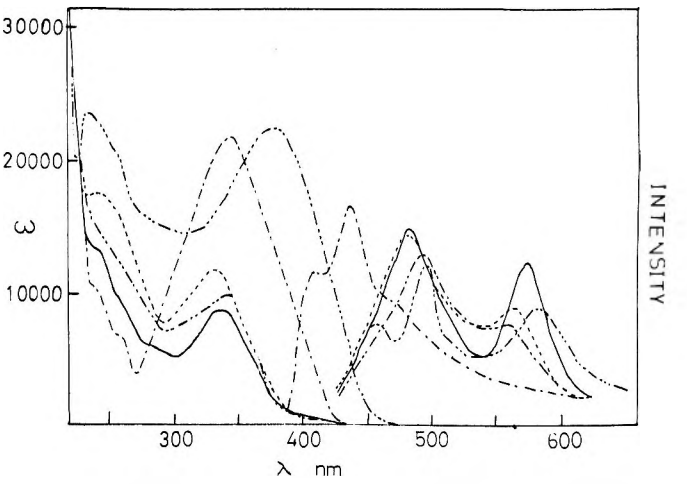


Figure 1. Electronic absorption and fluorescence spectra of 4-diphenylmethylene-4*H*-thiopyrans in ethanol: **3,** —; **4,** - - -; **5,** – – –; **6,** – - – -; 4-diphenylmethylene-2,6-diphenyl-4*H*-thiopyran, – – – –.

Table I. Quantum Yield for the Formation of 11 [a]

Solvent	Additive	ϕ
Benzene	None	0.99
Methylene chloride	None	1.01
Benzene	*cis*-Piperylene, 0.1 M	0.97
Benzene	Cyclooctatetraene, 0.26 M	0.074

[a] The concentration of **3** was 1.0–6.0 × 10^{-3} M.

(E_T > 40 kcal/mol[18]) quenched in part the photoisomerization of **3** to **11,** whereas *cis*-piperylene (E_T = 56.9 kcal/mol) did not quench this photorearrangement (Table I). These results, together with the sensitization experiment, suggest that the π,π^* triplet might mainly be responsible for the photoisomerization of **3** to **11**[19] and that the triplet energy lies between 45 and 57 kcal/mol.

Stern–Volmer analyses were undertaken in benzene using cyclooctatetraene as the quencher. The result is shown in Figure 2. The rationale for the Stern–Volmer plot can be seen in the following scheme and in eq 1

$$S \xrightarrow{h\nu} S^1$$

$$S^1 \rightarrow S^3$$

$$S^3 \xrightarrow{k_d} S$$

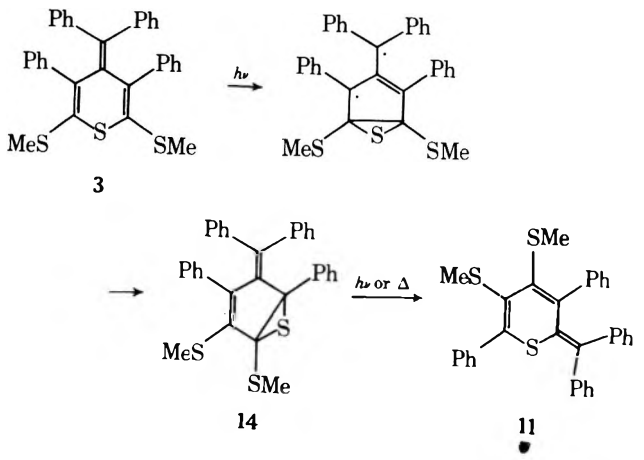
$$S^3 \xrightarrow{k_r} P$$

$$S^3 + Q \xrightarrow{k_q} S + Q^3$$

$$1/\phi = \frac{k_r + k_d}{k_r} + \frac{k_q}{k_r}[Q] \qquad (1)$$

where S, S^1, and S^3 are the ground state, first excited singlet state, and lowest triplet state, respectively, of **3;** P is product; [Q] is the concentration of quencher; k_d is the unimolecular rate of triplet decay of **3,** k_q is the bimolecular rate of quenching, and k_r is the desired unimolecular rate of triplet rearrangement. When we assumed that quenching of triplet is diffusion controlled with a bimolecular rate of 3.2 × 10^9 M^{-1} s^{-1},[21] solution of eq 1 indicates k_r = 7.3 × 10^7 s^{-1}. The reaction rate of photorearrangement of **3** to **11** is fast but slower by 1/100th order of magnitude than the rate of photorearrange-

Scheme II



ment of 4,4-diphenyl-2,5-cyclohexadienone,[16] which is diffusion controlled.

A proposed mechanism consistent with the observed rearrangement is depicted in Scheme II. In contrast to the photoisomerization of 1-methylenecyclohexa-2,5-dienes to 2-methylenebicyclo[3.1.0]hex-2-enes via their π,π^* singlet[22,23] the compound **14**, a possible intermediate, was not isolated in the photorearrangement of **3** and attempts to trap the intermediate in the presence of excess of triphenylphosphine have been unsuccessful. As pointed out previously[4] this differing behavior might derive from both a heavy-atom effect of a sulfur atom[24] and π electron conjugation of the triene through a sulfur atom in the heterocyclic ring. A very low quantum yield and elimination of a sulfur atom were observed in the photoreaction of **1** in contrast to the diphenylmethylene analogue **3**. However, it has been noted previously[3] that these reactions proceed via n,π^* triplet. Hence, the difference between the rearrangement of diphenylmethylene-4*H*-thiopyran and that of 4*H*-thiopyran-4-ones might be ascribed to the role of the nonbonding electron promoted to the π system in the excited state.[19]

Most of 4-diphenylmethylene-4*H*-thiopyrans (**4**, **5**, and **6**) were not affected by ultraviolet irradiation, although their absorption and emission spectra are similar to those of **3**. Steric repulsion between phenyl protons on C-3 and those on an exo-methylene carbon might prevent free rotation of an exo-methylene moiety which provides a mechanism for excited energy dissipation in the 1-methylene-2,5-cyclohexadienes.[25] On the other hand, the 4*H*-thiopyrans, **4**, **5**, and **6**, seem to be capable of dissipating excited energy because of free rotation of an exo-methylene bond. The photoreactivity of these 4-diphenylmethylene-4*H*-thiopyrans is, therefore, sensitive to the extent of substituents in the 4*H*-thiopyran ring and similar sensitivity to the extent of substituents was observed in the photoreaction of 4*H*-thiopyran-4-ones,[3] 4*H*-pyran-4-ones,[26] and 4-pyridones.[27]

Experimental Section

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. Ultraviolet spectra were recorded on a Hitachi 323 spectrophotometer. Infrared spectra were determined on a Jasco DS-402G grating spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian T-60A or HA-100 spectrometer and with a JEOL PS 100 spectrometer using tetramethylsilane as an internal standard. Mass spectral analyses were obtained on a Hitachi RMU-6L mass spectrometer. Microanalyses were performed at the Microanalytical Laboratory of Kyoto University, Kyoto, Japan.

4-Diphenylmethylene-2,6-bis(methylthio)-3,5-diphenyl-4*H*-thiopyran (**3**) and 4-diphenylmethylene-2,6-diphenyl-4*H*-thiopyran were prepared according to the reported method.[5]

2,6-Bis(methylthio)-3,5-dimethyl-4*H*-thiopyran-4-thione (8). A mixture of 2.21 g of 2,6-bis(methylthio)-3,5-dimethyl-4*H*-thiopyran-4-one[28] and 6 g of phosphorus pentasulfide in 100 ml of benzene was refluxed with stirring for 3 h. Aqueous ammonium sulfide was added to the reaction mixture. After separation of the organic layer, the aqueous solution was extracted with benzene. The combined benzene solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a green solid. Recrystallization from ethanol gave 1.78 g (75.6%) of **8**: mp 183.0–184.5 °C; ir (KBr) 2970, 1480, 1420, 1365, 1340, 1305, 1235, 1120, 1020, 925, 750 cm^{-1}; NMR ($CDCl_3$) δ 2.60 (s, 6 H), 2.66 (s, 6 H).

Anal. Calcd for $C_9H_{12}S_4$: C, 43.51; H, 4.87. Found: C, 43.47; H, 4.85.

3,5-Diphenyl-4*H*-thiopyran-4-thione (10). The procedure was the same as the one described for the preparation of **8**. From 1.6 g of 3,5-diphenyl-4*H*-thiopyran-4-one[3b] and 5 g of phosphorus pentasulfide in 100 ml of benzene there was obtained 1.33 g (78.2%) of **10** as a green solid: mp 171.5–174.0 °C; ir (KBr) 3040, 1600, 1540, 1440, 1320, 1310, 1120, 860, 830, 760, 695 cm^{-1}; NMR ($CDCl_3$) δ of 7.32 (s, 10 H), 7.49 (s, 2 H).

Anal. Calcd for $C_{17}H_{12}S_2$: C, 72.82; H, 4.31. Found: C, 72.68; H, 4.28.

4-Diphenylmethylene-2,6-bis(methylthio)-3,5-dimethyl-4*H*-thiopyran (4). A solution of 1.3 g of **8** and 1.1 g of diphenyldiazomethane in 100 ml of benzene was refluxed for 4 h. After addition of 300 ml of petroleum ether to the reaction mixture at room temperature a white solid was obtained. A mixture of this solid and 10 g of copper powder in 100 ml of xylene was refluxed for 8 h. After removal of unreacted copper powder by filtration and evaporation of the solvent in vacuo three fractional recrystallizations from benzene–ligroin gave 1.56 g (78%) of colorless crystals of **4**: mp 121–124 °C; ir (KBr) 3040, 2970, 1615, 1600, 1445, 1435, 1320, 1030, 915, 910, 900, 890, 770, 755, 705 cm^{-1}; NMR ($CDCl_3$) δ 1.61 (s, 6 H), 2.25 (s, 6 H), 7.25 (s, 10 H); mass spectrum *m/e* (rel intensity) 384 (17), 383 (26), 382 (100, M^+), 336 (9), 325 (20), 334 (38), 321 (9), 320 (20), 319 (37), 289 (12), 288 (35), 287 (21), 286 (12), 285 (10), 271 (14), 244 (20), 91 (34), 78 (56), 77 (18).

Anal. Calcd for $C_{22}H_{22}S_3$: C, 69.06; H, 5.80; S, 25.15. Found: C, 68.92; H, 5.78; S, 25.00.

4-Diphenylmethylene-4*H*-thiopyran (5). A similar procedure was employed to the one described in the preparation of **4**. From 0.93 g of 4*H*-thiopyran-4-thione and 1.45 g of diphenyldiazomethane 1.3 g (76%) of yellow crystals of **5** was obtained: mp 128–130 °C; uv (CH_2Cl_2) λ_{max} 344 nm (ϵ 20 800); ir (KBr) 3040, 3010, 1615, 1595, 1490, 1455 1370, 1030, 905, 785, 755, 700 cm^{-1}; NMR ($CDCl_3$) δ 6.21 and 6.43 (d of q, 4 H, J = 1.5, 11 Hz), 7.0–7.3 (m, 10 H); mass spectrum *m/e* (rel intensity) 264 (6), 263 (22), 262 (100, M^+), 261 (6), 229 (7), 228 (17), 185 (9), 184 (8), 101 (8), 100 (11).

Anal. Calcd for $C_{18}H_{14}S$: C, 82.40: H, 5.38. Found: C, 82.32; H, 5.33.

4-Diphenylmethylene-3,5-diphenyl-4*H*-thiopyran (6). A mixture of 1.3 g of 3,5-diphenyl-4*H*-thiopyran-4-thione and 1.1 g of diphenyldiazomethane in 100 ml of benzene was refluxed for 4 h. After evaporation of the solvent in vacuo, the residual solid was recrystallized from ethanol to afford 1.44 g (75%) of pale yellow crystals of **6**: mp 158–159 °C; uv (CH_2Cl_2) λ_{max} 334 nm (ϵ 13 200); ir (KBr) 3040, 1620, 1600, 1535, 1490, 1445, 1030, 800, 770, 760, 750, 735, 695 cm^{-1}; NMR ($CDCl_3$) δ 6.60 (s, 2 H), 6.8–7.2 (m, 20 H); mass spectrum *m/e*

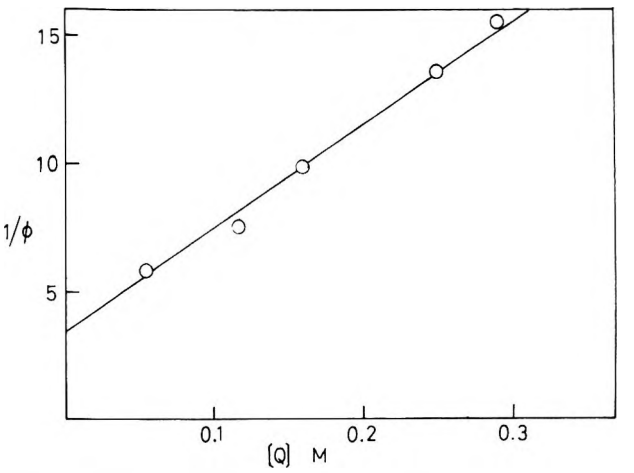


Figure 2. Plot of reciprocal of quantum yield for appearance of **11** vs. concentration of added cyclooctatetraene in the photorearrangement of **3**.

(rel intensity) 316 (9), 315 (34), 314 (100, M^+), 313 (19), 237 (21), 236 (9), 203 (10), 202 (8), 128 (9).

Anal. Calcd for $C_{30}H_{22}S$: C, 86.92; H, 5.35. Found: C, 87.08; H, 5.55.

Irradiation of 4-Diphenylmethylene-2,6-bis(methylthio)-3,5-diphenyl-4*H*-thiopyran (3). A solution of 0.5 g of 2,6-bis(methylthio)-3,5-diphenyl-4-diphenylmethylene-4*H*-thiopyran in 700 ml of benzene was irradiated with a 500-W Ushio medium-pressure mercury lamp using a Pyrex filter. The progress of the reaction was followed by TLC (silica gel), using benzene–cyclohexane (1:1) as eluent. After 2 h, nearly 100% of the starting material had reacted and the irradiation was halted. After evaporation of the solvent in vacuo, the residual solid was recrystallized from benzene–*n*-hexane to give 0.46 g (92%) of 2-diphenylmethylene-3,6-diphenyl-4,5-bis(methylthio)-2*H*-thiopyran, mp 207–210 °C, as yellow crystals: uv (CH_2Cl_2) λ_{max} 285 nm (ϵ 11 900), 328 (11 000), 403 (6900); ir (KBr) 3060, 3020, 2920, 1605, 1580, 1490, 1460, 1310, 1180, 1160, 1075, 1035, 910, 895, 845, 800, 770, 735, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.32 (s, 3 H), 6.6–7.4 (m, 20 H); mass spectrum *m/e* (rel intensity) 508 (22), 507 (40), 506 (100, M^+), 476 (34), 458 (47), 426 (44), 412 (73), 380 (30), 334 (31), 167 (28), 121 (33).

Anal. Calcd for $C_{32}H_{26}S_3$: C, 75.84; H, 5.17; S, 18.98. Found: C, 75.75; H, 5.35; S, 19.02.

Photooxygenation of 2-Diphenylmethylene-3,6-diphenyl-4,5-bis(methylthio)-2*H*-thiopyran. A solution of 0.4 g of 2-diphenylmethylene-4,5-bis(methylthio)-3,6-diphenyl-2*H*-thiopyran in 1000 ml of methylene chloride was irradiated with a Taika 300-W medium-pressure mercury lamp equipped with the filter system for 560-nm light described by Calvert and Pitts.[29] Oxygen was bubbled through the reaction solution while it was irradiated for 3 h. The residue obtained on evaporation was chromatographed on silica gel with benzene–cyclohexane (2:1) to give 0.075 g of benzophenone and 0.167 g of 4,5-bis(methylthio)-3,6-diphenyl-2*H*-thiopyran-2-one: mp 153.0–154.5 °C; ir (KBr) 3000, 1610, 1590, 1525, 1485, 1445, 1315, 1270, 1180, 980, 825, 725, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.79 (s, 3 H), 2.13 (s, 3 H), 7.3–7.5 (m, 10 H); mass spectrum *m/e* (rel intensity) 358 (8), 357 (10), 356 (32, M^+) 342 (14), 341 (48), 329 (25), 328 (100), 266 (52), 234 (32), 200 (22), 121 (33).

Anal. Calcd for $C_{19}H_{16}OS_3$: C, 64.01; H, 4.52; O, 4.49; S, 26.98. Found: C, 63.98; H, 4.43; O, 4.42; S, 27.17.

Desulfurization of 2-Diphenylmethylene-3,6-diphenyl-4,5-bis(methylthio)-2*H*-thiopyran. Redistilled anhydrous ethylamine (30 ml) was condensed into the reaction flask equipped with a dry ice condenser as designed by Truce.[30] When the lithium metal dissolved and a deep blue color developed, 0.6 g of 2-diphenylmethylene-4,5-bis(methylthio)-3,6-diphenyl-2*H*-thiopyran was added in portions under nitrogen atmosphere. After evaporation of ethylamine at room temperature, 50 ml of water was cautiously added with cooling. After neutralization this mixture was extracted with ether. The residue obtained on evaporation was separated by preparative thick layer chromatography on silica gel with benzene–cyclohexane (2:1) as eluent to give 0.008 g of benzophenone and 0.019 g of 3,6-diphenyl-2*H*-thiopyran-2-one, mp 182–183 °C (lit.[11] 183.5–184 °C). Its ir and NMR spectra were consistent with those of **13** prepared from *trans*-1,4-diphenylbutadiene and thiophosgene.[11]

Irradiation of 4-Diphenylmethylene-2,6-bis(methylthio)-3,5-dimethyl-4*H*-thiopyran, 4-Diphenylmethylene-4*H*-thiopyran, or 4-Diphenylmethylene-3,5-diphenyl-4*H*-thiopyran. A solution of the 4-diphenylmethylene-4*H*-thiopyrans (0.2–0.5 g) in benzene or methylene chloride (700 ml) was irradiated under nitrogen atmosphere for 14–20 h using a Ushio 500-W medium-pressure mercury lamp equipped with a Pyrex filter or a 313–436-nm solution filter.[13] The solution was concentrated to 10 ml. The reaction mixture showed only one spot on TLC (silica gel), the R_f value being the same as that of the starting material.

Quantum Yield Determinations. Solutions containing various weights of cyclooctatetraene and **3** were made up to 25 ml with Spectrograde benzene, and poured into the Pyrex tube. The tubes were degassed to a pressure of 10^{-3} Torr or less in three freeze–pump–thaw cycles, and then sealed. The samples were irradiated in a merry-go-round assembly using a 100-W medium-pressure mercury arc lamp as the central light source. The light source was filtered by a $CoSO_4 \cdot 7H_2O$–$CuSO_4 \cdot 5H_2O$ filter solution to isolate 313–436-nm light.[13] Potassium ferrioxalate actinometry[15] was used to determine the lamp intensity. After irradiation the concentration of the photoproduct **11** was determined at 403 nm by quantitative ultraviolet spectroscopy. The conversions of **3** were run 5% or less.

Measurement of Fluorescence Spectra. The fluorescence excitation and emission spectra were obtained on a Hitachi MPF-4 spectrofluorometer. The fluorescence spectra (uncorrected) were measured at 298 K in absolute ethanol (Wako Chemical). The concentration of the samples ranged from 10^{-5} to 10^{-7} M. Attempts to measure the phosphorescence excitation and emission spectra were carried out on a Hitachi MPF-4 spectrofluorometer at 77 K using Hitachi phosphoroscope attachments. Concentrations of these compounds ranged from 10^{-6} to 10^{-4} M.

Acknowledgment. We thank H. Minegishi, Application Laboratory, Hitachi Co., for making available a Hitachi spectrofluorometer and for help with measurement of emission spectra.

Registry No.—**3**, 58944-29-9; **4**, 58944-30-2; **5**, 58944-31-3; **6**, 58944-32-4; **7**, 14172-81-7; **8**, 24162-39-8; **9**, 1120-94-1; **10**, 21125-43-9; 2,6-bis(methylthio)-3,5-dimethyl-4*H*-thiopyran-4-one, 24215-64-3; phosphorus pentasulfide, 1314-80-3; 3,5-diphenyl-4*H*-thiopyran-4-one, 13700-75-9; diphenyldiazomethane, 883-40-9; 2-diphenylmethylene-3,6-diphenyl-4,5-bis(methylthio)-2*H*-thiopyran, 52680-68-9; 4,5-bis(methylthio)3,6-diphenyl-2*H*-thiopyran-2-one, 52577-73-8.

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(7) Raney Ni (W-2 and W-4) could not be used for desulfurization of the photoproduct, since the reaction mixture showed at least ten spots on silica gel TLC, along with a comparable amount of tarry material. The amount isolated from the reaction mixture was not sufficient for structure elucidation.
(8) It was anticipated to obtain 2-diphenylmethylene-3,6-diphenyl-2*H*-thiopyran[9] and/or 1,4,6,6-tetraphenylhexa-1,3,5-triene in this reaction. These compounds, however, were not isolated from the reaction mixture.
(9) Facile oxidation of 2-diphenylmethylene-3,6-diphenyl-2*H*-thiopyran by air[10] might give **13** and benzophenone.
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Comparison of the Solid and Solution Conformations of Methapyriline, Tripelennamine, Diphenhydramine, Histamine, and Choline. The Infrared–X-Ray Method for Determination of Solution Conformations

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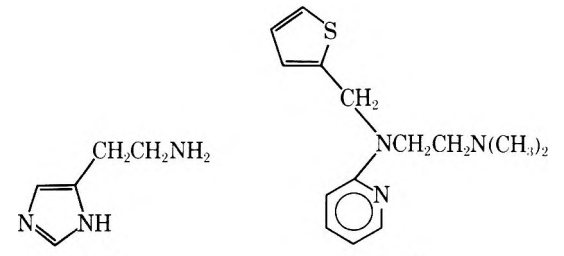
The ir–x-ray method for the determination of solution conformation is discussed and illustrated using choline chloride, histamine, and three antihistamines. Infrared spectroscopy was used as an experimental test of the equivalence of conformations in the solid state and solution, provided large groups do not obscure the fingerprint region. If the solid state and solution spectra are identical then a knowledge of the crystal structure gives the conformation in solution. This method indicated that as expected based on reports in the literature the conformation of choline was essentially the same in the solid state and solution. It also showed that, in contrast to reports in the literature, there was a predominance of the trans conformation of methapyriline hydrochloride (2-[(2-dimethylaminoethyl)-2-thenylamino]pyridine hydrochloride) in solution. Tripelennamine hydrochloride (2-[benzyl(2-dimethylaminoethyl)amino]pyridine hydrochloride) was also probably in the trans conformation both in solution and in the solid state. The solid state and solution infrared spectra of histamine were significantly different as expected based on reports in the literature. Similarly, differences in the published infrared spectra of solid acetyl choline chloride and bromide were consistent with x-ray studies which showed that there were different conformations about the ethyl carbon atom–ester oxygen bond in these two salts. The solid state and solution spectra of diphenhydramine hydrochloride are different suggesting that diphenhydramine has a different conformation in crystals and in solutions of this salt.

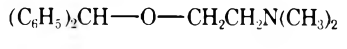
The conformations of molecules in the solid and solution have been compared using x-ray crystallography and NMR spectroscopy,[1] x-ray crystallography and circular dichroism,[2] x-ray crystallography and dipole moments,[3] infrared and NMR spectroscopy,[4] and infrared spectroscopy.[5]

In this paper we report the use of x-ray crystallography and infrared spectroscopy (the ir–x-ray method) to compare the solid and solution conformations of histamine (I), antihistamines (II–IV), and choline (V). These studies show that x-ray crystallography and infrared spectra can be combined to provide a reliable method for determination of solution conformations.

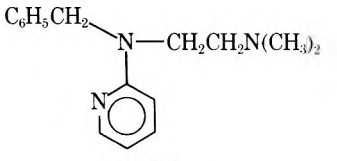


I

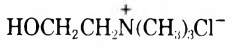
II



III



IV



V

Experimental Section

X-Ray Powder Diffraction Measurements. The 2-[(2-dimethylaminoethyl)-2-thenylamino]pyridine hydrochloride (methapyrilene hydrochloride) used was a gift from Abbott Laboratories, Chicago, Ill., for which we are grateful. The other compounds used were commercially available. The powder diffraction pattern of ground crystals of the material of interest was measured using a Debye-Scherrer powder camera with Ni-filtered Cu radiation. Intensities were estimated visually. The most intense observed bands of this pattern were then compared to the most intense bands calculated using the atom positions available from the crystal structure determination and the program POWD5.[6]

Infrared Difference Spectra. The ir difference spectra were measured by placing a Nujol mull of the material of interest and $CHCl_3$ solvent (in 0.5-mm NaCl cells) in the sample beam and a reference beam attenuator and a $CHCl_3$ solution of the material in the reference beam. The reference beam attenuator was used to adjust the % T (transmittance) of the mull spectra at 1800 cm^{-1} to approximately that of the solution. Before scanning the spectrum the pen was adjusted to about 50% T. To match the concentration of the $CHCl_3$ solution to that of the mull, the $CHCl_3$ solution was successively diluted, usually 3 parts of solution to 1 part of solvent, and the difference spectrum remeasured. This process was repeated until the difference spectra passed through a point where there was the least deviation from the 50% T line and began to resemble the mull spectra.

Spectral and Powder Diffraction Analysis of Choline Chloride (V) (Ethanaminium, 2-Hydroxy-*N,N,N*-trimethyl Chloride). Choline chloride was dried in a vacuum before use. It was extremely deliquescent and the Nujol mulls were prepared in a glove bag under nitrogen atmosphere. The capillary tubes for powder diffraction were also filled in this glove bag and sealed immediately upon removal.

The infrared spectra of choline chloride in Nujol mull and ca. 40% water solution are shown in Figure 1.

Spectral and Powder X-Ray Diffraction Analysis of Methapyrilene Hydrochloride (2-[(2-Dimethylaminoethyl)-2-thenylamino]pyridine Hydrochloride, II HCl). Methapyriline hydrochloride (II HCl) was recrystallized in plates from 2-propanol, acetone, or ethyl acetate, in fine needles from 1,2-dichloroethane, and in clumps from ethanol or chloroform. The ir spectra (Nujol mull) of these crystals were identical with each other and with the spectrum (Nujol mull) of a cooled melt of II HCl. The ir spectra of a Nujol mull and chloroform solution of II HCl are shown in Figure 2 along with the solution–solid state difference spectra. The ir spectrum of II HCl in these solvents was also virtually identical with the ir spectra of II HCl in H_2O in the regions not obscured by solvent absorption.

The free base, methapyriline (II), was prepared by making alkaline a H_2O solution of II HCl and extracting with ether. The ether was dried and then evaporated giving II which had an ir spectrum (in $CHCl_3$) which was virtually identical with that of II HCl except for the 2850-cm^{-1} peak due to the free base and the 990-cm^{-1} peak which was absent from the spectrum of II HCl.

The 60- and 100-MHz spectra of II HCl showed broadened triplets for the ethylene protons and this region of the spectrum is shown in Figure 3. The NMR spectra of II HCl in Me_2SO-d_6, CH_3CN, CD_3OD, and CH_3NO_2 were, in general, quite similar to these two spectra except for slight solvent-induced changes in chemical shift. Broadened triplets were observed for the $-CH_2-$ group when its absorbances were not obscured by absorptions of these solvents. Methapyrilene free base

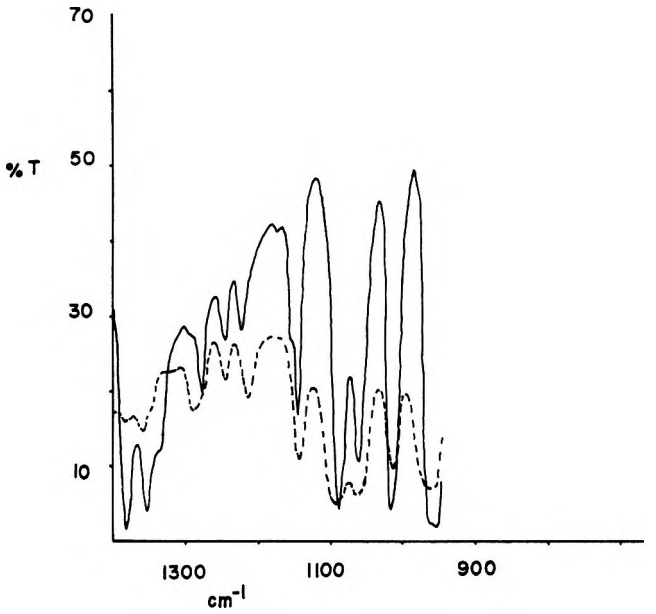


Figure 1. Ir spectra of choline chloride (V) in the solid state and in solution [(—) Nujol mull, (- - -) H_2O solution]. The peak at 1380 (cm^{-1}) in the mull spectrum is due to Nujol.

also exhibited broadened ethylene triplets ($W_{1/2} \approx 4$ Hz, $J \approx 7$ Hz) although their chemical shifts changed substantially as would be expected owing to deprotonation.

Spectral Analysis of 2-[Benzyl(2-dimethylaminoethyl)-amino]pyridine HCl (Tripelennamine HCl). Tripelennamine hydrochloride (IV HCl) was recrystallized from acetone in needles and plates and from 1,2-dichloroethane in plates. This antihistamine (IV HCl) was also recrystallized from ethanol, chloroform, methanol, water, methylene chloride, and from the melt. The ir spectra (Nujol mull) of all of these crystals were identical. The spectra of tripelennamine hydrochloride in $CHCl_3$ and Nujol mull and the solid state and solution difference spectra are shown in Figure 4. The ir spectrum of the free base of IV in $CHCl_3$ prepared in the same way as the free base of II was virtually identical with the spectra of IV HCl in $CHCl_3$ except for differences due to the deprotonation of the $-NMe_2$ group and a peak at 990 cm^{-1} in the free base which was absent in IV HCl.

The ethylene regions of the 60-MHz NMR spectra of IV HCl and IV were similar to the spectra of II HCl (see Figure 3).

Spectral and Powder X-Ray Diffraction Studies of Histamine (I). The free base of histamine was studied in the solid state and in solution. The ir spectra of histamine in Nujol mull and $CHCl_3$ solution along with the solid state and solution difference spectra are shown in Figure 5. The NMR spectrum of histamine in $CDCl_3$ showed the following absorptions (δ): 2.87 (4 H, 8-peak multiplet, $-CH_2CH_2-$), 5.12 (3 H, s, NH), 6.88 (1 H, s, ring CH), 7.12 (1 H, d, ring CH). The NMR spectrum (in $CDCl_3$) of the CH_2CH_2 group of histamine expanded and decoupled was nearly identical with the published decoupled spectrum of this group at pH 7.0 (monocation) in water solution.[7]

Spectral and Single-Crystal X-Ray Studies of Diphenhydramine Hydrochloride (2-Diphenylmethoxy-*N*,*N*-dimethylethylamine Hydrochloride, III HCl). Diphenhydramine hydrochloride (III HCl) was crystallized from acetone, ethyl acetate, ethanol–ethyl acetate, or benzene–chloroform (5:2) in needles, from ethanol in plates, from chloroform in clumps, and from the melt. The ir spectra (Nujol mull) of all of these crystals were essentially identical but differed from the spectrum of III HCl in $CHCl_3$ (see Figure 6). The ir spectrum of the free base (III) was different from both the solid state and solution spectra of III HCl. The 60-MHz NMR spectra of III HCl and III were also distinctly different. The ethylene protons of III were sharp triplets while those of III HCl were three-peak multiplets. However, these differences may be due to the fact that the chemical shift difference between the two methylene groups was much greater in the free base (III) than the hydrochloride (III HCl).

Diphenhydramine HCl (III HCl) crystallized [from benzene–$CHCl_3$ (5:2)] in hygroscopic needles which belong to the orthorhombic crystal class. Least-squares refinement of the 2θ values of 17 carefully centered reflections gave the following cell parameters (std dev): a = 10.596 (2), b = 14.311 (2), c = 10.773 (2) Å. The ρ calcd for $Z = 4$ molecules of III HCl ($C_{17}H_{21}NO$·HCl, mol wt 291.82) was 1.19 g/cm^3,

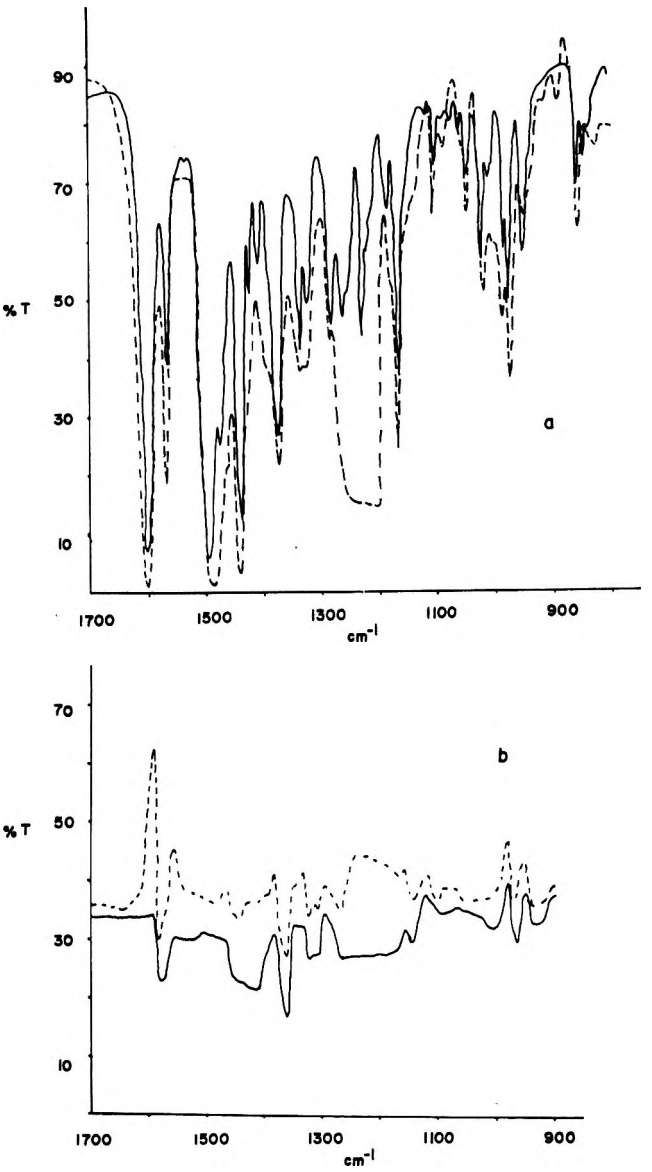


Figure 2. Infrared spectra (2a) of a Nujol mull (—) and $CHCl_3$ solution (- - -) of methapyriline hydrochloride (II HCl). Difference spectra (2b) between a Nujol mull and $CHCl_3$ solution of methapyriline hydrochloride. The dashed line (- - -) corresponds to a solution concentration slightly more than that of the mull and the solid line (—) corresponds to a solution concentration slightly less than that of the mull.

ρ obsd = 1.18 g/cm^3. The following systematic absences were observed: $0kl$, $k + l = 2n + 1$; $h0l$, $l = 2n + 1$ indicating that III HCl belonged to the space group $Pna2_1$ or to the space group $Pnma$ and the molecule situated on a mirror plane. Several attempts to determine the structure of III HCl in each of these space groups using both the programs of x-ray series[8] and the MULTAN[9] series were unsuccessful.

Results and Discussion

General Description of the Method. The method employed to determine the solution conformation of biologically important ethylene derivatives involves three steps: (1) determination of the crystal structure of the compound; (2) establishment that grinding the compound to a powder does not induce a crystalline phase transition; and (3) comparison of the infrared spectra in the solid state and in solution. Step 1 is accomplished using normal single-crystal x-ray techniques.

Since solid-state phase transformations have been reported to occur upon grinding,[10] step 2 was required to establish that the conformation of the compound in the powdered sample was identical with that in single crystals and step 2 was ac-

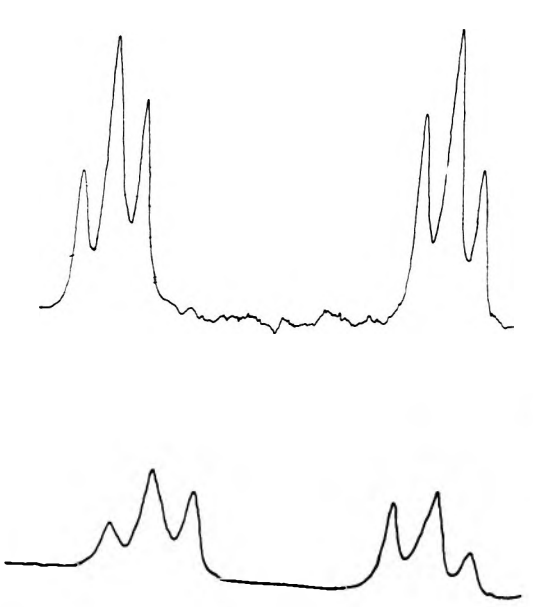


Figure 3. Observed 100-MHz (3a) and 60-MHz (3b) NMR spectra of methapyriline hydrochloride (II HCl) in $CDCl_3$. The scale in hertz is different for the two spectra.

complished by comparing the observed powder diffraction pattern to the theoretical diffraction pattern calculated from the atom coordinates available from the single-crystal x-ray study.

Three methods are available for comparison of solid-state and solution infrared spectra (step 3): (1) visual comparison by superposition of the two spectra; (2) measurement of difference spectra as suggested by Grutzner,[11] and (3) tabular comparison of the absorption maxima. All three methods were used; however, the quickest comparison can often be made using the solid-state and solution difference spectra. Perfect agreement between solid-state and solution spectra was not expected since there are differences in band widths and selection rules between the solid state and solution. We have adopted the working hypothesis that for organic molecules of this size and uneven shape solid state–solution difference spectra will be considered identical if there are three or fewer deviations of greater than 10% T from the center line and no deviation greater than 25% T.

If the solution and solid-state infrared spectra are different further studies are required to establish the bonds about which the conformations differ.

Cases Where the Solid State Conformation Predominates in Solution. A. Choline Chloride. Choline chloride has the gauche conformation in the solid state[12] and NMR studies indicated that the gauche conformation also predominated in water solution (ca. 90% gauche, 10% trans).[13] Powder diffraction experiments showed that a phase transition was not induced by grinding. The ten most intense observed peaks corresponded to eight of the ten most intense calculated peaks. Figure 1 shows that the solid and solution ir spectra of choline chloride are identical. Thus it has essentially the same conformation in the solid state and in solution and the ir studies confirm the NMR analysis.

B. Methapyriline Hydrochloride. The crystal structure of methapyriline hydrochloride (II HCl) showed that the NCH_2CH_2N group had the trans conformation in the solid state.[14] There were two molecules per asymmetric unit in crystals of II HCl; these two molecules had different conformations about the C–N–pyridyl(–thenyl) bond. The powder pattern of a sample of plates of II HCl grown from 2-propanol was very similar to the powder pattern calculated from the single-crystal atomic coordinates using the program POWD5.

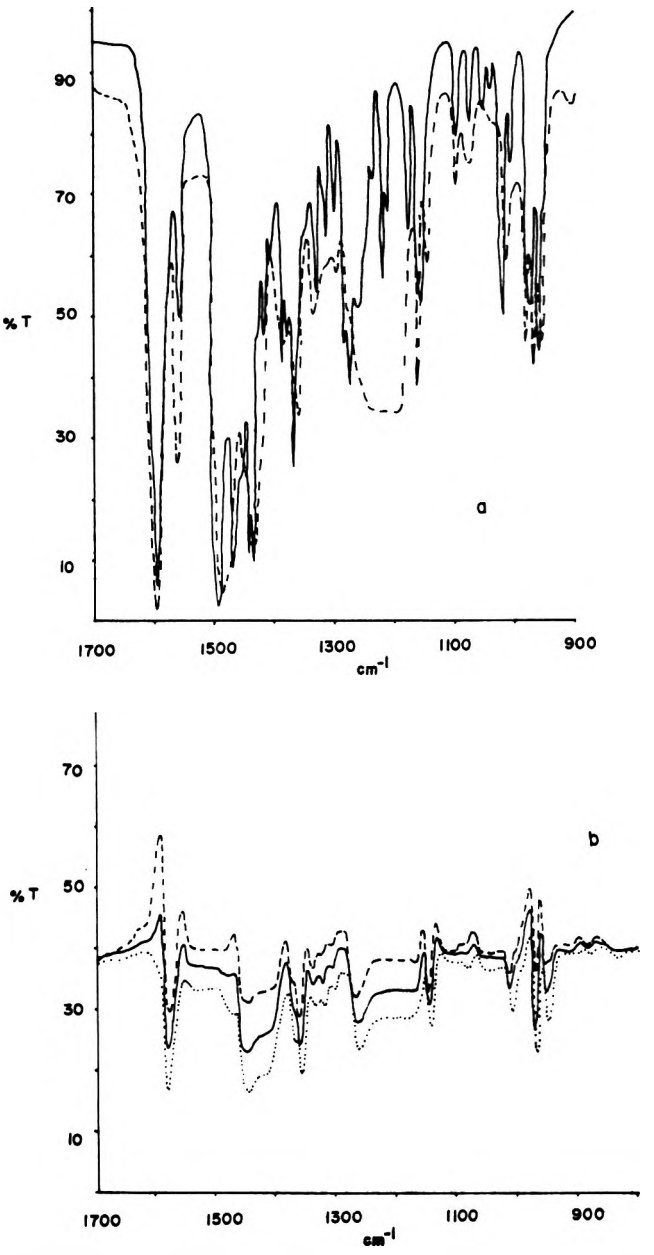


Figure 4. Infrared spectra (4a) of a Nujol mull (—) and $CHCl_3$ solution (- - -) of tripelennamine hydrochloride (IV HCl). Difference spectra (4b) between a Nujol mull and $CHCl_3$ solution of tripelennamine hydrochloride. The dashed line (- - -) corresponds to a solution concentration slightly more than that of the mull, the dotted line (· · ·) corresponds to a solution concentration slightly less than that of the mull, and the solid line (—) corresponds to a solution concentration nearly equal to that of the mull.

The 14 most intense observed lines in the powder pattern of ground II HCl corresponded to 14 of the 15 most intense calculated lines. This experiment showed that a phase transition was not induced upon grinding. The ir spectrum of these plates was virtually identical with the ir spectrum of needles grown from ethyl acetate and also with the ir spectra of crystals obtained from acetone, 1,2-dichloroethane, ethanol, or chloroform. These solid-state ir spectra were also very similar to the solution spectra of II HCl in chloroform, carbon tetrachloride, or water (see Figure 2a). The solid state and solution infrared difference spectra indicated that the spectra were similar although three deviations of greater than 10% T were observed. However, a solution concentration between that used for the difference spectra would almost certainly show no deviations of greater than 10% T. The ir spectrum of the free base, methapyriline (II), was also quite similar to these

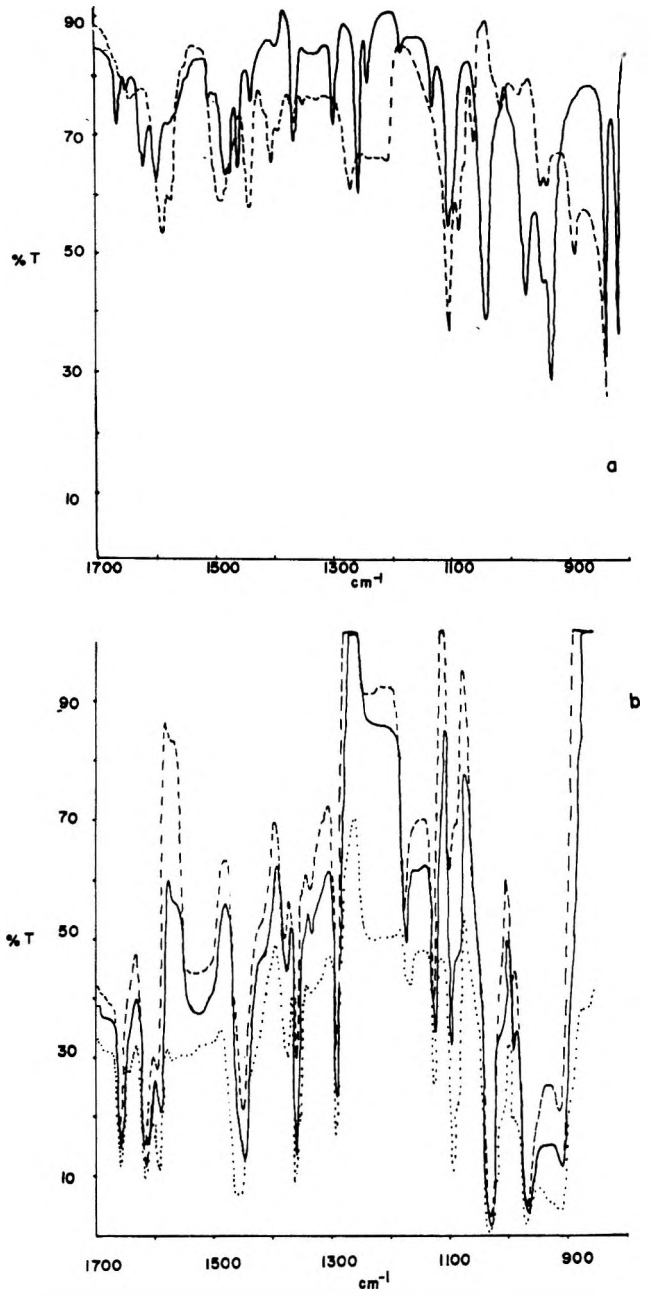


Figure 5. Infrared spectra (5a) of a Nujol mull (—) and $CHCl_3$ solution (- - -) of histamine (I). Difference spectra (5b) between a Nujol mull and a $CHCl_3$ solution of I. The dashed lines (- - -) corresponds to a solution concentration slightly more than that of the mull, the dotted line (· · ·) corresponds to a solution concentration slightly less than that of the mull, and the solid line (—) corresponds to a solution concentration nearly equal to that of the mull.

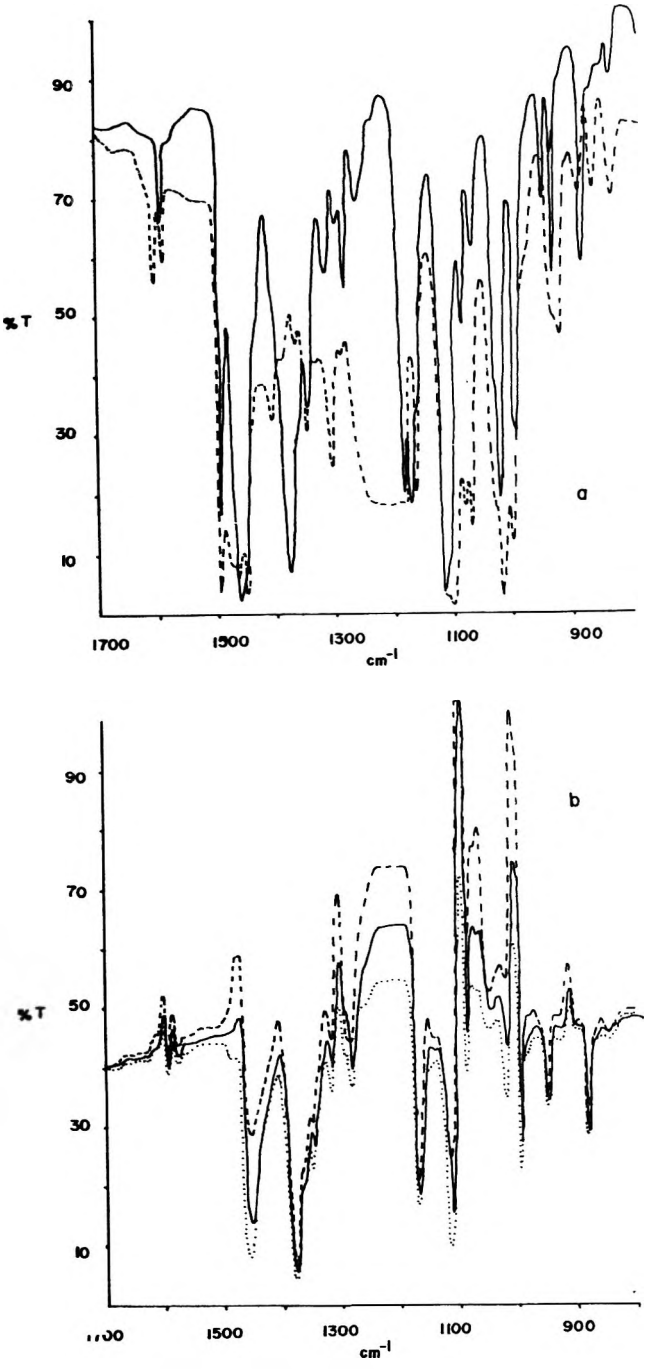


Figure 6. Infrared spectra (6a) of a Nujol mull (—) and $CHCl_3$ solution (- - -) of diphenhydramine hydrochloride (III HCl). Difference spectra (6b) between a Nujol mull and a $CHCl_3$ solution of III HCl. The dashed line (- - -) corresponds to a solution concentration slightly more than that of the mull, the dotted line (· · ·) corresponds to a solution concentration slightly less than that of the mull, and the solid line (—) corresponds to a solution concentration nearly equal to that of the mull.

solution spectra. This data indicates that methapyriline hydrochloride is in the same conformation in the solid state and in solution and the x-ray data show that this is the trans conformation. These data also indicate that there are two conformers about the C–N–pyridyl(–thenyl) bond in solution as in the solid.

The NMR spectra of methapyriline hydrochloride are also consistent with the assignment of a predominance of the trans conformation of methapyriline hydrochloride in solution. The spectra of the NCH_2CH_2N group of II HCl in chloroform-d_1, dimethyl sulfoxide-d_6, acetonitrile-d_3, methanol-d_4, and nitromethane were very similar except for slight solvent-induced chemical shift changes. Figure 3 shows expanded scale NMR spectra of the NCH_2CH_2N group of II HCl in $CDCl_3$ at 60 and 100 MHz.

The NMR spectra of methapyriline hydrochloride (II HCl) were calculated using coupling constants based on the solid state H–C–H and H–C–C–H angles and the Karplus[15] and Gutowsky–Karplus–Grant[16] relationships and the program NMRCAL.[17] These spectra were similar but not entirely consistent with the observed 60- and 100-MHz spectra (Figure 3). Nevertheless this exercise showed that these NMR spectra are "deceptively simple spectra"[18] and could be reproduced by a number of coupling constants and/or proportions of conformers. The ir–x-ray method allows clarification of such situations and is recommended in all cases where deceptively simple spectra are suspected.

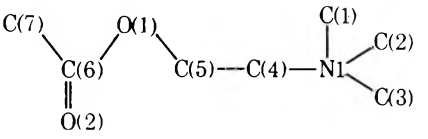
The evidence presented above, which is both experimental and theoretical, strongly suggests that the earlier suggestion[19] of methapyriline hydrochloride existing in an equally populated mixture of gauche and trans isomers in solution should be revised. The ir data in the solid state and in solution suggest that a conservative estimate of the percentage of trans conformer in solution would be 85–90%. The predominance of the trans ethylenediamine linkage is not consistent with experimental and theoretical studies of the parent compound ethylenediamine. These studies showed that gauche conformations were perferred over the trans by 1–2 kcal/mol in part due to the N–H···N hydrogen bond.[20] Electrostatic interactions rather than hydrogen bonding have been suggested to be the factors responsible for the predominance of gauche conformer in crystals and solutions of acetyl choline and derivatives.[13b] Apparently, the relatively weak N–H···N hydrogen bond and/or the H···N electrostatic interaction do not provide sufficient energy to overcome the steric repulsion involved in the gauche conformation of these substituted ethylenediamines. The NMR and ir spectra of the free base of methapyriline suggest that it is also in the trans conformation in solution.

C. Tripelennamine Hydrochloride. The solid-state infrared spectra (Nujol mull) of crystals of tripelennamine hydrochloride (IV HCl) grown from 1,2-dichloroethane, ethanol, chloroform, methanol, water, methylene chloride, or the melt were identical. These solid-state ir spectra were also virtually identical with the spectrum of IV HCl in chloroform (see Figure 4) and the solid-state and solution infrared difference spectra showed only three deviations of just slightly more than 10% T. The NMR spectra of the NCH_2CH_2N group of IV HCl in deuteriochloroform and D_2O were very similar to the spectra of the ethylenediamine portion of methapyriline hydrochloride.

These data suggest that tripelennamine hydrochloride, like methapyrilene hydrochloride, exists in solution as perhaps 85–90% of the trans conformer. This is consistent with the steric arguments used to explain the predominance of trans conformer in solutions of methapyrilene hydrochloride. The confirmation of the presence of trans conformer of tripelennamine hydrochloride in the solid state and in solution must await the determination of its crystal structure, which is in progress. The NMR and ir spectra of the free base of tripelennamine are also consistent with it being the trans conformer in solution.

Cases Where the Solution Conformation Differs from That in the Solid State. A. Histamine. The conformation of histamine (I) has been extensively studied in the solid state and in solution.[7,21,22] The solution NMR spectra of histamine (I) showed complex AA′BB′ multiplets for the ethylene group which led two groups of workers to conclude that I existed in a nearly equal proportion of gauche and trans conformers.[7,21] In the solid state histamine exists in the trans conformation,[22] and powder photographs of a ground sample of histamine matched the pattern calculated using the program POWD5 and crystallographic atom positions. Therefore, no phase transition occurred upon grinding and the mull spectrum was that of the pure trans conformer. If solutions of histamine consist of an equal proportion of gauche and trans rotamers, one would expect significant differences between the solid state and solution ir spectra. Figure 5 compares the spectra of histamine in the solid state (Nujol mull) and in solution ($CHCl_3$)[23] and shows the infrared difference spectra. As expected, there are significant differences between these spectra resulting in 13 deviations of greater than 10% T in the difference spectra. However, attempts to calculate the proportion of gauche and trans conformers from the changes in the relative peak heights of these absorptions have so far failed, perhaps due to deviations from Beer's law or to the fact that some of these absorptions may be due to different imidazole ring –C–C–N conformations between solution and the solid state. The fact that some of the bonds observed in the solid state are absent in solution substantiates this suggestion since both the gauche and trans forms of histamine are present in solution.

The possibility that differences in ir spectra may be due to differences in conformation about bonds other than the $-CH_2CH_2-$ group is consistent with infrared and x-ray crystallographic data on acetyl choline chloride and bromide. Crystallographic studies of these compounds showed that the O(1)–C(5)–C(4)–N(1), C(5)–O(1)–C(6)–O(2), and C(2)–



N(1)–C(4)–C(5) dihedral angles corresponded well, 84.7, 5.2, and 171.4° for the chloride and 78.4, 4.1, and 175.5° for the bromide. However, the C(4)–C(5)–O(1)–C(6) dihedral angle was 168.9° for the chloride and 78.9° for the bromide.[24] The ir spectra of acetyl choline chloride and bromide were different.[25] Absorptions at 916, 1077, 1135, and 1406 cm^{-1} in the Nujol mull spectra of the bromide were either weak or missing in mull spectra of the chloride while the 1456-cm^{-1} absorption in the chloride spectrum was missing in the bromide spectrum. Thus differences in ir spectra of molecules more complicated than the halogenated ethylenes studied by Mitzushima[5f] may arise from differences in conformation about bonds other than the bond of interest.

B. Diphenhydramine Hydrochloride. Infrared spectra of mulls of crystals of diphenhydramine hydrochloride (III HCl) grown from acetone, ethyl acetate, benzene–ethanol, chloroform, and the melt were identical with each other. However, these spectra were not identical with the ir spectrum of diphenhydramine hydrochloride in chloroform solution (see Figure 6). There were at least seven deviations of greater than 10% T in the difference spectra. Crystallographic studies indicate that there was either one or one-half molecule per asymetric unit ruling out the possibility that both the trans and gauche conformers were present in the solid state. Thus, in contrast to the ethylenediamine antihistamines there are different conformers present in the solid state and in solution. It is not clear whether these differences are due to rotation about the ethylene bond or some other bond in the molecule. There were also significant differences between the NMR and ir spectra of diphenhydramine hydrochloride and the free base; however, the reason for these differences in unclear.

Limits of the Method. The most serious limitation of this method is that it can probably only be successfully applied to relatively small molecules. Compounds with many functional groups which have conformations in the solid state and solution which differ by only a rotation about one bond would probably have identical infrared spectra. For example, our preliminary studies of diphenhydramine picrate indicate that the picrate anion obscures almost the entire fingerprint region of the spectrum. However, it is interesting to note that infrared spectra have been used to show that the solid state and solution conformations of some polypeptides are different.[26]

A second limitation is that infrared spectra cannot easily detect the presence of a few percent of a minor conformer. The large differences between the spectra of histamine in the solid and solution (Figure 5) showed that this method can easily detect 50% of another conformer; however, the similarities of the solid and solution spectra of choline chloride indicate that this method cannot detect the presence of a few percent of the minor conformer. Further studies are required to precisely

establish lower detection limits for the infrared–x-ray method; however, a conservative estimate is 15% of a minor conformer.

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Registry No.—I, 51-45-6; II HCl, 135-23-9; III HCl, 147-24-0; IV HCl, 22306-05-4; V, 67-48-1.

Supplementary Material Available. (1) Tables comparing the absorption maxima of the solid and solution ir spectra of choline chloride, methapyriline hydrochloride (II HCl), tripelennamine hydrochloride (IV HCl), histamine (I), and diphenhydramine hydrochloride (III HCl); and (2) detailed chemical shift data for the NMR spectra of methapyriline hydrochloride (II HCl), tripelennamine hydrochloride (IV HCl), and diphenhydramine hydrochloride (III HCl) (7 pages). Ordering information is given on any current masthead page.

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20-Methylcholesterol[1]

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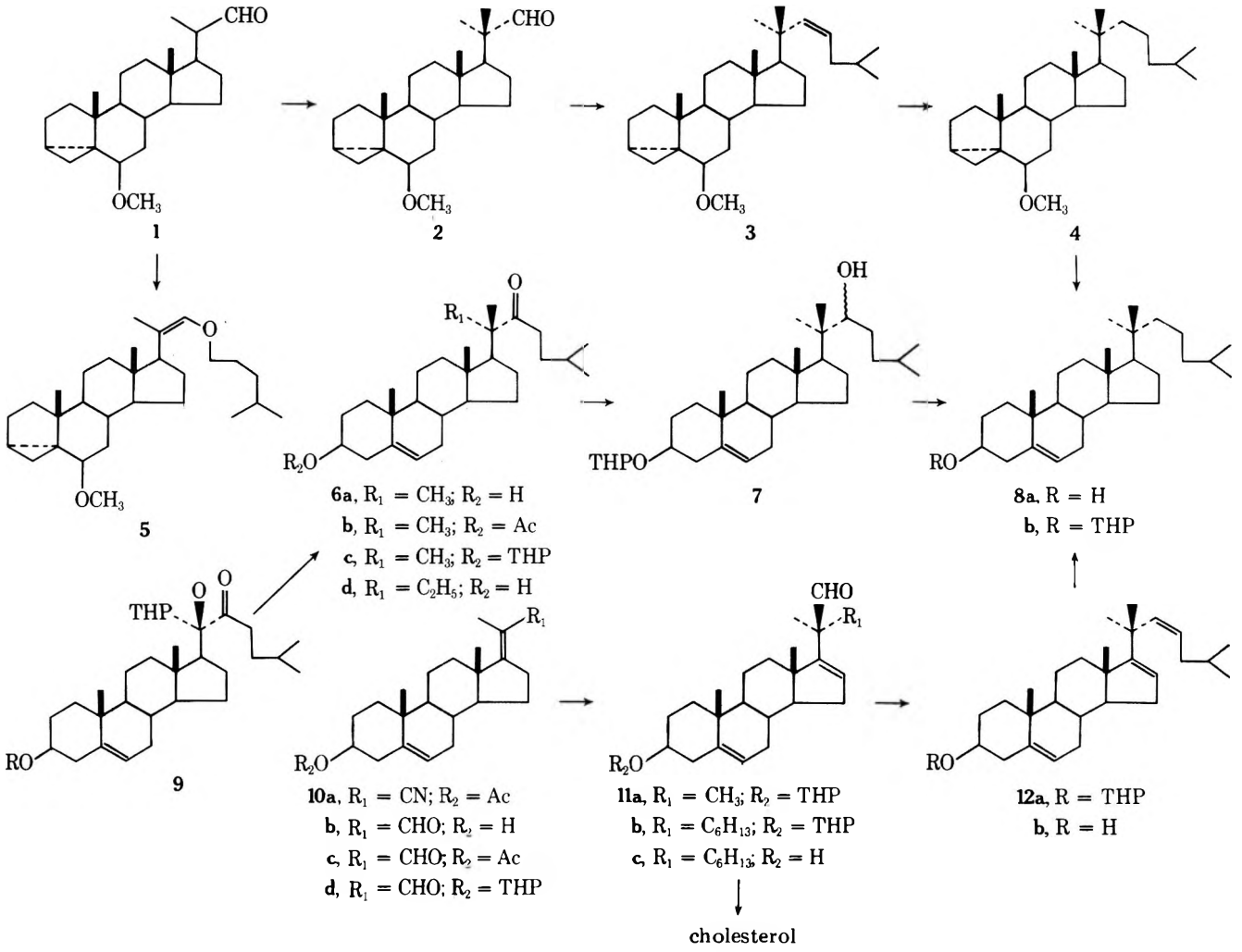
Three syntheses of 20-methylcholesterol (**8a**), resting on the alkylation of a C-20 anion with iodomethane, are described. The NMR signals of the 21- and the 28-methyl group are discussed in relation to the stereochemistry at C-20 of cholesterol and of 20-isocholesterol.

Within the framework of our studies[2] on the mechanism of the biodegradation of cholesterol to pregnenolone, we have investigated modifications[3] of the side chain of cholesterol. This paper describes syntheses of 20-methylcholesterol, a compound which cannot readily be metabolized by adrenals to pregnenolone and therefore was tested as a possible inhibitor both for the biosynthesis of cholesterol and for the biodegradation of cholesterol to pregnenolone.

The essence of the three syntheses described below consists in the generation of a carbanion at C-20, followed by its alkylation. Although there could be, a priori, a choice between the alkylation of a C-22 carbaldehyde with iodomethane, followed by the extension (of the aldehyde) to the complete cholesterol side chain, and the alkylation of a C-22 aldehyde with isohexyl bromide, followed by the conversion of the aldehyde to methyl, the second variant did not work: either the yield was poor, or the aldehyde suffered O-alkylation to give the enol ether **5**. This was revealed by its NMR spectrum, which lacked an aldehyde proton signal (δ 9–11) but indicated an olefinic methyl at δ 1.63, and also by its ir spectrum, giving a peak at 1660 cm^{-1}, commensurate with structures of similar enol ethers.[4]

The starting material for the first synthesis was the *i*-steroid aldehyde[5] **1**, which was alkylated with excess iodomethane (potassium *tert*-butoxide in *tert*-butyl alcohol) to give the α,α-dimethyl aldehyde **2** in 55% yield. The NMR spectrum of **2** shows a singlet at 9.66 ppm, in distinction to the doublet of the starting material **1**, where coupling (–CH–CHO) was observed. The stereoselectivity of this alkylation was studied by using iodomethane-d_3. The 250-MHz NMR indicates two



singlets for the C-20 methyls and the deuterated product shows relative intensities (for the two methyl peaks) of 3:2, indicating that the alkylation is only slightly stereoselective. The dimethyl aldehyde **2** was subjected to a Wittig reaction, according to Corey's procedure,[6] with isoamyltriphenylphosphonium bromide to give the olefin **3** in 60% yield. The olefin has the expected *Z* configuration as observed by Svoboda et al.[5] and others[7] in the formation of a cis olefin in similar cases. This is substantiated by the ir and NMR spectra (see Experimental Section). The dimethyl olefin **3** was catalytically reduced to give product **4**, which was solvolyzed to 20-methylcholesterol (**8a**) in 80% yield. The product is characterized by its two singlets at 0.85 and 0.92 ppm (*gem*-dimethyl) and by its mass spectrum, *m/e* 400.

The second synthesis involves the alkylation of (20*R*)-3β-hydroxy-20-tetrahydropyranyloxycholest-5-en-22-one (**9**).[8] This ketone was reduced in liquid ammonia with 2 equiv of calcium,[9] followed by the methylation of the resulting C-20 enolate with a large excess of iodomethane in tetrahydrofuran. The NMR of the alkylated product **6a** revealed an additional methyl peak (1.12 and 1.16 ppm, *gem*-dimethyl at C-20) and the mass spectrum showed the fragmentation of the 20–22 bond by the fragment *m/e* 315 ($M - C_6H_{11}O$).

The Alkylation at C-20 Is Stereospecific. The alkylation at the very hindered C-20 allows approach exclusively from the α side. The product of the iodomethane-d_3 alkylation shows in its NMR spectrum only one methyl peak at 1.11 ppm, indicative of a 28-CH_3 group and a 21-CD_3 group. The specific assignments for the C-20 *gem*-dimethyl peaks were obtained from the following considerations. (a) The doublet of the 21-methyl of (20*S*)-22-ketocholesterol is downfield (1.09 ppm), compared to the 21-methyl of its 20*R* isomer (1.00 ppm).[10] (b) The comparison of the 21-methyl peaks of a series of C-20 isomeric cholesteryl compounds[11] gave values of δ 0.91–0.95 for the 20*R* configuration and a range of δ 0.83–0.86 for the 20*S* configuration. In close analogy with these values, we assigned to the 21-methyl (below the plane) a value downfield relative to the 28-methyl (above the plane). After alkylation, the 3β-hydroxyl of **6a** was converted to its tetrahydropyranyl ether and the C-22 ketone reduced with lithium aluminum hydride. The mixture of epimeric alcohols at C-22 was mesylated and the mesylates reduced with lithium aluminum hydride to give 20-methylcholesterol tetrahydropyranyl ether (**8b**). Acid hydrolysis gave the desired 20-methylcholesterol (**8a**). The 100-MHz spectrum of 20-methylcholesterol (**8a**) reveals a downfield shift of the 18-methyl in comparison to cholesterol and to 20-isocholesterol.[12] The shift of 0.08 ppm is probably due to an interaction of the methyls 21 and 28.

The third synthesis rests on the alkylation of the aldehyde **10d.** This aldehyde was prepared by the reduction of the known (*E*)-3β-acetoxypregna-5,17(20)-diene-20-carbonitrile[13] (**10a**) with diisobutylaluminum hydride. Alkylation of the conjugated aldehyde **10d** with iodomethane gave product **11a** in a yield of 60%. The ir spectrum indicates the deconjugation of the carbonyl and the NMR spectrum shows singlets at 1.20 and 1.25 ppm, representing the *gem*-dimethyl at C-20. The stereoselectivity of this alkylation could be demonstrated since, contrary to the case of the saturated aldehyde **1** which was O-alkylated (see above) with isohexyl iodide, the conjugated aldehyde could be alkylated to 3β-hydroxycholesta-5,16-diene 20-carbaldehyde (**11c**) in 15% yield. The ir indicated a saturated aldehyde and the NMR spectrum showed a singlet for the 21-methyl at 1.22 ppm. The diene **11c** was

reduced over platinum oxide catalyst in 95% ethanol and gave 3β-hydroxycholest-5-ene 20-carbaldehyde which was not analyzed but directly decarbonylated to cholesterol with tris(triphenylphosphine)chlororhodium, a procedure[14] known to give a product with retention of configuration. The α,α-dimethyl aldehyde **11a** was subjected to a modified Wittig reaction[6] with isoamyltriphenylphosphonium bromide to give the triene **12a**, which was hydrolyzed to the 3β-hydroxy compound **12b** in an overall yield of 30%. Selective catalytic reduction of the triene **12b** with platinum oxide gave the title compound **8a**.

Assays[15] for inhibition of cholesterogenesis reveal 20-methylcholesterol to be inactive at a concentration of 1×10^{-4} M. The compound is equally inactive as inhibitor of cholesterol degradation (to pregnenolone) when tested in vivo under our standard conditions.[16]

Experimental Section

Melting points were determined on a Kofler melting point apparatus and are uncorrected. The NMR spectra were obtained in deuteriochloroform solution on a 60-MHz Varian EM360 and a 100-MHz Varian HA100D-15, with C1024 computer, using tetramethylsilane as an internal reference and the positions of the proton signals are expressed in parts per million downfield from tetramethylsilane signals. The mass analyses were obtained on an Atlas CH4, an ACI MS9, or an LKB 9000 spectrograph, using a direct insertion probe.

6β-Methoxy-20-methyl-3α,5-cyclo-5α-23,24-bisnorcholan-22-al (2) from 6β-Methoxy-3α,5-cyclo-5α-23,24-bisnorcholan-22-al (1). A solution of 1.4 g of potassium *tert*-butoxide in 30 ml of *tert*-butyl alcohol was added to a solution of 2.0 g of the aldehyde **1** in 20 ml of *tert*-butyl alcohol. After the addition of 3.5 ml (10 equiv) of methyl iodide the solution was stirred at room temperature for 18 h. Then the solution was poured on ice and the product isolated by extraction with ether. Chromatographic separation on Florisil gave, with the 2% ether in hexane eluates, 1.1 g (55%) of alkylated product **2** which could not be crystallized: ir 1705 (–CHO), 1090, 1010, and 960 cm^{-1} (6-OCH_3-*i*); NMR δ 0.75 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.12 [2s, 6, C-$(CH_3)_2$], 3.33 (s, 3, –OCH_3), 9.67 ppm (s, 1, –CHO).

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.67; H, 10.89.

Attempted C-Alkylation of Aldehyde 1 with Isohexyl Bromide. Formation of Ether 5. A solution of 800 mg of potassium *tert*-butoxide in 20 ml of *tert*-butyl alcohol was added to a solution of 1 g of the aldehyde **1** in 20 ml of *tert*-butyl alcohol. After the addition of 4 ml (10 equiv) of 1-bromo-4-methylpentane (isohexyl bromide) the solution was stirred at 25 °C for 18 h. A small sample was removed and worked up as described for the alkylation with methyl iodide. Only starting material could be isolated. Therefore the solution was heated under reflux for 3 h and then cooled and poured on ice. The crude product was isolated by ether extraction and purified by chromatography on preparative thin layer plates. The bulk of the material was the least polar (using 5% ether in hexane), leading to the isolation of 260 mg of pure syrupy enol ether **5**: ir 1660 (vinyl ether), 1170, 1120, 1080 (ether bands), 1010 and 960 cm^{-1} (6-OMe-*i*); NMR δ 0.62 (s, 3, 18-CH_3), 0.88 [d, 6, 26,27-$CH(CH_3)_2$], 1.02 (s, 3, 19-CH_3), 1.63 (s, 3, 21-CH_3), 2.78 (m, 1, 6α-H), 3.34 (s, 3, –OCH_3), 3.66 (t, 2, J = 6 Hz, –OCH_2–), 5.83 ppm (m, 1, 22-H).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.06; H, 11.30.

(*Z*)-6β-Hydroxy-3α,5-cyclo-5α-20-methylcholest-22-ene 6-Methyl Ether (3) from 2. The suspension of 900 mg of sodium hydride in 15 ml of dimethyl sulfoxide was heated with stirring under nitrogen at 70–75 °C. After the hydrogen evolution ceased (ca. 45 min), the solution was cooled and the solution of 15.5 g of isoamyltriphenylphosphonium iodide in 50 ml of dimethyl sulfoxide was added quickly. To this red solution was added rapidly the solution of 5.4 g of 6β-methoxy-3α,5-cyclo-20-methyl-5α-23,24-bisnorcholan-22-al (**2**) in 75 ml of dimethyl sulfoxide. The combined solutions were heated with stirring under nitrogen at 55–60 °C for 3 h, then cooled and poured on ice. The crude product was isolated by extraction with ether. Chromatography on alumina gave with the hexane fractions 3.8 g (60%) of pure **3** as a syrup: ir 1010 cm^{-1} (–OMe); NMR δ 0.79 (s, 3, 18-CH_3), 0.91 [d, 6, J = 6 Hz, 26,27-$CH(CH_3)_2$], 1.02 (s, 3, 19-CH_3), 1.12 and 1.14 (2 s, 3, 3, 21- and 28-CH_3), 5.13 (d of t, 1, J_{23-22} = 12 and J_{23-24} = 6 Hz, 23-H), and 5.45 ppm (d of t, J_{22-23} = 12 and J_{22-24} = 1 Hz, 22-H).

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.31; H, 11.72.

6β-Hydroxy-3α,5-cyclo-5α-20-methylcholestane 6-Methyl Ether (4) from 3. To the solution of 3.5 g of **3** in 200 ml of 95% ethanol was added 350 mg of 10% palladium on charcoal and the mixture was hydrogenated at room temperature and 30–35 psig for 18 h. The catalyst was removed by filtration and the ethanol evaporated. The 3.42 g (97%) of residue could not be crystallized, but appeared clean on TLC: ir 1010 and 960 cm^{-1} (6-OMe-*i*); NMR δ 0.77 (s, 3, 18-CH_3), 0.85 [d, 6, J = 6 Hz, 26,27-$CH(CH_3)_2$], 0.86 (s, 3, 28-CH_3), 0.92 (s, 3, 21-CH_3), 1.01 ppm (s, 3, 19-CH_3).

Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.27; H, 12.23.

20-Methylcholesterol (8a) from 4. The solution of 3.4 g of the ether **4** in 90 ml of dioxane was heated to 80 °C and then 160 mg of *p*-toluenesulfonic acid and 32 ml of water were added. The solution was kept at 80 °C for 6 h, then cooled in ice, whereby the product crystallized. After one recrystallization from methanol 2.6 g (81%) of pure 20-methylcholesterol (**8a**), mp 122–124 °C, was obtained: ir 3400 cm^{-1} (–OH); NMR δ 0.75 (s, 3, 18-CH_3), 0.85 [d, 6, J = 6 Hz, 26,27-$CH(CH_3)_2$], 0.85 (s, 3, 28-CH_3), 0.92 (s, 3, 21-CH_3), 0.98 ppm (s, 3, 19-CH_3).

Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.70; H, 12.06.

3β-Hydroxy-20-methylcholest-5-en-22-one (6a) from 9. Approximately 250 ml of anhydrous liquid ammonia was introduced into a 500-ml three-neck flask. While stirring vigorously 320 mg of calcium was added slowly. After the metal was dissolved, a solution of 2.0 g of (20*R*)-20-tetrahydropyranyloxy-22-ketocholesterol (**9**) in 30 ml of anhydrous tetrahydrofuran was added over a period of 0.5 h. After the blue-colored solution had turned colorless 50 ml of anhydrous tetrahydrofuran was added and the ammonia was allowed to evaporate. With most of the ammonia removed, 5 ml of methyl iodide in 10 ml of tetrahydrofuran was added and the solution was stirred at 25 °C overnight. A saturated solution of ammonium chloride was added and the mixture was extracted with ether. The ether solution was washed and dried and the solvent evaporated. The oily residue was chromatographed on a silica gel column which gave (5% ethyl acetate in benzene) 350 mg of pure alkylated product **6a**. Recrystallization from methanol furnished an analytical sample: mp 117–118 °C; ir 3330 (–OH) and 1680 cm^{-1} (>CO); NMR δ 0.73 (s, 3, 18-CH_3); 0.90 [d, 6, J = 6 Hz, 26,27-$CH(CH_3)_2$], 1.00 (s, 3, 19-CH_3), 1.12 (s, 3, 28-CH_3), 1.17 ppm (s, 3, 21-CH_3).

Anal. Calcd for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.10; H, 11.14.

3β-Acetoxy-20-methylcholest-5-en-22-one (6b). Acetylation of the alcohol **6a** with acetic anhydride and pyridine gave, after recrystallization from methanol, a pure analytical sample of the acetate **6b**: mp 119–120 °C; ir 1725 (–Ac), 1680 (–CO–), and 1240 cm^{-1} (Ac); NMR δ 0.72 (s, 3, 18-CH_3), 0.90 [d, 6, J = 6 Hz, 26,27-$CH(CH_3)_2$], 1.00 (s, 3, 19-CH_3), 1.13 (s, 3, 28-CH_3), 1.17 (s, 3, 21-CH_3), 2.04 ppm (s, 3, –$OCOCH_3$); mass spectrum *m/e* 396 (M – AcOH, 34%), 297 (M – AcOH – $C_6H_{11}O$, 100%).

Anal. Calcd for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 79.00; H, 10.46.

3β-Tetrahydropyranyloxy-20-methylcholest-5-en-22-one (6c). To the solution of 300 mg of the alcohol **6a** in 2 ml of 2,3-dihydropyran was added 1 drop of phosphorus oxychloride (25 °C, 18 h). The solution was poured into a chilled saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with water and dried over sodium sulfate and the solvent evaporated. After purification on TLC there was obtained 290 mg of solid **6c**, mp 104–105 °C, after recrystallization from methanol: NMR δ 0.71 (s, 3, 18-CH_3), 0.89 [d, 6, J = 6 Hz, 26,27-$CH(CH_3)_2$], 0.98 (s, 3, 19-CH_3), 1.12 (s, 3, 28-CH_3), 1.16 ppm (s, 3, 21-CH_3); mass spectrum *m/e* 396 (M – THPOH, 56%), 297 (M – THPOH – $C_6H_{11}O$, 57%), and 85 (100%).

Anal. Calcd for $C_{33}H_{54}O_3$: C, 79.46; H, 10.92. Found: C, 79.51; H, 10.76.

22-Hydroxy-20-methylcholesterol 3β-Tetrahydropyranyl Ether (22-Isomeric Mixture) (7). To the solution of 200 mg of the ketone **6c**, 100 mg of lithium aluminum hydride was added and the mixture heated under reflux for 18 h. The excess reagent was decomposed with 2 N sodium hydroxide. Solid sodium sulfate was added, and the precipitate was filtered off and washed with hot ethyl acetate. Evaporation of the filtrate gave, after purification on TLC, 120 mg of pure **7**, mp 139–140 °C after recrystallization from hexane: ir 3550 cm^{-1} (OH); NMR δ 0.78 (s, 3, 18-CH_3), 0.87 (s, 3, 28-CH_3), 0.89 [d, 6, J = 6 Hz, 26,27-$CH(CH_3)_2$], 0.97 (s, 3, 21-CH_3), and 1.00 ppm (s, 3, 19-CH_3); mass spectrum *m/e* 398 (M – THPOH, 16%), 297 (M – THPOH – $C_6H_{13}O$, 12%), and 85 (100%).

Anal. Calcd for $C_{33}H_{56}O_3$: C, 79.14; H, 11.27. Found: C, 78.82; H, 11.17.

20-Methylcholesterol 3β-Tetrahydropyranyl Ether (8b). To a solution of 100 mg of the alcohol **7** in 1 ml of pyridine 2 drops of mesyl chloride was added and the solution left at 23 °C for 18 h. After the addition of water the product was extracted with methylene chloride, the organic phase washed, then dried, and the solvent evaporated. The crude residue (105 mg) was dried in a desiccator over phosphorus pentoxide and then added to a solution of 50 mg of lithium aluminum hydride in 5 ml of tetrahydrofuran and this solution heated under reflux overnight. The usual workup (see **7** above) gave, after recrystallization from methanol, 43 mg of pure **8b:** mp 100–101 °C; ir 1025 and 960 cm^{-1} (ether); NMR δ 0.75 (s, 3, 18-CH_3), 0.85 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 0.85 (s, 3, 28-CH_3), 0.92 (s, 3, 21-CH_3), 0.99 ppm (s, 3, 19-CH_3).

Anal. Calcd for $C_{33}H_{56}O_2$: C, 81.75; H, 11.64. Found: C, 81.52; H, 11.57.

20-Methylcholesterol (8a). The solution of 50 mg of the ether **7** in 2 ml of ethanol containing 2.5 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 1 h. After cooling the solution was diluted with water and the product extracted with methylene chloride. After evaporation of the solvent the residue was recrystallized twice from methanol to give 35 mg of pure **8a:** mp 121–123 °C; ir 3400 cm^{-1} (-OH); NMR in all respects identical with that of the material obtained previously.

(20*S*)-3β-Hydroxy-20-ethylcholest-5-en-22-one (6d). The alkylation of 20α-tetrahydropyranyloxy-22-ketocholesterol (**9**) with ethyl bromide was carried out as described for the 20-methyl analogue above. Thus, 1.0 g of tetrahydropyranyloxy ketone gave 181 mg of alkylated material **6d,** mp 114–115 °C, after two recrystallizations from methanol: ir 3300 (-OH), 1680 cm^{-1} (CO); NMR δ 0.71 (s, 3, 18-CH_3), 0.80 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 0.98 (s, 3, 19-CH_3), and 1.12 ppm (s, 3, 28-CH_3); mass spectrum m/e 329 (M − $C_6H_{11}O$, 67%), 311 (M − $C_6H_{11}O$ − H_2O, 100%), and 271 (15%).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 79.10; H, 10.71. Found: C, 78.77; H, 10.73.

(*E*)-3β-Hydroxypregna-5,17(20)-diene 20-Carbaldehyde (10b) and Its Acetate from 10a. The solution of 10 g of the nitrile **10a** in 200 ml of dry toluene was cooled to −70 °C under a nitrogen atmosphere, while stirring. Then 65.0 ml of a 20% solution of diisobutylaluminum hydride in hexane was added. The solution was kept at −70 °C for an additional 30 min and then kept at room temperature overnight. The solution was then poured into an ice-cold saturated solution of ammonium chloride, 2 N sulfuric acid was added until pH 3, and finally the product was extracted with methylene chloride. The organic phase was washed with water and with a saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was chromatographed on a column of Florisil. The eluates with 10% ether in benzene furnished, after recrystallization from methanol, 8.1 g of **10b:** mp 137–138 °C; ir 3350 (-OH), 1645 and 1610 cm^{-1} (conjugated aldehyde); NMR δ 0.98 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.82 (s, 3, 21-CH_3), 2.90 (16-H), 5.42 (d, 1, 6-H), and 9.98 ppm (s, 1, -CHO).

Anal. Calcd for $C_{22}H_{32}O_2$·CH_3OH: C, 76.62; H, 10.07. Found: C, 76.57; H, 10.49.

Upon acetylation of the alcohol **10b** with acetic anhydride and pyridine, the acetate **10c** was obtained, mp 150–153 °C, after two recrystallizations from ether.

Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.95; H, 9.49.

(*E*)-3β-Tetrahydropyranyloxypregna-5,17(20)-diene 20-Carbaldehyde (10d) from 10b. To a solution of 8.1 g of the alcohol **10b** in 200 ml of tetrahydrofuran 8 ml of dihydropyran and 400 mg of *p*-toluenesulfonic acid were added. After standing for 4 h at room temperature, the solution was poured into a saturated solution of sodium bicarbonate and the mixture extracted with ether. The organic phase was washed with saline and water and dried, and the solvent was evaporated. The crude product was chromatographed on an alumina column, whereby the 10% ether in benzene eluates gave 8.9 g of ether **10d:** mp 143–146 °C; ir 1660 and 1610 (conjugated aldehyde), 1030 and 960 cm^{-1} (ether); NMR δ 0.98 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.82 (s, 3, 21-CH_3), 9.98 ppm (s, 1, -CHO).

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.40; H, 9.69.

3β-Tetrahydropyranyloxy-20-methylpregna-5,16-diene 20-Carbaldehyde (11a) from 10d. To the solution of the anion of dimethyl sulfoxide, prepared as described for the preparation of **3** from **2,** the solution of 16.0 g of the conjugated aldehyde **10d** in 100 ml of tetrahydrofuran was added while stirring. After 1 h 4.0 g of iodomethane was added and stirring continued for 18 h. The solution was then poured into ice-cold water and the product was isolated by ether extraction. The ether extract was washed with a saline solution, then dried, and the ether evaporated off to give 12.7 g of crude residue. Upon chromatography on silica the benzene fractions furnished 10.1 g of α,α-dimethyl aldehyde **11a:** mp 146–148 °C; ir 1730 (aldehyde), 1025 and 955 cm^{-1} (THP ether); NMR δ 0.82 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.20 and 1.25 [2 s, 3, 3, -C(CH_3)$_2$], 9.33 ppm (s, 1, -CHO).

Anal. Calcd for $C_{28}H_{42}O_3$: C, 78.82; H, 9.92. Found: C, 78.70; H, 10.21.

(*Z*)-3β-Hydroxy-20-methylcholesta-5,16,22-triene (12b) from 11a. To the solution of the anion of dimethyl sulfoxide, prepared as described above, a solution of 5.40 g of isoamyltriphenylphosphonium iodide in 50 ml of dimethyl sulfoxide was added at once. To this deep red solution was added rapidly a solution of 1.0 g of the aldehyde **11a** in 70 ml of dimethyl sulfoxide. The combined solutions were heated, while stirring under nitrogen, to 60 °C for 5 h, then cooled and poured on ice. The crude product was isolated by extraction with ether. Chromatography on an alumina column gave with the benzene eluates 502 mg of olefin **12a** as a yellow syrup which could not be crystallized: ir 960 and 1040 cm^{-1} (ether); NMR δ 0.83 (s, 3, 18-CH_3), 0.93 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.03 (s, 3, 19-CH_3), 1.23 [s, 3, 3, 21,28-C(CH_3)$_2$].

Without further purification, 400 mg of the ether **12a** was dissolved in 25 ml of methylene chloride and 25 ml of methanol. After the addition of 10 drops of concentrated hydrochloride acid the solution was left at room temperature overnight. The solvents were evaporated in vacuo and the residue chromatographed on silica TLC with benzene/10% ether. The product which was isolated by extraction from silica was recrystallized from acetone to give 286 mg of **12b:** mp 104–106 °C; ir 3350 cm^{-1} (OH); NMR δ 0.83 (s, 3, 18-CH_3), 0.95 [d, 6, 26,27-CH(CH_3)$_2$], 1.27 [2 s, 6, 21,28-C(CH_3)$_2$].

Anal. Calcd for $C_{28}H_{44}O$: C, 84.78; H, 11.18. Found: C, 84.64; H, 11.77.

20-Methylcholesterol (8a) from 12b. To a solution of 120 mg of the triene **12b** in 70 ml of 95% ethanol was added 12 mg of platinum oxide catalyst. The mixture was hydrogenated at 1 atm of hydrogen. After 110% of the calculated hydrogen was taken up the reaction was stopped, the ethanol evaporated in vacuo, the organic residue dissolved in methylene chloride, and the catalyst filtered off through Celite. The filtrate was evaporated to dryness and the residue crystallized from acetone to give 96 mg of **8a,** mp 120–123 °C, identical upon admixture with authentic standard. This material also had ir and NMR spectra indistinguishable from those obtained with material obtained previously by other syntheses.

3β-Hydroxycholesta-5,16-diene 20-Carbaldehyde (11c) from 10d. To a solution of the anion of dimethyl sulfoxide, prepared as described earlier, a solution of 2.0 g of the aldehyde **10d** in 20 ml of dimethyl sulfoxide was added. After 1 h 4.0 g of 1-bromo-4-methylpentane was added and the stirring continued overnight. The solution was now poured on ice and 2.1 g of crude product was isolated by ether extraction. Purification an preparative TLC gave 411 mg of relatively pure ether **11b** which could not be crystallized. Without further purification, the whole amount was hydrolyzed in a solution of 100 ml of tetrahydrofuran to which 5 drops of concentrated hydrochloric acid had been added and the solution let stand for 18 h. Dilution with water followed by extraction with methylene chloride gave 382 mg of a crude alcohol which was repeatedly recrystallized from methanol to give 315 mg of **11c:** mp 114–116 °C; ir 1680 (aldehyde), 960 and 1030 cm^{-1} (ether); NMR δ 0.82 (s. 3, 18-CH_3), 0.90 [d. 6, 26,27-CH(CH_3)$_2$], 1.03 (s, 3, 19-CH_3), 1.22 (s, 3, 21-CH_3), 9.32 ppm (s, 1, -CHO).

Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.53; H, 11.03.

Cholesterol from 3β-Hydroxycholesta-5,16-diene 20-Carbaldehyde (11c). A solution of 450 mg of the diene **11c** in 100 ml of 95% ethanol was reduced, at 1 atm, with hydrogen and 40 mg of prereduced platinum oxide. The reaction was stopped after 1.1 equiv of hydrogen was absorbed and the mixture was evaporated to dryness. The product was dissolved in methylene chloride and the catalyst was removed by filtration through Celite. The filtrate was evaporated to dryness and the residue filtered through a small column of alumina. The eluates gave 410 mg of 3β-hydroxycholest-5-ene 29-carbaldehyde which appeared as a single spot on TLC and was different from its starting material. The solution of 410 mg of this aldehyde and 1.0 g of tris(triphenylphosphine)chlororhodium in 50 ml of xylene was refluxed for 18 h, then cooled and 100 ml of ethanol added. The precipitated bis(triphenylphosphine)carbonylchlororhodium (670 mg, >80%) was removed by filtration, the filtrate evaporated to dryness in vacuo, and the residue chromatographed on an alumina column to give with the 5% ether in benzene eluates 211 mg of cholesterol, mp 149–150 °C, unchanged by admixture to an authentic sample. The ir and NMR spectra were idencal with those of an authentic standard.

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Registry No.—**1**, 25819-77-6; **2**, 58958-20-6; **3**, 58958-21-7; **4**, 58958-22-8; **5**, 58958-23-9; **6a**, 58958-24-0; **6b**, 58958-25-1; **6c**, 58958-26-2; **6d**, 58958-27-3; **7**, 58958-28-4; **8a**, 58958-29-5; **8b**, 58958-30-8; **9**, 26622-97-9; **10a**, 3092-00-0; **10b**, 58958-31-9; **10c**, 58958-32-0; **10d**, 58958-33-1; **11a**, 58958-34-2; **11b**, 58958-35-3; **11c**, 58958-36-4; **12a**, 58966-79-3; **12b**, 58958-37-5; methyl iodide, 74-88-4; 1-bromo-4-methylpentane, 626-88-0; isoamyltriphenylphosphonium iodide, 52710-37-9; cholesterol, 57-88-5.

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Synthesis and Cyclization of 21-Hydroxyethylthioprogesterone Derivatives

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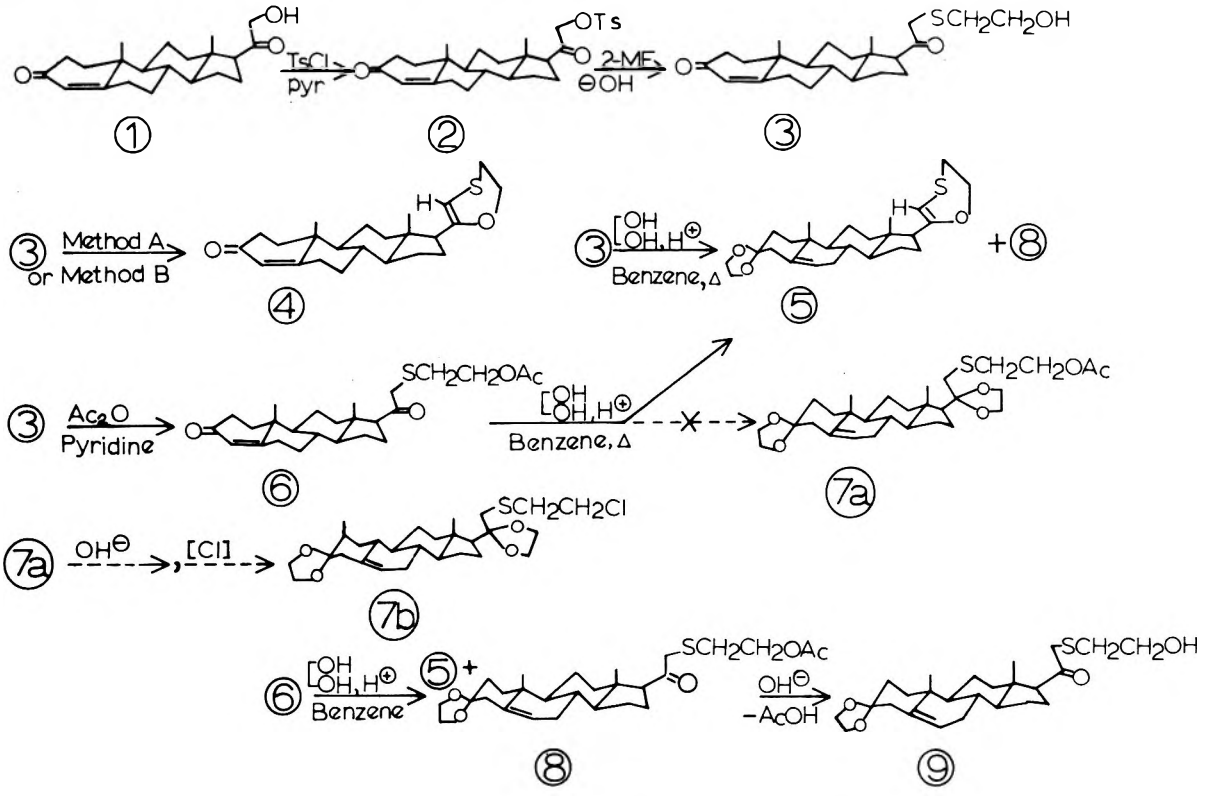
Treatment of 21-*p*-toluenesulfonyloxyprogesterone with 2-mercaptoethanol gives 21-hydroxyethylthioprogesterone. Under reaction conditions which usually produce chlorination of primary alcohols 21-hydroxyethylthioprogesterone cyclizes to 17β-(5′,6′-dihydro-1′,4′-oxathiin-2′-yl)-4-androsten-3-one. Following acetylation of the 21-hydroxyethylthio group of the title compound, acid-catalyzed ketalization of the resulting acetate gives a resolvable mixture of 3-ethylene ketals of 21-acetoxyethylthio-5-pregnene-3,20-dione and 17β-(5′,6′-dihydro-1′,4′-oxathiin-2′-yl)-5-androsten-3-one. The anticipated 3,20-diethylene ketal of 21-acetoxyethylthio-5-pregnene-3,20-dione could not be detected in the reaction mixture using a variety of reaction conditions. The C-21 sulfur atom is believed to influence the courses of the deacetylation and cyclization reactions. Mechanisms are proposed to account for these results. Nuclear magnetic resonance, infrared, and ultraviolet spectral properties of the new steroid dihydroxathiins are discussed.

Steroid alkylating agents were previously synthesized in this laboratory to serve as active site directed irreversible inhibitors for studies of the steroid binding site of 20β-hydroxy steroid dehydrogenase (E.C.1.1.1.53).[1-3] One of a series of isomeric bromoacetoxyprogesterone derivatives, 4-pregnen-16α-ol-3,20-dione 16-bromoacetate, terminates pregnancy in rats.[4] Similarly, the steroid alkylating agent 4-estren-17β-ol-3-one 17-bromoacetate is an interceptive agent in rats and primates.[5] The benzylic halide 1,3,5(10)-estratriene-2,4-dibromomethyl-3-ol-17-one 3-*O*-methyl ether was found to be a persistent anti-estrogen.[6] Predictably, all of the bromoacetoxyprogesterone derivatives which were synthesized are susceptible to hydrolysis in aqueous media possessing pH values above 7.0. Indeed, following inactivation of 20β-hydroxy steroid dehydrogenase with 4-pregnen-6β-ol-3,20-dione bromoacetate, or 4-pregnen-11α-ol-3,20-dione bromoacetate, at pH 7.0, the enzyme is readily reactivated by adjusting the pH to 8.0 or 9.0.[7] Similar alkaline conditions produce hydrolytic cleavage of the ester bond in conjugates between steroid bromoacetates and nucleophilic amino acids.[2]

Steroid alkylating agents possessing greater stability toward hydrolysis over a broad pH range compared to the bromoacetates are desirable for our biological experiments. Therefore, we attempted to synthesize 21-(2′-chloroethylthio)progesterone, which was expected to have the desired chemical properties. The present report describes the synthesis of 21-(2′-hydroxyethylthio)progesterone and the results obtained when this steroid and its derivatives were treated under conditions conventionally employed for chlorination of primary alcohols.

11-Deoxycorticosterone (**1**, Scheme I) was converted to the corresponding 21-toluenesulfonate (**2**) by Borrevang's procedure.[8] Upon treatment of **2** with alkaline 2-mercaptoethanol 21-(2′-hydroxyethylthio)-4-pregnene-3,20-dione (**3**) was obtained. Reaction of **3** with thionyl chloride in chloroform,[9] or hexamethylphosphorus triamide and carbon tetrachloride in chloroform,[10] did not provide the expected 21-(2′-chloroethylthio)-4-pregnene-3,20-dione (**3b**) but instead gave a new compound **4**. This steroid does not exhibit a 1700-cm^{-1} ir absorption (characteristic of a C-20 carbonyl), but has a strong 1630-cm^{-1} absorption. Compound **4** possesses an unusually strong ultraviolet absorption [λ_{max} (CH_3OH) 238 nm (ϵ 24 000)], more thoroughly discussed below. Elemental analysis, NMR, ir, and uv spectral data of **4** support the structural

Scheme I



assignment as represented in Scheme I. The NMR signal due to the C-4 proton appears as a broad singlet at τ 4.31 (similar to that observed for the corresponding vinyl protons in **1**, **2**, and **3**). The resonance signal due to the C-3′ vinyl proton in the 5′,6′-dihydro-1′,4′-oxathiin system is observed as a sharp singlet at τ 5.19. Group contribution calculations[11] predict this value for the C-3′ vinyl proton resonance signal.

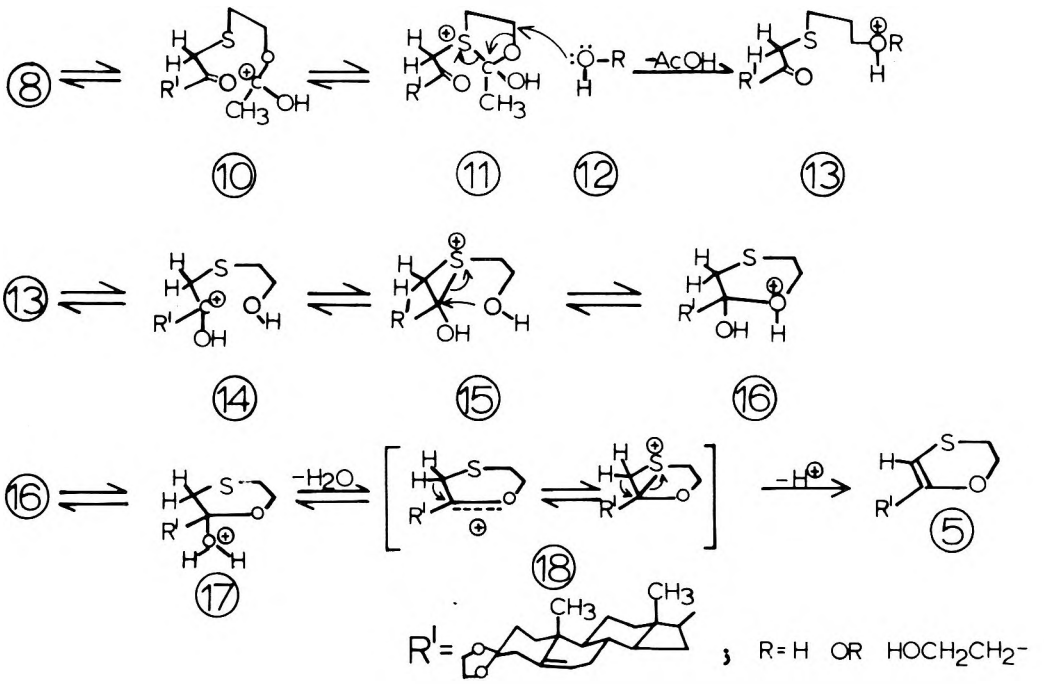
In an attempt to prepare the 3,20-diethylene ketal of **3**, the steroid was treated with ethylene glycol and *p*-toluenesulfonic acid in benzene under reflux. The only product obtained from the reaction was the monoketal **5**, containing the 5′,6′-dihydro-1′,4′-oxathiin system on the steroid D ring. The structure of **5** was established by elemental analysis and spectroscopic data. The ir spectrum of **5**, compared with that of **3**, lacks absorption at 3400 (C-2′, OH, 1700 (C-20, C=O), and 1650 cm^{-1} (C-3, C=O). However, a new band at 1630 cm^{-1} (–SCH=CO–), similar to that seen in the ir spectrum of **4**, is observed. Interestingly, compound **5**, which does not possess a 3-keto-Δ^4 chromophore, exhibits an uv absorption at λ_{max} (MeOH) 238 nm (ϵ 8500). This absorption must be due to the 5′,6′-dihydro-1′,4′-oxathiin system.[12] Moreover, this explains the unusually large uv extinction coefficient observed for **4** (i.e., ϵ 24 000). This is an ϵ value of 7000–8000 greater than that expected for a 3-keto-Δ^4 steroid. The NMR spectrum of **5** contains two vinyl proton signals: a sharp singlet at τ 5.15 (due to H-3′, as seen in **4**) and a narrow multiplet at τ 4.70 (H-6) which is slightly shifted upfield compared to the H-4 signal in **4**.

Acetylation of **3** with acetic anhydride in pyridine provided the corresponding acetate **6**. Conversion of the acetate **6** to the diketal **7a**, then deacetylation and chlorination of the hydroxyethyl side chain with hexamethylphosphorus triamide and CCl_4, had been planned (Scheme I). The C-20 ketal group was expected to prevent cyclization during the chlorination reaction. However, a mixture of **6**, ethylene glycol, and *p*-toluenesulfonic acid in benzene, heated under reflux for 18 h (in a Dean-Stark water separator), produced a reaction mixture containing only **5** and **8**. Base-catalyzed hydrolysis of **8** gave **9** which was isolated by short column silica gel chromatography. Longer periods of heating **6** produced **5** as the major product while shorter reaction times gave more of **8**, as determined by TLC analysis of the reaction mixtures. The structure of **9** was established by elemental analysis and comparison of the ir and NMR spectra of this compound with those discussed above. This steroid did not exhibit any uv absorption in the 210–290-nm region.

The relative ease with which **3** cyclizes to **4**, and **8** is deacetylated and cyclizes to **5**, is interesting. Cyclization of **3** to **4** by an acid-catalyzed sequence involving intermediates analogous to **14** → **16** → **17** (Scheme II) is well known for δ-hydroxybutyl alkyl ketones.[13] Conditions under which we first attempted to chlorinate **3** (Experimental Section, method A) contain a strong acid, and could well promote this sequence. However, the hexamethylphosphoramide–CCl_4 conditions of chlorination (method B) are not acidic and the by-products of this reaction are neutral.[10] Therefore, it is entirely likely that chlorination of the 21-(2′-hydroxyethylthio) group of **3** does occur, but that the resulting chloroethylthio steroid undergoes a rapid cyclization (**3** → **3b** ⇄ **3c** → **4**, Scheme III). This could occur by an internal nucleophilic displacement of the chlorine atom by the C-20 oxygen in the carbonyl or enol form, represented by equations in Scheme III. Neighboring group participation involving a β-thio atom is classical in nucleophilic reactions,[14] and thus can account for the results that we obtain from attempts to produce 21-(2′-chlorethylthio)progesterone directly from 21-(2′-hydroxyethylthio)-progesterone.

The tendency of the acetoxy group of **8** to be deacetylated under conditions which do not ordinarily bring about this reaction[15] may be associated with participation of the C-21 sulfur atom. Deacetylation of **8**, leading to cyclization of the resulting hydroxyethylthio group in **13** or **14** (Scheme II), can be rationalized by a mechanism involving C-21 sulfur participation through intermediate structures **10** and **11**, wherein **12** (R = H) is a water molecule. However, the reaction mixture which produces **5** and **8** contains a large excess of ethylene glycol, relative to water. If ethylene glycol (**12**, R = $HOCH_2CH_2$, Scheme II) would react with **11** then formation

Scheme II



of the 2′-hydroxyethoxy ether of **14** (i.e., **13**, R = $HOCH_2CH_2$–) would occur. Cyclization of this compound is not expected to take place. There is no evidence that this ether is formed in the reaction mixture.

An alternative mechanism which accounts for the deacetylation and cyclization of **8** promoted by the C-21 sulfur atom is represented by equations in Scheme III. In this case protonation of the acetoxy group of **8** gives **10**, in equilibrium with the enol intermediate **21**. The sulfur atom forms the respective cyclic sulfonium intermediates **19** and/or **23**. Deprotonation of these species gives **5**. Although the cyclization mechanisms represented in Schemes II and III appear to be equally probable in terms of sulfur participation, our failure to detect a product resulting from the reaction of **11** + **12** (Scheme II), where **12** is ethylene glycol, leads us to favor the mechanism shown in Scheme III.

Experimental Section

All melting points were determined in a Mel-Temp apparatus and are reported uncorrected. Ultraviolet spectra were determined in methanol with a Beckman Model 25 spectrophotometer. Infrared spectra were determined in KBr, unless otherwise stated, with a Beckman Acculab 4 spectrometer. Nuclear magnetic resonance spectra were determined in deuteriochloroform with tetramethylsilane as internal standard, in a Varian T-60 spectrometer, and are reported as τ values. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. All the reactions were monitored by thin layer chromatography with Eastman silica gel sheets (no. 6060 containing a fluorescent indicator). Chloroform (Fisher Scientific, C-574, containing 0.75% ethanol) was used to develop the chromatograms. Iodine and/or ultraviolet light were used for visualization. Silica gel G, E. Merck AG-Darmstadt, was used as adsorbent for short column chromatography.[16] Optical rotations were determined in chloroform using 2% solutions in a 1-dm semimicro (2.5 ml) tube with a Dr. Steeg & Reuter Model SR-5 polarimeter. Removal of solvents was carried out under reduced pressure in a Buchler flash evaporator.

4-Pregnene-21-ol-3,20-dione 21-*p*-Toluenesulfonate (2). Compound **2** was prepared by a method similar to that described by Borrevang[8] for the synthesis of 4-pregnene-17α,21-diol-3,20-dione 21-*p*-toluenesulfonate. A solution of 5.0 g of deoxycorticosterone (**1**) in 30 ml of dry pyridine was cooled to −20 °C, then mixed with a solution of 3.0 g of *p*-toluenesulfonyl chloride in 30 ml of CH_2Cl_2 at −20 °C. The resulting solution was allowed to stand at −15 °C for 14 h. Following dilution with 200 ml of methylene chloride, the mixture was washed thrice with dilute HCl, four times with dilute $NaHCO_3$, and twice with water. After drying (Na_2SO_4) the solution was concentrated to dryness. Crystallization of the residue from acetone–ethanol gave 5.0 g (76%) of **2**, mp 151–153 °C, $[\alpha]^{25}D$ +131° (lit.[17] mp 170–171 °C) (Borrevang states that steroid tosylates generally exhibit variable melting points.[8]). Anal. Calcd for $C_{28}H_{36}O_5S$: C, 69.39; H, 7.49; S, 6.62. Found: C, 69.54; H, 7.19; S, 6.86. Ir ν_{max} (KBr) 2950, 1707, 1668, 1370, 1177 cm^{-1} supports structure **2**.

21-(2′-Hydroxyethylthio)-4-pregnene-3,20-dione (3). To 400 mg of **2** in 10 ml of ethanol were added in succession 160 mg of 2-mercaptoethanol dissolved in 5 ml of ethanol and 80 mg of NaOH dissolved in 1 ml of water. The resulting mixture was heated under gentle reflux with magnetic stirring for 30 min, then cooled and an equal volume of water was added, giving an oily precipitate. The mixture was distributed between 50 ml of ether and an additional 25 ml of water and separated. The ethereal layer was washed twice with 25 ml of water, dried (Na_2SO_4), and concentrated to dryness. Crystallization of the residue from acetone–cyclohexane gave 110 mg (34%) of **3**: mp 110 °C; $[\alpha]^{25}D$ +164°; λ_{max} 240 nm (ϵ 20 000). Anal. Calcd for $C_{23}H_{34}O_3S$: C, 70.73; H, 8.77; S, 8.21. Found: C, 70.58; H, 8.60; S, 8.05. The ir data, ν_{max} (KBr) 3410 (OH), 1700 (C-20, C=O), 1662 cm^{-1} (C-3, C=O), support structure **3**. The structural assignment was further confirmed by the NMR spectrum of this compound.

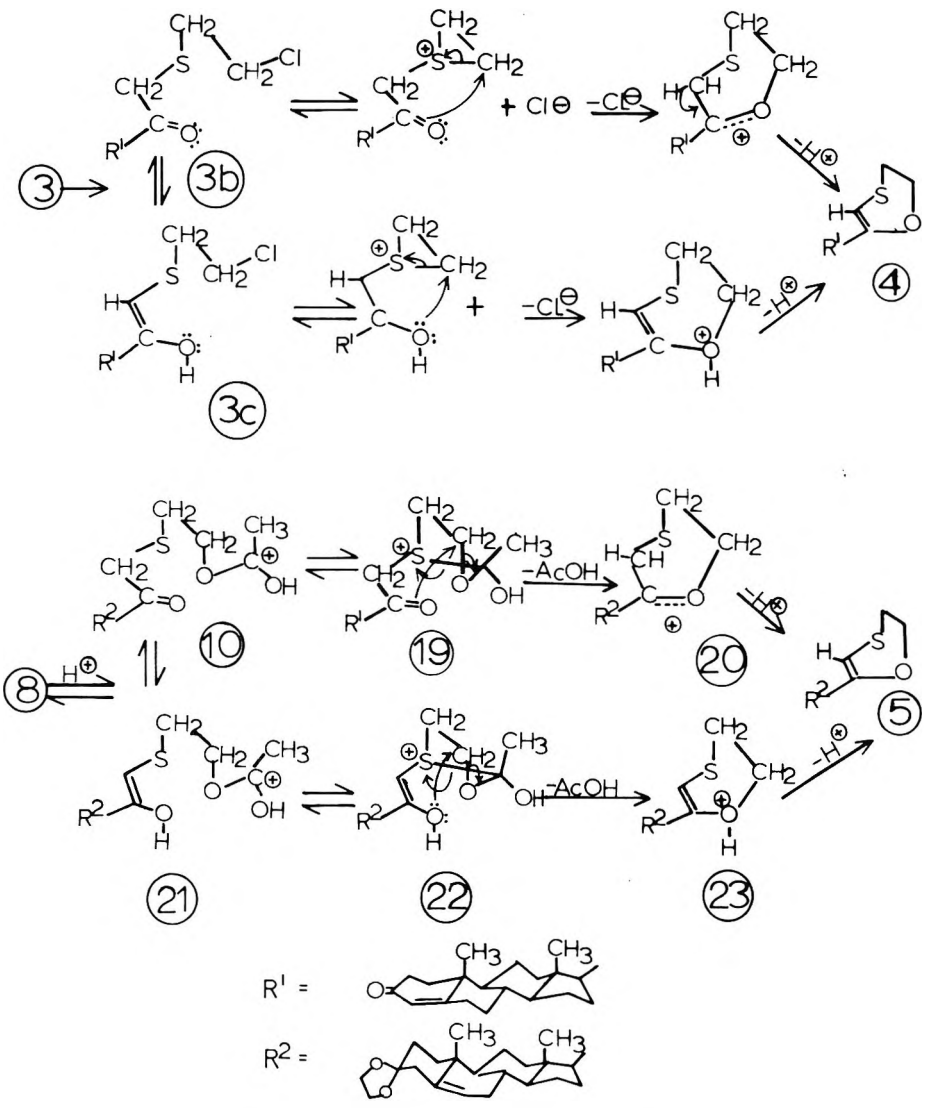
17β-(5′,6′-Dihydro-1′,4′-oxathiin-2′-yl)-4-androsten-3-one (4). Method A. To a solution of 300 mg of **3** in 1 ml of chloroform was added dropwise and with stirring 0.06 ml of thionyl chloride in 0.5 ml of chloroform and the resulting solution was stirred for 3.5 h, then concentrated to dryness. Residual thionyl chloride was chased by evaporating CCl_4 from the oily residue. Crystallization of the residue from acetone gave 60 mg of **4**: mp 168–171 °C; $[\alpha]^{25}D$ +145°; λ_{max} 238 nm (ϵ 24 000). Anal. Calcd for $C_{23}H_{32}O_2S$: C, 74.16; H, 8.66; O, 8.59; S, 8.59. Found: C, 73.76; H, 9.02; O, 8.76; S, 8.58.

Ir spectrum of **4** shows the absence of an hydroxyl group (3400 cm^{-1}), or a band (1700 cm^{-1}) characteristic of the C-20 keto group, but exhibits a strong ν_{max} (KBr) at 1630 cm^{-1}, which is characteristic of the 5′,6′-dihydro-1′,4′-oxathiin system.[18,19] The structure **4** was further confirmed by NMR spectroscopy (see the discussion above).

Method B. A solution of 170 mg of hexamethylphosphorus triamide in 0.5 ml of chloroform was added dropwise and with stirring to an ice–water cooled solution of **3** (390 mg) dissolved in a mixture of 1 ml of chloroform and 4 ml of CCl_4. The resulting solution was heated under gentle reflux for 5 h. The solution was then concentrated under vacuum to about 1 ml and was washed with three 15-ml portions of water. The organic residue was dissolved in 20 ml of chloroform, washed with water, dried (Na_2SO_4), and concentrated to dryness. Crystallization of the residue from acetone gave 120 mg of **4**, mp 169–171 °C. Compound **4** was found to have identical melting point, TLC, and ir spectra with the material obtained from method A.

17-(5′,6′-Dihydro-1′,4′-oxathiin-2′-yl)androst-5-en-3-one Cyclic Ethylene Ketal (5). Compound **3** (390 mg), 0.375 ml of ethylene glycol, and 51 mg of *p*-toluenesulfonic acid in 30 ml of benzene were heated under reflux for 19 h, using anhydrous Na_2SO_4 in the side arm of a Dean-Stark apparatus to remove water. The reaction mixture

Scheme III



was allowed to come to room temperature, and then was stirred for 0.5 h, after addition of 3 drops of tributylamine. The resulting mixture was washed with water and dried (Na_2SO_4). Evaporation of solvent followed by crystallization of the residue from ethyl acetate gave 220 mg of **5**: mp 226–227 °C; λ_{max} 230 nm (ϵ 8500). Anal. Calcd for $C_{25}H_{36}O_3S$: C, 72.08; H, 8.71; O, 11.52; S, 7.69. Found: C, 72.12; H, 8.82; O, 11.53; S, 7.70.

The ir spectrum of **5** contained no carbonyl or hydroxyl absorptions. Presence of strong ν_{max} at 1630 cm^{-1} supports structure[18,19] **5**, which was further confirmed by its NMR spectrum. The integrated NMR spectrum of **5** contains the signals τ 4.70 (one proton, broad singlet, H-6), 5.15 (one proton, singlet, H-3′), 5.43–5.84 (two protons, multiplet, H-6′), 6.9–7.23 (two protons, multiplet, H-5′), 8.94 (three protons, singlet, H-19), 9.3 (three protons, singlet, H-18), 6.07 (four protons, singlet, OCH_2CH_2O ketal).

21-(2′-Acetoxyethylthio)-4-pregnene-3,20-dione (6). A solution of **3** (200 mg) in 0.5 ml of pyridine and acetic anhydride (0.5 ml) was heated on a steam bath for 0.5 h. The reaction mixture was allowed to come to room temperature, then ice water was added and the mixture was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and concentrated to dryness. TLC analysis indicated the presence of one component in the residue. The ir bands, in CCl_4 solutions, ν_{max} 1743 (acetate C=O), 1708 (C-20, C=O), and 1680 cm^{-1} (C-3, C=O), support structure **6**. Compound **6** resisted crystallization, and was therefore used as an oil in the ketalization experiment described below.

Ketalization of 21-(2′-Acetoxyethylthio)-4-pregnene-3,20-dione to 8. Compound 6 (475 mg), 0.4 ml of ethylene glycol, 50 mg of *p*-toluenesulfonic acid, and 30 ml of benzene were heated under reflux for 18 h with anhydrous Na_2SO_4 in the side arm of a Dean-Stark apparatus. The cooled solution was stirred for 0.5 h with 0.65 ml of tributylamine. The resulting solution was washed with water, dried, and concentrated to dryness. Treatment of the solid residue with ethyl acetate gave 80 mg of a crystalline material, mp 206–212 °C which increased to 225–227 °C after two crystallizations from ethyl acetate. This product was found to be identical with **5** by a comparison of its melting point, mixture melting point, TLC, and ir with those of an authentic sample of **5** which had been prepared from **3**. The TLC of the mother liquor from the first ethyl acetate crystallization contained a forward migrating spot with mobility similar to **6**, but was not uv absorbing. This solution containing compound **8** was concentrated to dryness, and the residue was subjected to base-catalyzed hydrolysis, described below.

21-(2′-Hydroxyethylthio)-5-pregnene-3,20-dione Cyclic 3-Ethylene Ketal (9). To a solution of 380 mg of **8** in 5 ml of CH_3OH was added 90 mg of sodium methoxide dissolved in 5 ml of CH_3OH. The resulting solution was stirred at room temperature for 23 h, then concentrated to dryness. The semisolid residue was extracted with chloroform, the chloroform extract was washed with water and dried (Na_2SO_4), and the solvent was removed, leaving an oily residue (280 mg) which resisted crystallization. The oil was chromatographed on a short column of silica gel G (15 g) with chloroform, giving **9** as a white, crystalline material, mp 101–104 °C. Recrystallization of **9** from acetone–petroleum ether gave crystals of mp 117–119 °C; $[\alpha]^{25}D$ +50°; no detectable uv absorption in the range 215–300 nm. Anal. Calcd for $C_{25}H_{38}O_4S$: C, 69.09; H, 8.81; S, 7.38. Found: C, 68.99; H, 8.85; S, 7.16. The strong ir bands, ν_{max} 3220 (C-2′, OH) and 1690 cm^{-1} (C-20, C=O), support structure **9**. The structure assigned to **9** was confirmed by the NMR spectrum.

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Registry No.—1, 64-85-7; 2, 58958-13-7; 3, 58958-14-8; 4, 58958-15-9; 5, 58958-16-0; 6, 58958-17-1; 8, 58958-18-2; 9, 58958-19-3; *p*-toluenesulfonyl chloride, 98-59-9; 2-mercaptoethanol, 60-24-2.

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Daunomycinone Analogues via the Diels–Alder Reaction. Synthesis and Chemistry of Some 6,11-Dihydroxy-5,12-naphthacenediones[1]

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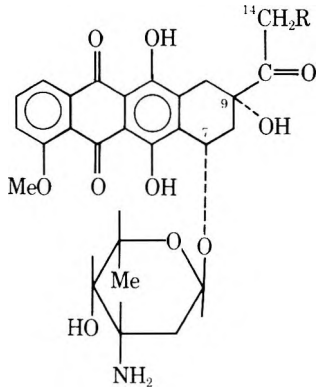
Quinizarinquinone reacts with 1,3-butadiene and 1-acetoxy-1,3-butadiene, but not 2-methoxy-1,3-butadiene, mainly at the external double bond to give end adducts **5a** and **5b**, respectively. Their transformation into, and the chemistry of, various dihydroxynaphthacenedione derivatives are described. These include **13d** (a simplified aglycone of daunomycinone), the 5,6,11,12-tetramethoxynaphthacenes, **17** and **19a**, and the oxidative demethylation of **17** to a 5,6,11,12-naphthacenetetrone, **18**, as well as the dihydroxytrione **22b**.

The anthracycline antibiotics daunorubicin (1) and adriamycin (2) have shown promise for clinical use against a variety of tumors, including solid ones.[2] In addition, daunorubicin benzhydrazone (**3**, methyl ketone O of 1 replaced by $NNHCOC_6H_5$) has clinical activity against acute myeloblastic and lymphoblastic leukemia.[3] Thus, various changes in this system appear compatible with retention of antitumor properties.



1, R = H, daunorubicin
2, R = OH, adriamycin

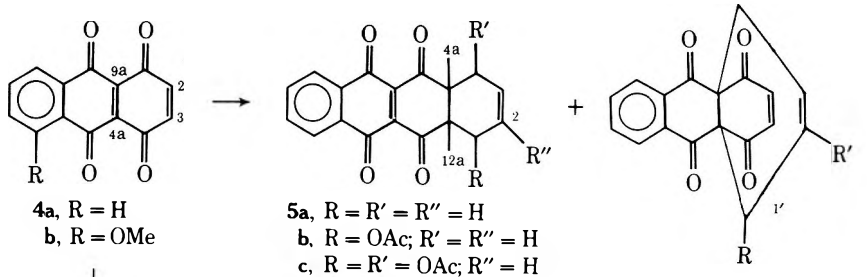
A number of derivatives at the ketone and amine functions of daunorubicin and adriamycin synthesized in our laboratories[4] and elsewhere[5,6] show a modified spectrum of both toxicity and antitumor activity against various experimental tumors in mice. These results led us to examine other structural variations and also routes that may lead to a synthesis of 1 and 2.

This paper reports some studies on (1) the Diels–Alder reaction as a route to the 6,11-dihydroxy-5,12-naphthacenedione ring system of 1 and 2, (2) some chemistry of, and blocking methods for, the quinizarin system of these rings, (3) an assessment of this route to the aglycones of 1 and 2 and their analogues.

The Diels–Alder reaction of quinizarinquinone (**4a**) with suitable butadienes offers a possible quick entry into the dihydroxynaphthacenedione ring system if addition occurs at the C-2 double bond. Inhoffen et al.[7] studied the reaction of several dienes with **4** and observed that the internal double bond competed with the double bond at C-2. Only with 1,4-diacetoxybutadiene was any end adduct **5c** isolated. In the other cases, they found that the formation of an internal adduct (e.g., **6c**) or diadduct (e.g., **7b**[8] or an isomer; isolated as **10b**) predominated. We find that under proper reaction conditions, the desired end adducts of structure **5** may become the predominant products for some, but not all, butadienes.

Reaction of quinizarinquinone (**4a**) with excess 1,3-butadiene in hot benzene for several hours afforded the red end adduct **5a** as the main product, the pale-beige internal adduct **6a** as a minor product, and only TLC and mass spectral indications of the diadduct **7a**. Unlike butadiene, excess 1-acetoxy-1,3-butadiene[9] reacted with **4a** in hot benzene to give mainly the diadduct **7b**, essentially as reported.[7] However, **4a** and a limited excess of 1-acetoxy-1,3-butadiene reacted in acetonitrile to afford primarily **5b**,[8] together with some internal adduct **6b**[8] and some diadduct **7b**.

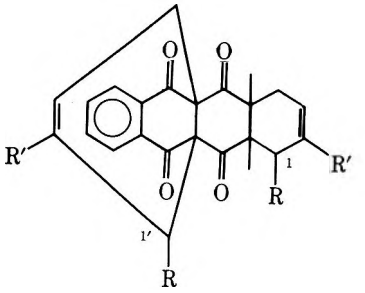
The reaction of **4a** with 2-methoxybutadiene was disappointing. Under a wide variety of conditions, the major product was the center adduct **6d**, accompanied by some diadduct **7c**. The desired end adduct **5d** was never formed in sufficient quantity to warrant attempts at its separation from the major product **6d**. Compound **5d** is wanted as the precursor to the versatile ketone **22b**. Thus the reaction of butadienes with **4** cannot always be directed to give the end ad-



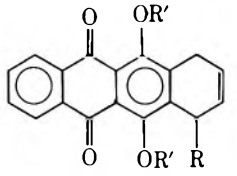
4a, R = H
b, R = OMe

5a, R = R′ = R″ = H
b, R = OAc; R′ = R″ = H
c, R = R′ = OAc; R″ = H
d, R = R′ = H; R″ = OMe

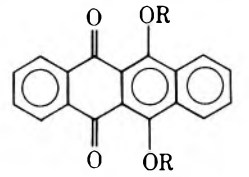
6a, R = R′ = H
b, R = OAc; R′ = H
c, R = OMe; R′ = H
d, R = H; R′ = OMe



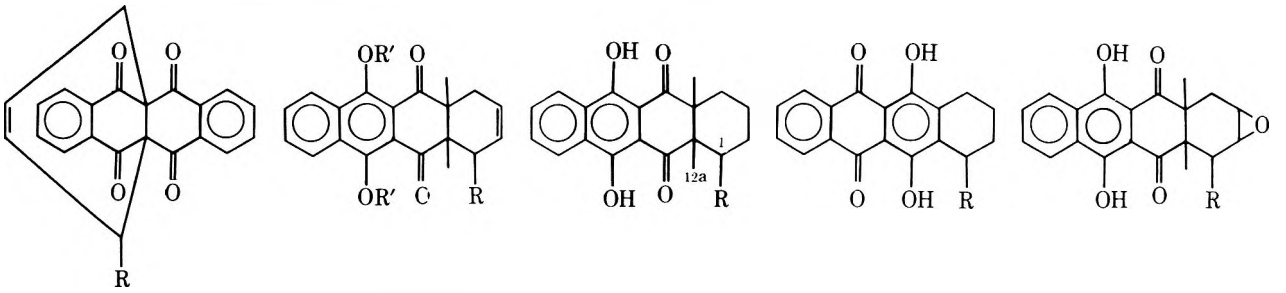
7a, R = R′ = H
b, R = OAc; R′ = H
c, R = H; R′ = OMe



8a, R = H; R′ = H
b, R = OAc; R′ = H
c, R = H; R′ = Me
d, R = H; R′ = Ac



9a, R = H
b, R = Me



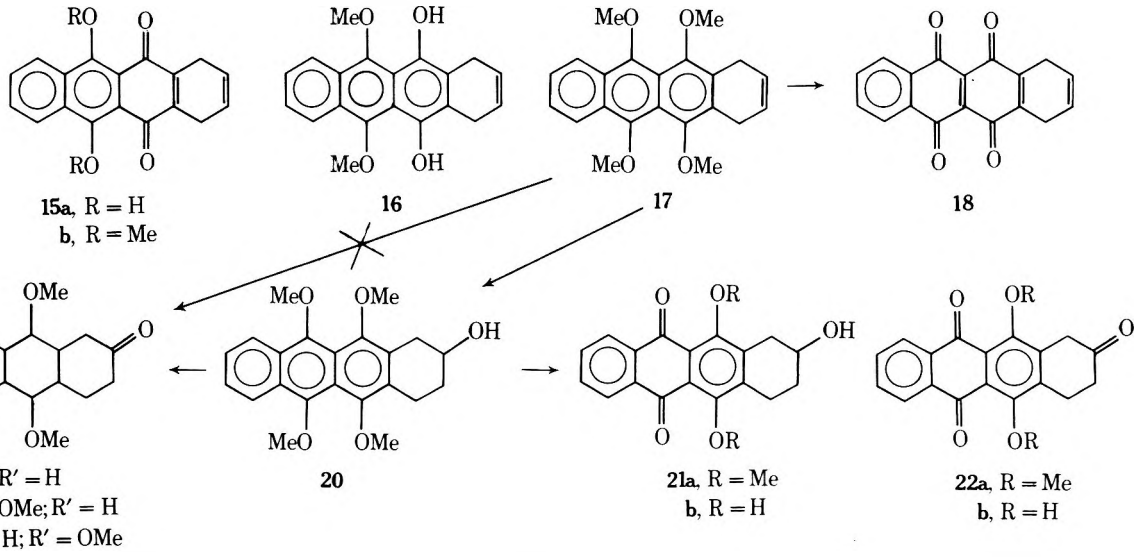
10a, R = H
b, R = OAc

11a, R = H; R′ = H
b, R = OAc; R′ = H
c, R = H; R′ = Me

12a, R = H
b, R = OAc

13a, R = H
b, R = OAc
c, R = O_2CCF_3
d, R = OH

14a, R = H
b, R = OAc



15a, R = H
b, R = Me

16

17

18

19a, R = R′ = H
b, R = OMe; R′ = H
c, R = H; R′ = OMe

20

21a, R = Me
b, R = H

22a, R = Me
b, R = H

duct by choice of reaction conditions. The products formed depend also on the nature of the substituents of the butadiene.[10]

The structural assignments in the above series of Diels–Alder reactions were based on the chemistry and spectral properties of the products. When the end adduct **5a** was heated in xylene, it tautomerized to the quinizarin form **8a**. Adduct **5a** also could be aromatized to **9a**. In the acetoxybutadiene series, the end adduct **5b** readily lost acetic acid and aromatized to **9a** under a wide variety of conditions. Only by carefully heating **5b** in acetonitrile containing molecular sieves was tautomerization to the quinizarin form, **8b**, achieved. Heating the diadduct **7b** in xylene and acetic acid caused aromatization to **10b**.[7] In contrast to **5b**, the internal adduct **6b** was only slowly changed by hot methanolic sodium methoxide to give anthraquinone.

Table I. NMR Data[a]

Compd	Allyl H	Vinyl H	H-4a,12a	Other
4a		6.90 s 2[b,c]		
5a	2.37 m 4	5.67 m 2	3.51 m 2	
5b	2.0–2.3 m 2	6.00 m 2	3.62 m 2	1.68 s 3 OAc
	5.37 m 1			
6a	2.66 d 4	5.72 t 2		
		6.78 s 2[b]		
6b	2.12 m 1[d]	6.64 d 1[b,e]		1.88 s 3 OAc
	3.24 m 1[d]	7.11 d 1[b,e]		
	6.06 m 3			
6d	2.70 m 4	4.60 t 1		3.50 s 3 OMe
		6.79 s 2[b]		
7b	1.7–4.0 m 6[f]	5.97 m 4	*f*	1.27 s 3 OAc
	5.72 m 2			1.88 s 3 OAc
8c	3.48 d 4	5.92 t 2		3.92 s 6 OMe
8d	3.34 br s 4	5.87 br s 2		2.51 s 6 OAc
10b	1.5–3.7 m 2	6.05 m 2		1.28 s 3 OAc
	6.18 m 1			
11a	2.45 m 4	5.72 m 2	3.30 m 2	13.35 s 2 OH[g]
11b	1.5–3.2 m 2	6.06 m 2	3.42 m 2	1.40 s 3 OAc
	5.54 m 1			13.08 s 1 OH
				13.52 s 1 OH
11c	2.4–3.1 m 6[f]	5.78 m 2	*f*	4.07 s 6 OMe
12b	1.5–3.0 m 6[h]		3.22 m 2	1.42 s 3 OAc
	5.35 m 1[i]			13.30 s 1 OH
				13.60 s 1 OH
14b	5.68 m 1[i]			1.43 s 3 OAc
	1.5–3.32 m 6[h]			13.00 s 1 OH
				13.50 s 1 OH
15b	3.20 s 4	5.80 s 2		4.02 s 6 OMe
16	3.52 d 4	6.01 m 2		9.55 s 2 OH[g]
17	3.62 d 4	6.04 m 2		3.86 s 6 OMe
				4.00 s 6 OMe

[a] See Experimental Section for details. Results are given in the order δ, multiplicities and number of protons; and s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Aromatic protons are omitted. [b] Quinone H-2, 3 protons. For 1,4-benzoquinone, these appear at δ 6.72. [c] Acetone-d_6 was solvent. [d] $J_{4'}$ geminal = 18 Hz. [e] $J_{2,3}$ = 10 Hz. [f] These 6 include 4 allyl and 2 H-4a,12a protons. [g] All OH in table are phenolic OH. All are chelated with quinone except those for **16** which are hydrogen bonded to OMe. [h] These include all other aliphatic protons except those listed. [i] H-1 proton.

The ir spectra of **5a** and **5b** had carbonyl adsorption at 5.8–6.0 μ instead of the chelated hydroxy quinone absorption at 6.1–6.3 μ shown by **8a, 8b,** and quinizarin. The NMR spectra of both **5a** and **5b** showed clearly the protons H-4a and H-12a and lacked the phenolic protons of quinizarin, which are chelated with the quinone oxygens. The NMR spectra of the internal adducts **6a, 6b,** and **6d** clearly showed the H-2 and H-3 protons typical of quinones that were absent from the NMR spectra of **5a** and **5b.** Table I presents the NMR data. The ir spectra of **6a** and **6b** are distinguishable from those of **5a** and **5b,** although they all show carbonyl bands in the same region. The mass spectral fragmentation patterns are also distinctive and helpful in making the structural assignments. Thus, end adduct **5b** tends to lose acetic acid to give **9a,** whereas internal adduct **6b** tends to undergo a reverse Diels–Alder reaction that ultimately gave quinizarin while losing acetic acid to a lesser extent. Likewise, **6d** tends to reverse to quinizarin.

We next chose to demonstrate that **5b** could be converted into the trihydroxynaphthacenedione **13d** that had been prepared previously in our laboratories.[11] Compound **8b** could not be reduced successfully to **13b;** acetic acid was eliminated rapidly to form **9a** under all the reaction conditions studied. However, **5b** rapidly absorbed 1 mol of hydrogen with a variety of catalysts to give **11b** in which the double bond still remained at C-2. Introduction of 2 mol of hydrogen was achieved by hydrogenation of **5b** in benzene in the presence of palladium black. The product **12b** could be reoxidized to **13b** by the use of silver oxide in benzene. Application of the previously developed[11] transesterification procedure to form **13c** and subsequent hydrolysis afforded the desired **13d.** Less effectively **12b** could be air oxidized by treatment with sodium carbonate in acetonitrile to give a mixture of **13b** and **13d.** The whole mixture could be treated with trifluoroacetic acid and hydrolyzed to afford **13d.** Compared with the original synthesis,[11] the reaction sequence to **13d** via **4a, 5b, 12b,** and **13b** is shorter and affords a greater yield (about 18% overall from **4a**). Farina and Vega[12] have recently prepared the methyl ether of **13d** (where R = OMe) by another route. The coupling of **13d** with daunosamine to give the simplified analogue of **2** has already been reported[13] using the techniques recently developed for the successful coupling of daunomycinone and daunosamine to afford **2.**[13,14]

The catalytic hydrogenation of **5a** did not proceed selectively. After the uptake of 1 mol of hydrogen, **11a** and **12a** were both present according to NMR data. Complete hydrogenation to **12a** was accomplished with palladium black as catalyst. Pure **11a** was obtained readily by chemical reduction of **5a** with zinc and acetic acid. With proper care, this reagent combination also could be applied to **5b** for the preparation of **11b** without appreciable aromatization of **5b** to **9a.**

The C-2 double bond of **5, 8,** and **11** would seem to provide the means for further modification of these molecules. However, **5** and **8** were very insoluble compounds, and **5b** and **8b** lost acetic acid very easily. Compounds **11a** and **11b** were more soluble and more stable. Both **11a** and **11b** have been successfully converted to the 2,3-epoxides, **14a** and **14b,** respectively, by the action of peracid. Surprisingly, they were not oxidized from the leuco to the quinizarin form. The diacetyl quinizarin **8d,** a protected and more soluble form of **8a,** was

obtained readily by treatment of **5a** with trifluoroacetic anhydride and acetic acid.

Leuco **12b** is completely converted by treatment with triethylamine in benzene into quinizarin **13a**. This transformation probably begins with the elimination of acetic acid from **12b** to afford the $\Delta^{1(12a)}$ olefin. This isomerizes to a quinone—**15a** without the Δ^2 double bond—which in turn readily tautomerizes to the quinizarin **13a**. This sequence follows the suggested mechanism by which the condensation of leucoquinizarin with aldehydes affords 2-alkyl quinizarins.[15]

Ketone **22b**, or an appropriately protected form, appears to be a versatile intermediate. It seems suitable not only for conversion to the 4-demethoxy derivatives of daunomycinone[16] and adriamycinone, but the carbonyl group seems suitable for transformation into widely different kinds of side chains also. Protection of the quinizarin system of **22b** by conversion to the tetramethoxy derivative **19a** may be practical, providing that the mild, oxidative demethylation procedure for dimethyl ethers of hydroquinones[17,18] is applicable. To test this, we proceeded as follows.

Methylation of leuco **11a** in acetone with methyl sulfate and barium oxide as base gave consistent yields (50–57%) of tetramethoxy **17**. When potassium carbonate was used as base, the yields of **17** were erratic and dimethyl products leuco **11c**, leuco tautomer **16**, and quinone **15b** were isolated, depending on reaction conditions. The presence of these compounds show that the tetramethyl **17** is formed in a stepwise fashion, e.g., **11a** → **11c** → **16** → **17**. Product is lost when leuco **11c** or **16** is oxidized to quinone **15b**. Interestingly, the formation of **15b** is suppressed, but not eliminated, when zinc dust is added to the reaction mixture.

Assignment of structure to leuco **11c** was on the same basis as for leuco **11a** and **11b**. Initial assignment of structure to **15b** was based on its rapid isomerization in acid (with concomitant air oxidation) to **9b**, and was confirmed by the synthesis of the different dimethyl **8c** from **8a**. Dimethyl **8c** was unaffected by the acid conditions that converted **15b** to **9b**. The structure of **16** was assigned on the basis of its ir that showed the presence of OH (3 μ) and absence of C=O, its NMR that showed two phenolic H (δ 9.55)[19] and two methoxy groups, as well as its MS (*m/e* 322, M^+, 100% rel abundance) and analysis. Furthermore, when a solution of **16** was left in air, it was converted to quinone **15b**. A solution of **16** left overnight in an NMR tube was only half oxidized; its spectrum showed **16** and **15b** in a 1:1 ratio, perhaps stabilized as a molecular complex like quinhydrone.

The four methyl groups in **17** were readily removed by silver(II) oxide[17] treatment to give a high yield of the diquinone **18** whose ir spectrum was similar to that of **4a** and lacked the chelated quinone adsorptions of **8a** and **9a**. Two of the methyl groups in **17** were readily removed by a number of reagents (see Experimental Section) as well as by treatment with (1) mercuric acetate, palladium chloride, and cupric chloride in methanol,[20] or (2) one-pot treatment with sodium borohydride–zinc chloride and then chromic acid,[21] two sets of reagents that are used to convert olefins to ketones; ketone **19a** was not obtained. The product was **8c**.

The four methyl groups remained intact when **17** was converted to the alcohol **20** by hydroboration and subsequent oxidation with alkaline hydrogen peroxide. Alcohol **20** was best oxidized to tetramethoxy ketone **19a** (50% yield) with dimethyl sulfoxide (Me_2SO)–dicyclohexylcarbodiimide (DCC) in the presence of pyridinium trifluoroacetate.[22] Crystalline ketone **19a** was stable. It was unstable in solution or in the noncrystalline but chromatographically homogeneous form and decomposed rapidly to give a mixture of several components by TLC.

Oxidative demethylation[17] of **20** gave only the partially demethylated **21a** instead of a diquinone that corresponded to **18**, the diquinone that was smoothly obtained from **17**. However treatment of **20** with aluminum chloride in nitrobenzene afforded the completely demethylated **21b** in over 90% yield.

Work in this area is being discontinued in view of concurrent work elsewhere[10] and plans to examine a stereospecific route to daunomycinone and adriamycinone. Results thus far show that the Diels–Alder reaction of quinizarinquinone with various butadienes is a possible but not general entry to dihydroxynaphthacenediones. Results also show that a quinizarin system can be protected as the tetramethoxy derivative, e.g., as in **17**, **19a**, and **20**, but the usefulness of these blocking groups is somewhat limited by their instability and by methods for their removal.

Twenty-four compounds have been evaluated under the auspices of the National Cancer Institute against lymphoid leukemia L1210 in the mouse. All were found inactive at doses ranging as high as 400 mg/kg. The compounds tested were **4a**, **5a**, **5b**, **6a**, **6b**, **6d**, **7b**, **8a–d**, **9a**, **9b**, **11a**, **11b**, **12a**, **12b**, **14a**, **16**, **17**, **19a**, **20**, **21a**, and **21b**.

Experimental Section

Melting points were taken on a Fisher-Johns hot stage and were not corrected. Ultraviolet–visible spectra (methanol solution, Cary 11 instrument), infrared spectra (Nujol, Beckman IR-4 instrument), and 60-MHz NMR (Varian Associates, A-60 spectrometer) measurements were made by the Pharmaceutical Analysis Group under the direction of Dr. Peter Lim. Measurements of 100-MHz NMR were performed by Mr. L. Cary, using a Varian XL-100 spectrometer. The NMR spectra were run in $DCCl_3$ as solvent, unless otherwise noted, with Me_4Si as internal solvent. Elemental microanalyses were provided by Ms. E. M. McCarthy. Mass spectra were recorded by Dr. D. W. Thomas on an LKB Model 9000 mass spectrometer at 12 eV.

For thin layer chromatography, silica gel HF-254 plates were used and visualized with uv or iodine. The solvent systems used were (A) acetone–cyclohexane (20:80); (B) methylene chloride; (B-1) same solvent as B except with a silica gel slurry for plates, prepared with 0.05 M KH_2PO_4 instead of water, as suggested by Dr. Carol Mosher; (C) tetrahydrofuran–CH_2Cl_2 (30:70); (C-1) same as C but a silica gel slurry, prepared with 0.05 M KH_2PO_4 instead of water; (D) CH_2Cl_2; (E) acetone–cyclohexane (40:60); (F) $CHCl_3$, plates as in B-1; (G) THF–benzene (1:4), plates as in B-1. All evaporations were carried out in a spin evaporator at a bath temperature of 45 °C under vacuum (either water aspirator and/or mechanical pump, as required), unless specified otherwise. Anhydrous Na_2SO_4 was used for drying solutions, unless otherwise specified.

1,4,4a,12a-Tetrahydro-5,6,11,12-naphthacenetetrone (5a). A cooled, stainless steel bomb was loaded with 50 g (0.21 mol) of quinizarinquinone, 300 ml of benzene, and 42 ml (0.48 mol) of 1,3-butadiene, heated for 20 h at 45–50 °C with stirring, and evaporated to afford 44.8 g of crude product. This was stirred with 1.0 l. of boiling acetone for 10 min to afford 25.13 g (41%) of **5a**: mp >315 °C; ir max 5.81, 6.00, 6.26, and 7.79 μ; uv max 315 nm (ϵ 4100), 253 (14 700), 230 sh (16 700), 213 (20 700); MS *m/e* 292 (M^+, 90), 290 (30), 274 (40), 240 (quinizarin, 20); R_f 0.23 in solvent A. Anal. Calcd for $C_{18}H_{12}O_4 \cdot \frac{1}{2}H_2O$: C, 72.3; H, 3.70; Found: C, 72.3; H, 3.70.

4a,9a-[2]Buteno-1,4,9,10-anthracenetetrone (6a). The organic liquors from the purification of 60.0 g of **5a** were evaporated to dryness, and the residues were triturated with 200 ml of tetrahydrofuran to give crystalline quinizarin, 31.2 g. The liquors were concentrated to 50 ml to yield 7.35 g of crude **6a**. Recrystallization from 75 ml of tetrahydrofuran and 150 ml of cyclohexane afforded the off-white solid **6a**, 2.82 g (1.9%), mp 205–207 °C. One recrystallization from ethanol afforded the analytical sample of **6a**: mp 207–208 °C; ir max 5.85, 5.95 (C=O), 7.95 μ; uv max 296 nm (ϵ 6300), 245 sh (30 000), 227 (44 700); MS *m/e* 292 (M^+, 80), 274 (20), 264 (40), 210 (64), 134 (100); R_f 0.46 in solvent A. Anal. Calcd for $C_{18}H_{12}O_4$: C, 74.0; H, 4.14. Found: C, 74.0; H, 3.84.

The crystallization liquors from **6a** on concentration afforded crude **6a** containing some diadduct **7a** (1,4,4a,12a-tetrahydro-5a,11a-[2]-buteno-5,6,11,12-naphthacentetrone) which was detected by TLC (R_f 0.07 in solvent A) and characterized by MS, *m/e* 346 (M^+, 2) and 292 (100).

1,4,4a,12a-Tetrahydro-1-acetoxynaphthacene-5,6,11,12-tetrone (5b).[8] **A. Benzene Solvent.** A benzene solution of 0.22 g (2.0

mmol) of 1-acetoxy-1,3-butadiene and 0.48 g (2.0 mmol) of quinizarinquinone, (**4a**) in 35 ml of benzene reacted at 40 °C for 2 h to afford 0.35 g of crystalline product from cyclohexane. Recrystallization from acetone–cyclohexane (1:1) afforded 0.18 g (26%) of **5b**, a deep-red, crystalline material: mp ~150 °C, changes color, >315 °C; ir max 5.75, 5.82, 5.98, 6.25 μ; uv max 348 nm (ε 4200), 278 shoulder (11 100), 257 (17 400), 239 (17 700), 217 (17 400); MS *m/e* 290 (only major peak, M − HOAc); R_f 0.65 in solvent C. Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.6; H, 4.03. Found: C, 68.8; H, 4.09.

B. Acetonitrile Solvent. A mixture of 50.0 g (0.178 mol) of **4a** and 23.5 g (0.21 mol) of 1-acetoxy-1,3-butadiene in 250.0 ml of acetonitrile was heated for 20 min at 50 °C to afford 7.64 g (15.3%) of precipitated quinizarin, and a filtrate that afforded a red, slightly tacky solid. Trituration in 250 ml of ether afforded 45.64 g (76%) of **5b** that decomposed on TLC plates. Recrystallization from 25% methylene chloride in ethanol, 13.5 ml/g, afforded the pure product 58% yield: ir max 5.72, 5.80, 5.88 w, 5.97, 6.22 μ. The ir spectrum was different from that of the analytical sample, but the benzene reaction product gave the same ir when the workup was as above.

The purity of **5b** cannot be established by TLC and melting point since it decomposes to **9a**. The ir spectrum is helpful, but the NMR spectrum is essential to show that **5b** is free of quinizarin, quinizarinquinone, internal adduct **6b**, and diadduct **7b**.

11-Acetoxy-4a,9a-[2]buteno-1,4,9,10-anthracenetetrone (6b).[8] The mother liquors from the crystallization of **5b** (method B above) were evaporated to dryness, and the residue was extracted with ether. The ether-soluble material was recrystallized from methylene chloride–cyclohexane to afford crystalline, off-white **6b**: mp 207–208 °C; ir max 5.70 (C=O ester), 5.84 and 5.93 (C=O), 8.00, 8.18 (C–O–C); uv max 228 nm (ε 35 700), 310 (2200); MS (12 eV) *m/e* (rel intensity) 308 (M − CH_2O, 4), 290 (M − HOAc, 15), 240 (M − acetoxybutadiene, 70). Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.6; H, 4.03. Found: C, 68.5; H, 4.19.

Extended heating of **6b** in methanolic sodium methoxide afforded a high yield of anthraquinone, identical with authentic anthraquinone by ir, TLC, and melting point.

1,13-Diacetoxy-1,4,4a,12a-tetrahydro-5a,11a-[2]buteno-naphthacene-5,6,11,12-tetrone (Diadduct 7b).[8] A stirred mixture of 0.80 g (3.36 mmol) of **4a** and 0.90 g (8.0 mmol) of 1-acetoxy-1,3-butadiene in 25 ml of benzene was heated for 15 h in an oil bath of 38 °C. The homogeneous, reddish solution was diluted with 25 ml of carbon tetrachloride and evaporated to dryness. The residue was slurried in 25 ml of carbon tetrachloride and again evaporated to dryness to remove excess acetoxybutadiene. The residue was then stirred in 25 ml of carbon tetrachloride for 24 h. The tan, crystalline product **7b** was collected and dried to afford 1.13 g (74%), mp 175–178 °C, R_f 0.29 in B. One recrystallization afforded the crystalline analytical sample of **7b**: mp 162.0–163.5 °C; ir max 5.70, 5.75 (sh), 5.86, 6.25; uv max 305 nm (ε 2700), 260 (10 500), 232 (32 000); MS *m/e* 402 (M − HOAc); R_f 0.30 in solvent D. Anal. Calcd for $C_{26}H_{22}O_8$: C, 67.5; H, 4.80. Found: C, 67.5; H, 4.60.

4a,9a-[2]buteno-12-methoxy-1,4,9,10-anthracenetetrone (6d). Reaction of 2.1 g of 75% purity (58 mmol) of **4a** and 0.82 g (63 mmol) of 2-methoxybutadiene[23] in 10 ml of acetonitrile containing a little hydroquinone for 6 h at 55 °C afforded, after column chromatography (silica gel, 150, benzene) and crystallization from ether–petroleum ether (bp 30–60 °C), 0.85 g (41%) of pale orange **6d**: mp 68–70 °C; ir max 5.85, 5.95 (C=O), 6.28 (C=C), 7.95, 8.15 μ; uv max (95% EtOH) 2.98 nm (ε 2390), 253 (11 250), 227 (37 400); MS *m/e* 323 (M + 1, 11), 322 (M^+, 58), 240 (100). Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.81; H, 4.38. Found: C, 71.0; H, 4.45.

Use of other temperatures (23–160 °C), many other solvents (cyclohexane, benzene, DMF, etc.), various reaction times (up to 30 h), and different mole ratios all gave **6d** as the major product (81–100% of any reaction mixture) as indicated by examination of the NMR spectra. The presence of traces of end adduct (**5d**) was inferred. With large excesses of 2-methoxybutadiene (10 ×), the presence of some diadduct (**7c**) was observed (NMR and TLC) but no isolation was attempted.

7,10-Dihydro-6,11-dihydroxynaphthacene-5,12-dione (8a). A mixture of 0.70 g (2.39 mmol) of **5a** in 75 ml of xylene was heated for 20 h at reflux, and then chilled in ice. The crystalline material was collected and dried to afford 0.40 g (57%) of **8a** as dark-red needles, mp >310 °C, very insoluble in most solvents. Trituration with boiling chloroform and drying at 80 °C (1.0 mm pressure) afforded the analytical sample of **8a**: ir max 6.11, 6.28 μ (chelated C=O); MS *m/e* 290 (M − H_2, 52), 292 (M^+, 50). Anal. Calcd for $C_{18}H_{12}O_4$: C, 74.0; H, 4.14. Found: C, 74.2; H, 3.96.

7-Acetoxy-7,10-dihydro-6,11-dihydroxy-5,12-naphthacenedione (8b). A mixture of 0.20 g (0.57 mmol) of **5b** and 1.2 g of 3 A molecular sieves in 25 ml of acetonitrile was stirred for 20 h at ~30 °C in a stoppered flask. The reaction mixture was diluted with 50 ml of CH_2Cl_2 and filtered through a Celite pad. The filtrate was evaporated to dryness to afford 0.14 g (70%) of **8b**. Trituration of 0.11 g of the crude product with 20 ml of ether afforded 0.10 g (63%) of the analytically pure, red **8b**: mp >300 °C; ir max 5.75, 6.10, and 6.24 (chelated quinone), 7.88, 8.00 μ; uv max 251 nm (ε 37 000), 256 (36 100), 281 sh (9600); MS *m/e* 290 (M − HOAc, 100). Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.6; H, 4.03. Found: C, 69.1; H, 3.57.

No tautomerization of **5b** to **8b** occurred in acetonitrile alone or in acetone containing 3 A molecular sieves.

7,10-Dihydro-6,11-dimethoxy-5,12-naphthacenedione (8c). Methylation of 5.00 g of **8a** with 20 ml of methyl sulfate and 30 g of potassium carbonate in 200 ml of methyl ethyl ketone at reflux for 20 h afforded 3.14 g (58%) of **8c**, mp 190–191 °C. The product from an earlier run using acetone as a solvent (which gave lower yield) was recrystallized from methylene chloride–methanol (1:5) to afford the analytical sample of **8c**: mp 193–193.5 °C; ir max 6.00 (C=O), 6.28, 6.42, 7.46, 7.53, and 10.02 μ (this band not in **15**); uv max 376 nm (ε 8300), 261 (29 300); MS *m/e* 320 (M^+, 100); R_f 0.38 in solvent F. Anal. Calcd for $C_{20}H_{16}O_4$: C, 75.0; H, 5.04. Found: C, 74.8; H, 5.07.

This was identical by ir, TLC, and melting point with product formed from **17** by treatment (1) with mercuric acetate, palladium chloride, and cupric chloride[20] and (2) one-pot treatment with diborane (from $NaHB_4$ and $ZnCl_2$) and chromic acid.[21] Probably no reaction with diborane occurred and **17** was partially demethylated and oxidized to **8c** (cf. **20** giving **21a** with CrO_3).

7,10-Dihydro-6,11-diacetoxy-5,12-naphthacenedione (8d). A mixture of 300 mg (1.03 mmol) of **5a** in a solution of 5.0 ml of trifluoroacetic anhydride and 2.0 ml of glacial acetic acid was stirred for 15 min in a stoppered flask. The resulting red solution was poured with stirring into 100 ml of cold water to afford a yellow, crystalline precipitate. This was collected after 2 h, washed thoroughly with water, and dried to afford 0.34 g (88%) of **8d**, R_f 0.16 and 0.64 (trace) in solvent B-1. One recrystallization from methylene chloride–ethanol afforded **8d**: mp 256–257 °C; ir max 5.69, 5.99, 6.30, 7.47 μ; MS *m/e* 376 (M^+, 5), 334 (M − CH_2CO, 30), 292 (M − $2CH_2CO$, 100); R_f 0.04 in solvent B. Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.2; H, 4.29. Found: C, 70.4; H, 3.90.

6,11-Dihydroxy-5,12-naphthacenedione (9a). A mixture of 0.26 g (0.74 mmol) of **5b** and 0.50 g of commercial sponge nickel (water suspension) in 5.0 ml of DMF was stirred for 16 h at ambient temperature to afford 0.20 g (93%) of **9a**, mp >300 °C, homogeneous by TLC: R_f 0.55 in solvent E.

The analytical sample of **9a** obtained from a previous experiment had mp >315 °C (lit. mp 333[7] and 289–290 °C[24]); ir max no OAc at 5.75, 6.12, and 6.30 (chelated quinone), 6.61, 11.55, and 13.79 μ; uv max (cyclohexane) 452, 484, 503, and 518 as compared with literature values[24] of uv max (cyclohexane) 457, 488, 511, and 524 nm; MS *m/e* 290 (M^-, 100).

Compound **5b** also was converted completely to **9a** by boiling xylene (20 h), nitrobenzene at 100 °C, and methanolic sodium methoxide at reflux for 0.5 h. At 23 °C, aromatization to **9a** also occurred with nickel boride in 1,2-dimethoxyethane, potassium diazocarboxylate in acetonitrile, and trifluoroacetic acid in benzene for 1 h. A solution of **5b** in $(Me_2N)_3PO$–H_2O (10:1) was converted rapidly to **9a** by warming on a steam bath for 15 min; $(Me_2N)_3PO$ alone was ineffective.

6,11-Dimethoxy-5,12-naphthacenedione (9b). A solution of 200 mg of the dimethoxy quinone **15b** in 10 ml of trifluoroacetic acid was left for 20 h at room temperature, then the solvent was removed. The residue was crystallized from methylene chloride–petroleum ether, bp 65–110 °C (1:9), 20 ml, to afford 50 mg (25%) of **9b** as a bright yellow solid: mp 183–184 °C; ir max 6.00, 6.22 (weak), 6.25, 6.32-(weak), 7.43, 7.90 μ; uv max 403 nm (ε 71 300), 293 (18 500), 281 (20 000 sh), 249 (42 500); NMR δ 4.12 (s, 6 H, 2 OCH_3) and eight aromatic protons; MS *m/e* 318 (M^+, 100). Anal. Calcd for $C_{20}H_{14}O_4 \cdot \frac{1}{4}HO$: C, 74.5; H, 4.53. Found: C, 74.5; H, 4.80.

13-Acetoxy-5a,11a-[2]butenonaphthacene-5,6,11,12-tetrone (10b). A solution of 6.0 g (13.0 mmol) of **7b** in 400 ml of toluene and 32 ml of glacial acetic acid was heated for 20 h at 75 °C and then evaporated. The residue was triturated with 25 ml of carbon tetrachloride and crystallized from 100 ml of ethanol to afford 4.2 g (81%) of **10b**: mp 188–190 °C (lit.[7] mp 190 °C); R_f 0.25 in B, 0.25 in toluene, and 0.10 in acetone; ir max 5.69 (C=O, ester), 5.80, 5.90, 6.28 μ; uv max 313 nm (ε 5500), 262 (16 400), 232 (39 800); MS *m/e* 400 (M^+, 5), 357 (M − CH_3CO, 5), 340 (M − HOAc, 28), 290 (M − 1 − acetoxybutadiene, 25).

1,4,4a,12a-Tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (11a). A mixture of 1.50 g (5.12 mmol) of **5a** and 4.0 g of zinc dust in 50 ml of glacial acetic acid was stirred under nitrogen for 3.0 h to afford 1.20 g (79%) of yellow-green, homogeneous **11a**. This was recrystallized

once from 2-propanol–cyclohexane to afford the analytical sample of **11a**: ir max 6.10, 6.20, 6.35, 6.70 μ; MS *m/e* 294 (M^+, 100); R_f 0.69 in solvent B-1. Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.5; H, 4.80. Found: 73.7; H, 5.17.

1-(Acetoxy)-1,4,4a,12a-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (11b). To a 200-mg portion of 5% $Pd/BaSO_4$ in 50.0 ml of cold benzene, presaturated with hydrogen, was added 1.06 g (3.0 mmol) of **5b**. The cooled mixture was hydrogenated at 1 atm until hydrogen uptake ceased after 44 min. The catalyst was removed by filtration, and the filtrate was evaporated to afford 1.01 g of **11b**, which was freed of insoluble quinizarin (19%) by trituration with ether. The product was recrystallized twice from ether to afford analytically pure **11b**: mp 164–165 °C; ir max 5.75, 6.10, 6.20, 6.32, 6.65 (characteristic of leucc), 8.02, 8.15 μ; uv max 237 nm (ε 26 700), 252 (23 000), 277 (22 000), 285 (20 200), 397 (12 800), 417 (12 300); MS *m/e* 352 (M^+, 18), 292 (M − HOAc, 40), 240 (M − acetoxybutadiene, 68); R_f 0.70 in solvent E. Anal. Calcd for $C_{20}H_{16}O_6$: C, 68.2; H, 4.58. Found: C, 68.6; H, 4.80.

Reaction of **5b** to **11b** with zinc dust and acetic acid with toluene as solvent at 0 °C proceeded with aromatization to **9**; yields of **11b** ranged between 75 and 80%.

1,2,3,4,4a,12a-Hexahydro-6,11-dihydroxy-5,12-naphthacenedione (12a). Hydrogenation of 2.00 g (6.85 mmol) of **5a** with 0.20 g of palladium black (Engelhard's catalytic grade) in 100 ml of benzene at 1 atm, overnight, afforded 2.0 g (98%) of crude product, homogeneous by TLC. Recrystallization from methylene chloride and 2-propanol gave 138 mg (68%) of yellow-orange **12a**: mp 172–73 °C; ir max 6.11, 6.20, 6.30, 6.65 μ (characteristic of leuco compounds); NMR δ 1.3–3.5 m 10; 13.42 s ½ and 13.69 s 1½, phenolic H; MS *m/e* 296 (M^+, 100). Anal. Calcd for $C_{18}H_{16}O_4$: C, 73.0; H, 5.44. Found: C, 72.8; H, 5.17.

1-Acetoxy-1,2,3,4,4a,12a-hexahydro-6,11-dihydroxy-5,12-naphthacenedione (12b). A mixture of 1.5 g of palladium black (Engelhardt catalytic grade) in 250 ml of benzene was cooled to 10 °C while 15.0 g of **5b** was added. The cold mixture was hydrogenated at 48 psig. The hydrogen uptake showed that 83% of **5b** had been reduced to **11b** in 5 min. The theoretical amount of hydrogen for reduction to **12b** was taken up in 5 h. Recrystallization from tetrahydrofuran–cyclohexane (1:4) afforded 11.7 g (78%) of **12b**: mp 170–172 °C; ir max 5.75, 6.10, 6.20, 6.32, 6.64 (characteristic of leuco), 8.15, 11.92, 12.30 μ; uv max 417 nm (ε 12 500), 398 (13 100), 285 (20 500), 277 (22 000), 252 (23 600), 237 (27 100); MS *m/e* 354 (M^+. 6), 312 (M − CH_2CO, 2), 294 (M − HOAc, 100); R_f 0.37 in solvent B-1. Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.8; H, 5.12. Found: C, 68.8; H, 5.13.

7,8,9,10-Tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (13a). A stirred solution of 0.55 g (1.52 mmol) of **12b** in 50.0 ml of benzene was treated overnight at 20 °C with 5.0 ml of triethylamine. The red precipitate was collected, washed thoroughly with water (50 ml) and benzene (50 ml), then dried at 100 °C (1.0 mm) for 6 h to afford 0.425 g (93%) of the bright red **13a**: mp >300°; ir max 6.12, 6.28, 7.95, 12.0, 13.75 μ; NMR δ 1.85 m 4, 2.81 m 4, 7.80 q 2 (aryl), 8.35 q 2 (aryl), 14.1 s 2 (chelated OH); MS *m/e* 294 (M^+, 100). Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.5; H, 4.79. Found: C, 73.4; H, 4.84.

These properties agreed well with those of **13a** synthesized earlier.[11]

7-Acetoxy-6,11-dihydroxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (13b). A mixture of 6.68 g (18.9 mmol) of leuco **12b** and 10.0 g (43 mmol) of silver oxide in 500 ml of benzene was stirred and heated at reflux for 1 h, an additional 2.0 g (8 mmol) of silver oxide was added, and the reaction was continued for a total of 6.5 h. After filtration, the filtrate was saturated with H_2S and filtered, and the filtrate was evaporated to dryness. Recrystallization from absolute ethanol afforded 4.8 g (73%) of homogeneous **13b** in two crops (second crop, 15%), R_f 0.70 in solvent A-1 (developed twice) identical with that of authentic **13b**[10] by TLC and ir. Compound **13b** had ir max 5.75 (C=O ester), 6.15, 6.3, 8.1 μ; mp 210–212 °C, red melt. When the melt was cooled and reheated above 220 °C gradually, a solid glass formed and gave off the odor of acetic acid, and then decomposed >280 °C (lit.[11] mp 286 °C dec).

7,8,9,10-Tetrahydro-5,7,11-trihydroxynaphthacene-5,12-dione (13d). A. By Air Oxidation in Carbonate. A mixture of 0.50 g (1.4 mmol) of **12b** and 0.32 g (3.0 mmol) of sodium carbonate, anhydrous, in 25 ml of acetonitrile was heated for 18 h at 40 °C with stirring to afford 0.42 g of a mixture of acetoxy **13b** and the hydroxy **13d**, by TLC. This mixture was treated first with trifluoroacetic acid and then with cold methanolic sodium methoxide to afford 0.23 g (52%) of **13d**, ir and TLC identical with those of authentic **13d**; ir max 5.72 (C=O of OAc), 6.13 and 6.30; R_f 0.10 in B-1.

This procedure did not scale up well, probably because the rather insoluble **13d** tended to coat the reactants and reduce the likelihood for further reaction.

B. By Literature Method.[11] A mixture of 4.2 g (12.0 mmol) of **13b** and 90 ml of trifluoroacetic acid was stirred for 2.0 h at 25 °C. The mixture was diluted with 75 ml of toluene and evaporated to dryness. This was repeated to remove the excess trifluoroacetic acid, leaving 4.70 g of **13c**. The trifluoroacetate **13c** in 275 ml of cold methanol was treated with 110.0 ml of 1 N methanolic sodium methoxide for 1.5 h at ice-bath temperature, acidified with 25.0 ml of glacial acetic acid, and evaporated to dryness. The residue was triturated with 1.0 l. of water to afford 3.25 g of product. Recrystallization from 200 ml of 1,2-dichloroethanol afforded 2.40 g (64.5%) of **13d**, mp 278–279 °C, changing to dark needles which decomposed at 295 °C (lit. mp 292 °C dec);[11] R_f 0.25 in solvent C-1; MS *m/e* 310 (M^+, 40), 292 (M − H_2O, 100).

2,3-Epoxy-1,2,3,4,4a,12a-hexahydro-6,11-dihydroxy-5,12-naphthacenedione (14a). Reaction of 0.29 g (1.0 mmol) of **11a** with 0.20 g (1.16 mmol) of *m*-chloroperbenzoic acid in 100 ml of benzene with stirring at room temperature for 86 h in a stoppered flask afforded a yellow solid. This was collected and washed with cyclohexane to afford 100 mg of impure product. The mother liquors deposited a second yellow, crystalline crop of 50 mg (16%) of analytically pure **14a**: mp 187–188 °C; NMR δ 2.80–3.50 m 8, 13.30 s 2; MS *m/e* 310 (M^+, 100), 290 (20), 274 (22), 254 (30); R_f 0.63 in solvent C-1. Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.7; H, 4.55. Found: C, 69.9; H, 4.72. From the impure product and the mother liquors was obtained an additional 157 mg (49%) of **14a**.

1-Acetoxy-2,3-epoxy-1,2,3,4,4a,12a-hexahydro-6,11-dihydroxy-5,12-naphthacenedione (14b). A solution of **11b** in benzene was stirred with 40% aqueous peracetic acid for 5 days and worked up. Two recrystallizations from benzene afforded the analytical sample of **14b**: mp 264–265 °C; ir max 5.72, 6.10, 6.20, 6.31, 6.69 μ; MS *m/e* 368 (M^+, 100), 308 (M − HOAc, 60), 290 (M − HOAc − H_2O, 60); R_f 0.10 in solvent B. Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.2; H, 4.38. Found: C, 65.3; H, 4.76.

1,4-Dihydro-5,6,11,12-tetramethoxynaphthacene (17). A mixture of 100 g of leuco **11a**, 320 g of barium oxide, 1.67 l. of acetone, and 322 ml of dimethyl sulfate was stirred under a nitrogen atmosphere at reflux for 5 h. The mixture was filtered (through Celite), the filter was thoroughly washed with acetone, and the combined filtrates were evaporated. The residue was diluted with 200 ml of acetone, kept overnight at 5 °C, and the precipitate was collected, washed (cold acetone), and air dried to give 68.5 g (57.6%) of orange-yellow, crystalline **17**, mp 191–193 °C. Recrystallization from methylene chloride–petroleum ether (bp 65–110 °C) afforded **17**: mp 197–198 °C; ir max 5.99, 6.19, 6.22, 6.91, 7.52 μ; uv max 420 nm (ε 6500), 397 (8000), 377 (7800), 359 (4300), 269 (107 000), 240 (27 800); MS *m/e* 350 (M^+, 100); R_f 0.70 and 0.55 in solvent D and F, respectively. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.5; H, 6.33. Found: C, 75.6; H, 6.33.

The use of barium oxide gave very consistent results in experimants ranging in size from 3 g to 100 g of **11a**. Earlier experiments with calcined potassium carbonate instead of barium oxide required longer reaction times (40–89 h), and gave erratic yields (20–60%) of **17** and increasing amounts of leuco dimethyl **11c** with shorter reaction times. Overly long reaction times gave dimethyl **15b**, an oxidized form of **11c**. Addition of zinc dust to the reaction decreased the formation of **15b**.

The stability of **17** was examined. **17** was relatively unchanged (by TLC) by the following: 20-h reflux or 8 days at room temperature in 1 N NaOMe–MeOH; 48 h at room temperature in lithium aluminum hydride and diglyme; 24 h at room temperature in glacial acetic acid. **17** was all decomposed (by TLC) by the following at room temperature: 2 h in trifluoroacetic acid; 20 h in sodium hydride and DMF; 6 days (or less) in 1 N hydrochloric acid and 1,2-dimethoxyethane; and 4 days when a methylene chloride solution of **17** was exposed to air and repeatedly allowed to evaporate to dryness and then redissolved. In the last case, the product was **8c**. When **17** (30 mg) was treated with excess sodium hydride in DMF for 2 days, the homogenous (R_f 0.73 in chloroform) product (20 mg) appeared to be 5,6,11,12-tetramethoxynaphthacene (mp 158–170 °C from 2-propanol–cyclohexane) on the basis of its molecular weight [MS 348 (M^+, 100)], its symmetrical aryl and methyl protons by NMR (δ 4.06 s, 12 protons of 4 OMe; 7.37 q 4, aryl H; and 8.29 q, 4, aryl H), and analysis fitting solvated 5,6,11,12-tetramethoxynaphthacene (Anal. Calcd for $C_{22}H_{20}O_4$·*i*-PrOH·⅓C_6H_{12}: C, 74.3; H, 7.40. Found: C, 74.4; H, 7.67).

1,4-Dihydro-6,11-dimethoxy-5,12-naphthacenedione (15b). After 3.0 g (43%) of crystalline **17** had been obtained from a methylation of 5.8 g of **11a**, using K_2CO_3 and 89-h reaction time, the mother liquors were evaporated. Recrystallization of the residue from 25 ml of 1,2-dimethoxyethane afforded 1.02 g (16%) of orange-yellow **15b**: mp 196.5–197.5 °C; ir max 6.00 (s), 6.20, 6.33, 7.4 (s), 12.70 (this band not in **8c**); uv max 412 nm (ε 6600), 295 (15 600), 284 (16 200), 233

(50 400); MS *m/e* 320 (M^+, 100); R_f 0.37 in solvent F. Anal. Calcd for $C_{20}H_{16}O_4$ (320.3): C, 75.0: H, 5.04. Found: C, 75.1; H, 5.11.

6,11-Dimethoxy-1,4,4a,12a-tetrahydro-5,12-naphthacenedione (11c). After unreacted **4a** (recovered by base extraction) and 50 mg (14%) of crystalline **17** had been obtained from a methylation of 0.29 g of **11a** using K_2CO_3 and 18-h reaction time, the mother liquors (consisting of 1 ml of methylene chloride and 15 ml of 2-propanol) were diluted with an equal volume of cyclohexane to afford 30 mg (9%) of leuco dimethyl **11c:** mp 164–165 °C; ir max 5.92, 6.05 (C=O), 6.20, 6.37, 6.70, 6.89 μ; uv max 368 nm (ϵ 5000), 296 (6800), 263–267 (36 400), 235 (27 400); MS *m/e* 322 (M^+, 100); R_f 0.24 in solvent F. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.4; H, 5.62. Found: C, 74.4; H, 5.77.

1,4-Dihydro-5,12-dihydroxy-6,11-dimethoxynaphthacene (16). A mixture of 1.5 g (7.75 mmol) of leuco **11a,** 10.0 g of freshly calcined potassium carbonate, 25 ml of methyl ethyl ketone, and 10 ml of methyl sulfate was heated for 3 h at reflux temperature. Filtration of the salts and concentration of the solvent afforded a reddish-brown precipitate that was triturated with methanol and dried to give 1.38 g (55%) of **16,** identical by TLC and ir with the analytical sample of **16.** This was purified through a silica gel column (methylene chloride eluent) to yield brownish **16:** mp 162–163 °C; ir max 2.98 (OH), 6.05 (m), 7.35–7.40 (s), 8.00, 11.90 μ (not in **11c** or **15b**); uv max 413 nm (ϵ 5600), 272 (28 000), 218 (46 600); MS *m/e* 322 (M^+, 100); R_f 0.10 in benzene. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.5; H, 5.63. Found: C, 74.3; H, 5.71.

A solution of **16** in methylene chloride left open to air overnight was oxidized to **15** according to TLC and ir of the isolated product.

Smaller amounts of **16** was also formed in some methylations of **11a** with acetone as solvent, generally in cases where little **17** was formed.

1,4-Dihydro-5,6,11,12-naphthacenetetrone (18). The literature procedure[17] was followed. A mixture of 63 mg (0.18 mmol) of **17** and 262 mg (2.1 mmol) of silver(II) oxide was sonificated for 15 s, then treated with 0.40 ml of 85% H_3PO_4. After stirring at room temperature for 45 min, the mixture was diluted with 150 ml of water and extracted with methylene chloride (3 × 60 ml). Evaporation of the dried organic extracts left 52 mg (100%) of dull red **18:** mp 205 °C dec; ir max 5.87 (C=O), 6.00, 6.25, 7.72, 7.82 μ; uv max 315 nm (ϵ 4100), 252 (14 700), 230 (16 700 sh), 213 (20 700); MS *m/e* 290 (M^+, 100), 288 ($M - H_2$, 80). Anal. Calcd for $C_{18}H_{10}O_4 \cdot \frac{1}{2}H_2O$: C, 72.2; H, 3.70. Found: C, 72.3; H, 3.70.

1,2,3,4-Tetrahydro-2-hydroxy-5,6,11,12-tetramethoxynaphthacene (20). A tetrahydrofuran (THF) solution (20 ml) of diborane (1 M in BH_3) was added to a stirred solution of 4.20 g (12.0 mmol) of olefin **17** in 60 ml of THF under nitrogen. After 3.5 h, the solution was cooled (ice bath) and stirred while treated carefully with 14.5 ml of 30% hydrogen peroxide in 60 ml of 6 N sodium hydroxide. Most of the THF was removed and the aqueous solution was extracted with methylene chloride to afford 4.1 g (92%) of homogeneous (by TLC) **20.** Recrystallization from benzene gave yellow, crystalline **20:** mp 212–213 °C; ir max 2.85 μ (OH); NMR δ 3.83 (s, 6 H) and 3.99 (s, 6 H) of 4 OCH_3; uv max 430 nm (ϵ 6200), 396 (7900), 378 (7700), 359 (3900); NMR 1.3–3.0 m 8, 3.83 s 6 (2 OMe), 3.99 s 6 (2 OMe), and 4 aryl H; MS *m/e* 310 (M^+, 100); R_f 0.11 in solvent F. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.7; H, 6.55. Found: C, 72.1; H, 6.70.

3,4-Dihydro-5,6,11,12-tetramethoxy-2(1*H*)-naphthacenone (19a). The literature procedure[22] was followed using 1.00 g (2.71 mmol) of alcohol **20,** 8 ml of dimethyl sulfoxide, 30 ml of benzene, 2 ml pyridine, and 1.0 ml of trifluoroacetic acid; 2.00 g of dicyclohexylcarbodiimide was added initially and 2.00 g more (total, 19.4 mmol) after 3.75 h. After a total reaction time of 5.75 h, no **20** was left (by TLC). The reaction mixture was treated with 6.0 g (67.5 mmol) of oxalic acid and 25 ml of methanol and worked up, using additional benzene to extract the product (1.77 g). This was chromatographed (100 g silica gel, 200–325 mesh, pretreated with KH_2PO_4 buffer; 2.25 × 47 cm column; 1% THF in benzene as eluent) to give 0.50 g (50%) of **19a,** homogeneous by TLC. Identical material from an earlier run was recrystallized from ether–hexane (1:5) to afford dark tan **19a:** mp 130 °C sintered; 142–145 °C dec; ir max 5.80 μ (C=O); uv max 413 nm (ϵ 5100), 390 (6200), 325 (5900), 266 (72 500), 227 (20 000); NMR δ 2.65 t 2, 3.48 t 2, 3.88 d 8 (2 OMe + benzylic CH_2), 4.04 d 6 (2 OMe), 7.52 q 2 (aryl), 8.36 q 2 (aryl); MS *m/e* 366 (M^+, 100); R_f 0.58 in solvent G. Anal. Calcd for $C_{22}H_{22}O_5 \cdot \frac{1}{4}H_2O$: C, 71.2; H, 6.10. Found: C, 71.1; H, 5.77.

6,11-Dimethoxy-8-hydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (21a). The literature procedure[17] used in preparing the naphthacenetetrone **18** was applied to 500 mg (1.36 mmol) of tetramethoxy **20** using 2.0 g (16.2 mmol) of silver(II) oxide, 30 ml of dioxane, and 3.2 ml of 85% phosphoric acid to afford the theoretical yield of **21a** that crystallized on standing. Recrystallization from acetonitrile–petroleum ether (bp 30–60 °C) afforded orange **21a:** mp 182–183 °C; ir max 2.88 (OH), 5.97 μ; uv max 370 nm (ϵ 5300), 260 (34 800). 223 (19 500); MS *m/e* 338 (M^+, 100), 320 ($M - H_2O$, 25); R_f 0.15 in solvent G. Anal. Calcd for $C_{20}H_{18}O_5$: C, 70.8; H, 5.35. Found: C, 70.6; H, 5.42.

The identical product (ir, TLC, MS) was obtained on treatment of **20** with either *N*-bromoacetamide in *tert*-amyl alcohol or with chromium trioxide in pyridine.

7,8,9,10-Tetrahydro-6,8,11-trihydroxy-5,12-naphthacenedione (21b). A mixture of 2.00 g (5.40 mmol) of **20,** 100 ml of nitrobenzene, and 10.0 g (75 mmol) of aluminum trichloride was stirred at ambient temperature for 20 h and then poured into a mixture of 500 g of ice, 200 ml of water, and 300 ml of concentrated hydrochloric acid. After the nitrobenzene was removed by ether extraction (2 × 600 ml), the aqueous phase stood for 12 days during which the precipitated 1.54 g (92%) of **21b** was collected. This was almost homogeneous (R_f 0.30 + trace at R_f 0.95). Trituration with boiling methylene chloride afforded red, crystalline **21b:** mp 313–315 °C dec; ir max 3.00 (OH), 6.15, 6.30 μ (phenolic OH chelated with quinone); uv max 514 nm (ϵ 6000), 481 (9700), 457 (8700), 287 (9600), 256 sh (38 600), 252 (39 700); NMR δ 2.0–3.2 m 6, 4.30 m 2, 7.84 q 2 (aryl), 8.38 q 2 (aryl), 13.62 s 2 (chelated OH); MS *m/e* 310 (M^+, 100); R_f 0.32 in solvent G. Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.7; H, 4.54. Found: C, 70.1; H, 4.80.

3,4-Dihydro-6,11-dihydroxy-5,8,12(1*H*)-naphthacenetrione (22b). By the procedure used to prepare **19a,** 0.35 g (1.13 mmol) of **21b** was allowed to react with 1.30 g (6.32 mmol) of dicyclohexylcarbodiimide and excess dimethyl sulfoxide for 3 h and worked up to afford 0.29 g (83%) of crude **22b,** still containing a trace of dicyclohexylurea according to its ir spectrum. Addition of water to a sulfolane solution of this afforded red crystals which were triturated with boiling methanol to afford the analytical sample of **22b:** mp >310 °C dec; ir max 5.79 (C=O), 6.15, 6.30 μ (chelated quinone); uv max 514 nm (ϵ 5300), 482 (7300), 457 sh (6400), 288 (7000), 256 (26 900), 252 (27 300); NMR δ 2.67 t 2 (H-9), 3.30 t 2 (H-10), 3.68 s 2 (H-7), 7.84 q 2 and 8.38 q 2 (aryl H), 13.35 s 1 and 13.45 s 1 (chelated OH) with MeOH solvate also detectable; R_f 0.65 in solvent G. Anal. Calcd for $C_{18}H_{12}O_5 \cdot 0.2CH_3OH$: C, 69.3; H, 4.09. Found: C, 69.1; H, 4.15.

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Registry No.—**4a,** 1709-63-3; **5a,** 58976-81-1; **5b,** 58976-82-2; **6a,** 58976-83-3; **6b,** 58976-84-4; **6d,** 58976-85-5; **7b,** 58976-86-6; **8a,** 58976-87-7; **8b,** 58976-88-8; **8c,** 58976-89-9; **8d,** 58976-90-2; **9a,** 1785-52-0; **9b,** 36831-93-3; **10b,** 58976-91-3; **11a,** 58976-92-4; **11b,** 58976-93-5; **11c,** 58976-94-6; **12a,** 58976-95-7; **12b,** 58976-96-8; **13a,** 58976-97-9; **13b,** 58976-98-0; **13d,** 20494-73-9; **14a,** 58976-99-1; **14b,** 58977-00-7; **15b,** 58977-01-8; **16,** 58977-02-9; **17,** 58977-03-0; **18,** 58977-04-1; **19a,** 58977-05-2; **20,** 58977-06-3; **21a,** 58977-07-4; **21b,** 58977-08-5; **22b,** 58977-09-6; 1,3-butadiene, 106-99-0; 1-acetoxy-1,3-butadiene, 1515-76-0; 2-methoxybutadiene, 3588-30-5; 5,6,11,12-tetramethoxynaphthacene, 58977-10-9.

References and Notes

(1) A portion of this paper was presented by A. P. Martinez, W. W. Lee, and D. W. Henry at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974, Abstract No. MEDI-58. The work with 2-methoxybutadiene, contributed by T.H.S., was added during revision of this manuscript.

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Chemical Transformations of 7,9-Disubstituted Purines and Related Heterocycles. Selective Reduction of Imines and Immonium Salts

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Ten 7,9-disubstituted purines and related heterocycles were reduced with borohydride to afford the corresponding 7,8-dihydro species, a type of heterocycle which has not previously been studied in any detail. The reduced species were found to reoxidize quantitatively at rates characteristic of and predictable for the individual heterocycles; the reoxidation phenomenon was investigated and shown to involve reaction with water or oxygen. In solutions containing mixtures of reduced and oxidized heterocycles, the two species were found to be in rapid equilibrium, undoubtedly via hydride transfer. This observation prompted the utilization of the 7,8-dihydro-7,9-disubstituted heterocycles for the novel and selective reduction of imines and immonium salts. Benzylideneaniline, benzylidenebenzylamine, and cyclohexylidenepyrrolidinium perchlorate, e.g., were converted to their respective amines in excellent yields. Over the range of conditions employed for these transformations, no significant reduction of aldehydes, ketones, or several other common organic functional groups was observed, so the heterocycles may prove useful as selective reducing agents. The reactivity of the disubstituted heterocycles with nucleophiles was also studied. Certain of the oxidized compounds, e.g., were found to undergo ring opening at high pH, as has been observed previously. Treatment of the reduced, ribosylated species with aniline at pH 4.5 resulted in deribosylation of the nucleosides. This transformation, which previously has been possible only after opening of the imidazole moiety at high pH, should be of considerable utility to biochemists for the depurination of 7-methylguanosine moieties in transfer and messenger RNA's.

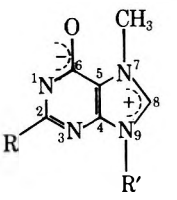
Many reports concerned with alkylated purines and their derivatives and analogues have appeared in recent years. These investigations have dealt with the synthesis of substituted heterocycles and with the effects of specific alkylating agents and reaction conditions on the position and extent of alkylation. The relevance of these alkylations as models for mutagenic change at the nucleic acid level has also been considered, as have the biological and physical properties of the alkylated species. However, substantially less work descriptive of the chemistry of the individual alkylated compounds themselves is available.

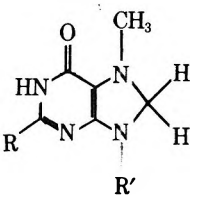
One alkylated nucleoside of special interest in this regard is 7-methylguanosine, which occurs in unique positions in certain transfer[3] and messenger[4] RNA's, and is the only naturally occurring nucleoside known to exist as a zwitterion at physiological pH. Owing to its zwitterionic character, 7-methylguanosine may undergo facile and reversible reduction,[5] a transformation first noted[6] for 1,3-dimethylbenzimidazolium iodide and 9-methylcaffeine perchlorate. 7-Methylguanosine also undergoes ring opening in strong aqueous base,[7] depurination in strong acid,[8] and selective demethylation in the presence of a powerful nucleophile.[9]

To determine the possible generality of these transformations for related heterocycles, as well as additional reaction pathways which may be available, we have studied the chemistry of ten 7,9-disubstituted purines and related compounds and report on the nature of the pH-dependent reoxidation of the reduced heterocycles, the utilization of the reduced species in the selective reduction of imines and immonium salts, and the interaction of certain of the oxidized and reduced heterocycles with strong bases and nucleophiles.

Results and Discussion

Synthesis of Disubstituted Heterocycles. The 7,9-disubstituted purines **1a**–**8a** were prepared by known procedures[10] and converted to the corresponding 7,9-disubstituted 7,8-dihydropurines by reduction with sodium borohydride in water. Isolation of the reduced purines free from boron hydrides was accomplished by concentration of the reaction mixtures to a small volume, treatment with acetone, and concentration to dryness under diminished pressure. This

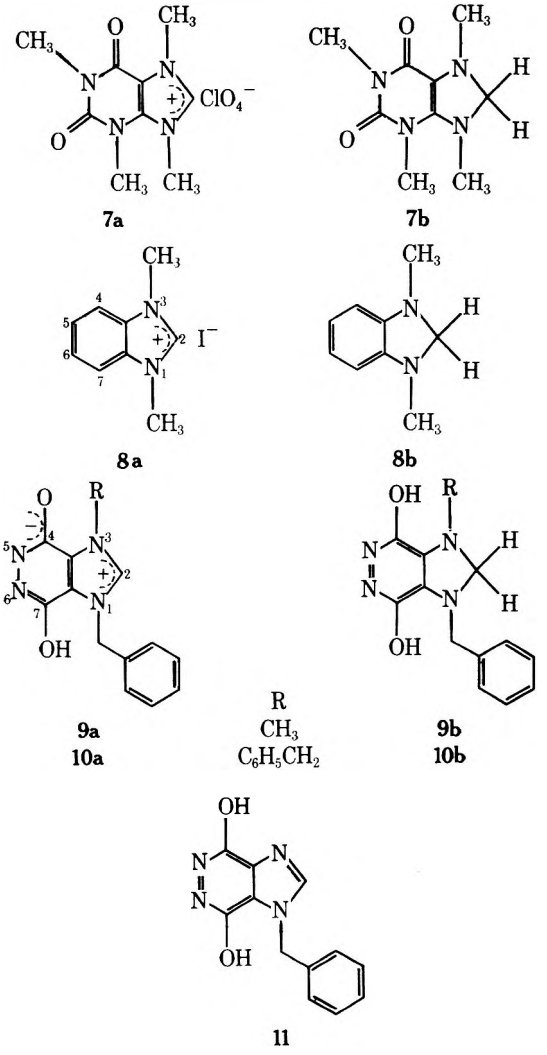




	R	R′	
1a	NH_2	β-D-ribofuranosyl	**1b**
2a	NH_2	CH_3	**2b**
3a	H	β-D-ribofuranosyl	**3b**
4a	H	CH_3	**4b**
5a	OH	β-D-ribofuranosyl	**5b**
6a	OH	CH_3	**6b**

procedure afforded the reduced compounds as their respective sodium salts.

1-Benzyl-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine



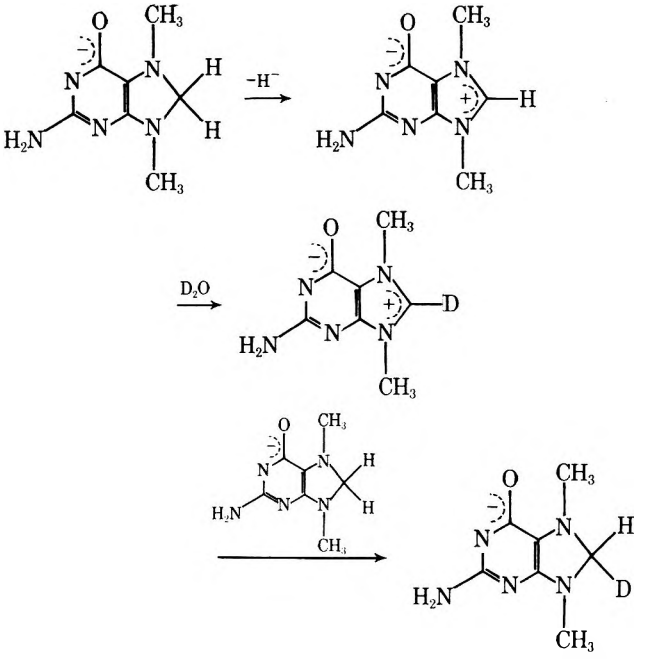
(**9a**) was obtained in 95% yield by methylation of 1-benzyl-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**11**)[11] with methyl iodide at room temperature. The ultraviolet spectrum, high- and low-resolution mass spectra, and NMR data of **9a** were consistent with the assigned structure. 1,3-Dibenzyl-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**10a**) was produced in similar fashion, by treatment of **11** with benzyl bromide in DMF at reflux.[12] Compounds **9a** and **10a** were converted to the respective 3-substituted 1-benzyl-2,3-dihydro-4,7-dihydroxyimidazo[4,5-*d*]pyridazines by treatment with sodium borohydride and could be isolated as the sodium salts by the evaporative procedure outlined above for the 7,9-disubstituted 7,8-dihydropurines. Alternatively, the reduced imidazo[4,5-*d*]pyridazines (**9b** and **10b**) could be obtained in protonated form rather than as the sodium salts by treatment of concentrated aqueous solutions of **9a** and **10a** with excess borohydride and then with acetic acid. The resulting suspensions of **9b** and **10b** were filtered, washed with water and tetrahydrofuran, and then dried under vacuum.

Physical and Spectral Properties of the Disubstituted Heterocycles. All of the disubstituted heterocycles studied, as well as the corresponding disubstituted dihydro species, were found to be soluble in water and to a lesser extent in ethanol, methanol, and dimethylformamide. Some of the reduced species, particularly **4b, 5b, 7b,** and **9b,** were also soluble in ethyl acetate, which permitted their extraction from aqueous media in pure form after borohydride reduction of the individual oxidized heterocycles.[13]

The ultraviolet spectra of the 7,9-dialkyl-7,8-dihydropurines and related analogues all had longer wavelength absorption than did the respective oxidized heterocycles (Table I). Thus 7,9-dimethyl-7,8-dihydroguanine (**2b**) had an absorption maximum in the ultraviolet at 304 nm at neutral pH. This absorption was characteristic of the reduced species (λ_{max} for **2a** itself were at 281 and 251 nm) and permitted the course of borohydride reduction of purine **2a,** or reoxidation of dihydropurine **2b,** to be followed conveniently by changes in the ultraviolet.[14]

The ^{1}H NMR spectra of the heterocycles were also characteristic of oxidation state, as was apparent for **9a** and **9b** (Table II). For 9-methylcaffeine perchlorate (**7a**), e.g., the NMR spectrum determined in D_2O (external Me_4Si) revealed singlets of equal intensity at δ 3.34, 3.78, 4.11, and 4.17, corresponding to the four methyl groups. The C-8 proton was not observed, owing presumably to rapid exchange with solvent.

This type of exchange has been noted previously[15] and parallels the exchange of tritium observed between T_2O and the C-8 proton of adenosine or guanosine.[16] The exchange suggested that the C-8 position in the disubstituted heterocycles possessed both positive and negative character. In fact, when the spectrum of 9-methylcaffeine perchlorate was recorded in dimethyl sulfoxide-d_6, in which proton exchange would be expected to be much slower, the C-8 proton was observed to resonate at δ 9.29. As expected, reduction of 9-methylcaffeine perchlorate with sodium borohydride to afford **7b** resulted in the shielding of the four methyl groups, which gave signals at δ 2.57, 3.09, 3.17, and 3.45 when measured in D_2O. The C-8 methylene protons resonated as a singlet at δ 4.35. These protons did not exchange readily in D_2O at room temperature or at 45 °C, although under more favorable conditions the corresponding methylene protons in **2b** were observed to undergo some exchange with solvent at 45 °C. This may be attributed to exchange of the following type:



Reoxidation of the Reduced Heterocycles. The reoxidation of 8,9-dihydro-7-methylguanosine (**1b**) has been studied as a model for the reversible reduction of the 7-methylguanosine moiety (which occurs in certain transfer RNA's.)[5] It was reported that the reduced species reoxidized to 7-methylguanosine with a $t_{1/2}$ of 20–35 min in 0.5 M sodium phosphate buffer at pH 7.0 and the conversion was attributed to reaction of **1b** with O_2 dissolved in the aqueous medium, although neither the experimental basis for this conclusion nor its generality were described. Investigation of reduced

Table I. Ultraviolet Absorption Maxima of the Reduced, Disubstituted Heterocycles

Compd	pH 2, λ_{max}, nm	pH 7, λ_{max}, nm	pH 10, λ_{max}, nm
7,8-Dihydro-7-methylguanosine (**1b**)	274	302	293
7,8-Dihydro-7,9-dimethylguanine (**2b**)	272	304	292
7,8-Dihydro-7-methylinosine (**3b**)	286	289	287
7,8-Dihydro-7,9-dimethylhypoxanthine (**4b**)	289	292	285
7,8-Dihydro-7-methylxanthosine (**5b**)	305, 271	300, 246	297
7,8-Dihydro-7,9-dimethylxanthine (**6b**)	291	292	288
7,8-Dihydro-9-methylcaffeine (**7b**)	277	309	310
1,2-Dihydro-1,3-dimethylbenzimidazole (**8b**)	293	302	302
1-Benzyl-1,2-dihydro-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine (**9b**)	361	340	342
1,3-Dibenzyl-1,2-dihydro-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**10b**)	372	342	342

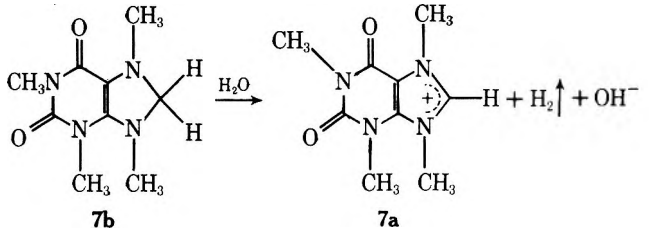
Table II. Rates of Reoxidation of the Reduced Heterocycles in Aqueous Solution at Variable pH[a]

Compd	$t_{1/2}$ values for reoxidation, min						
	pH 2	pH 3.5	pH 5	pH 6	pH 7	pH 8	pH 10
7,8-Dihydro-7-methylguanosine (**1b**)	7	8	6	13	12	22	*b*
7,8-Dihydro-7,9-dimethylguanine (**2b**)	4	3	7	10	11	6	3
7,8-Dihydro-7-methylinosine (**3b**)	35	40	52	42	50	65	*b*
7,8-Dihydro-7,9-dimethylhypoxanthine (**4b**)	18	42	50	47	50	45	40
7,8-Dihydro-7-methylxanthosine (**5b**)	1	1.5	1.5	1.5	5	12	*b*
7,8-Dihydro-7,9-dimethylxanthine (**6b**)	1	1	1	1	2	4	2
7,8-Dihydro-9-methylcaffeine (**7b**)	6	10	15	17	55	86	160
1,2-Dihydro-1,3-dimethylbenzimidazole (**8b**)	46	75	61	95	230	220	500
1-Benzyl-1,2-dihydro-4,7-dihydroxy-3-methylimidazo[4,5-*d*]-pyridazine (**9b**)	10	19	17	24	12	2[illegible]	*b*
1,3-Dibenzyl-1,2-dihydro-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**10b**)	2	3	12	22	24	19	*b*

[a] The pH was maintained within 0.2 unit by the use of acetate buffer at pH 2, 3.5, 5, and 6 and borate buffer at pH 7, 8, and 10. [b] Unstable at pH 10.

heterocycles **1b–10b** revealed that reoxidation in aqueous solution was a general phenomenon. Each compound was reduced in aqueous solution with sodium borohydride and, after destruction of excess borohydride, the individual solutions were adjusted to appropriate concentrations and pH values by the addition of aliquots of the concentrated solutions containing the heterocycles to acetate or borate buffer solutions. The ultraviolet spectra of the reduced heterocycles were then recorded at predetermined time intervals, as illustrated in Figure 1 for the reoxidation of 7,8-dihydro-9-methylcaffeine (**7b**) in aqueous solution at pH 4.5. The ultraviolet spectra were then utilized to calculate the $t_{1/2}$ values for reoxidation at individual pH values and the results are given in Table II. For 8,9-dihydro-7-methylguanosine (**1b**), e.g., the $t_{1/2}$ value at pH 7.0 was found to be 13 min, which was the same as the rate determined in unbuffered solution but somewhat less than the reported[5] value of 20–35 min. However, when the experiment was repeated in the presence of 0.1 M phosphate buffer, the value of $t_{1/2}$ changed to approximately 25 min, in agreement with the published value obtained under similar conditions.

If the reversible reduction of compounds **1a–10a** were to involve the type of transformation previously proposed for compounds **1a**, **7a**, and **8a**, then oxidation of the reduced



7b **7a**

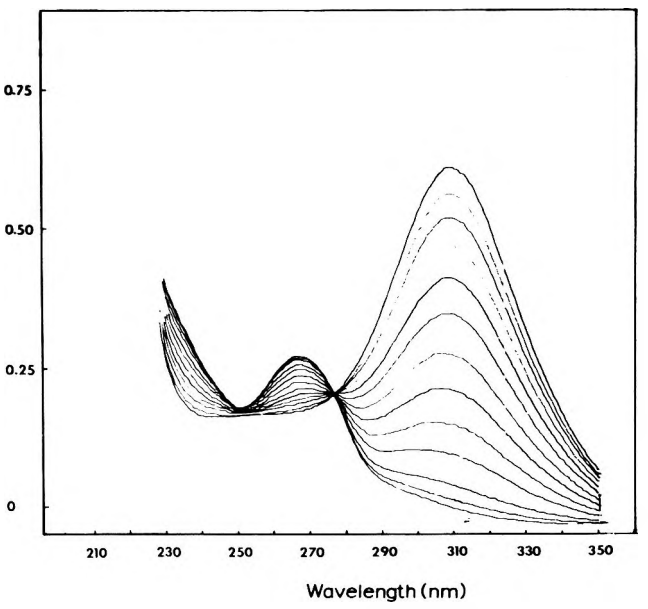


Figure 1. Reoxidation profile of 7,8-dihydro-9-methylcaffeine (**7b**) at pH 4.5. The ultraviolet spectrum of **7b** (λ_{max} 309 nm) was recorded at regular time intervals. The increase in absorbance at 266 nm was due to the formation of **7a**.

species via reaction with water or oxygen would necessarily result in the formation of equivalent molar amounts of hydroxide ion, hydrogen, and the oxidized heterocycles (**1a–10a**). Consistent with this scheme was the change in pH from 4.5 to 8.5 which accompanied the reoxidation of a 0.3 M aqueous solution of 7,8-dihydro-9-methylcaffeine (**7b**). Also of interest in this regard was the recovery in quantitative yield of a

Table III. Approximate Rates of Reoxidation of the Reduced Heterocycles in Degassed, Aqueous Solution at Variable pH[a]

Compd	$t_{1/2}$, min						
	pH 2	pH 3.5	pH 5	pH 6	pH 7	pH 8	pH 10
7,8-Dihydro-7-methylguanosine (**1b**)	7	55	100	82	20	27	*b*
7,8-Dihydro-7,9-dimethylguanine (**2b**)	18	30	24	13	6	3	4
7,8-Dihydro-7-methylxanthosine (**5b**)	12	47	68	22	15	8	*b*
7,8-Dihydro-7,9-dimethylxanthine (**6b**)	11	50	70	9	13	5	11
1,2-Dihydro-1,3-dimethylbenzimidazole (**8b**)	30	105	110	95	155	300	>600
1-Benzyl-1,2-dihydro-4,7-dihydroxy-3-methylimidazo[4,5-*d*]-pyridazine (**9b**)	30	35	25	40	35	80	*b*

[a] The pH was maintained within 0.2 unit by the use of acetate buffer at pH 2, 3.5, 4, 5, and 6 and borate buffer at pH 7, 8, and 10. [b] Unstable at pH 10.

sample of 1-benzyl-4,7-dihydroxy-3-methylimidazo[4,5-*d*]-pyridazine (**9a**) which had been reduced with borohydride and allowed to reoxidize in aqueous solution. The recovered sample was identical with authentic **9a** as judged by its melting point and ultraviolet spectrum, as well as its chromatographic properties (TLC on silica gel). An experiment was also carried out in which a sample of 7,8-dihydro-7,9-dimethylxanthine (**6b**) was treated with 3 M aqueous hydrochloric acid in a sealed system and the evolved gas was trapped in a gas collection apparatus and subsequently shown to be flammable.

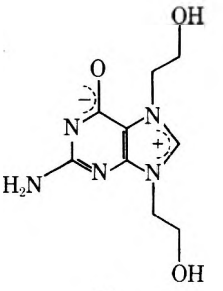
To determine if reoxidation of the reduced heterocycles did indeed involve reaction with molecular oxygen, the reoxidation experiment with 7,8-dihydro-7,9-dimethylxanthine (**6b**) was repeated in an aqueous buffer (pH 3.5) which had been carefully degassed to remove dissolved oxygen. The measured $t_{1/2}$ value in the degassed solution was 50 min (as compared with the original value of 1 min in oxygen-saturated solution) and brief agitation of the degassed solution in the presence of air reestablished reoxidation at the faster rate.[17,18] Since a substantial portion of the observed reoxidation of **6b** at pH 3.5 had obviously occurred via reaction with oxygen, the $t_{1/2}$ values for several of the heterocycles were also determined in degassed aqueous solutions to provide an approximate measure of the rate of reoxidation in the absence of oxygen (Table III). Comparison of the $t_{1/2}$ values for reoxidation obtained in the presence and absence of oxygen (Tables II and III) indicated that most of the reoxidation occurred via reaction with oxygen, especially at moderate pH values.

To demonstrate that reaction could occur between the reduced heterocycles and water at neutral pH, a sample of 7,8-dihydro-7,9-dimethylguanine (**2b**) was dissolved in degassed, aqueous solution and a portion was sealed in a tube whose volume was such that it could have contained no more than 13% of the oxygen required to effect oxidation of **2b** to **2a**. The sealed tube was maintained at room temperature for 2 weeks, during which time **2a** was formed in quantitative yield. In experiments in degassed aqueous solutions at lower pH values, all of the compounds studied oxidized faster than at neutral pH, presumably reflecting reaction of the reduced species with hydronium ions, according to the scheme

$$\mathbf{7b} + \overset{+}{H_3O} \longrightarrow \mathbf{7a} + H_2O + H_2\uparrow$$

Consistent with this scheme were the rates of reoxidation of species **7b** and **8b**, which varied inversely with pH (Tables II and III). However, a more complicated pH profile was observed for several other species, notably **1b, 2b, 5b,** and **6b** (Table III). For these compounds, the rate of reoxidation was also faster at high pH. The difference in the shape of these rate curves is presumably due to the presence of ionizable hydrogens in compounds **1b, 2b, 5b,** and **6b**. At high pH the pyrimidine ring could thus have substantial negative character. Since **1a, 2a, 5a,** and **6a** are resonance stabilized, with considerable delocalization of the net positive and negative charges formally written for each, the presence of negative charge in the pyrimidine moiety of **1b, 2b, 5b,** and **6b** would be expected to facilitate the development of positive charge in the imidazole moiety, e.g., by promoting the net loss of hydride.

Ring Opening of the Oxidized Heterocycles. At high pH, an additional effect is operative which affects the observation of the reoxidation phenomenon but not its kinetics, namely hydrolysis of the imidazolium ring in the oxidized heterocycles. Hydrolytic opening of the imidazolium ring has been reported for several 7,9-disubstituted purines and for the 1,3-dimethylbenzimidazolium ion. Brooks and Lawley, e.g., studied the base-promoted hydrolysis of 7,9-di(2-hydroxyethyl)guanine (**12**) and reported the product as 2-amino-4-hydroxy-5-[*N*-(2-hydroxyethyl)formamido]-6-*N*-(1-hydroxyethyl)pyrimidine (**13**).[19] No evidence was presented in support of the position assigned to the formyl group, however, in spite of earlier evidence for the formation of two products from the ring opening of 1,2,3,5-tetramethylbenzimidazole.[20] Similarly, Haines et al.[7] studied the decomposition of 7-methylguanosine (**1a**) in aqueous ammonium hydroxide at pH



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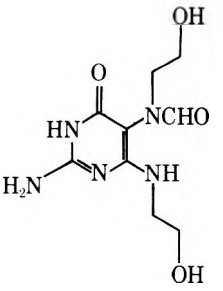

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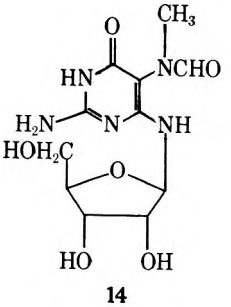

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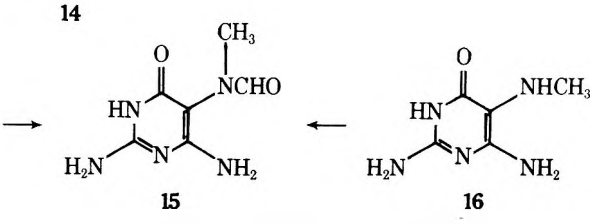


15 **16**

Table IV. Rates of Ring Opening of Disubstituted Heterocycles[a]

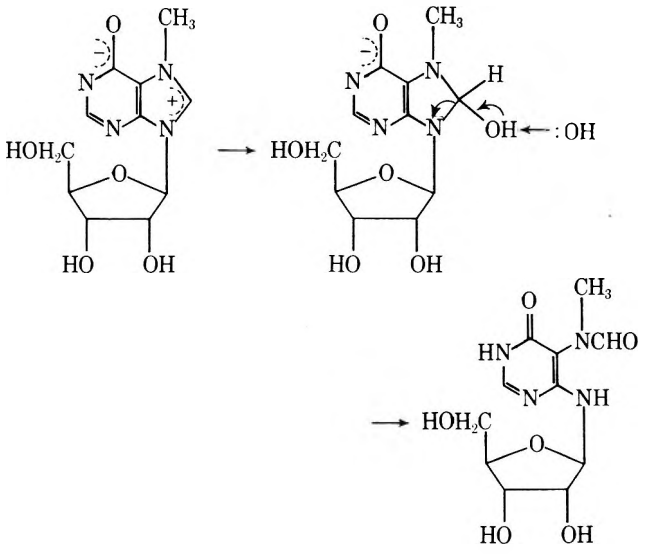
Compd	$t_{1/2}$, min
7-Methylguanosine (**1a**)	25
7,9-Dimethylguanine (**2a**)	>120
7-Methylinosine (**3a**)	5
7,9-Dimethylhypoxanthine (**4a**)	*b*
7-Methylxanthosine (**5a**)	10
7,9-Dimethylxanthine (**6a**)	*b*
9-Methylcaffeine percholorate (**7a**)	1.5

[a] Aqueous Tris–HCl, pH 10.0. [b] Stable under the reaction conditions.

11 and observed the formation of a pyrimidine which was homogeneous as judged by paper chromatography. This species was assigned the N^5-formyl structure **14** by virtue of the fact that a compound identical with its aglycone (**15**) could be obtained by formylation of **16**.[21] By analogy with the earlier work, the 5-formyl isomers have also been reported as the exclusive products resulting from the ring opening of 7-methylxanthosine[22] and 6-thio-7-methylguanosine.[23]

We have monitored the ring opening of several 7,9-disubstituted purines by ultraviolet and NMR spectrometry. For 7-methylguanosine (**1a**), e.g., treatment with 0.1 M Tris–HCl at pH 10.0 effected ring opening, which was monitored by a decrease in λ_{max} 283 nm and an increase in λ_{max} 266 nm (Figure 2), and by the appearance of the formyl proton in the NMR. For 7-methylguanosine (**1a**), the $t_{1/2}$ value for ring opening was approximately 25 min (Table IV). Rapid hydrolytic cleavage was also observed for 7-methylinosine (**3a**, $t_{1/2}$ = 5 min) and 7-methylxanthosine (**5a**, $t_{1/2}$ = 10 min) in 0.1 M Tris–HCl, pH 10.0, while the corresponding 9-methyl analogues (**2a**, **4a**, and **6a**, respectively) were much more stable. The rate differences may be attributed to the ribosyl substituents in compounds **1a**, **3a**, and **5a**, which may facilitate the ring opening via inductive stabilization of reaction intermediates and which undoubtedly cause some distortion of the imidazole ring, resulting in ring strain which can be relieved by ring opening. No comparable effects would be anticipated for compounds **2a**, **4a**, or **6a**.

The mechanism of ring opening is postulated to involve addition of hydroxide ion at C-8 (numbered as in the purine series), followed by base-catalyzed displacement of one of the two possible anionic aminopyrimidine species. This scheme would predict that to the extent that it is delocalized into the imidazole ring, a negative charge in the six-membered ring would substantially diminish the rate of ring opening.[24] In fact



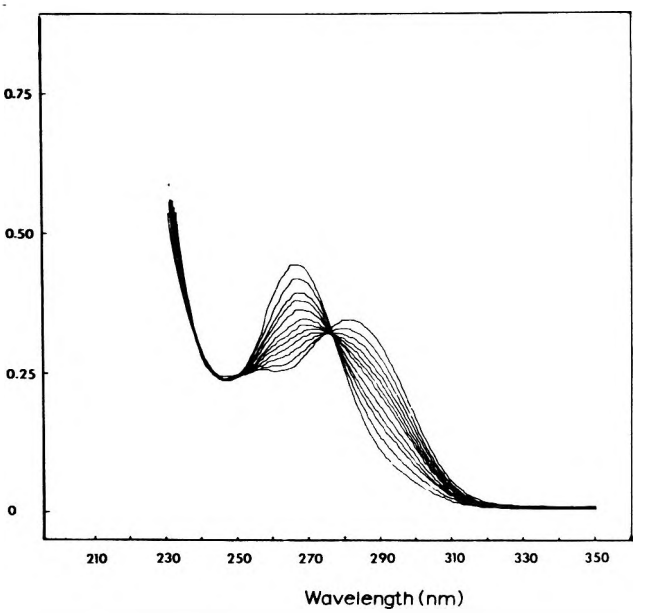
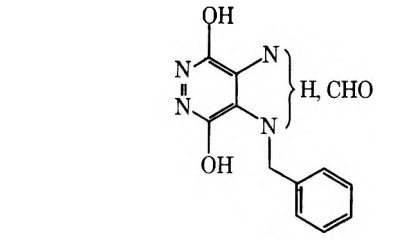


Figure 2. Base-induced ring opening of 7-methylguanosine (**1a**) in 0.1 M Tris–HCl, pH 10.0. The ultraviolet spectrum of **1a** (λ_{max} 283 nm) was recorded at 5-min time intervals. The increase in absorbance at 266 nm corresponded to the formation of ring-opened product.

treatment of 9-methylcaffeine perchlorate (**7a**) with 0.1 M Tris–HCl at pH 10.0 resulted in extremely rapid cleavage of the imidazole ring, consistent with the absence of negative charge in the pyrimidine moiety.

Treatment of the Disubstituted Heterocycles with Nucleophiles Other Than Hydroxide Ion. In analogy with the results obtained for compounds **1a**, **5a**, and **7a**, treatment of 1-benzyl-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine (**9a**) with aqueous base afforded N-formylated, ring-opened product **17**. In contrast, treatment of **9a** with ethoxide under anhydrous conditions afforded no N-formylpyridazine. Obtained instead in 44% yield was 1-benzyl-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**11**). The formation of **11** presumably



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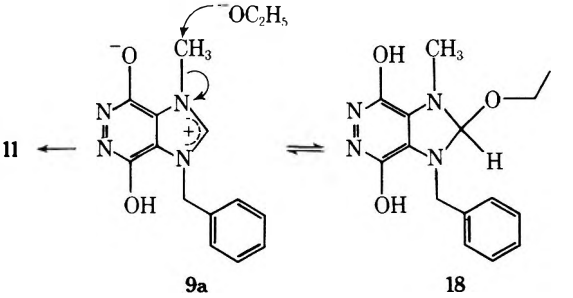


reflected the fact that the expected addition of ethoxide to C-2 in **9a** would afford species **18**, which cannot undergo ring opening in the same sense as the hydrate of **9a**. It is anticipated that formation of **18** would be reversible, as is observed for imino esters[25] and for the addition of hydride to C-2 in **9a**, and that the slower, but irreversible displacement of the 3-methyl substituent may therefore occur.[26]

Table V. Reduction of Imines with 1,2-Dihydro-1,3-Disubstituted Imidazo[4,5-*d*]pyridazines

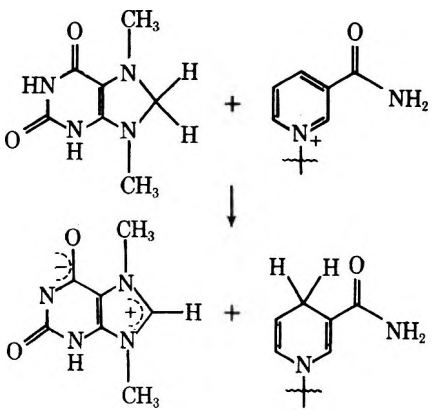
Compd[a]	Solvent[b]	Percent reduction: Benzylideneaniline (20) 8 h, room temp	Benzylideneaniline (20) 3 h, 55 °C	Benzylidenebenzylamine (21) 8 h, room temp	Benzylidenebenzylamine (21) 3 h, 55 °C
1-Benzyl-1,2-dihydro-4,7-dihydroxy-3-methylimidazo-[4,5-*d*]pyridazine (**9b**)	CH_3OH	1	35	6	11
9b	DMF		0		
9b	CH_3OH + 10 μl CH_3COOH		87		
9b	CH_3OH + 25 μl CH_3COOH		97		
9b	2:1 DMF–CH_3COOH		80		
1-Benzyl-1,2-dihydro-4,7-dihydroxy-3-methylimidazo-[4,5-*d*]pyridazine (**9b**) Na salt	CH_3OH		0		
9b Na^+ salt	CH_3OH + 25 μl CH_3COOH	43	67	15	31
9b Na^+ salt	CH_3OH + 40 μl CH_3COOH	88	95	70	69
1,3-Dibenzyl-1,2-dihydro-4,7-dihydroxylimidazo[4,5-*d*]pyridazine (**10b**)	CH_3OH	15	34	12	40
1,3-Dibenzyl-1,2-dihydro-4,7-dihydroxylimidazo[4,5-*d*]pyridazine (**10b**) Na^+ salt	CH_3OH		0		0
10b Na^+ salt	CH_3OH + 25 μl CH_3COOH	47	49	42	51
10b Na^+ salt	CH_3OH + 40 μl CH_3COOH	56	53	58	69

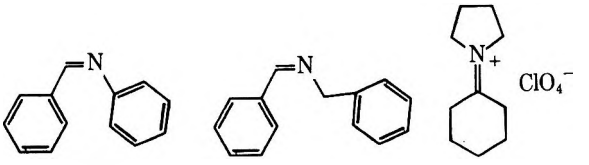
[a] The reductions utilized reducing agent and imine in a ratio of 4:1. [b] The reactions were carried out in a total volume of 200 μl (excluding added acetic acid, where indicated).

Certain of the reduced heterocycles also underwent nucleophilic displacement reactions. For example, treatment of 7,8-dihydro-7-methylguanosine (**1b**) with an aqueous 1 M solution of anilinium acetate, pH 4.5, afforded several products, including 7-methylguanine,[27] which was obtained in 68% yield and identified by comparison of ultraviolet and chromatographic properties with those of an authentic sample.

The mild conditions utilized for the reduction of **1a** with sodium borohydride or other reducing agents (e.g., **1b**), suggests the possible utility of a reducing agent–aniline treatment for depurination of the 7-methylguanosine moieties in tRNA and mRNA.

Hydride Transfer Experiments. While the reoxidation of 7,9-dialkyl-7,8-dihydropurines and related compounds apparently proceeds primarily via reaction with oxygen, the reduced compounds can effect the net transfer of hydride ions to other organic compounds. For example, mass spectrometric analysis of a sample of 7,9-dimethylguanine isolated after incubation in aqueous solution with reduced [8-^{2}H]-7-methylguanosine (**1b**) revealed 12% incorporation of deuterium.[29] Similarly, treatment of $NADP^+$ with an excess of reduced 7,8-dihydro-7,9-dimethylxanthine (**6b**) at pH 10 for 5 min afforded 25% reduction to NADPH, as judged by the change in A_{340}.[30] The reduced heterocycles were also capable of the reduction of aliphatic and aromatic imines and immonium ions. Thus treatment of a methanolic solution of benzylideneaniline (**20**) or benzylidenebenzylamine (**21**) with a fourfold excess of reduced heterocycles **9b** or **10b** at 55 °C for 3 h gave reduction in moderate yields to *N*-benzylaniline and dibenzylamine, respectively.





20 **21** **22**

Certain factors were found to affect the extent of reduction of imines and immonium ions. For example, while treatment of a methanolic solution of benzylideneaniline with a sample of **9b** afforded *N*-benzylaniline in 35% yield (Table V), the addition of acetic acid to the reaction mixture increased the yield to 97%, presumably via protonation of the imine.[31,32] The extent of reduction of imines and immonium salts was also found to depend on the specific heterocycle utilized for the transformation. Thus reduction of benzylideneaniline with 1,2-dihydro-1,3-dimethylbenzimidazole (**8b**) in methanol–acetic acid afforded 16% of *N*-benzylaniline after 8 h at room temperature and 20% of the product after 3 h at 55 °C. Under the same conditions 7,8-dihydro-7,9-dimethylguanine (**2b**) gave 91 and 94% reduction, respectively. As shown in Table VI, the extent of reduction of **21** effected by individual compounds was generally consistent with the rate at which those

Table VI. Reduction of Benzylideneaniline, Benzylidenebenzylamine, and Cyclohexylidenepyrrolidinium Perchlorate[a]

Compd	Percent reduction: Benzylideneaniline (20) 8 h, room temp	Benzylideneaniline (20) 3 h, 55 °C	Benzylidenebenzylamine (21) 8 h, room temp	Benzylidenebenzylamine (21) 3 h, 55 °C	Cyclohexylidenepyrrolidinium perchlorate (22) 1 h, room temp
7,8-Dihydro-7,9-dimethylguanine (**2b**)	91	94	46	62	36
7,8-Dihydro-7-methylinosine (**3b**)	70	77	25	34	31
7,8-Dihydro-7,9-dimethylhypoxanthine (**4b**)	81	82	49	59	71
7,8-Dihydro-7-methylxanthosine (**5b**)	50	42	15	39	38 (96)[b]
7,8-Dihydro-7,9-dimethylxanthine (**6b**)	76	84	38	40	58
7,8-Dihydro-9-methylcaffeine (**7b**)	95	89	42	49	64
1,2-Dihydro-1,3-dimethylbenzimidazole (**8b**)	16	20	28	22	51 (76)[b]
1-Benzyl-1,2-dihydro-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine (**9b**)	43	67	15	31	25 (55)[c]
1,3-Dibenzyl-1,2-dihydro-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**10b**)	47	49	42	51	(48)[c]

[a] The reductions were carried out with a fourfold excess of reducing agent in 200 μl of methanol and 25 μl of acetic acid. [b] This reduction was carried out with a fivefold excess of reducing agent in 200 μl of ethyl acetate at 40 °C for 16 h. [c] This reduction was carried out with a fivefold excess of reducing agent in 200 μl of ethyl acetate at 40 °C for 3 h.

Table VII. Reduction of Benzylideneaniline and Benzylidenebenzylamine under Optimized Conditions[a]

Compd	Percent reduction: Benzylideneaniline (20)	Benzylidenebenzylamine (21)
7,8-Dihydro-7,9-dimethylguanine (**2b**)	89	86
7,8-Dihydro-7,9-dimethylhypoxanthine (**4b**)	96 (81)[b]	85 (76)[b]
7,8-Dihydro-7-methylxanthosine (**5b**)	94	80
7,8-Dihydro-7,9-dimethylxanthine (**6b**)	98 (84)[b]	97 (82)[b]
1,2-Dihydro-1,3-dimethylbenzimidazole (**8b**)	42	40
1-Benzyl-1,2-dihydro-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine (**9b**)	98	94
1,3-Dibenzyl-1,2-dihydro-4,7-dihydroxylimidazo[4,5-*d*]pyridazine (**10b**)	79	77

[a] The reductions were carried out with an eightfold excess of reducing agent in 250 μl of 20% acetic acid in methanol at reflux for 1 h. [b] Isolated yield.

compounds were found to reoxidize in aqueous solution.[33,34]

The reductions shown in Table VI were carried out for comparative purposes and do not represent the best yields which can be obtained with the individual reducing agents. For example, the low yields of *N*-cyclohexylpyrrolidine were due in part to the instability of cyclohexylidenepyrrolidinium perchlorate in methanol–acetic acid. The same reduction can be effected in ethyl acetate, utilizing reduced heterocycles which were isolated after borohydride reduction by extraction into ethyl acetate. Thus treatment of the immonium salt with 5 equiv of 7,8-dihydro-7-methylxanthosine (**5b**) in ethyl acetate at 40 °C for 16 h afforded *N*-cyclohexylpyrrolidine in 96% yield. When the same reduction was carried out on a larger scale to permit isolation of *N*-cyclohexylpyrrolidine, the use of 1.7 equiv of **5b** for each equivalent of **22** afforded the pyrrolidine in 75% isolated yield (90% by GLC). As shown in Table VII, higher yields of dibenzylamine and *N*-benzylaniline were also obtained by treatment of imines **20** and **21** with a greater excess of reducing agent and acetic acid. These were verified by isolating the products from larger scale reactions in similar yield.

It is of interest that the reduced compounds reported here are very specific in their reduction of imines and immonium salts as compared with other common functional groups such as aldehydes, ketones, etc., and may prove useful as selective reducing agents. This is particularly true since the rate and extent of reductions obtained with these reduced heterocycles varies substantially from compound to compound and according to the reaction conditions.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are corrected. Ultraviolet spectra were recorded on a Cary 15 spectrophotometer, fluorescence spectra on a Turner Model 430 spectrofluorometer, and low-resolution mass spectra on a Perkin-Elmer Hitachi RMU-6 spectrometer using a direct inlet. The high-resolution mass spectra were obtained by Professor K. Biemann and Dr. C. Costello on a CEC-21-110B high-resolution mass spectrometer. NMR spectra were recorded on a Perkin-Elmer Hitachi R22 spectrometer at 90 MHz.

1-Benzyl-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine (9a). A solution of 10.0 g (41 mmol) of 1-benzyl-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**11**)[11] and 10.0 g (70 mmol) of methyl iodide in 250 ml of dimethylformamide was stirred at room temperature for 48 h. The solution was concentrated to afford a viscous oil which was treated with 100 ml of absolute ethanol and 400 ml of petroleum ether and allowed to stand overnight. The resulting solid was filtered, redissolved in aqueous ammonium hydroxide, and treated with hydrochloric acid to adjust to pH 5. The white precipitate was filtered and dried to afford **9a:** yield 10.0 g (95%); mp 222–224 °C dec; $C_{13}H_{12}N_4O_2$ (M^+ calcd, 256.0960; found, 256.095); λ_{max} (H_2O) (pH 2) 273 nm (ε 3400), λ_{min} 248 (2400); λ_{max} (H_2O) (pH 7) 299 (3500), λ_{min} 251 (1100); λ_{max} (H_2O) (pH 12) 307 (3800), λ_{min} 253 (1100); fluorescence spectrum $\lambda_{excitation}$ 355 nm, $\lambda_{emission}$ 470 nm; ir (KBr) 3510, 3440, 3110, 3015, 1700, 1400, 1225, 1165, and 710 cm^{-1}; NMR (Me_2SO-d_6) δ 3.97 (3 H, s), 5.65 (2 H, s), 7.22 (5 H, m) and 9.58 (1 H, s); mass spectrum *m/e* 256.095 (M^+), 242.077, 180.063, 166.048, and 134.037.

1-Benzyl-1,2-dihydro-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine (9b). To 50 mg (0.20 mmol) of 1-benzyl-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine (**9a**) in 0.5 ml of water was added 50 mg (1.3 mmol) of sodium borohydride. Glacial acetic acid (ca. 0.5 ml) was added dropwise to destroy the excess borohydride and the yellow precipitate was filtered, washed with water and THF, and dried in vacuo to afford **9b** as a yellow solid: yield 25 mg (50%); mp 196–200 °C dec; λ_{max} (H_2O) (pH 7) 340 nm (ε 4000), λ_{min} 279 (1900);

λ_{max} (H_2O) (pH 10) 342 (4100), λ_{min} 278 (1600); NMR (Me_2SO-d_6) δ 2.77 (3 H, s), 4.26 (2 H, s), 4.56 (2 H, s) and 7.39 (5 H, s); mass spectrum *m/e* 258 (M^+) 257, 242, 181, 180, 167, 166, 109, 108, 91, and 90.

1,3-Dibenzyl-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (10a). A solution of 0.51 g (2.1 mmol) of 1-benzyl-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**11**)[11] and 0.72 g (4.2 mmol) of benzyl bromide in 25 ml of DMF was heated at reflux for 24 h. The cooled solution was concentrated and the residue was treated with 10 ml of ethanol and 150 ml of petroleum ether. The viscous oil which separated was dried in vacuo to afford an off-white solid which was recrystallized from methanol–aqueous ammonium hydroxide to give **10a** as white crystals: yield 0.38 g (54%); mp 110 °C dec; $C_{19}H_{16}N_4O_2$ (M^+ calcd 332.1273; found 332.125); λ_{max} (H_2O) (pH 2) 277 nm (ϵ 3400), 268 (3400), and 264 (3200), λ_{min} 270 (3300) and 247 (2400); λ_{max} (H_2O) (pH 7) 299 (3300), λ_{min} 252 (1500); λ_{max} (H_2O) (pH 12) 306 (3400), λ_{min} 253 (1300); fluorescence spectrum $\lambda_{excitation}$ 358 nm, $\lambda_{emission}$ 471 nm; NMR (Me_2SO-d_6) δ 5.77 (4 H, s), 7.33 (10 H, m) and 10.18 (1 H, s); mass spectrum *m/e* 332.125 (M^+), 242.079, 183.055, and 129.058.

1,3-Dibenzyl-1,2-dihydro-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (10b). 1,3-Dibenzyl-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**10a**) was reduced with borohydride and precipitated with acetic acid as described above for **9a**: yield 40%; mp 193–197 °C dec; λ_{max} (H_2O) (pH 2) 372 nm, λ_{min} 329; λ_{max} (H_2O) (pH 7) 342, λ_{min} 279; λ_{max} (H_2O) (pH 10) 342, λ_{min} 281; mass spectrum *m/e* 334, 333, 332, 243, 242, 183, 106, 92, 91, and 65.

Preparation of Reduced Dialkylated Heterocycles. Individual dialkylated heterocycles (100 mg, **1a**–**10a**) were dissolved in 25 ml of water and treated with 50 mg (1.3 mmol) of sodium borohydride. The reaction mixture was maintained at room temperature for several minutes and then concentrated to 1 ml, treated with 2 ml of acetone, and evaporated to dryness to afford approximately 130 mg of a white solid, approximately 75% of which consisted of the reduced dialkylated heterocycle. In several cases, the pure heterocycle could be separated from the inorganic salt by trituration with hot ethyl acetate and concentration of the ethyl acetate extract under diminished pressure.

Exchange of the C-8 Protons in 7,8-Dihydro-7,9-dimethylguanine (2b) in D_2O. A sample of 7,9-dimethylguanine (100 mg, 0.56 mmol) was reduced with borohydride and isolated as the sodium salt. The reduced heterocycle (**2b**) was dissolved in 0.5 ml of degassed D_2O and sealed in an NMR tube. After an initial NMR spectrum was recorded, the sample was heated at 50 °C for 4 h and then maintained at room temperature for an additional 6 h. An NMR spectrum was again recorded and revealed that the total intensity of resonances at δ 2.78 and 2.60 (*N*-methyl peaks) relative to that at δ 4.31 (C-8 protons) had changed from approximately 3:1 to 6:1, reflecting net exchange of deuterium into the C-8 position.

Measurement of $t_{1/2}$ Values for Reoxidation. Stock stolutions of the individual heterocycles (**1a**–**10a**) were prepared by dissolving approximately 5 mg of each compound and 5 mg of $NaBH_4$ in 1 ml of water. A 10-μl aliquot was withdrawn, treated with 20 μl of glacial acetic acid or 1 M hydrochloric acid to quench excess borohydride, and then combined with 1 ml of (degassed or aerated) 0.1 M acetate or 0.1 M borate buffer at the appropriate pH. Ultraviolet spectra were taken at predetermined time intervals and the spectra were used to obtain $t_{1/2}$ values for reoxidation.

Reoxidation of 7,8-Dihydro-7,9-dimethylguanine in a Sealed Tube. A solution of 21 mg (0.21 mmol) of 7,8-dihydro-7,9-dimethylguanine in 1.5 ml of degassed water was sealed in a tube (under N_2) having a total volume of 2.5 ml. The tube was maintained at room temperature for 2 weeks, then opened and immediately analyzed by TLC on silica gel which gave a single spot with R_f 0.14 (development with methanol) corresponding to 7,9-dimethylguanine (**2a**), and by its ultraviolet spectrum which had λ_{max} (H_2O) (pH 7) 252 and 279 nm, characteristic of **2a**.

Ring-Opening Reactions. The individual disubstituted heterocycles were dissolved in 2 M ammonium hydroxide and maintained at room temperature for 2 h. The solution was evaporated to dryness, redissolved in D_2O, and concentrated. This process was repeated and the final white solid was dissolved in D_2O and used to record an NMR spectrum. Descending paper chromatography (Whatman No. 1 paper) of the products derived from **1a**, **5a**, and **7a** gave only one spot in each of three solvent systems (A, 6:4 5% aqueous ammonium carbonate–methanol; B, 65:16.7:18.3 2-propanol–concentrated hydrochloric acid–water; C, 7:3 ethanol–water.) The product(s) derived from the ring opening of **1a** had R_f values of 0.86 (solvent A), 0.68 (B), and 0.80 (C). The product(s) derived from **5a** had values of 0.84 (A), 0.74 (B), and 0.84 (C), while the values for the product(s) from **7a** were 0.89 (A), 0.98 (B), and 1.00 (C).

Treatment of 1-Benzyl-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine (9a) with Sodium Ethoxide. To a stirred solution of 1.02 g (4.0 mmol) of 1-benzyl-4,7-dihydroxy-3-methylimidazo[4,5-*d*]pyridazine in 50 ml of absolute ethanol was added 2 g of sodium metal at a rate which maintained the temperature of the solution at about 55 °C. The resulting solution was stirred overnight and the precipitate which formed was filtered, washed with ethanol, and dried, affording 0.57 g of a white solid. The solid was dissolved in 5 ml of water and treated with acetic acid to afford a white precipitate which was filtered and dried, giving 0.42 g (44%) of pure 1-benzyl-4,7-dihydroxyimidazo[4,5-*d*]pyridazine (**11**), identical in all respects with an authentic sample.

Treatment of 7,8-Dihydro-7-methylguanosine with Aniline. A solution of 119 mg (0.40 mmol) of 7-methylguanosine in 2 ml of water was treated with 50 mg (1.3 mmol) of sodium borohydride at room temperature for 10 min. Acetic acid (0.5 ml) was added to quench excess borohydride and to adjust the pH to 4.5. The solution was treated with 5 ml of 1 M aniline–HCl, pH 4.5, and maintained at room temperature for 5 h, during which time the solution became dark in color. An aliquot of the reaction mixture was analyzed by ascending paper chromatography on Whatman No. 1 paper in 60:40 5% aqueous ammonium carbonate–methanol. Several spots were observed and one of these (R_f 0.63) was believed to be the ribose–aniline adduct **19** on the basis of its mass spectrum [*m/e* 225 (M^+), 224, 106, 93, 73, 64, and 30] and ultraviolet spectrum [λ_{max} (H_2O) (pH 1) 248 nm; λ_{max} (H_2O) (pH 7) 274; λ_{max} (H_2O) (pH 12) 274]. Another aliquot was analyzed by paper chromatography in 5:1:4 1-butanol–acetic acid–water and several products were observed, one of which had an R_f (0.60) identical with that of 7-methylguanine. The original reaction mixture was maintained at 0 °C for 48 h and the precipitate which had formed was filtered after treatment of the reaction mixture with 20 ml of ethanol. The solid was washed with ethanol and dried to afford 7-methylguanine as a tan solid, yield 45 mg (68%), identical with authentic 7-methylguanine, as judged by comparison of their ultraviolet spectra and paper chromatographic characteristics.

Condensation of Ribose and Aniline. Ribose (135 mg, 0.90 mmol) and aniline (84 mg, 0.90 mmol) were heated at 70 °C in a solution of 5 ml of absolute ethanol and 5 ml of benzene containing 0.5 ml of 6 M hydrochloric acid. After 15 min the solution had turned reddish-brown and the cooled reaction mixture was concentrated to 2 ml. Petroleum ether (30 ml) was added and the dark oil which formed was separated and washed with petroleum ether (15 ml). The crude product (235 mg) was purified by ascending paper chromatography on Whatman No. 1 paper (60:40 5% aqueous ammonium carbonate–methanol). Three bands were observed (R_f 0.0, 0.68, and 0.80) and the band at R_f 0.68 was fluorescent and contained material whose ultraviolet and mass spectra were identical with those of the material isolated from the decomposition of **1b** in the presence of aniline.

Hydride Transfer from 7,8-Dihydro-7,9-dimethylxanthine (6b) to $NADP^+$. To 11 mg (62 μmol) of 7,9-dimethylxanthine (**6a**) in 3 ml of water was added an excess of sodium borohydride. The excess borohydride was decomposed by the addition of aqueous acetic acid and the pH was adjusted from 3.6 to 4.5 by the addition of aqueous ammonia. Nicotinamide adenine dinucleotide phosphate ($NADP^+$) (0.74 mg, 1.1 μmol) was added and the pH was quickly readjusted to 10.0 with aqueous ammonia. After 5 min, the absorbance at 340 nm was measured by dilution of the sample with 0.1 M Tris–HCl, pH 10.0. The net A_{340} value was 0.10, after correction for a control which contained no $NADP^+$, corresponding to 25% reduction of $NADP^+$ to NADPH. An additional control was run in the absence of **6b** to verify that the formation of NADPH was not due to incomplete decomposition of sodium borohydride.

Reduction of Imines with Reduced Disubstituted Heterocycles. To 50 mg (~0.2 mmol) of the reduced disubstituted heterocycles in 200 μl of solvent was added 10 mg (~0.05 mmol) of the appropriate imine. The reaction was maintained at room temperature for 8 h or heated at 55 °C for 3 h. The reaction mixture was then examined by GLC on a 6 ft × 0.25 in. copper column packed with 20% Carbowax 20M on Chromosorb W. The percent reduction was determined by comparison of the imine and secondary amine peaks. External standards of authentic products were used to verify the absolute recovery.

Reduction of Cyclohexylidenepyrrolidinium Perchlorate (22) with Reduced Disubstituted Heterocycles. To 50 mg (~0.2 mmol) of the reduced disubstituted heterocycles in 200 μl of solvent was added 10 mg (0.04 mmol) of cyclohexylidenepyrrolidinium perchlorate. The reaction mixture was warmed at 40 °C for 3 h and analyzed by GLC relative to a sample of *N*-cyclohexylpyrrolidine prepared under identical conditions using borohydride as the reducing agent.

Dibenzylamine. To 2.0 g (11 mmol) of 7,8-dihydro-7,9-dimethylxanthine in a solution consisting of 20 ml of methanol and 2

ml of acetic acid was added 0.50 g (2.5 mmol) of benzylidenebenzylamine (21). The reaction mixture was heated at reflux for 3 h and maintained overnight at room temperature. The reaction mixture was concentrated and the residue was partitioned between ether and 10% aqueous sodium hydroxide. The aqueous layer was extracted with two additional portions of ether and the combined ether extract was dried and concentrated to afford dibenzylamine as a clear liquid, yield 0.41 g (82%), identified by comparison of its GLC retention time and NMR spectrum with those of an authentic sample. Utilization of 7,8-dihydro-7,9-dimethylhypoxanthine as the reducing agent afforded dibenzylamine in 76% isolated yield.

***N*-Benzylaniline Hydrochloride.** To a solution of 4.0 g (22 mmol) of 7,8-dihydro-7,9-dimethylxanthine in 25 ml of methanol and 3 ml of acetic acid was added 1.0 g (5.4 mmol) of benzylideneaniline (**20**). The reaction mixture was heated at 55 °C for 1 h and maintained overnight at room temperature. The mixture was concentrated to remove excess methanol, neutralized with 10% aqueous sodium hydroxide, and extracted with benzene. Saturation of the benzene extract with hydrogen chloride effected precipitation of *N*-benzylaniline hydrochloride, which was isolated as white crystals by filtration: yield 1.0 g (84%); mp 210–212 °C (lit.[35] mp 210–212 °C); NMR ($CDCl_3$, Me_4Si) δ 4.35 (2 H, s) and 7.25 (12 H, s). Also utilized for the reduction was 7,8-dihydro-7,9-dimethylhypoxanthine. The reaction mixture was worked up as indicated above for dibenzylamine and afforded *N*-benzylaniline (identical with an authentic sample as judged by NMR spectra and GLC retention times) in 81% yield.

***N*-Cyclohexylpyrrolidine.** A solution of 0.50 g (2.0 mmol) of cyclohexylidenepyrrolidinium perchlorate[36] and 1.0 g (3.3 mmol) of 7,8-dihydro-7-methylxanthosine (**5b**) in 20 ml of ethyl acetate was heated at 40 °C for 16 h. The mixture was filtered and the residue was washed with ether. The combined organic solution was concentrated to afford 0.40 g (75%) of *N*-cyclohexylpyrrolidine, which was purified further by chromatography on alumina and elution with chloroform. The identity of the product was verified by comparison of NMR and mass spectral data with published values.[37]

Acknowledgment. We thank Miss Virginia Lightner for the preparation of several synthetic intermediates and Professor George M. Whitesides for the use of his polarographic analyzer and for a helpful discussion during the course of this work. This investigation was supported by Public Health Service Research Grant CA-15535 from the National Cancer Institute.

Registry No.—**1a,** 22164-16-5; **1b,** 15313-37-8; **2a,** 524-35-6; **2b,** 55235-22-8; **3a,** 22163-89-9; **3b,** 58526-72-0; **4a,** 5752-16-9; **4b,** 25472-81-5; **5a,** 58526-73-1; **5b,** 58526-74-2; **6a,** 5752-21-6; **6b,** 58526-75-3; **7a,** 17749-99-4; **7b,** 17749-90-5; **8b,** 3204-31-7; **9a,** 58526-76-4; **9b,** 58526-77-5; **9b** Na salt, 58958-41-1; **10a,** 58526-78-6; **10b,** 58526-79-7; **10b** Na salt, 58944-52-8; **11,** 5424-28-2; **19,** 55782-50-8; **20,** 538-51-2; methyl iodide, 74-88-4; benzyl bromide, 100-39-0; 7-methylguanine, 578-76-7; ribose, 50-69-1; aniline, 62-53-3.

References and Notes

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(12) The compound was also characterized by its NMR, ultraviolet, and high- and low-resolution mass spectra, all of which were consistent with the assigned structure and similar to the analogous data obtained for **9a.**
(13) Analysis of the reduced species could be effected by thin layer chromatography on silica gel, development with methanol. In this system the less polar reduced heterocycles had larger R_f values than their respective oxidized forms, all of which exist as charged species.
(14) Compounds **1a–6a,** as well as **8a,** were also found to be fluorescent while the respective reduced species were not, so that the course of reduction or reoxidation could also be monitored by the disappearance or appearance of fluorescence. A similar characteristic was noted for the 1,3-disubstituted 4,7-dihydroxyimidazo[4,5-*d*]pyridazines **9a** and **10a,** which were fluorescent only in their respective reduced forms (i.e., **9b** and **10b**).
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(17) Although the addition of metal ions, such as copper and silver, to solutions of **6b** markedly increased its rate of reoxidation (as did the presence of benzoyl peroxide), treatment of **6b** with 0.05 M EDTA at pH 5.5 (in degassed or oxygenated solutions) had essentially no effect on the rate of reoxidation. It was also found that reoxidation of **6b** at pH 3.5 in the presence of 6.5 mM dithiothreitol (in degassed or oxygenated solutions) had no effect on the rate of reoxidation.
(18) Since reoxidation of the heterocycles via reaction with water would result in the formation of hydrogen peroxide, the reactivity of hydrogen peroxide with the reduced heterocycles was tested. It was found that treatment of a degassed solution (pH 7.0) of 7,8-dihydro-7,9-dimethylhypoxanthine (**4b**) with a large molar excess of hydrogen peroxide increased the rate of reoxidation by a factor of 10.
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(21) Compound **19** was assumed to formylate on N^5 by analogy with earlier work on 2,5,6-triamino-4-pyrimidone. See W. Traube and H. W. Dudley, *Chem. Ber.*, **46,** 3839 (1913).
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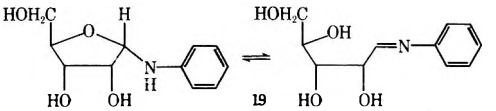
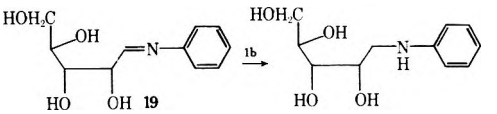
(26) This transformation parallels the demethylation of 7-methylguanosine by lithium *tert*-butylmercaptide in hexamethylphosphoramide[9] and is analogous to the SN2 displacement of methyl groups from quaternary ammonium salts [M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Lett.*, 1375 (1966)].
(27) Also obtained was the imine derived from ribose and aniline (**19**).[28] The latter was identified by its low-resolution mass spectrum (*m/e* 225) and by its ultraviolet and chromatographic properties, all of which were identical with those of an authentic sample derived from a 1:1 ethanol–benzene



solution of ribose and aniline which was heated in the presence of a catalytic amount of concentrated hydrochloric acid for 15 min.
(28) Although **1b** should certainly be capable of reducing imine **19** to the corresponding amine, the formation of **19** was effected under mild conditions



which disfavor its reduction and no significant amount of the amine has been observed.
(29) The theoretical incorporation of deuterium into 7,9-dimethylguanine by a pathway involving reoxidation of [8-^{2}H]-7,8-dihydro-7-methylguanosine (**1b**), deuterium exchange of [8-^{2}H]-7-methylguanosine (**1a**) with water, and subsequent exchange of deuterated water with 7,9-dimethylguanine would give <0.05% deuterium incorporation. A control reaction, run with sodium borodeuteride that had been pretreated with acetic acid, gave no detectable [8-^{2}H]-7,9-dimethylguanine.
(30) Control reactions were run without $NADP^+$ and without **6b.**
(31) In those cases in which the reduced heterocycles were utilized as their sodium salts, no reduction of **20** or **21** was observed in alcoholic media owing to the low solubility of the reducing agents. In these cases, the addition of acetic acid served to solubilize the reduced heterocycles in addition to protonating the imines.
(32) The extent of reduction was also affected by the choice of solvent. Although some reduction of **21** by **9b** was observed in neutral ethanolic or methanolic solutions, none was observed when 2-propanol, dimethylacetamide, dimethyl sulfoxide, or dimethylformamide–methanol (2:1 or 1:1) were employed as solvents. Moreover, while the addition of acetic acid did facilitate the reduction in some of these cases, as may be appreciated from the 80% yield of *N*-benzylaniline obtained by reduction in 2:1 dimethylformamide–acetic acid, no *N*-benzylaniline was formed in the presence of 4:1 dimethyl sulfoxide–acetic acid. (In the last case a portion of the reducing agent was utilized in the conversion of dimethyl sulfoxide to dimethyl sulfide, but this transformation did not consume all of the available reducing agent.)
(33) As would be expected, reduction of benzylidenebenzylamine proceeded in lower yield than reduction of benzylideneaniline in almost every case, although the extent of reduction was generally still in agreement with the relative rates of reoxidation for individual heterocycles. The few exceptions evident in Table VI can probably be attributed to phenomena such as side reactions between the heterocyclic species and reduced imines, the instability of cyclohexylidenepyrrolidinium perchlorate (**22**) to the reaction conditions, and differences in solubility of the heterocyclic species in the reaction media.
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A Convenient Route to the Dihydroxyacetone Substituent

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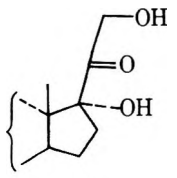
A method for the conversion of a ketone to the dihydroxyacetone substituent has been developed. This reaction of the ketone with methoxyvinyllithium (MVL) yields after oxidation with peracids the dihydroxyacetone derivative directly. Alternately the intermediate adduct, as its *p*-nitrobenzenesulfinyl ester, can be rearranged to the isomeric sulfone, oxidation of which may yield the hydroxy keto sulfone, thereby providing an alternative stereochemistry at the tertiary alcohol center. These reactions were exemplified by cyclohexanone and estrone-3-methyl ether.

The dihydroxyacetone unit is a structural feature common to the corticoid hormones, as **1**, and also the antitumor agent, adriamycin, as **2**. In an effort to develop a scheme for



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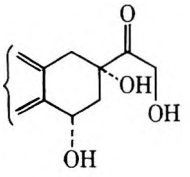
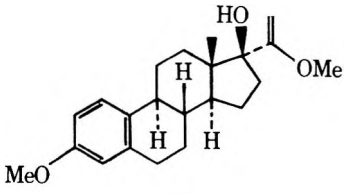


2

the introduction of this functionality we have examined transformations of the adducts from methoxyvinyllithium (MVL) with ketones.[1] Thus estrone methyl ether reacted with MVL to yield the 17α adduct **3** (83%), which was smoothly hydrolyzed (aqueous methanolic acetic acid, 76%) to the corresponding 17α-acetyl-17β-alcohol **4**. When the adduct **3** was oxidized with osmium tetroxide in pyridine or with *m*-chloroperbenzoic acid in wet ether it was transformed to the dihydroxy ketone derivative **5**, readily acetylated to the 21-acetate **6**. The stereochemical assignments are based on the



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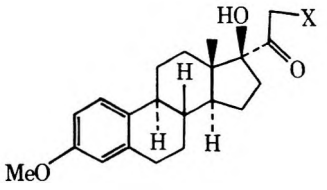
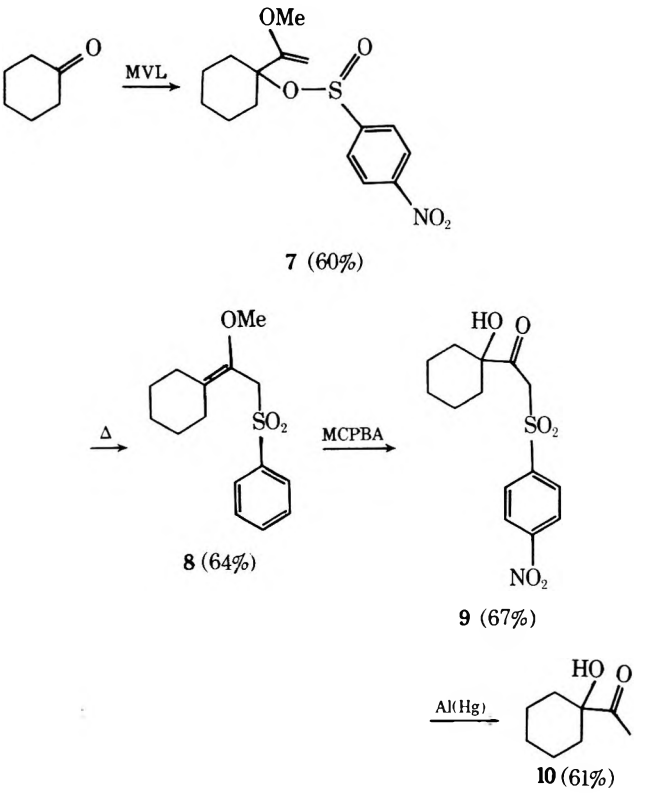


4, X = H
5, X = OH
6, X = OAc

known tendency for α-addition of organometallic reagents to the 17-ketone.[2] Thus the stereochemistry of the side chain is necessarily controlled by the stereochemistry of the initial adduct. In order to allow some control over this point we have developed the alternative process shown in Scheme I.

The initial adduct of MVL with the ketone, in this case cyclohexanone, was treated with *p*-nitrobenzenesulfinyl chloride to yield the sulfinate **7**, which on heating to 100 °C underwent a [2,3]-sigmatropic rearrangement[3] to the enol ether sulfone **8**. Such a rearrangement of an allylic sulfinate has precedence[4] but this appears to be the first example in which an enol ether has participated. The *p*-tolylsulfinate corresponding to **7** could be prepared but its thermolysis gave rise to a complicated series of products. Oxidation of **8** to **9** was

Scheme I



7 (60%)

8 (64%)

9 (67%)

10 (61%)

achieved (67%) with *m*-chloroperbenzoic acid in moist methylene chloride. Compounds of type **8** and **9** are certainly amenable to further transformation, e.g., alkylation α to the sulfonyl group. Removal of this sulfonyl function was readily achieved by reduction with aluminum amalgam in aqueous THF (61%) to the hydroxy ketone derivative **10**. Methods exist for the elaboration of such methyl ketones to the dihydroxyacetone substituent.[2a]

These two paths to the dihydroxyacetone substituent provide alternative sequences for the formation of the tertiary alcohol moiety of this substituent. It is reasonable to expect, therefore, that they may provide different stereochemistry at this center, since in the first case control is provided by the direction of addition of MVL and in the second case the stereochemistry emanates from the direction of epoxidation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and have not been corrected. Microanalyses were performed by Midwest Microlabs, Inc. Indianapolis, Ind. Ir spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer. NMR spectra were recorded on a Varian Associates T-60 spectrometer or a Hitachi Perkin-Elmer R-22B instrument. Silica gel for column chromatography was Davison Chemicals grade 950 (60–200 mesh) or Merck silica gel 60, no. 7734.

3-*O*-Methyl-17α-(α-methoxyvinyl)estra-3,17β-diol (3). To a

stirred solution of α-methoxyvinyllithium[1] (12 mmol) in THF–pentane at −60 °C under nitrogen was added estrone methyl ether (1.15 g, 4 mmol) dropwise in THF (20 ml). The reaction mixture was warmed to 0 °C over a period of 0.5 h, then quenched with aqueous ammonium chloride and extracted with ether. The organic layer was dried ($MgSO_4$) and most of the ether was removed under reduced pressure. Addition of hexane (50 ml) induced crystallization of the product in 74% yield (1.02 g), mp 144–146 °C (it should be noted that when the reaction was carried out with a twofold excess of MVL, crystalline **3** was obtained in 83% yield, mp 141–143 °C): ir (CCl_4) 3650, 1665, 1620 cm^{-1}; NMR (CCl_4) δ 0.90 (s, 3 H), 1.0–2.4 and 2.6–3.0 (m, 16 H), 3.54 (s, 3 H), 3.70 (s, 3 H), 4.02 and 4.15 (AB quartet, J_{AB} = 2 5 Hz, 2 H), 6.5–6.8 and 7.05–7.3 (aryl m, 3 H). Recrystallization from hexane–ether provided colorless plates, mp 147.5–149 °C.

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.20; H, 8.83. Found: C, 77.50; H, 8.55.

3-*O*-Methyl-17α-acetylestra-3,17β-diol (4). A solution of steroidal enol ether **3** (70 mg, 0.204 mmol) in methanolic acetic acid (1:1, 6 ml) containing a little water (0.5 ml) was stirred at 20 °C for 2 h, then taken up in ether (50 ml). The ethereal solution was washed with water, dried ($MgSO_4$), and concentrated to give a white solid (67 mg, 100%, mp 108–111 °C) which was recrystallized from hexane–methylene chloride to provide **4** 51 mg (76%), as colorless needles (mp 121–122 °C): ir ($CHCl_3$) 3600, 3450, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.3–3.1 (series of multiplets with a three-proton singlet visible at δ 2.00, total integral 19 H), 3.77 (s, 3 H), 6.53–6.8 and 7.0–7.12 (aryl m, 3 H).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.7; H, 8.59. Found: C, 76.7; H, 8.65.

3-*O*-Methyl-17α-(α-hydroxyacetyl)estra-3,17β-diol (5). To a solution of 3-*O*-methyl-17α-(α-methoxyvinyl)estra-3-17β-diol (539 mg, 1.58 mmol) in pyridine (10 ml) was added osmium tetroxide in pyridine (0.158 M, 10 ml, 1.58 mmol); a black color developed immediately and the reaction mixture was stirred at room temperature for 18 h. The osmate ester was reduced by shaking vigorously with an aqueous pyridine (10 ml H_2O/50 ml pyridine) solution of sodium bisulfite (4.0 g) for 3 h. The resulting solution was extracted with 5 × 50 ml of chloroform, and the chloroform was washed with 1 N HCl, saturated bicarbonate, and brine, dried (Na_2SO_4), and evaporated to leave a black tar.

The tar was chromatographed on silica gel; elution with benzene/ethyl acetate (9:1) gave estrone methyl ether. Ethyl acetate elution afforded 3-*O*-methyl-17α-(α-hydroxyacetyl)estra-3,17β-diol (**5**) as a white solid, 163 mg (30%), mp 139–145 °C.

The analytical sample was recrystallized from a boiling solution of 10% chloroform in hexane, and had mp 145–147 °C: ir ($CHCl_3$) 3575, 3455, 1710, 1610 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 7.1–6.45 (m, 3 H), 4.41 (br s, 2 H), 3.64 (s 3 H), 0.92 (s 3 H), 3.2–0.90 (complex m, 17 H); mass spectrum (70 eV) *m/e* 344 (M^+).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.2; H, 8.19. Found: C, 73.1; H, 7.8.

To a cold (6 °C) solution of 95% *m*-chloroperbenzoic acid (106 mg, 585 μmol peracid) was added enol ether **3** (200 mg, 585 μmol) in *wet* ether (30 ml) at a rate such that the temperature remained below 6 °C, and was stirred at 0–6 °C for 1 h. The ethereal solution was washed with saturated bicarbonate and brine, dried (Na_2SO_4), and evaporated to leave 180 mg of **4** as a white solid (90% crude). The solid was recrystallized as above to give 130 mg (65%) of 3-O-methyl-17α(α-hydroxyacetyl)estra-3,17β-diol, mp 145–147 °C.

3-*O*-Methyl-17α-(α-acetoxyacetyl)estra-3,17β-diol (6). The steroidal keto diol **5** (176 mg, 570 μmol) in dry pyridine (3 ml) was stirred overnight under nitrogen with acetic anhydride (87 mg, 855 μmol). The excess acetic anhydride was hydrolyzed by stirring with water (4 drops) for 30 min and the acetate was precipitated upon addition of 1 N HCl (25 ml). The white solid was filtered and recrystallized from hexane/dichloromethane to afford **6** as colorless needles: mp 129–130 °C; 177 mg (83%); ir ($CHCl_3$) 3600–3200 br, 1745, 1721, 1605 cm^{-1}; NMR (90 MHz) ($CHCl_3$) δ 7.18–6.52 (m, 3 H), 5.22, 4.91 (AB q, *J* = 18 Hz), 3.77 (s, 3 H), 2.19 (s, 3 H), 0.99 (s, 3 H), 3.0–1.2 (complex multiplet, 16 H); uv (EtOH) λ_{max} 278 nm (ε 9300), 287 (8600).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.5; H, 7.82. Found: C, 69.8; H, 7.45.

1-(α-Methoxyvinyl)-1-cyclohexyl *p*-Nitrosulfinate (7). To a stirred solution of α-ketol, 1-hydroxy-1-(α-methoxyvinyl)cyclohexane[1] (1.0 g, 6.4 mmol) in dry tetrahydrofuran (15 ml) at 0 °C under dry nitrogen was added dropwise ethereal methyllithium (3.1 ml, 20 M, 6.2 mmol). After stirring for 5 min at 0 °C, the solution was cooled to −70 °C and *p*-nitrobenzenesulfinyl chloride[5] (1.25 g, 6.1 mmol) was added dropwise as a solution in tetrahydrofuran (10 ml). After stirring for 0.5 h at −70 °C and 0.5 h at 20 °C, the reaction mixture was taken up in ether (80 ml) and washed with aqueous sodium bicarbonate (three 100-ml portions), then brine (50 ml). After drying ($MgSO_4$) and concentration in vacuo, there was obtained a dark yellow oil (2.00 g) which was triturated thoroughly with ten portions (20 ml) of pentane. The residual gum (62 mg) was discarded and the combined extracts were concentrated and cooled to furnish the sulfinate **7**, 1.19 g (60%), as very pale yellow needles (mp 89–90 °C): NMR ($CDCl_3$) δ 1.4–2.4 (m, 10 H), 3.64 (s, 3 H), 4.36 and 4.56 (AB quartet, *J* = 3 Hz, 2 H), 7.83 and 8.3 (AB quartet, *J* = 8 Hz, 4 H); ir ($CHCl_3$) no hydroxyl present; the analytical sample was recrystallized from pentane as colorless needles, mp 89.5–90 °C.

Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89. Found: C, 55.22; H, 6.06.

1-(2-Cyclohexylidene-2-methoxy)ethyl *p*-Nitrophenyl Sulfone (8). Thermal Rearrangement of 1-(α-Methoxyvinyl)-1-cyclohexyl *p*-Nitrosulfinate (7). The sulfinate **7** was observed to undergo rapid thermal reorganization at 130 °C. For example, in 60 s 40% sulfone was present, and after 90 s, 78%. However, in runs where rearrangement was complete (120–180 s), other products had been formed in small, but variable, amounts.[6] The reaction was more sluggish at 100 °C, i.e., 25% conversion in 7.5 min, but it was observed that the rearrangement could be carried to completion by heating for 30–70 min at 100 °C without significant decomposition. All glassware was washed with concentrated ammonium hydroxide and dried at 130 °C before use.

Pyrolysis at 130 °C. The sulfinate (231 mg) was heated under nitrogen at 130 ±1 °C for 130 s, and then the flask was immediately cooled in ice–water. Thorough treatment with carbon tetrachloride (8 ml) brought all but a small amount of dark solid into solution. Filtration and concentration provided a dark yellow solid (220 mg) which was triturated with pentane (1 ml), ether (0.5 ml), then pentane (1 ml) to furnish pale yellow crystals of the sulfone **8**, 129 mg (56%), with mp 118–120 °C. In another experiment, treatment of the melt with 1 ml of 1:1 pentane–ether gave a 41% yield of crystals with mp 121–123 °C.

Pyrolysis at 100 °C. A sample (0.500 g) of the sulfinate was heated at 100 ± 1 °C under nitrogen for 70 min. Thorough extraction with carbon tetrachloride (13 ml) followed by filtration and concentration provided yellow crystals (0.480 g, 96%) which upon trituration with ether (1 ml) provided pale yellow crystals, 0.32 g (64%), of the sulfone **8**, mp 121–123 °C: NMR ($CDCl_3$) δ 1.46 (bm, 8 H), 1.88 (m, 2 H), 2.18 (m, 2 H), 3.32 (s, 3 H), 4.05 (s, 2 H), 8.02 and 8.32 (AB quartet, *J* = 9 Hz, 4 H).

The analytical sample was recrystallized from pentane–ether, mp 121.5–123 °C.

Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89. Found: C, 55.14; H, 6.14.

1-[α-(p-Nitrobenzenesulfonyl)]acetylcyclohexanol (9). To a stirred solution of the sulfonyl enol ether **8** (0.390 g, 1.20 mmol) in methylene chloride (15 ml) at 0 °C was added dropwise a solution of *m*-chloroperbenzoic acid (85%, 0.245 g, 1.20 mmol) in methylene chloride (10 ml). After 0.5 h at 0 °C and 0.5 h at 20 °C, the solution was washed twice with aqueous sodium bicarbonate (20 ml), then water (20 ml). After drying ($MgSO_4$) and evaporation of solvent there remained a yellow solid (0.390 g) which was recrystallized from benzene to provide the product **9** as faintly yellow crystals: 0.219 g (67%), mp 155–157 °C; ir ($CHCl_3$) 3540, 1710, 1540, 1360, 1330, 1170 cm^{-1}; NMR ($CDCl_3$) δ 1.61 (bs, 10 H), 2.88 (s, 1 H, exchangeable with D_2O), 4.59 (s, 2 H), 8.05 and 8.44 (AB quartet, *J* = 9 Hz, 4 H). The analytical sample was prepared by recrystallization from benzene, mp 162–163°.

Anal. Calcd for $C_{14}H_{17}NO_6S$: C, 51.4; H, 5.24. Found: C, 51.7; H, 5.44.

The crude sulfone obtained from pyrolysis of the sulfinate could be epoxidized without purification, e.g., the pyrolysate from 136 mg of sulfinate was epoxidized as described above to afford a waxy solid (103 mg) which upon trituration with ether (1 ml) provided the hydroxy keto sulfone (mp 155–157 °C), 58 mg (43% based on sulfinate).

Reduction of 1-(α-*p*-Nitrobenzenesulfonyl)acetylcyclohexanol (9) with Aluminum Amalgam. 1-Acetylcyclohexanol (10). Aluminum foil (430 mg) was cut into strips (ca. 1 × 5 cm) and immersed for 15 s in 2% aqueous mercuric chloride, then rinsed with absolute ethanol followed by anhydrous ether, and cut into 1-cm squares directly into a flask containing the hydroxy keto sulfone **9** (510 mg, 1.56 mmol) in 10% aqueous tetrahydrofuran (30 ml). The stirred mixture was gently refluxed in a 65 °C bath for 70 min, at which time it was cooled and filtered through sintered glass. The solids were washed with ether, and then combined filtrate and washings were concentrated to a volume of several milliliters at 1 atm (15-cm Vigreux column). Ether (10 ml) was added, the water layer separated, and the dried ($MgSO_4$) ether layer concentrated at 1 atm (Vigreux). Methylene chloride (10 ml) was added and the solution concentrated under reduced pressure to leave a pale yellow oil (233 mg) which was extracted thoroughly with two portions of warm distilled pentane (10

ml). Removal of solvent then furnished 1-acetylcyclohexanol (**10**), 136 mg (61%), as a colorless liquid: ir (film) 3600–3150, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.0 (m, 10 H), 2.27 (s, 3 H), 3.65 (br s, 1 H, exchanges with D_2O).

Acknowledgments. We wish to thank the National Science Foundation, the National Institutes of Health, and Merck Sharp and Dohme for their generous support and Dr. V. Kane for estrone methyl ether.

Registry No.—**3,** 58873-40-8; **4,** 34965-67-8; **5,** 58917-11-6; **6,** 58917-12-7; **7,** 58873-41-9; **8,** 58873-42-0; **9,** 58873-43-1; **10,** 1123-27-9; 2-methoxyvinyllithium, 42722-80-5; estrone methyl ether, 1624-62-0; 1-hydroxy-1-(α-methoxyvinyl)cyclohexane, 54123-63-6; *p*-nitrobenzenesulfinyl chloride, 13088-17-0; *m*-chloroperbenzoic acid, 937-14-4.

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(6) At 30 °C, the sample began to darken rapidly after heating in the melt ca. 90 s and rearrangement was still incomplete. At 100 °C, the melt did not become darkened even upon heating for over 1 h.

Macrocycles. Synthesis and Thermal Decomposition of 3-Benzosuberone Diperoxide

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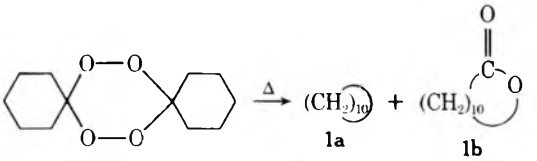
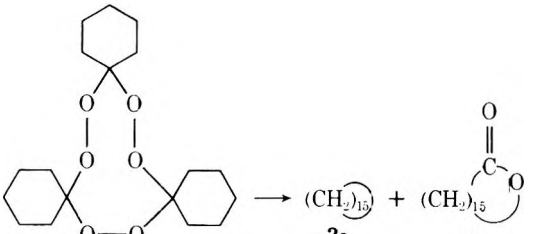
The synthesis and pyrolysis of 3-benzosuberone diperoxide (**4**) gave a fair yield of the macrocyclic hydrocarbon (**5**) and the lactone (**6**). The hydrocarbon (**5**) was converted to 1,6,11,16-tetraketocyclocosane (**9**) using conventional synthetic procedures.

It has been previously reported that cyclic ketone peroxides such as dicyclohexylidene diperoxide (**1**) and tricyclohexylidene triperoxide (**2**) are precursors to macrocyclic hydrocarbons (**1a, 2a**) and macrocyclic lactones (**1b, 2b**).[1] The reactions are illustrated in Scheme I.

Scheme I



1 **1a** **1b**

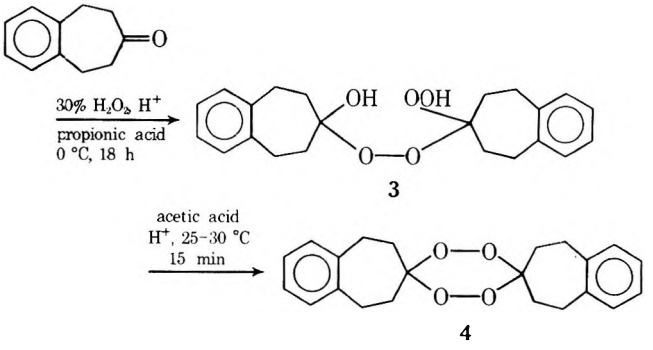


2 **2a** **2b**

The thermal decomposition of these peroxides was found to give higher, more reproducible yields of the macrocyclic products than photolysis and these results were reported.[2] Improvements have also been reported on synthesis of the precursor triperoxide,[3] diperoxides,[4] and mixed triperoxides.[5]

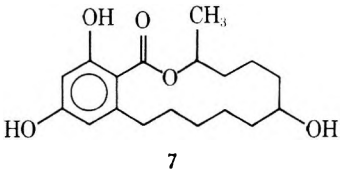
As an extension of the earlier work reported by Story and co-workers,[1] we have undertaken a study of the thermal decomposition of a variety of cyclic ketone peroxides for the purpose of macrocyclic synthesis. In this note, we wish to report our results on the synthesis and thermal decomposition of 3-benzosuberone diperoxide (**4**). The synthesis of this peroxide is outlined in Scheme II.

Scheme II



4 was decomposed in refluxing hydrocarbon solvent to yield the macrocyclic products shown in Scheme III. The products (**5** and **6**) were isolated by a combination of vacuum distillation and column chromatography.

This work greatly extends the utility of the macrocyclic synthesis[1] because it suggests a new approach to the synthesis of molecules similar to animal growth regulators.[6–10] For example, zeranol (**7**) has been used to improve the growth in livestock.[8,9]

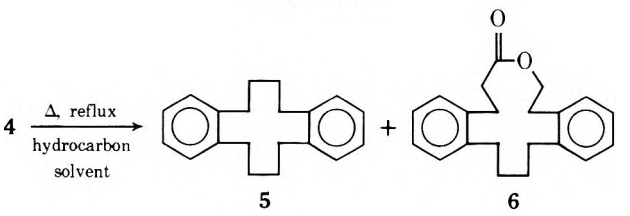


7

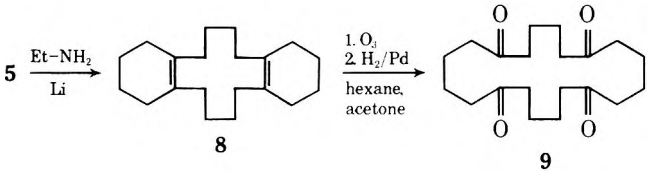
5 was converted by the known procedures shown in Scheme IV to 1,6,11,16-tetraketocyclododecosane (**9**). **9** was tested and found to be unsuccessful as a selective ion reagent.[11]

In conclusion, the synthesis of **5, 6,** and **9** would be difficult to accomplish by conventional syntheses alone. Indeed, the procedures outlined in this paper may be used to synthesize a variety of novel large-ring compounds.

Scheme III



Scheme IV



Experimental Section

Benzosuberone was prepared according to the procedure by Allinger.[12]

Preparation of 1-Hydroxy-1'-hydroperoxydibenzosuberyl Peroxide (3). Benzosuberone (110 g, 0.625 mol) and 30% hydrogen peroxide (71.3 g, 0.625 mol) were dissolved in 300 ml of propionic acid and cooled to 0 °C. Perchloric acid (10%, 20 ml) was added and the solution stirred at 0 °C for 18 h. Water (400 ml) was added to the mixture and the crystals were filtered and washed well with water. The crystals were air dried to yield 103 g (90%) of 1-hydroxy-1'-hydroperoxydibenzosuberyl peroxide (3), mp 114–116 °C. After recrystallization three times from benzene, the melting point was 122–123 °C.

Ir (KBr) 3380 (s), 3250 (s), 3070 (w), 2950 (s), 2860 (m), 1490 (m), 1440 (s), 1390 (m), 1335 (w), 1265 (m), 1230 (w), 1210 (m), 1170 (w), 1140 (w), 1080 (s), 1030 (s), 980 (s), 940 (m), 920 (m), 900 (m), 875 (m), 760 (s), 745 cm^{-1} (s).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.31; H, 7.08. Found: C, 71.00; H, 7.08.

Preparation of Benzosuberone Diperoxide[13] (4). To a solution of 5.1 l. of acetic acid and 330 ml of 10% perchloric acid in acetic acid, 66 g of 1-hydroxy 1'-hydroperoxydibenzosuberyl peroxide was added. The temperature was maintained at 25–30 °C. The solid 1-hydroxy-1'-hydroperoxydibenzosuberyl peroxide went completely into solution and the diperoxide (4) precipitated 15 min later (26 g, 40% yield, mp 195 °C). The diperoxide was recrystallized twice from acetone, mp 220 °C.

Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.94; H, 6.86. Found: C, 75.29; H, 7.23.

Pyrolysis of Benzosuberone Diperoxide[14] (4). The following pyrolysis procedures were tried in an attempt to maximize the yields of the macrocyclic products.

(a) Benzosuberone diperoxide (0.50 g) was dissolved in 10 ml of Isopar-K (a hydrocarbon solvent available from Humble Oil) and refluxed for 3 h.

(b) Benzosuberone diperoxide (0.50 g) was dissolved in 10 ml of *n*-decane and refluxed for 3 h.

(c) Benzosuberone diperoxide (0.50 g) was dissolved in 10 ml of Isopar-L (a hydrocarbon solvent available from Humble Oil) and refluxed for 3 h.

(d) Benzosuberone diperoxide (0.50 g) was dropped slowly into an open test tube suspended in an oil bath heated to 230 °C.

The yields were determined by VPC using a 5 ft × 0.25 in. 20% SE-30 column. The yields were as follows.

Procedure	% benzosuberone	% 5	% 6
a	11	13	21
b	10	11	18
c	N.D.	10	13
d	10	9	5

Large-Scale Pyrolysis of Benzosuberone Diperoxide (4). Benzosuberone diperoxide (130 g) was refluxed in 2.6 l. of Isopar-K for 3 h. (Behind a safety shield!). The solvent was removed under reduced pressure. The pressure was reduced to 2.2 mmHg, pot temperature up to 135 °C. Only solvent and benzosuberone were collected up to this time. The pressure was reduced to 0.5 mmHg and the distillate collected at 190–260 °C. The distillate was dissolved in a minimum amount of hexane and placed on the top of a column which contained 500 ml of silica gel. The silica gel was eluted with hexane until no more hydrocarbon could be detected in the elute. The hexane was removed under vacuum and the residue recrystallized from anhydrous ethanol to yield 6.7 g (7% yield) of 1,7-dibenzocyclododecane (5): mp 104–105 °C; ir (CCl_4) 3090 (w), 3055 (w), 3009 (m), 2985 (sh), 2923 (s), 2900 (sh), 2878 (m-s), 1495 (m-s), 1474 (m-s), 1450 (m), 1352 (w), 1343 (w), 1290 (w), 1241 (w), 1175 (w-m), 1056 (w), 1033 cm^{-1} (3).

Anal. Calcd for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found: C, 90.56; H, 9.45.

The lactone 6 was eluted from the silica gel column with benzene and recrystallized from absolute ethanol: yield 6%; mp 98–99 °C; ir (CCl_4) 2922 (s), 2850 (m-s), 1715 (s), 1464 (m), 1450 (m), 1413 (m), 1370 (m), 1441 (sh, w), 1372 (w), 1200 (w), 1135 (w-m), 1121 cm^{-1} (w-m).

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.93; H, 8.06.

Reduction of 1,7-Dibenzocyclododecane[15] (5). 1,7-Dibenzocyclododecane (5, 6.7 g, 0.025 mol) was placed in a 300-ml, three-necked flask equipped with a thermometer, stirrer, and dry ice condenser. The flask was purged with nitrogen and warmed to drive out moisture. Ethylamine (100 ml) and lithium metal (2.1 g, 0.030 mol) were added. The mixture was stirred for 8 h at reflux temperature and the excess lithium removed. The ethylamine was allowed to evaporate (at room temperature) in the fume hood. Water was added slowly to the residue and the crystals collected, washed with water, and air dried to give 8 (85% yield, mp 95–98 °C). The crude material was recrystallized from absolute ethanol: mp 103–104 °C; ir (CCl_4) 3080 (sh), 2918 (s), 2850 (s), 2814 (m-s), 1469 (m), 1450 (m), 1438 (w-w), 1368 (w), 1347 (w), 1287 (w), 1264 (w-m), 1241 (w), 1163 (w), 1142 cm^{-1} (w).

Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 87.97; H, 12.01.

Preparation of 1,6,11,16-Tetraketocyclododecane (9). Diolefin 8 (0.65 g) was dissolved in 30 ml of hexane and ozonized at room temperature. A white solid precipitated after several minutes and no more ozone was taken up. (An ir spectrum of the solid showed that the reaction was incomplete.) The hexane was removed; the solid was dissolved in acetone and again ozonized until no more ozone was absorbed.

The acetone solution was hydrogenated at 1 atm pressure and room temperature using 10 mg of palladium on charcoal as catalyst until no more hydrogen was absorbed. The catalyst was filtered and the solvent removed under vacuum. The residue was recrystallized several times from hexane to give 0.090 g (14% yield) of the tetraketone 9: mp 76–77 °C; ir (CCl_4) 2930 (s), 2890 (sh), 2860 (sh), 1712 (s), 1450 (sh), 1438 (m-w), 1408 (m), 1368 (m), 1341 (sh), 1270 (w), 1190 (w), 1164 (w), 1140 cm^{-1} (w).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.55.

Acknowledgment. We would like to thank Story Chemical Corp. for permission to publish that part of the work performed in their laboratories.

Registry No.—3, 58815-90-0; 4, 58815-91-1; 5, 58815-92-2; 6, 58815-93-3; 8, 58815-94-4; 9, 58815-95-5; benzosuberone, 4443-91-8; hydrogen peroxide, 7722-84-1.

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Boron Compounds. 40.[1] *O*-Ethylboranediyl Derivatives of Dulcitol

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1,6-Bis-*O*-diethylboryl-2,3:4,5-bis-*O*-ethylboranediyldulcitol (**2**) and 1,6:2,3:4,5-tris-*O*-ethylboranediyldulcitol (**3**) are prepared from dulcitol and ethylboron compounds. 2,3:4,5-Bis-*O*-ethylboranediyldulcitol (**4**) is prepared by selective deborylation of **2** and **3** using methanol. The regioselective O-derivatization of **4** is investigated with benzoyl chloride, acetic anhydride, and tosyl chloride. One obtains the boron-containing **5a** and the boron-free dulcitol derivatives **6a–c** and **7**.

Much interest has been centered on the use of the phenylboranediyl protective group for the selective O-derivatization of polyalcohols and carbohydrates.[2] The fact that the reaction of phenylboronic acid with glycerol yields a mixture of phenylboranediyl derivatives of glycerol with five- and six-membered *O*-phenylboranediyl rings[3] prompted us to investigate new routes which allow the selective introduction of *O*-ethylboranediyl groups into polyhydroxy systems. The availability of triethylborane,[4] coupled with the fact that the *O*-ethylboranediyl derivatives of polyalcohols have not been described, motivated our present investigations[5–9] into the possible structures and some specific reactions of the *O*-ethylboranediyl derivatives of polyhydroxy compounds.

Conflicting structural assignments have been made for the *O*-phenylboranediyldulcitol derivative,[10–12] and also an extremely low yield was obtained in the derivatization of "1,3:4,6-bis-*O*-phenylboranediyldulcitol" to 1,3,4,6-tetra-*O*-acetyl-2,5-di-*O*-benzoyldulcitol.[11] The use of alcohols and water for washing[2,11] *O*-phenylboranediyl derivatives is a questionable practice as the selective deborylation of *O*-ethylboranediyl groups with methanol has been observed.[8,9]

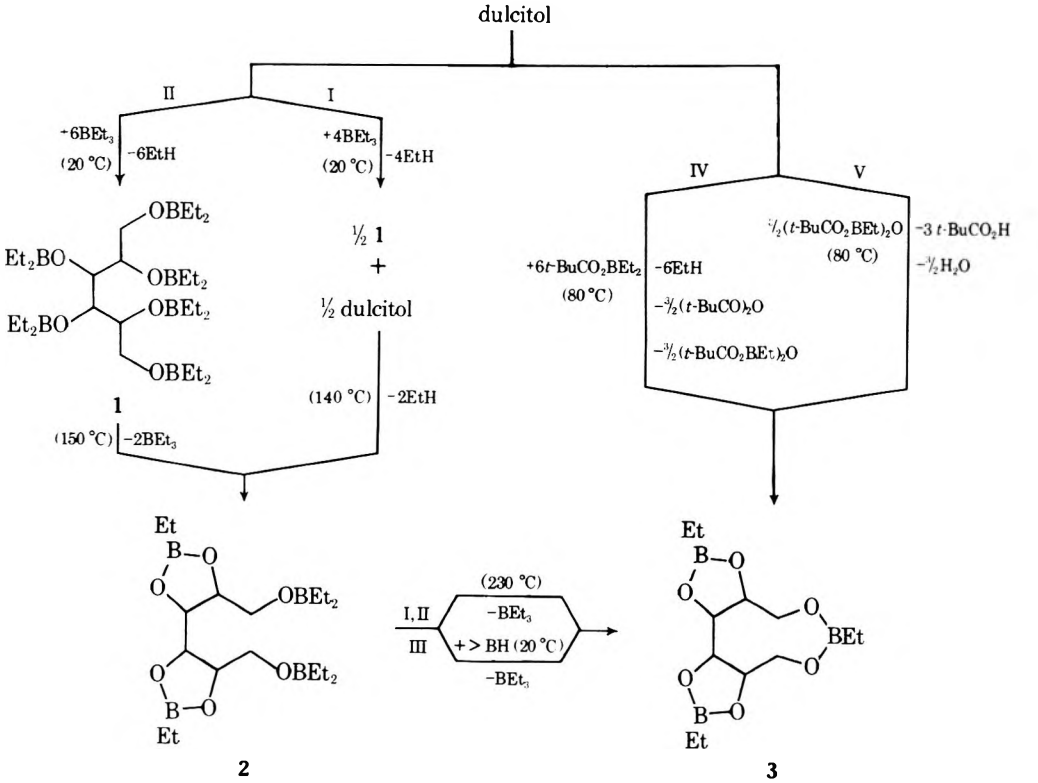
Results and Discussion

A. O-Diethylborylation and O-Ethylboranediylation of Dulcitol. 1,6-Bis-*O*-diethylboryl-2,3:4,5-bis-*O*-ethylboranediyldulcitol (**2**) can be prepared in two ways (Scheme I). The first method involves two stages. Firstly 1,2,3,4,5,6-hexakis-*O*-diethylboryldulcitol (**1**) is prepared analogously to the previously described perdiethylborylation of polyols,[5] by reaction of dulcitol with activated triethylborane[13] in an exothermic reaction at room temperature. Two moles of triethylborane is then eliminated from **1** by heating to 150 °C and **2** is obtained in 96% yield. **2** can also be prepared, without isolating **1**, by reaction of dulcitol with 4 mol of triethylborane. In the first part of this reaction dulcitol is added to activated triethylborane[13] at room temperature and 4 mol of ethane are evolved. The resultant mixture of dulcitol and **1** is subsequently heated to 140 °C causing a further 2 mol of ethane to be liberated, generating **2** in 93% yield.

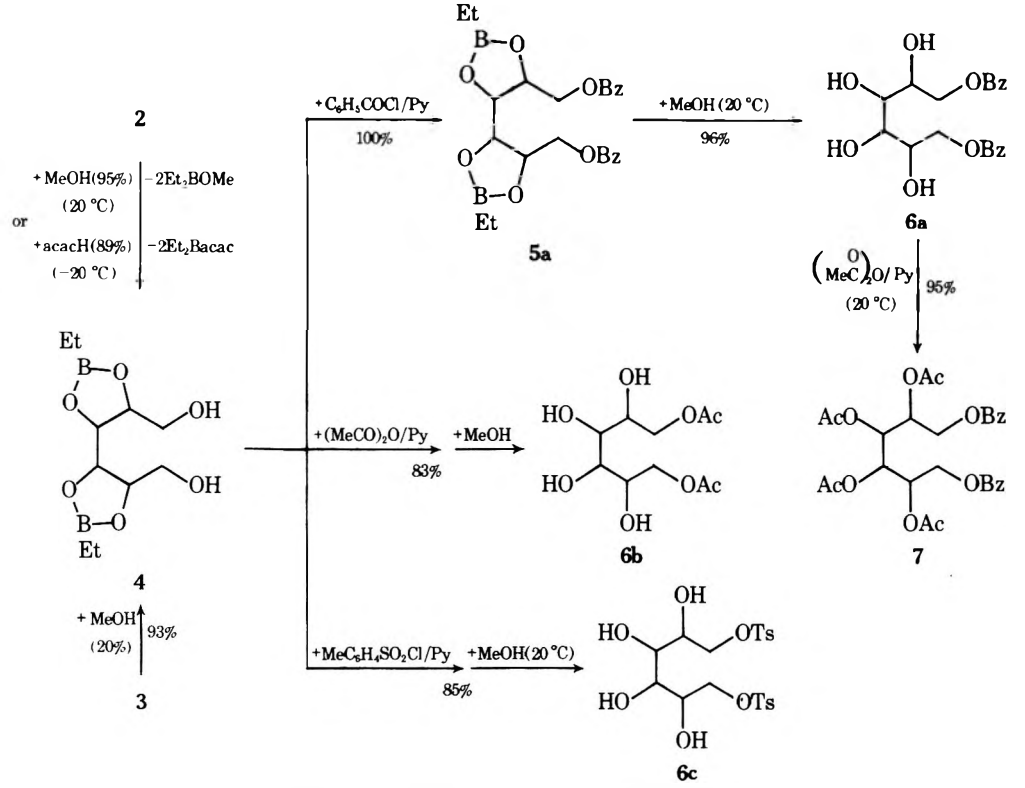
1,6:2,3:4,5-Tris-*O*-ethylboranediyldulcitol (**3**) can be prepared using the five routes I–V (see Scheme I).

3 can be obtained by pyrolysis of **1** (route I) or **2** (route II). The thermal elimination of 2 mol of triethylborane from **1** to yield **2** occurs at 150 °C, whereas 230 °C is required in order to eliminate the third mole. This temperature lies in the range for intermolecular elimination of triethylborane[6] from two *O*-diethylboryl groups. Intramolecular ring formation occurs exclusively in the pyrolyses of **1** and **2**. The addition of catalytic amounts of >BH[14] to **2** at room temperature also leads to the formation of **3** (route III) in 98% yield.

Scheme I



Scheme II



Bz = C_6H_5CO–; Ac = CH_3CO–; Ts = p-$CH_3C_6H_4SO_2$–

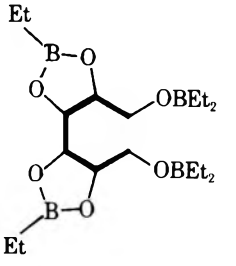
Reaction between dulcitol and diethylboryl pivalate[13] gives directly **3** at 80 °C, accompanied by evolution of 6 mol of ethane and formation of 1.5 mol of bis(ethylpivaloyloxy)-diboroxane[7] and 1.5 mol of pivalic acid anhydride (route IV). The relatively low yield (66%) of **3** is due to the difficulty encountered in the separation of this compound from the bis(ethylpivaloyloxy)diboroxane.[15] **3** can, however, be prepared in 87% yield by reaction of the latter with dulcitol at 80 °C (route V); pivalic acid (3 mol) and water (1.5 mol) in this case are formed as side products.

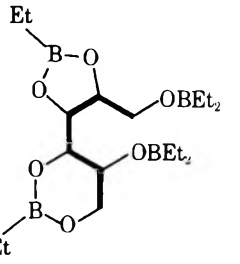
B. Regioselective O-Derivatization of Dulcitol. The diethylboryl groups of **2** can be selectively removed by addition of methanol at room temperature.[9] The solid 2,3:4,5-bis-*O*-ethylboranediyldulcitol (**4**) is obtained in 95% yield (see Scheme II). Selective deborylation of **3** may also be effected using methanol at room temperature; the nine-membered ethylboranediyl ring is opened, and **4** is obtained in 93% yield.

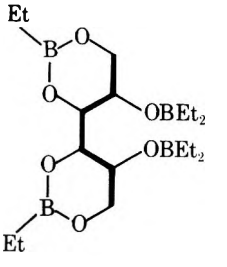
By the normal procedure benzoylation of **4** gives 1,6-di-*O*-benzoyl-2,3:4,5-bis-*O*-ethylboranediyldulcitol (**5a**); this can be deborylated with methanol to give the known 1,6-di-*O*-benzoyldulcitol[16] (**6a**). Analogously **6b**[17] is formed in 95% yield by deborylation of the di-*O*-acetyl derivative of **4**.

The selective deborylation of **2** with acetylacetone to give pure **4** can only be achieved below 0 °C; at room temperature a mixture of compounds is obtained. A study of the temperature dependence of this reaction shows that the yield of **4** decreases with increasing temperature, whereas the yield of **3** increases and rises to ca. 50% at 100 °C. At this temperature an, as yet, unidentified solid containing four hydroxyl groups and one *O*-ethylboranediyl group is obtained. This compound is also formed when pure **4** is heated to 100 °C in the presence of acetylacetone. However, **4** remains unchanged after 1 h at 120 °C in the absence of acetylacetone.

C. Structure Determination of 2, 3, and 4. The fact that the pyrolysis of **1** between 140 and 180 °C causes the elimination of only 2 mol of triethylborane, rather than 3 as in the case of mannitol[9] and sorbitol,[18] indicates that two five- or







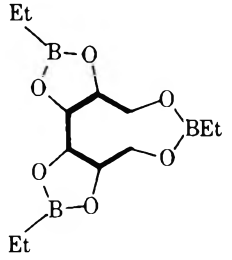
six-membered ethylboranediyl rings are formed in this reaction, and hence the three structures **2**, **2a**, and **2b** are possible. The symmetry of **2** is reflected in its ^1H NMR spectrum (see Experimental Section). The ^{11}B NMR spectrum of a neohexane (2,2-dimethylbutane) solution of **2** verifies the presence of two *O*-diethylboryl groups and two *O*-ethylboranediyl groups.[5] The position of the symmetrical signal for the *O*-ethylboranediyl boron atoms at δ 34 ppm indicated the presence of the structure **2** with two five-membered 1,3,2-dioxaborolane rings.[6] Higher membered OBO rings have signals at δ 30 ppm.[6-8]

Further proof for this structural assignment is given by the fact that the high-yield selective deborylation of **2** to **4** is possible. The two hydroxyl groups appear as a triplet at τ 5.07 ppm with J = 5.5 Hz in the ^1H NMR spectrum of a dimethyl

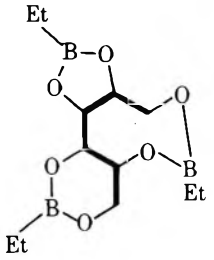
sulfoxide solution of 4. This triplet indicates that the two hydroxy groups are primary.[19]

Benzoylation and deborylation of 4 can be effected in 96% yield to give the known 1,6-di-*O*-benzoyldulcitol,[10] thus giving final proof of the structure of 2.

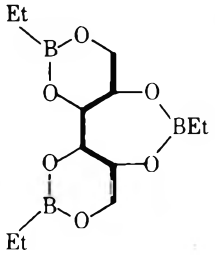
An extremely high temperature (230 °C) is required for the formation of the third *O*-ethylboranediyl ring. This is the temperature required for intermolecular elimination of triethylborane;[6] it is reasonable, therefore, to assume that a seven-, eight-, or nine-membered ring is formed under these reaction conditions. No intermolecular products are formed; thus structures 3, 3a, and 3b are possible.



3



3a



3b

The ^{11}B NMR spectrum of 3 in neohexane shows the presence of five-membered rings; however, the breadth of the signal observed does not allow an unequivocal interpretation. The nine-membered ring would be expected to have a signal at ca. δ 30 ppm, this being the range for six- and higher membered rings.

Proof of the structure of 3 is furnished by its facile selective deborylation to 4 (see Scheme II), which involves opening of the nine-membered ethylboranediyl ring.

Comparison of *O*-Ethyl- with *O*-Phenylboranediyl Derivatives of Dulcitol. The first *O*-phenylboranediyl derivative of dulcitol was prepared in 1958. However, no structural assignment was attempted.[10] In the latter paper it is mentioned that the ratio of dulcitol to phenylboroxine is unimportant, and tris-*O*-phenylboranediyldulcitol is always obtained. Later, the preparation and derivatization of 1,3:4,6-bis-*O*-phenylboranediyldulcitol in poor yield (10%) is described.[11] It is interesting to note that the preparation involves the use of hot water and methanol. We suggest that the use of such solvents leads to either the selective deborylation of one *O*-phenylboranediyl ring or an intermolecular linkage. This is comparable with the selective deborylation of 2 to 4.

The reaction of dulcitol with triphenylborane in toluene (see Experimental Section) gives a tris-*O*-phenylboranediyldulcitol in a yield of 93% which has mp 162 °C; this is identical with the derivative prepared from phenylboronic acid and dulcitol in acetone.[10] Treatment of this derivative with warm water leads to the selective cleavage of one of the *O*-phenylboranediyl rings.

It was recently proposed, on the basis of fragmentation in the mass spectrometer, that the *O*-phenylboranediyl derivative of dulcitol is 1,3:2,4:5,6-tris-*O*-phenylboranediyldulcitol without giving the means of preparation of this derivative.[12]

Summary. The use of the protective *O*-ethylboranediyl group offers distinct advantages over the *O*-phenylboranediyl group. A choice of five routes (I–V) is available for introducing the *O*-ethylboranediyl groups into polyalcohols. The products can be distilled in vacuo, and in several cases[6–9] the analyses by GLC methods are possible. A useful tool in the determination of the structure of *O*-ethylboranediyl derivatives is ^{11}B NMR spectroscopy, where characteristic high-field chemical shifts (δ 34.5 ppm) are obtained specifically for five-membered rings.

Many of the dulcitol derivatives can be selectively deborylated with methanol at room temperature. The number of hydroxy groups in the products can be quickly and accurately determined with the help of activated triethylborane.[5,26] The selectively deborylated products can be O-derivatized with benzoyl chloride, acetic anhydride, or tosyl chloride in good yield.

Experimental Section

General. All experiments were carried out in dry, deoxygenated solvents under an atmosphere of argon.

Analyses. Ethane was measured with a mass spectrometer CEC 103. The purity of 3 was determined gas chromatographically[20] with a M + F 720 (3-m steel column filled with SF 96 on Embacel). The ^1H NMR,[21] ir,[22] and mass spectra[23] were obtained using the instruments Varian A-60 or HA-100, Perkin-Elmer 125, and Varian MAT CH5, respectively. ^{11}B NMR[24] spectra were recorded at 32.1 MHz with $Et_2O{\cdot}BF_3$ as an external standard (deshielding $\delta > 0$). Boron was determined by flame photometry of methanol solutions with a M4QIII from Carl Zeiss. C, H analyses were carried out by Dornis and Kolbe, Mülheim-Ruhr. The B_C values were obtained by the described quantitative analysis using anhydrous trimethylamine *N*-oxide in boiling benzene.[25a] The BC_2 values were obtained by oxidation with anhydrous trimethylamine *N*-oxide in boiling pentane.[25b] The hydroxy groups were determined using activated triethylborane.[5,26]

Reagents. Dulcitol was obtained from Baker Chemical Co. Triethylborane,[4] tetraethyldiborane,[27] diethylboryl pivalate,[13] and bis(ethylpivaloyloxy)diboroxane[14] have been synthesized in our pilot plant and laboratory, respectively.

Preparation. A. 1,2,3,4,5,6-Hexakis-*O*-diethylboryldulcitol (1). Triethylborane (84 g, 0.857 mol), which was activated by 0.2 ml of diethylboryl pivalate, was added dropwise (2 h) to a stirred suspension of dulcitol (23.2 g, 127 mmol) in heptane (120 ml) and ethane (17.74 nl, MS) was evolved. The temperature rose to 45 °C. After the removal of the excess of triethylborane and heptane in vacuo colorless 1 (73.5 g, 98%) was obtained as residue: MS (70 eV) no M^+; found *m/e* 561 (B_6, rel intensity 5), 462 (B_5, 22), 407 (B_4, 66), 309 (B_4, 89), 99 (B_1, 100); ^1H NMR (CCl_4, 60 MHz) τ 5.48 (m, 4 H), 5.92 (m, 4 H), 9.13 (s, 60 H).

Anal. Calcd for $C_{30}H_{68}B_6O_6$ (589.7): B, 11.00; B_C, 7.33. Found: B, 11.15; B_C, 7.13.[25a]

B. 1,6-Bis-*O*-diethylboryl-2,3:4,5-bis-*O*-ethylboranediyldulcitol (2). Route I (Pyrolysis of 1). 1 (56 g, 95 mmol) was heated to 150 °C and pure (GLC) triethylborane (18.5 g, 189 mmol) distilled over. Distillation of the residue in vacuo yielded colorless 2 (35.8 g, 95%), bp 120 °C (10^{-3} Torr).

Route II (Dulcitol and BEt_3 in the Ratio 1:4). Dulcitol (20 g, 110 mmol) was added in portions over 4 h to triethylborane (43 g, 439 mmol) containing 0.2 ml of diethylboryl pivalate. The temperature rose to a maximum of 50 °C and ethane (9.59 nl, 97.5%, MS) was liberated. The mixture was then heated to 130 °C (bath) and a further 5.25 nl (107%) of ethane (MS) was evolved. Distillation yielded 2 (40.3 g, 93%): bp 130 °C (10^{-3} Torr); MS (70 eV) no M^+; found *m/e* 365 (B_4, rel intensity 19), 197 (B_2, 13), 125 (B_1, 20), 111 (B_1, 47), 99 (B_1, 100), 98 (B_1, 44), 57 (B_1, 27); ^1H NMR (100 MHz, CCl_4) τ 5.65 (m, 2 H) [5.86 (m), 6.00 (d, J = 4 Hz), 4 H], 6.17 (dd, J = 11.5, 3 Hz, 2 H), 9.12 (m, 30 H); ^{11}B NMR (neohexane) δ 55 (1 B, half-width = 600 Hz) and 35 ppm (1 B, half-width ~ 600 Hz).

Anal. Calcd for $C_{18}H_{38}B_4O_6$ (393.8): B, 10.98; B_C, 5.49; B_{C_2}, 1.83. Found: B, 10.89; B_C, 5.34;[25a] B_{C_2}, 1.91.[25b]

Tris-1,6:2,3:4,5-*O*-ethylboranediyldulcitol (3). Route IV (Dulcitol and Diethylboryl Pivalate). Dulcitol (10.4 g, 57.1 mmol) was added in portions in 2 h to diethylboryl pivalate (61.7 g, 363 mmol) at 80 °C and ethane (MS) (7.85 nl, 102%) evolved. Fractionation yielded excess diethylboryl pivalate (3.4 g) (^1H NMR), bp 68 °C (12 Torr), 97% (GC) pivalic acid anhydride (15 g), bp 84 °C (12 Torr), 28 g of a mixture of 80% bis(ethylpivaloyloxy)diboroxane, and 20% 3 (^1H NMR), bp 108 °C (0.2 Torr), and 3 (11.2 g, 66%), bp 114 °C (5×10^{-3} Torr).

Dulcitol and Bis(ethylpivaloyloxy)diboroxane. Route V. A mixture of dulcitol (3.2 g, 17.6 mmol) and bis(ethylpivaloyloxy)diboroxane (16.4 g, 55 mmol) was heated to 80 °C for 30 min. Distillation in vacuo yielded **3** (4.5 g, 87%), bp 100 °C (10^{-3} Torr).

From 1 and 2 with Ethyldiborane (Route III). A mixture of **1** (51.6 g, 87.5 mmol) and ethyldiborane (882.3 mg, 15.05‰ H^-, 13.6 mmol BH) was stirred for 4 days at room temperature. The >BH was then destroyed by bubbling in ethylene for 0.5 h and the triethylborane (21.4 g) was distilled in vacuo. Further distillation yielded **2** (16 g, 62%), bp 99 °C (10^{-3} Torr), and **3** (13.2 g, 38%), bp 131 °C (10^{-3} Torr).

From 2 with >BH (Route III). A mixture of **2** (11.6 g, 29.5 mmol) and 0.2 ml of ethyldiborane (with 15.1‰ H^-) was stirred for 6 h at room temperature. Triethylborane (2 g) was removed in vacuo and **3** (8.5 g, 98%), bp 99 °C (10^{-3} Torr), was obtained.

3 by Pyrolysis of 2 (Route I). **2** (7.8 g, 19.8 mmol) was heated to 230 °C for 5 h during which time triethylborane (1.6 g) distilled over. Pure (GLC) **3** (5.4 g, 92%) was obtained by distillation of the residue: MS (70 eV) no M^+; found *m/e* 197 (B_2, rel intensity 18), 111 (B_1, 44), 99 (B_1, 100), 57 (B_1, 22); ^1H NMR (CCl_4, 100 MHz) τ 5.60 (m, 2 H), 5.80 (m, 3 H), 6.04 (d, J = 2 Hz, 2 H), 6.16 (br s, 1 H), 9.14 (m, 15 H); ^{11}B NMR (neohexane) δ 34 ppm with shoulder (30 ppm) (half-width = 600 Hz).

Anal. Calcd for $C_{12}H_{23}B_3O_6$ (295.8): B, 10.97; B_C, 3.66. Found: B, 10.84; B_C, 3.63.[25a]

C. 2,3:4,5-Bis-O-ethylboranediyldulcitol (4). 4 from 2 with Methanol. Methanol (10 ml) was added to **2** (6.4 g, 16.3 mmol). The mixture was stirred for 30 min at room temperature. After removal of the methanol and diethylmethoxyborane mixture (8.6 g with 4.09% B), **4** (4 g, 95%) remained as a colorless powder, mp 97 °C.

4 from 3 with Methanol. Methanol (10 ml) was added to **3** (11 g, 37.2 mmol). The mixture was stirred for 15 min at room temperature. After removal of the methanol and ethyldimethoxyborane mixture (15.8 g with 2.34% B) in vacuo (15 Torr), **4** (8.9 g, 93%) was obtained as residue: mp 97–98 °C; MS (70 eV) no M^+, found *m/e* 227 (B_2, rel intensity 2), 197 (B_2, 13), 129 (B_1, 18), 111 (B_1, 44), 99 (B_1, 100), 98 (45), 31 (B_0, 6); ir (Nujol) 3285 (OH), 1355 cm^{-1} (BO); ^1H NMR (Me_2SO-d_6, 60 MHz) τ 5.07 (t, J = 5.5 Hz, 2 H), 5.5–6.2 (m, 4 H), 6.5 (m, 4 H), 9.16 (m, 10 H); ^{11}B NMR (Me_2SO) δ 33 ppm (half-width ~ 1300 Hz).

Anal. Calcd for $C_{10}H_{20}B_2O_6$ (257.9): B, 8.38; B_C, 2.79; H^+, 0.782. Found: B, 8.36; B_C, 2.72;[25a] H^+, 0.774.

4 from 2 with Acetylacetone. Acetylacetone (10 ml) was added dropwise to a stirred solution of **2** (5 g, 12.7 mmol) in hexane (20 ml) at −20 °C. After 1 h, **4** was filtered off, washed with hexane, and vacuum dried. The yield of **4** was 2.9 g (89%), mp 97 °C.

4 with Acetylacetone at 100 °C. A mixture of **4** (1.4 g, 5.4 mmol) and acetylacetone (5 ml) was heated to 100 °C for 1 h. After cooling to room temperature hexane (10 ml) was added, and the solid was filtered off, washed with hexane, and dried in vacuo giving mono-O-ethylboranediyldulcitol (0.5 g, 84%), mp ~156 °C. On concentrating the filtrate **3** (0.8 g, ~100%) (^1H NMR) was obtained: MS (70 eV) no M^+; found *m/e* 129 (B_1, rel intensity 24), 111 (B_1, 41), 99 (B_3, 100); ^1H NMR (Me_2SO-d_6; 60 MHz) τ 5.65 (m, 6 H), 6.60 (m, 6 H), 9.18 (m, 5 H).

Anal. Calcd for $C_8H_{17}BO_6$ (220.0): B, 4.92; B_C, 1.64; H^+, 1.83. Found: B, 4.93; B_C, 1.54;[25a] H^+, 1.83.

Pyrolysis of 4. **4** (1.8 g) remained unchanged (melting point) after being heated to 120 °C for 1 h.

D. O-Derivatization of 4. 1,6-Di-O-benzoyl-2,3:4,5-bis-O-ethylboranediyldulcitol (5a). From 4 with Benzoyl Chloride. Benzoyl chloride (3.63 g, 25.8 mmol) was added dropwise in 30 min to a stirred solution of **4** (3.3 g, 12.8 mmol) in pyridine (20 ml) at 0 °C. The mixture was then stirred for 8 h at room temperature before filtering off the pyridine hydrochloride. Concentration of the filtrate in vacuo yielded **5a** (6.0 g, 100%): mp 121 °C; MS (70 eV) no M^+; found *m/e* 331 (B_2, rel intensity 12), 270 (B_1, 12), 233 (B_1, 12), 111 (B_1, 82), 105 (B_0, 100), 77 (B_0, 28); ^1H NMR (CD_3CN, 60 MHz) τ 1.98 (m, 4 H), 2.43 (m, 6 H), 5.39 (m, 2 H), 5.56 (m, 6 H), 9.16 (m, 10 H).

Anal. Calcd for $C_{24}H_{28}B_2O_8$ (466.1): B, 4.64; B_C, 1.55. Found: B, 4.71; B_C, 1.79.[25a]

1,6-Di-O-benzoyldulcitol (6a). 6a from 5a with Methanol. 5a (5.5 g, 11.8 mmol) and methanol (40 ml) yielded **6a** (4.4 g, 96%): mp 206 °C; MS (70 eV) no M^+; found *m/e* 237 (rel intensity 38), 207 (19), 196 (74), 178 (23), 165 (69), 123 (95), 105 (100), 77 (22).

Anal. Calcd for $C_{20}H_{22}O_8$ (390.4): C, 61.53; H, 5.86; H^+, 1.033. Found: C, 61.56; H, 5.66;[25a] H^+, 1.056.

1,6-Di-O-benzoyl-2,3,4,5-tetra-O-acetyldulcitol (7). From 6a with Acetic Anhydride. Acetic anhydride (10 ml) was added dropwise to a solution of **6a** (2.1 g, 5.4 mmol) in pyridine (10 ml). After stirring for 3 h at room temperature the solution was concentrated in vacuo to yield crude **7** (2.85 g, 95%): mp 224 °C (recrystallized once from glacial acetic acid); MS (70 eV) found *m/e* 436 (rel intensity 3), 423 (8), 351 (34), 279 (54), 207 (54), 105 (100), 43 (57).

Anal. Calcd for $C_{28}H_{30}O_{12}$ (558.5): C, 60.21; H, 5.41. Found: C, 60.19; H, 5.30.

1,6-Di-O-acetyldulcitol (6b). From 4 with Acetic Anhydride. Acetic anhydride (10 ml) was added to **4** (0.7 g, 2.7 mmol) in pyridine (10 ml). The mixture was stirred for 1 h at room temperature. Pyridine and acetic anhydride were removed in vacuo (10^{-2} Torr). Two 15-ml portions of methanol were added to the residue and the solution was concentrated in vacuo (15 Torr). **6b** (0.6 g, 83%), mp 168 °C, was obtained: ^1H NMR (Me_2SO-d_6, 60 MHz) τ 5.55 (m, 2 H), 6.0 (br s, 6 H), [6.57 (m), 6.67 (s), 5 H)], 7.99 (s, 5 H).

Anal. Calcd for $C_{10}H_{18}O_8$ (266.3): C, 45.11; H, 6.81; H^+, 1.51. Found: C, 45.14; H, 6.80; H^+, 1.51.

1,6-Di-O-p-tosyldulcitol (6c). From 4 with Tosyl Chloride. *p*-Tosyl chloride (2.7 g, 14.2 mmol) was added in portions to a stirred solution of **4** (1.8 g, 7 mmol) in pyridine (15 ml). The temperature rose to a maximum of 29 °C. After stirring for 10 h at room temperature, water (40 ml) was added dropwise causing the pyridine hydrochloride to go into solution and **6c** to precipitate out. After filtration, washing with water, and drying in vacuo **6c** (2.9 g, 85%), mp 128–130 °C (mp 134 °C from THF), was obtained: MS (70 eV) no M^+; found *m/e* 275 (rel intensity 3), 172 (30), 155 (22), 103 (51), 91 (100), 73 (76).

Anal. Calcd for $C_{20}H_{26}S_2O_{10}$ (490.6): C, 48.97; H, 5.34; S, 13.07; H^+, 0.822. Found: C, 49.05; H, 5.08; S, 13.05; H^+, 0.79.

Dulcitol and Triphenylborane. Dulcitol (5.5 g, 30.2 mmol) was added to triphenylborane (55.4 g, 0.23 mmol) in toluene (75 ml) at room temperature and the mixture was then heated under reflux for 3 h. After removal of solvent (GC: 19.19% benzene and 80.7% toluene) the solid residue (41.4 g) was heated to 180 °C at 10^{-3} Torr to remove the excess triphenylborane (28 g) and crude tris-O-phenylboranediyldulcitol (12.4 g, 93%) was obtained: mp 162 °C[10] (from diethyl ether); MS (70 eV) M^+ *m/e* 440 (B_3, rel intensity 41), 159 (B_1, 51), 147 (B_1, 100), 91 (B_0, 30); ^1H NMR (Me_2SO-d_6, 60 MHz) τ 2–2.8 (m, 15 H), 4.9–5.9 (m, 8 H).

Anal. Calcd for $C_{24}H_{23}B_3O_6$ (440.0): B, 7.37; B_C, 2.46. Found: B, 7.27 B_C, 2.50.

Bis-O-phenylboranediyldulcitol. A mixture of tris-O-phenylboranediyldulcitol (0.4 g, 0.9 mmol) and water (20 ml) was heated to 60 °C for 2 h. The insoluble material product was filtered off and dried in vacuo to give bis-O-phenylboranediyldulcitol hydrate (0.3 g, 89%): mp 137 °C[11]; ^1H NMR (Me_2SO-d_6, 60 MHz) τ 2–2.7 (m, 9 H), 5–6.5 (m, 11 H).

Anal. Calcd for $C_{18}H_{20}B_2O_6 \cdot H_2O$ (372.2): H^+, 1.08. Found: H^+, 1.17.

Registry No.—**1**, 58881-46-2; **2**, 58881-47-3; **3**, 58881-48-4; **4**, 58881-49-5; **5a**, 58881-50-8; **6a**, 20847-03-4; **6b**, 58917-44-5; **6c**, 20847-02-3; **7**, 58881-51-9; triethylborane, 97-94-9; dulcitol, 608-66-2; diethylboryl pivalate, 34574-27-1; bis(ethylpivaloyloxy)diboroxane, 52164-70-2; ethyldiborane, 16924-34-8; mono-O-ethylboranediyldulcitol, 58881-52-0; benzoyl chloride, 98-88-4; acetic anhydride, 108-24-7; *p*-tosyl chloride, 98-59-9; triphenylborane, 960-71-4; tris-O-phenylboranediyldulcitol, 58881-53-1; bis-O-phenylboranediyldulcitol, 4248-37-7.

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Electron Adducts of Acrylic Acid and Homologues. Spectra, Kinetics, and Protonation Reactions. A Pulse-Radiolytic Study

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Pulse radiolysis–kinetic absorption spectrophotometry has been employed to study the addition of electrons to acrylic acid and to several of its homologues in aqueous solution as well as spectral properties and subsequent chemical transformations of the electron adducts. Specific rates of reaction of e_{aq}^- with the acid anions at room temperature in units of 10^{10} M^{-1} s^{-1} are acrylate, 0.53 ± 0.05; methacrylate, 0.45 ± 0.4; *trans*-crotonate, 0.13 ± 0.01; β,β-dimethylacrylate, 0.059 ± 0.002; *trans,trans*-sorbate, 0.58 ± 0.03; *trans*-cinnamate, 1.4 ± 0.1. The specific rates of reaction of e_{aq}^- with the corresponding un-ionized carboxylic acids are all in the range (1.5–2.9) × 10^{10} M^{-1} s^{-1}. Spectra of reversibly diprotonated (i.e., uncharged) and monoprotonated (mononegative) electron adducts were characterized for all six acids. The main features of the spectra of the diprotonated adducts are an intense band, λ_{max} ~250–350 nm, ϵ_{max} ~(1–4) × 10^4 M^{-1} cm^{-1}, and a weaker band, λ_{max} ~350–490 nm, ϵ_{max} ~10^3 M^{-1} cm^{-1}. Spectra of the monoprotonated adducts are red shifted ~10–40 nm relative to corresponding diprotonated adducts. The spectrum of the unprotonated (dinegative) adduct could be determined only for cinnamate; it is additionally red shifted ~25 nm. Values of pK_a (radical) for the process $RCO_2H_2\cdot \rightleftarrows RCO_2H\cdot^- + H^+$ fall in the range 5–8 for the six acids; pK_a (radical) for the second dissociation of the electron adduct of cinnamic acid is 11.6. An anomalous spectral change was observed with acrylic acid around pH 5. Decay of the diprotonated electron adducts of all the acids except β,β-dimethylacrylic is second order, $2k$ ~ (1–7) × 10^9 M^{-1} s^{-1}. Decay of the monoprotonated electron adducts of all the acids in the absence of catalytic species is first order, k_{H_2O} ~ (0.1–2) × 10^5 s^{-1}. α-Carbon radicals, $RR'\dot{C}HCO_2^-$, were identified spectrally as the products of irreversible decay of the monoprotonated electron adducts of acrylic, methacrylic, β,β-dimethylacrylic, and crotonic acids; catalysis of the decay process by OH^- was observed for all the adducts except that of cinnamic acid. More detailed investigation of the decay of $CH_2CHCO_2H\cdot^-$ established general acid (Bronsted $\alpha = 0.43 \pm 0.04$) and general base catalysis as well. Electron transfer from the monoprotonated electron adducts of acrylic and crotonic acids to a number of acceptors was studied as a function of $E^{0\prime}$ of acceptor and pH. Spectra of α-carbon radicals generated by addition of H atoms to each of the acids (except cinnamic) at pH ~1 have λ_{max} ~290–300 nm, ϵ_{max} ~450–1800 M^{-1} cm^{-1}, and $2k_{decay}$ ~ (1–2) × 10^9 M^{-1} s^{-1}. Results of these studies are compared with those of a similar investigation involving acrylamide and its homologues.

In a recent communication,[2a] we described two types of protonation reactions of the electron adduct of acrylic acid in aqueous solution. We now report a detailed study of the reactions of electron adducts of several substituted acrylic acids by the technique of pulse radiolysis–kinetic spectrometry.

Pulse radiolytic studies of α,β-unsaturated acids have been reported for acrylic acid,[2,3] benzoic acid,[4] and maleic and fumaric acids.[5] A number of related studies by ESR technique have also been reported. In the reaction of e_{aq}^- with acrylic acid at pH 12,[6] only the C-protonated electron adduct, $CH_3\dot{C}HCO_2^-$, was observed. The electron adducts of a large number of α,β-unsaturated acids produced by the reaction of ammoniated electrons have also been characterized by means of the ESR technique.[7]

An ESR spectrum observed when neat acrylic acid was irradiated with ^{60}Co γ rays at 77 K was attributed to the electron adduct.[8] Exposure of neat acrylic acid to externally generated H atoms under the same conditions gave a product which was identified as the H atom adduct to the β carbon.[9] ^{60}Co γ ray irradiation of acrylic acid at 77 K in frozen solutions in several aprotic solvents, e.g., triethylamine, methyltetrahydrofuran, or 3-methylhexane, gave stable electron adducts, while the species observed in frozen protic solutions was the same as that resulting from addition of H to β carbon.[10] An optical absorption spectrum attributed to the electron adduct of cinnamic acid has also been measured in solution at 77 K in 2-methyltetrahydrofuran.[11]

Experimental Section

Radiolysis of water produces e_{aq}^- along with other species, eq 1.

$$H_2O \longrightarrow e_{aq}^-,\ OH,\ H,\ H_2O_2,\ H_2,\ \text{and}\ H_3O^+ \qquad (1)$$

Hydroxyl radicals were scavenged by the addition of *tert*-butyl alcohol to the solutions, eq 2.

$$OH + (CH_3)_3COH \rightarrow \dot{C}H_2C(CH_3)_2OH + H_2O \qquad (2)$$

$$k_2 = 5.2 \times 10^8\ M^{-1}\ s^{-1}\ (\text{ref } 12)$$

The alcohol radicals formed in reaction 2 are generally unreactive and do not have significant absorption in the wavelength region involved in this work.[13] The contribution of transient species formed from the reaction of H atoms (yield ~20% that of e_{aq}^-) to the net observed spectra and kinetics is considered to be relatively small (see below).

Single pulses of 30-ns duration from a Febetron 705 machine were employed to produce the short-lived electron adducts. The technique employed has been described in detail.[13,14]

Materials. The following chemicals were used as received: Ma-

Table I. Specific Rates of Reaction of Hydrated Electrons

Registry no.	Acid	k, 10^{10} M^{-1} s^{-1} Anion[a]	Undissociated acid[b]
79-10-7	Acrylic	0.53 ± 0.05	2.4 ± 0.1
79-41-4	Methacrylic	0.45 ± 0.04 0.84[c]	1.9 ± 0.1
107-93-7	*trans*-Crotonic	0.13 ± 0.01[d]	1.8 ± 0.2
541-47-9	β,β-Dimethylacrylic	0.059 ± 0.015	1.5 ± 0.1
22500-92-1	*trans,trans*-Sorbic	0.58 ± 0.03	2.9 ± 0.1
140-10-3	*trans*-Cinnamic	1.4 ± 0.12[d] 0.72[c]	2.2 ± 0.1

[a] Uncertainties are mean deviations. [b] Uncertainties are standard deviations. [c] From ref 16. [d] Determined by monitoring both kinetics of decay of e_{aq}^- and of formation of the transient.

theson N_2O and gold label Ar; Mallinckrodt 70% AR $HClO_4$ and *tert*-butyl alcohol; Baker and Adamson AR KOH, NaH_2PO_4, KH_2PO_4, Na_2HPO_4, K_2HPO_4, $Na_2B_4O_7 \cdot 10H_2O$, KSCN, and NH_4Cl; Fisher or G. Frederick Smith $NaClO_4 \cdot H_2O$; G. Frederick Smith $Ba(ClO_4)_2$; Baker and Adamson K_2SO_4; Aldrich Analyzed 99.9+% zone refined *trans*-cinnamic acid.

Eastman or Matheson Coleman and Bell acrylic acid was recrystallized from the melt, distilled twice under ~20 Torr of N_2, and the middle fraction of the distillate recrystallized again from the melt. The resulting crystals were stored in a refrigerator. Purified acid was used to make up solutions for radiolysis for no more than 2 weeks after purification. Eastman or Matheson Coleman and Bell methacrylic acid was purified and handled in the same way as acrylic acid. Aldrich 98% *trans*-crotonic acid was recrystallized from 30–60 °C petroleum ether, mp found 71–72 °C (uncorrected) (lit.[15] 71.5 °C). Aldrich β,β-dimethylacrylic acid was recrystallized twice from petroleum ether, mp found 67.5–68.5 °C (uncorrected) (lit.[15] 70 °C). Eastman sorbic acid was recrystallized twice from ethyl acetate, then once from hot distilled water and dried by storing in a vacuum desiccator, mp found 130–131.5 °C (uncorrected) (lit.[15] 134.5 °C).

Dosimetry. The concentration of electron adducts produced in solution was calculated from measured doses based on $G(e_{aq}^-) = G(OH) = 2.8$. Doses per pulse were calculated from the measured absorbance at 500 nm due to $(SCN)_2^{\cdot -}$ produced upon irradiation of N_2O-saturated 0.04 M aqueous KSCN solutions,[13] taking $\epsilon_{500} = 7600$ M^{-1} cm^{-1}. Initial concentration of e_{aq}^- was usually 3–20 μM, but sometimes as much as 10^{-4} M. Under all conditions, the concentration of the substrates was high enough to scavenge >95% of e_{aq}^-.

Results

Reactivity with e_{aq}^-. The specific rates of reaction of e_{aq}^- with acid anions and undissociated acids are presented in Table I. The solutions were deaerated by sweeping with Ar, contained 0.10 M *tert*-butyl alcohol (10^2–10^3-fold excess over substrate) and were buffered at pH 9.2 with ~1 mM borate. The rates of reaction of the anions were determined by following the decay of absorbance of e_{aq}^- at 700 nm under pseudo-first-order conditions. In two cases, growth of absorbance of the electron adduct was also followed.

Rates of reaction of the undissociated acids with e_{aq}^-, eq 3, could not be measured directly at pH ≤ 3 because of the competition of H_3O^+ for hydrated electrons, eq 4.

$$R_2C{=}CRCO_2H + e_{aq}^- \rightarrow \text{adduct} \quad (3)$$

$$H_3O^+ + e_{aq}^- \rightarrow \cdot H \quad (4)$$

$$k_4 = 2.3 \times 10^{10}\ M^{-1}\ s^{-1} \text{ (ref 16)}$$

Such low pH values are required to keep the acids (pK_a = 4.25–5.15, see Table II) largely undissociated. The rates were determined, however, from experiments based on the competition between reactions 3 and 4. In these experiments, 2–5 mM acid solutions were irradiated at several pH values in the range 2.0–3.7, and the initial absorbance was measured at wavelengths where absorbance was due primarily to the electron adducts. Absorbance values obtained with a given acid decreased with decrease in pH. The ratio of the absorbance at the highest pH to absorbance at the lower values of pH varied linearly with the ratio $(H_3O^+)/(\text{substrate acid})$. The slopes can be shown to be equal to k_4/k_3.[17] With solutions at the lower end of the pH range, a small correction for absorbance by H atom adducts was necessary.[17]

As seen in Table I, rates of reaction of the undissociated acids with e_{aq}^- do not vary with structure as much as those of the anions. With the anions, the most prominent effect is the lowering of reactivity by substitution of β hydrogen by methyl. β-Phenyl increases reactivity of the anion while β-vinyl does not lead to any significant change. As expected, the anions are less reactive than the undissociated acids.

Absorption Spectra of Initially Formed Transient Species. Spectra of initially formed transients were usually

Table II. λ_{max}, ϵ_{max}, pK_a, and Decay Kinetics of Initial Transient Species Produced by Reaction with e_{aq}^-

		Diprotonated electron adduct					Monoprotonated electron adduct			
Acid	pK_a of parent acid[a]	pH	λ_{max}, nm	ϵ_{max}, mM^{-1} cm^{-1}	$2k$, 10^9 M^{-1} s^{-1}	pK_a[e] of radical	pH	λ_{max}, nm	ϵ_{max}, mM^{-1} cm^{-1}	k,[g] 10^4 s^{-1}
Acrylic	4.25	3.7	255	19.	4.0	5.0,[f] 7.0[f]	6.0[f]	265	7.7	4.0
			265[b]	16.				350[c]	1.0	
			350[c]	0.7			9.5	285	9.7	3.0
								350[c]	1.3	
Methacrylic	4.36	3.2	255	14.4	4.0	5.3	9.0	290	4.7	20.
			380	0.8				380[c]	1.0	
Crotonic	4.69	3.8	250	18.	0.7	7.5	10.4	280	11.4	1.0
			400	0.6				380[c]	1.0	
β,β-Dimethylacrylic	5.12	3.8	<255	9.5	(k = 6.0 × 10^3 s^{-1})[d]	8.0	11.0	270	8.8	0.9
								420	0.75	
trans,trans-Sorbic	4.76	4.2	292	33.	2.6	6.4	11.1	320	27.	5.0
								450[c]	0.5	
trans-Cinnamic	4.44	3.7	340	36.	7.2	5.6,[f] 11.6[f]	9.5	375	36.	0.2[h]
			490	1.0				500	2.5	
							13.0	395	37.	8.[i]
								530	4.6	

[a] From ref 15. [b] From ref 2. [c] Shoulder. [d] *first*-order decay. [e] Uncertainties are 0.1–0.2. [f] See discussion of assignment. [g] Extrapolated to zero concentration of buffer and added OH^-. [h] At pH 7.5. [i] Independent of concentration or buffer and OH^-.

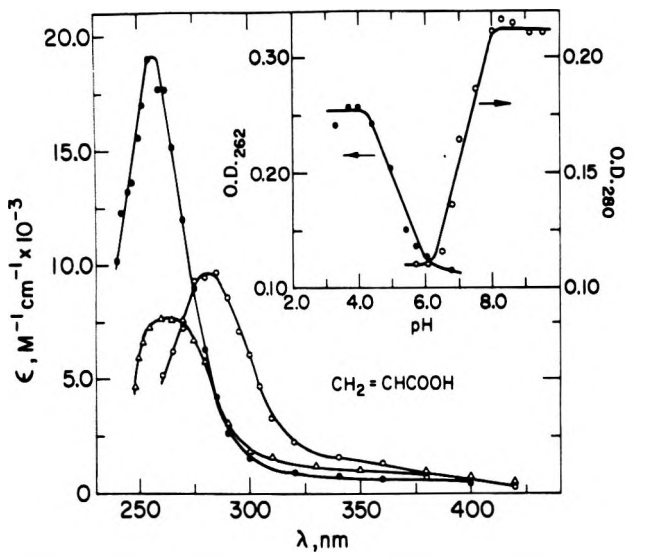

Figure 1. Initial transient absorption spectra produced by the reaction of e_{aq}^- with 2–8 mM acrylic acid at pH 9.5 (O), 6.0 (△), and 3.8 (●) in 1–1.5 M aqueous *t*-BuOH under 1 atm of Ar; dose ~8 krad/pulse. Insert: Change in absorbance with pH at 262 and 280 nm.

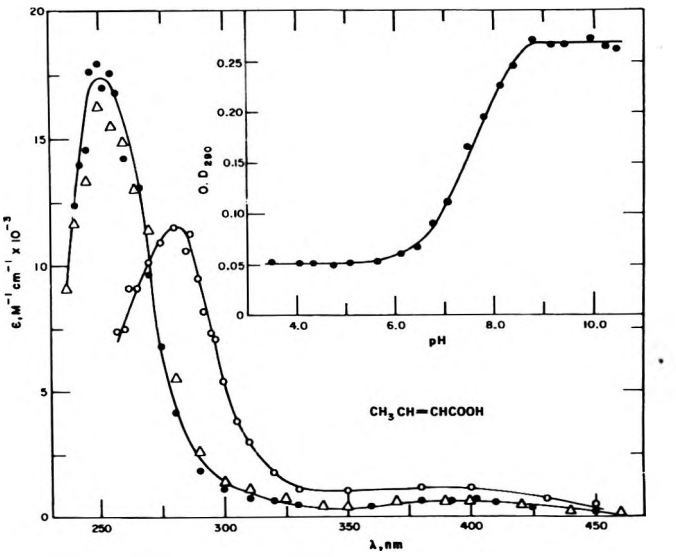

Figure 3. Initial transient absorption spectra produced by reaction of e_{aq}^- with 5 mM *trans*-crotonic acid at pH 9.2 (O), 6.3 (△), and 4.0 (●) in 1.0–1.5 M aqueous *t*-BuOH under 1 atm of Ar; dose ~4 krad/pulse. Insert: Change in absorbance with pH at 290 nm.

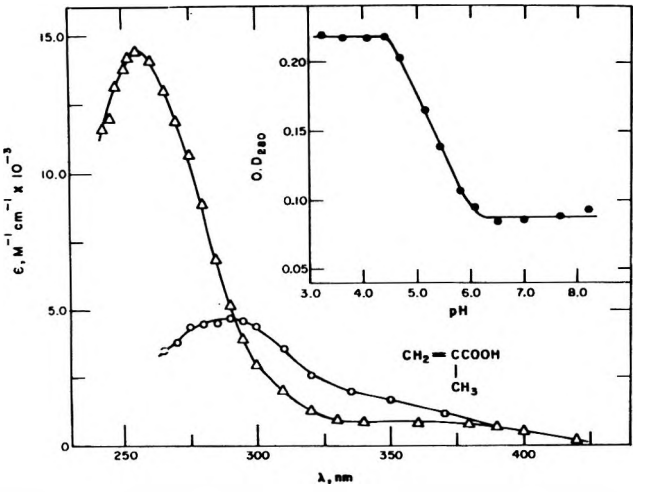

Figure 2. Initial transient absorption spectra produced by the reaction of e_{aq}^- with 3–8 mM methacrylic acid at pH 9.0 (O) and 3.7 (△) in 1.0 M aqueous *t*-BuOH under 1 atm of Ar; dose ~8 krad/pulse. Insert: Change in absorbance with pH at 280 nm.

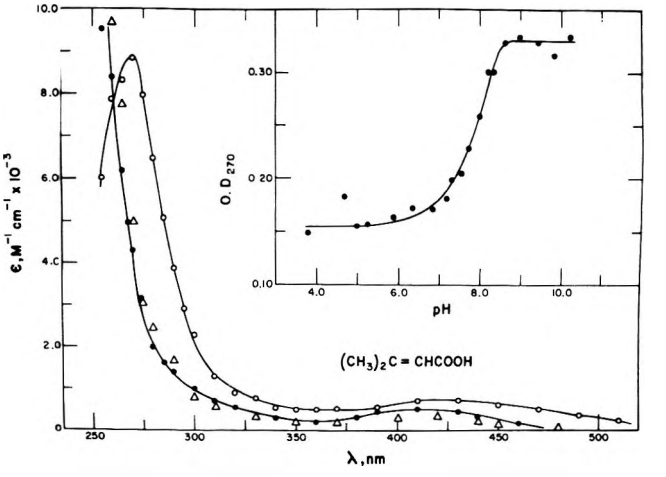

Figure 4. Initial transient absorption spectra produced by the reaction of e_{aq}^- with 5 mM β,β-dimethylacrylic acid at pH 9.7 (O), 6.6 (△), and 3.8 (●) in 1.0 M aqueous *t*-BuOH under 1 atm of Ar; dose ~8 krad/pulse. Insert: Change in absorbance with pH at 270 nm.

measured at pH 3.5, 6.0, 9.5, and 12.2, or similar pH values. Absorbances were either measured "immediately," i.e., ~0.1 μs after the pulse, or were extrapolated to zero time from measurements made up to several μs after the pulse. All spectral measurements were corrected for depletion of substrate. Spectral data are presented in Figures 1–6. pK_a values for the *reversible* protonation of the electron adducts were determined by measuring absorbance of irradiated solutions at a fixed wavelength at several different pH values. The resulting titration curves are shown as inserts in Figures 1–6. Values of λ_{max}, ϵ_{max}, and pK_a of the initial transients formed by electron addition are collected in Table II.

The main features of all the initial transient spectra are a prominent absorption band at short wavelengths, centered ~280–300 nm in most cases, and a relatively weak band ~100 nm to the red of the main band. The main band is shifted to longer wavelengths at higher pH values. Acrylic and *trans*-cinnamic acids gave rise to three distinct transient spectra as pH was varied. The other acids, namely, methacrylic, crotonic, β,β-dimethylacrylic, and sorbic, gave rise to only two distinct spectra. The apparent large difference between the second pK_a of the acrylic acid and *trans*-cinnamic acid radicals is discussed below.

Kinetics of Decay of Initially Formed Transient Species. Kinetic data summarized in Table II were obtained by following change in absorbance as a function of time at several pH values. Kinetics were generally followed to ~80–90% decay of initial transient spectra. Spectra of secondary transients were also characterized.

Acrylic Acid. Decay of the electron adduct of acrylic acid in the pH range 8.2–11.5 was cleanly first order, independent of initial concentrations of e_{aq}^- ($1–2.5 \times 10^{-5}$ M) and acrylic acid (2–5 mM). At pH 8–9 (1 mM borate buffer) the first-order rate of decay was also independent of the ionic strength (0.01–0.10 M $NaClO_4$). At pH above 9, decay rates depended significantly on the concentration of hydroxide ion (see below) and also on the nature and concentration of buffers. The roles of buffer acids and their conjugate bases in these rate effects were determined by varying buffer ratios at constant total buffer concentration and constant ionic strength.[17,18]

The second-order catalytic constant for each active buffer species was evaluated from the linear dependence of the first-order decay constant on the concentration of the active

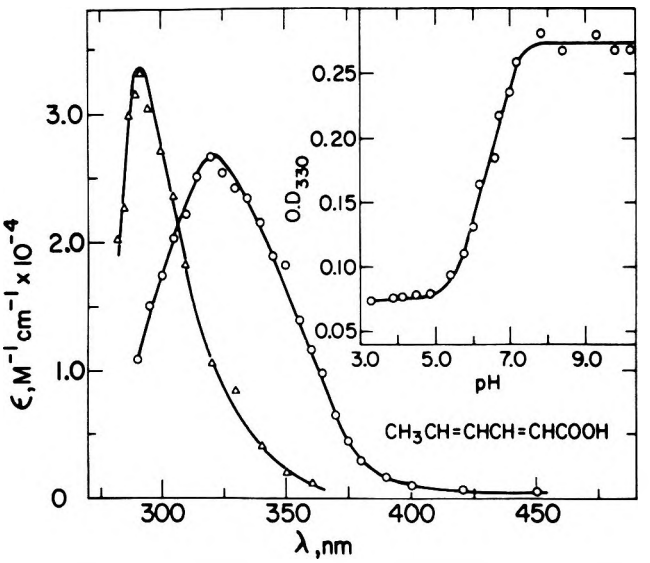

Figure 5. Transient absorption spectra produced by the reaction of e_{aq}^- with 10 mM sorbic acid at pH 9.2 (○) and 3.1 (△) in 1.5 M aqueous *t*-BuOH under 1 atm of Ar; dose ~2 krad/pulse. Insert: Change in absorbance with pH at 330 nm.

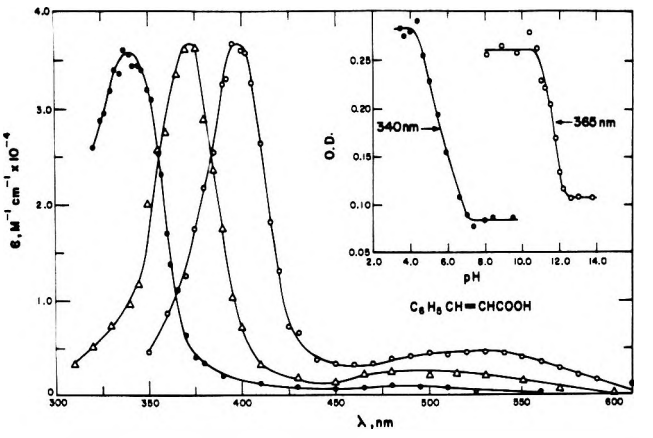

Figure 6. Transient absorption spectra produced by the reaction of e_{aq}^- with 0.2–2 mM *trans*-cinnamic acid at pH 13.0 (○), 9.3 (△), and 3.7 (●) in 1.0 M aqueous *t*-BuOH under 1 atm of Ar; dose ~2 krad/pulse. Insert: Change in absorbance with pH at 340 and 365 nm.

species at constant pH and nearly constant ionic strength. In solutions at pH above 9, and at constant ionic strength and low buffer concentration, the first-order decay rate varied linearly with $[OH^-]$. The second-order catalytic constants for buffer components and OH^- were derived from the slopes of such linear plots and are given in Table III.

The rate constants for the reaction of buffer acids with the electron adduct of acrylic acid adhere to the Bronsted catalysis equation $k_{cat.} = (qK_a/p)^\alpha$ with $\alpha = 0.43 \pm 0.04$.[17]

Primary salt effects on the first-order rate constant for the reaction of the electron adduct with OH^- ions were examined in 1 mM tetraborate buffer at pH 10.5 with the objective of determining the overall charge on the electron adduct, i.e., its state of protonation. Linear plots of log k_{decay} vs. $\mu^{1/2}/(1 + \mu^{1/2})$ were obtained for several inert salts but their slopes depended on the nature of the anion. Thus, the apparent magnitude of the negative charge of the electron adduct calculated from the data for various salts was 2.5 ± 0.4 from experiments with $NaClO_4$, 2.4 ± 0.5 for $Ba(ClO_4)_2$, 1.2 ± 0.3 for K_2SO_4, and 0.8 ± 0.2 for $(n\text{-}Bu_4N)_2SO_4$.

Decay of the electron adduct at pH 6.0, i.e., between its two apparent pK_a values, 5.0 and 7.0, adhered to first-order kinetics, as it did at pH 6.0 and 9.5, while at pH 3.1 its decay was second order (see Table II).

Methacrylic Acid. The initial transient formed by electron addition to methacrylic acid at pH 8–9 was also found to decay by first-order kinetics with the rate independent of radiation dose, initial concentration of the substrate, and pH. As can be seen from Table II, the uncatalyzed first-order rate of decay of the electron adduct of methacrylic acid is considerably higher than that of acrylic acid. Substitution of hydrogen attached to α-carbon atom by a methyl group apparently accelerates decay of the electron adduct.

At higher pH values, viz., 10.1–11.1, the rate was found to be linearly dependent on the concentration of OH^-, with $k = 1.0 \times 10^9\ M^{-1}\ s^{-1}$ (see Table III), a value only slightly higher than for the electron adduct of acrylic acid.

At pH 3.2, the presumably doubly protonated electron adduct decayed completely by a second-order process (see Table II).

***trans*-Crotonic Acid.** At pH 10.4, the electron adduct of *trans*-crotonic acid decayed by a first-order process the rate of which did not change significantly with threefold variation in concentration of the adduct or a 15-fold variation in the concentration of the substrate. As can be seen from Table II, the uncatalyzed first-order rate of decay of the electron adduct is considerably less than that of acrylic acid. In contrast to α-methyl substitution, β-methylation apparently inhibits decay of the radical.

In the pH range 11.1–12.2, the decay rate was linearly dependent on OH^- concentration, with $k = 1.5 \times 10^8\ M^{-1}\ s^{-1}$

Table III. Rate Constants for Reaction of Electron Adducts with Buffer Components[a] and OH^-

Substrate acid	Buffer species	k_μ, $M^{-1}\ s^{-1}$	μ, M	$k_{\mu=0}$
Acrylic	$H_2PO_4^{-1}$	1.6×10^7	0.22	5.7×10^{6b}
	$HP_2O_7^{-3}$	1.4×10^6	0.50	9.1×10^{4b}
	NH_4^+	8.5×10^5	0.10	1.8×10^{6b}
	$B(OH)_3$	2.8×10^5	0.10, 0.50	2.8×10^{5c}
	HPO_4^{-2}	4.0×10^4	0.20	7.0×10^{3b}
	NH_3	$(2.8 \pm 1.0) \times 10^6$	0.10	2.8×10^{6d}
	$B(OH)_4^-$	$(4.9 \pm 1.5) \times 10^5$	0.10	2.3×10^{5b}
	OH^-	$(7.7 \pm 0.3) \times 10^8$	0.026	7.7×10^{8b}
Methacrylic	OH^-	$(1.0 \pm 0.1) \times 10^9$	0.013	8×10^{8b}
trans-Crotonic	OH^-	$(1.5 \pm 0.1) \times 10^8$	0.005–0.022	$\sim 1.2 \times 10^{8b}$
β,β-Dimethylacrylic	OH^-	$(1.9 \pm 0.1) \times 10^7$	0.20	3×10^{6b}
Sorbic	OH^-	$(3.0 \pm 0.2) \times 10^7$	0.005–0.045	$\sim 2 \times 10^{7b}$
trans-Cinnamic	OH^-	$\ll 10^4$	0.1	$\ll 10^4$

[a] All data are at pH greater than first pK_a of electron adducts except for acrylic acid. In latter case pH was greater than apparent second pK_a. [b] Extrapolated to $\mu = 0$ by means of the relationship $\log k = \log k_0 + z_a z_b \mu^{1/2}$, assuming a charge of −1 on every electron adduct. [c] k independent of μ. [d] k assumed to be independent of μ.

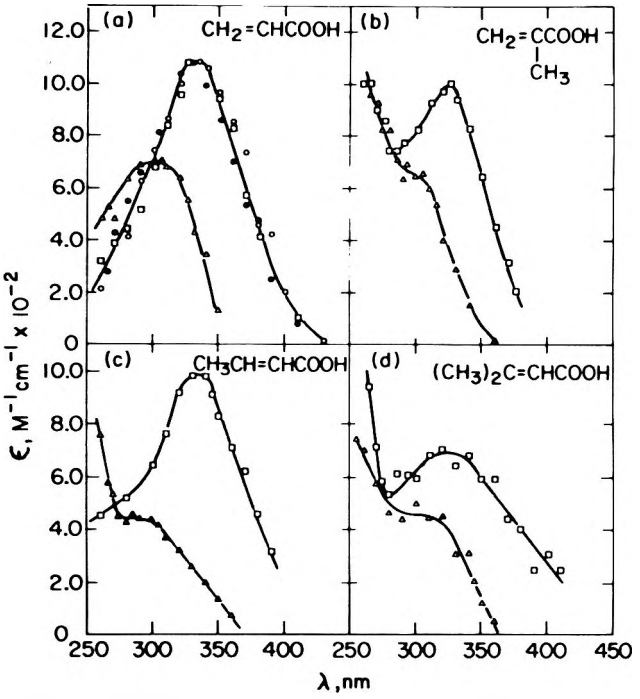

Figure 7. Secondary spectra formed in the decay of electron adducts and primary spectra of H atom adducts of (a) acrylic, (b) methacrylic, (c) crotonic, and (d) β,β-dimethylacrylic acids. Dose per pulse 8–36 krad. (a) 2 mM acrylate, 1.0 M *t*-BuOH, under 1 atm of Ar read 0.2 μs (pH 12.0) (○) and 20 μs (pH 10.0) after the pulse (●); spectrum of $CH_3\dot{C}HCO_2^-$ radical from reaction 5 at pH 9.2 (□); 2 mM acrylic acid, 0.5 M *t*-BuOH, under 1 atm Ar, pH 0.5 (△). (b) 2 mM methacrylate, 1.0 M *t*-BuOH, under 1 atm of Ar, measured at pH 12.2 ~0.2 μs after the pulse (□); 0.4 mM methacrylic acid, 0.4 M *t*-BuOH under 1 atm of Ar, pH 1.0 (△). (c) 5 mM crotonate, 1.5 M *t*-BuOH under 1 atm of Ar, measured at pH 12.9 ~0.2 μs after the pulse (□); 2 mM crotonic acid, 1 M *t*-BuOH, under 1 atm Ar, pH 0.9 (△). (d) 5 mM β,β-dimethylacrylic acid, 1.0 M *t*-BuOH, under 1 atm Ar, measured at pH 13.1, 0.2 μs after the pulse (□); 1 mM β,β-dimethylacrylic acid, 0.4 M *t*-BuOH, under 1 atm Ar at pH 0.7 (△).

(Table III), considerably lower than that for the electron adducts of acrylic and methacrylic acids.

Using the same electrolytes as with acrylic acid [$NaClO_4$, K_2SO_4, and $Ba(ClO_4)_2$], the results of primary salt effect experiments did not help in establishing the state of protonation of the electron adduct at pH 11.6. Results were essentially the same as those described above for the reaction of the electron adduct of acrylic acid with OH^-.

At pH 3.8, the presumably doubly protonated electron adduct decayed via a second-order process (see Table II).

β,β-Dimethylacrylic Acid. At pH 10.0, the uncatalyzed first-order rate of decay of the electron adduct was the same as the corresponding value for crotonic acid (see Table II). In the pH range 11.0–12.2 the rate of pseudo-first-order decay of the electron adduct of β,β-dimethylacrylic acid (measured in the presence of 0.2 M $NaClO_4$) was linearly dependent on $[OH^-]$. As can be seen from Table III, the second-order rate constant for reaction with OH^- is considerably smaller than the corresponding value for crotonic acid.

At pH 3.8, the presumably doubly protonated electron adduct decayed completely by a first-order process (Table II), the chemical course of which was not investigated.

Sorbic Acid. The uncatalyzed first-order rate of decay of the electron adduct differed relatively little from the corresponding value for acrylic acid. The rate of pseudo-first-order decay of the electron adduct of sorbic acid at pH 11.1–12.3 varied linearly with $[OH^-]$. The second-order rate constant for reaction with OH^- (see Table III) is lower than that of acrylic acid by a factor of ~25.

At pH 4.2, the presumably doubly protonated electron adduct decayed by a second-order process (see Table II).

***trans*-Cinnamic Acid.** At pH 10.1 (1 mM tetraborate-buffer), the singly protonated electron adduct decayed by a first-order process considerably slower than the uncatalyzed rate of decay of the electron adduct of acrylic acid. At lower pH values, the decay was slower and followed mixed kinetics. At pH 13.2, the electron adduct of cinnamic acid, i.e., the radical dianion, decayed by a clean first-order process. In the limited pH range available around 13 (radical $pK_a = 11.6$), its decay was not influenced by changes in OH^-, cinnamic acid concentration, or ionic strength. The first-order character of this decay as well as the absence of catalysis by OH^- is discussed below.

The doubly protonated electron adduct at pH 3.7 decayed via mixed kinetics showing a strong second-order component.

Secondary Transient Species and H Atom Adducts. Acrylic Acid. In alkaline solutions, the decay of the initial electron adduct species was found to produce another transient. This was identified as the radical $CH_3\dot{C}HCO_2^-$ by comparison of its spectrum with that generated[1,19] via reaction 5.

$$CH_3CHClCO_2^- + e_{aq}^- \rightarrow CH_3\dot{C}HCO_2^- + Cl^- \quad (5)$$

In Figure 7a spectra of the secondary transient generated under two different conditions are compared with the spectra produced by reaction 5 and by addition of H atoms to acrylic acid. It is apparent that, after normalization at 330 nm, the secondary spectrum observed 20 μs after the pulse at pH 10.0, the spectrum observed 0.2 μs after the pulse under conditions of accelerated decay of the primary transient, i.e., at pH 12.2, and the spectrum produced by reaction 5 at pH 9.2 do not differ significantly. This spectral similarity indicates that protonation at the β-carbon atom takes place during the decay reaction.

The spectrum resulting from addition of H atoms to acrylic acid at pH 0.5 is similar to one which has been reported for the $CH_3\dot{C}HCO_2H$ radical.[19] The shift of λ_{max} to shorter wavelength is consistent with the behavior of a number of radical acid–base pairs.[19]

The decay of the spectra of the secondary transient generated at pH 12.2 and of the H atom adduct generated at pH 0.9 followed second-order kinetics.

Other Acids. The secondary spectra formed from the decay of the electron adducts at pH ~12, as well as the spectra of the H atom adducts of methacrylic, crotonic, and β,β-dimethylacrylic acid at pH ≤1, are shown in Figures 7b–d. The secondary spectra have maxima around 325 nm, with another peak below 260 nm. The spectra of the H atom adducts have a poorly defined band at ~300 nm, with another stronger absorption below ~260 nm. Spectra of H atom adducts were generated under conditions of pH and concentration of the acid substrates such that >99% of e_{aq}^- reacted directly with H^+. From these spectra, one can conclude that decay of the electron adduct results in protonation at the β-carbon atom in these cases.

The secondary spectrum from the decay of the electron adduct of cinnamic acid was very weak, with no characteristic features above 320 nm. The two corresponding spectra of sorbic acid were also weak and featureless above 300 nm.

Oxidation Reactions of the Electron Adducts of Acrylic and Crotonic Acids. The oxidation reactions of the electron adducts of acrylic and crotonic acids with several oxidants of known redox potential were examined by a technique which is described in detail elsewhere.[20] Experiments were done at pH ~3.4, 6.0, and 8–9. The extent of reaction 6 can be represented by the percent electron transfer

$$S\cdot^- + Ox \rightarrow S + Ox\cdot^- \quad (6)$$

Table IV. λ_{max}, ϵ_{max}, and Decay Kinetics of α-Carbon Radicals of Acrylic Acids in Aqueous Solution

	From decay of electron adducts				From H atom adduct			
Acid	pH	λ_{max} nm	ϵ_{max}, M^{-1} cm^{-1}	$2k$, M^{-1} s^{-1} [a]	pH	λ_{max}, nm	ϵ_{max}, M^{-1} cm^{-1}	$2k$, M^{-1} s^{-1} [a]
Acrylic	12.2	330	1100	1.3×10^9	0.9	300	700	2.0×10^9
		335 [b]	950 [b]	1.2×10^9 [b]		300 [b]	700 [b]	2.2×10^9 [b]
Methacrylic	12.2	325	1000	5.7×10^8	1.0	300	600	1.0×10^9
Crotonic	12.9	330	1000	9.3×10^8	1.0	290 [c]	450	1.2×10^9
β,β-Dimethylacrylic	13.1	330	650		0.7	300 [c]	450	1.2×10^9
Sorbic	13.2	380 [d]	~60		0.8	295 [c]	1800	
Cinnamic	13.0	300 [d]	4000					

[a] Mean deviations ~20%. [b] Reference 19 for $CH_3\dot{C}HCO_2^-$ and $CH_3\dot{C}HCO_2H$ radicals. [c] Well-developed shoulder masked by a strong tail absorption. [d] Absorption tail poorly characterized.

where S and $S\cdot^-$ represent the solute and its electron adduct, respectively, while Ox and $Ox\cdot^-$ represent the oxidant and the reduced oxidant.

The maximum absorbance at a characteristic wavelength of the reduced oxidant was measured for a pulse-radiolyzed solution containing an excess of acrylic or crotonic acid (5–10 mM) and a small known concentration of oxidant (0.05–0.1 mM). This absorbance was compared with that produced via reaction 7, taken as 100% reduction.

$$e_{aq}^- + Ox \rightarrow Ox\cdot^- \quad (7)$$

The results are shown in Figure 8. From the middle point of these curves an apparent oxidation potential value for the electron adduct can be derived. The values at various pH's do not differ appreciably, 1.1 ± 0.1 V, and are with reference to two-electron redox potential values of the oxidants.

There is a noticeable difference in the behavior of the electron adducts of acrylic and crotonic acids, Figures 8a and 8b. Whereas the electron adduct of crotonic acid was nearly completely oxidized by oxidants of suitable potential at all pH values, electron transfer from the electron adduct of acrylic acid at pH 6.0 and 8.2 apparently proceeded to only 50–60% of completion.

The results of experiments where the oxidant was maintained the same but where the pH of the solution was continuously varied are shown in Figure 8c. The pK_a values determined from these sigmoidal curves agree well with the values determined directly from the dependence of the absorbance of the electron adduct on pH. The pK_a values obtained in these experiments validates the assumption that protonation equilibria of the electron adducts are established well within the time required for the electron transfer reaction. This assumption is important as a primary objective in doing these experiments was to help determine the number of distinct states of protonation of the electron adducts in question.

The rates of these electron transfer reactions, determined from rates of formation of transient absorption of the reduced oxidants, were generally $\leq 4 \times 10^9$ M^{-1} s^{-1}.

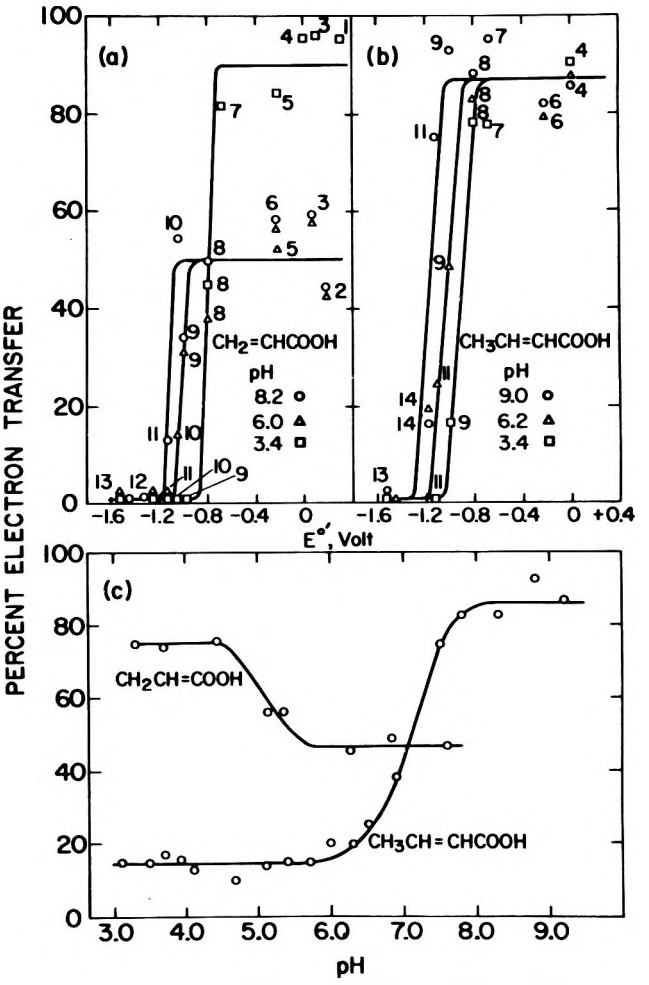

Figure 8. Plot of percent electron transfer from electron adducts of (a) acrylic and (b) crotonic acid to various oxidants vs. $E^{0\prime}$ values for two-electron reduction of the oxidants at various pH values. Solutions contained 10 mM crotonic acid, 1.5 M t-BuOH, and 0.05 mM oxidant or 10 mM acrylic acid, 1.5 M t-BuOH, and 0.1 mM oxidant both under 1 atm of Ar: 1, benzoquinone; 2, 2,5-dimethylbenzoquinone; 3, duroquinone; 4, 2-methyl-1,4 naphthoquinone; 5, 9,10-anthraquinone-1-sulfonate; 6, 9,10-anthraquinone-2-sulfonate; 7, fluorenone; 8, p-cyanoacetophenone; 9, benzophenone; 10, 4,4-dimethoxybenzophenone; 11, 4,4-dihydroxybenzophenone; 12, p-chlorobenzophenone; 13, benzamide; 14, fumaric acid. (c) Variation of percent electron transfer with pH: 10 mM crotonic acid and 0.05 mM benzophenone, or 10 mM acrylic acid and 0.1 mM 2-methyl-1,4-naphthoquinone.

Discussion

Rates of Reaction with e_{aq}^-. The specific rates of reaction of the undissociated acids, $(1.5–2.9) \times 10^{10}$ M^{-1} s^{-1}, are near the diffusion controlled limit. The observed variations of reactivity with structure are similar in sign but smaller in magnitude compared to those observed[18] in the reaction of acrylamides with e_{aq}^-. Rates of the latter reaction are also near the diffusion-controlled limit. The somewhat slower reactions of the acid anions with e_{aq}^- display a larger variation of rate with structure. In all three cases the most prominent effect is deceleration by β-methyl. This effect is an example of the frequently observed systematic dependence upon structure of reaction rates near the diffusion-controlled limit.

Initial Transient Spectra. The main feature in the spectra of the electron adducts is the band at ~300 nm with ϵ_{max} of ~10^4 M^{-1} cm^{-1}. The longer wavelength bands are not well characterized and have a small contribution from the spectra of H atom adducts. Change of initial transient spectra with

pH can reasonably be attributed to rapid reversible protonation of the electron adducts at the oxygen atom.[18] A linear relationship which exists[17] between the reciprocals of the wavelength maxima of the electron adducts and those of the corresponding parent molecules includes the amides,[18] carboxylic acids, and carboxylate anions.

pK_a (Radical) Values. The number of distinct spectra and pK_a values measured is important in the context of spectral assignment. Only for the electron adducts of acrylic and cinnamic acids were two pK_a (radical) values (see Table II) observable. Transients from electron adducts of the other acids gave rise to single pK_a values in the range 5.3–8.0. These pK_a values of electron adducts can be compared with pK_a = 5.3 and 12.0 for the electron adduct of benzoic acid[4] as well as 10.9 and 13.5, respectively, for the last stage of deprotonation of the electron adducts of fumaric and maleic acids.[5] By comparison with these cases, the electron adducts of acrylic acids in this study can be expected to have pK_a values for the last stage of deprotonation above 10. This equilibrium has not been observed for most of the substituted acrylic acids, presumably because the electron adducts undergo fast irreversible protonation at β carbon at pH values above 9.

Thus, the following assignments can be made: (a) the electron adduct spectra around pH 9 are probably those of the *singly protonated* mononegative electron adducts; (b) the spectra around pH 3.5 are probably those of the *doubly protonated* uncharged electron adducts and (c) the spectrum of cinnamic acid at pH 13.2 is that of the *unprotonated dinegative electron adduct.*

These assignments do not account for the three spectra and two pK_a values (5.0 and 7.0) observed with acrylic acid. The origin of these observations is not understood at present. Fessenden and Chawla[5] have presented evidence for the monoprotonated mononegative nature of the electron adduct of acrylic acid at pH 9.5 by measuring the conductance of a solution of acrylate ions at this pH after a pulse of radiation.

Using a generalized formula for the electron adducts, the dissociation equilibria can be represented as

$$R_2CCRCO_2H_2\cdot \underset{pK_a\ 5\text{–}8}{\rightleftharpoons} R_2CCRCO_2H\cdot^- + H^+ \quad (8)$$

$$R_2CCRCO_2H\cdot^- \underset{pK_a\ >10}{\rightleftharpoons} R_2CCRCO_2\cdot^{2-} + H^+ \quad (9)$$

(No attempt is made here to represent delocalization of the odd electron.) Reaction 9 was observed in this work only with cinnamic acid. The rate of reaction 10

$$R_2CCRCO_2H\cdot^- \xrightarrow[\text{or buffer}]{OH^-} R_2CHCRCO_2\cdot^- \quad (10)$$

with all the other monoprotonated radicals is very high. Hence equilibrium 9 cannot be achieved.

Decay Kinetics of Electron Adducts and Formation of β-Carbon Protonated Radicals. The dependence on structure of rate of isomerization of O-monoprotonated (mononegative) electron adducts of the acrylic acids into their β-protonated isomers parallels the behavior of the mononegative electron adducts of the corresponding amides.[18] The trends in both uncatalyzed (Table II) and hydroxide ion catalyzed (Table III) reactions are $k(\alpha\text{-methyl}) > k(\text{unsubstituted}) > k(\beta\text{-methyl})$. These relative reactivities have been discussed previously.[18] Acid catalysis of protonation at β carbon has been observed with the electron adducts of both acrylic amides[18] and acrylic acids. Base catalysis has only been observed with electron adducts of acrylic acids. The magnitude of the Bronsted coefficient, α, characterizing catalysis by oxo acids and NH_4^+ is the same for the electron adducts of acrylamide[18] and acrylic acid. Failure to observe base catalysis of β-protonation of the electron adducts of acrylamides can be ascribed to the relatively low pK_a values of their monoprotonated forms (7–9.5).[18] Presumably base catalysis acts by deprotonation of the functional group which is either concerted with or is rapidly followed by protonation at β carbon, e.g., eq 11.

$$AH + CH_2CHCO_2H\cdot^- + B \rightarrow A^- + CH_3CHCO_2\cdot^- + BH^+ \quad (11)$$

The role of either AH or B, or both, can be played by H_2O. In the special case of the electron adduct of cinnamic acid, the deprotonated dinegatively charged radical is sufficiently stable to be observed directly (Figure 6). The first-order decay of this species, e.g., at pH 13 (Table II), quite possibly involves protonation at β carbon with water functioning as the acid.

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Addition of Thiophenol to Polycyclic Vinylarenes[1]

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The relative rates of the free-radical addition of thiophenol to several vinylarenes have been determined. The reactions were run in benzene at a temperature of 70 °C. A good correlation was found between reactivity and the total energy difference between the reactant olefin and the carbon-centered radical intermediate. The calculations were carried out utilizing a semiempirical self-consistent field molecular orbital method. A variable bond length technique was incorporated into this approach. A much poorer correlation was found utilizing the free valence, calculated by the same method, for the terminal methylene position of the olefin. These results can be interpreted as showing that the transition state for the addition of thiyl radical to a vinylarene has a considerable contribution from a form that resembles the intermediate carbon-centered radical

The reaction between an alkyl or aryl mercaptan and an olefin (eq 1) to yield a sulfide is a well-known example of a free-radical addition process.[2]

$$RCH{=}CH_2 + R'SH \longrightarrow RCH_2CH_2SR' \qquad (1)$$

Its radical nature was based on evidence that included the anti-Markownikoff orientation[3] and the rate enhancement both by light[4] and the peroxides.[5] Such evidence led to the formulation of the chain mechanism[6] shown below.

Initiation: $$R'SH \xrightarrow{k(I)} R'S\cdot + H\cdot \qquad (2)$$

Addition: $$R'S\cdot + RCH{=}CH_2 \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} R\dot{C}HCH_2SR' \qquad (3)$$

Chain transfer: $$R\dot{C}HCH_2SR' + R'SH \xrightarrow{k_{ct}} RCH_2CH_2SR' + R'S\cdot \qquad (4)$$

Polymerization: $$R\dot{C}HCH_2SR' + RCH{=}CH_2 \xrightarrow{k_p} RCH(CH_2SR')CH_2\dot{C}HR \qquad (5)$$

Termination: $$2R'S\cdot \xrightarrow{2k_{t1}} R'SSR' \qquad (6)$$

$$2R\dot{C}HCH_2SR' \xrightarrow{2k_{t2}} RCH(CH_2SR')CH(CH_2SR')R \qquad (7)$$

$$R\dot{C}HCH_2SR' + R'S\cdot \xrightarrow{k_{t12}} RCH(SR')CH_2SR' \qquad (8)$$

One of the interesting aspects of this reaction is the reversibility of the addition step (eq 3). It has been shown that *cis*-2-butene is isomerized to the trans compound by methanethiol.[7] This result contrasts, for example, with the observation that during the addition of trichloromethyl radical to 2-butenes no isomerization of the starting materials is observed.[8] Further, it has been suggested that for reactions in which an unstable alkyl thiyl radical adds to an olefin to give a stable carbon-centered radical, the addition is irreversible.[9] However, evidence for this assertion is not conclusive, and the reaction is generally regarded as a facile, reversible addition followed by a rate-determining chain transfer step.[2b,6,10,11]

Several studies have qualitatively[12] and quantitatively[13-15] indicated that substituents in the olefin moiety which donate electrons to the site of the carbon-centered radical (i.e., that would tend to stabilize the intermediate) enhance the rate of the addition reaction, while electron-withdrawing substituents retard it. This effect has been attributed to a contribution by the charge-separated form (I) to the transition state.[12,15] Such a form represents electron transfer to an electronegative attacking radical that precedes atom transfer and bond formation.

$$R{-}\overset{+}{\underset{H}{C}}{-}CH_2\!:\!\overset{\cdot\ \ -}{SR'}$$

I

It was felt that an interesting, complementary adjunct to the work dealing with the relationship between the reactivity toward thiyl radical and the electronic characteristics of the olefin moiety would be an examination of the correlation of the rates of reaction for a series of compounds with quantities calculated utilizing a semiempirical self-consistent field approach.[16,17] Unruh and Gleicher[17] have demonstrated that this method gives a good correlation between the relative rates of abstraction from arylmethanes by trichloromethyl radical and the π energy difference between the intermediate carbon-

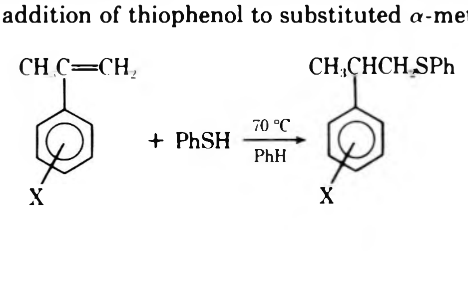
$$ArCH_3 + \cdot CCl_3 \longrightarrow Ar\dot{C}H_2 + HCCl_3 \qquad (9)$$

centered radical and the arylmethane reactant. This result was taken as evidence that the transition state of the abstraction process had considerable productlike character.[18] On the other hand, if a better correlation had been observed utilizing some ground-state property of the reactant—free valence, charge density, etc.—then the transition state might be stabilized to a large extent by a contributing form that resembles the reactants.[19] It was felt that a similar study could be made by doing calculations on the olefin reactant and carbon-centered radical intermediate (eq 3).

Results and Discussion

The technique used for the calculations in this study differed somewhat from that used previously by Unruh and Gleicher.[17] Here, a variable bond length approach has been incorporated into the semiempirical PPPSCF method wherein a new set of bond lengths for the molecule is calculated at the end of each iteration via a linear bond order–bond length relationship.[20,21] These new bond lengths are then used to calculate new values of the repulsion and resonance integrals in the following iteration. Furthermore, the σ energy can be determined using localized-bond models and bond length–bond energy relationships. The total energy is, then, the sum of the carbon–carbon σ and π energies and may more closely reflect the bond length variation observed for "real" molecules than did the earlier method.

The system examined in previous work at this laboratory was the addition of thiophenol to substituted α-methylsty-



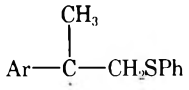
(10)

Table I. Relative Reactivities of Isopropenylarenes toward Thiophenol at 70 °C

Compd (Chart I)	k_x/k_{std}	$\Delta\Delta E_{total}$[a]	F[b]
Phenyl (III)	0.65 ± 0.17[c]	0	0.7816
1-Naph (IV)	0.095 ± 0.01	0.170	0.7859
2-Naph (V)	1.00	0.056	0.7810
9-Anth (VIII)	0.015 ± 0.005	0.507	0.7807
9-Phenanth (IX)	0.033 ± 0.005	0.173	0.7869

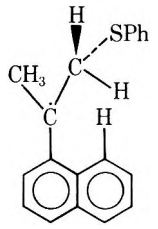
[a] Energy change in eV relative to α-methylstyrene (III). [b] Free valence at the terminal methylene position. [c] Average deviation.

renes at 70 °C in benzene.[15] Originally, it was hoped that a direct extension of this system could be carried out, wherein a series of isopropenylarenes would be allowed to react with thiophenol under the same conditions as before. Two olefins would compete for a limited amount of thiophenol. The relative rates were then to be correlated with either the binding energy differences between the starting olefin and the intermediate free radical (II) or with a ground-state property of the



II

olefin reactant. It is clear from the results in Table I, however, that steric factors are playing a significant role in determining the rate. For any of the compounds with the isopropenyl moiety in a peri position, the rate is lower than expected. This is most likely explained by nonbonded interactions of the type depicted for the structure XII below, where the carbon-cen-



XII

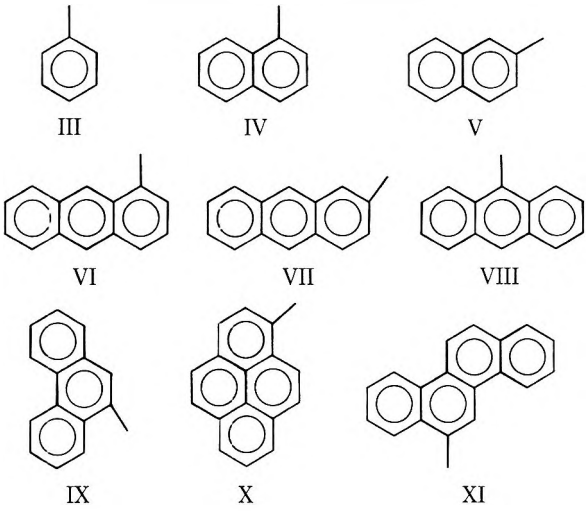
tered radical is forced from planarity, thus decreasing the resonance stabilization of the radical.

Although interesting, these effects cannot easily be quantitatively incorporated into correlations of reaction rates.

$$ArCH{=}CH_2 + PhSH \xrightarrow[PhH]{70\ ^\circ C} ArCH_2CH_2SPh \qquad (11)$$

Therefore, an alternative system was utilized—thiophenol and vinylarenes. Although these olefins might be thought to have a greater tendency to polymerize than do the corresponding isopropenyl compounds,[22] such reactions were not observed

Chart I. Polycyclic Arene Systems



III IV V VI VII VIII IX X XI

under the experimental conditions. However, it was discovered that the more reactive of these former compounds did seem to polymerize under the conditions encountered during the gas–liquid chromatographic analyses of the reaction mixtures. This problem necessitated a modified method of analyzing the reaction mixtures. The technique finally used involved the measurement of the disappearance of thiophenol and standard olefin (*p*-methoxy-α-methylstyrene). The amount of the vinylarene that disappeared was then calculated by assuming that thiophenol reacted only by addition to the olefins. The amount of the vinylarene that had reacted was then set equal to the difference between the amount of reacted thiophenol and reacted reference olefin. The assumption that thiophenol disappeared only by reaction with the olefins was supported by the apparent lack of any phenyl disulfide or ring-substitution products being formed.

As a test of this modified method of analysis, the original data for the addition of thiophenol to substituted α-methylstyrenes[15] were reexamined. A ρ value of -0.36 ± 0.08 was thus obtained from the correlation of reactivity with the σ^+ substituent parameters. This value is in reasonable agreement with the original value of -0.38 ± 0.02, although the greater uncertainty of the ρ value calculated by the modified method is apparent.

Table II shows the results of the competitive addition of thiophenol to vinylarenes, together with several of the calculated quantities utilized in the attempted correlations with the experimental relative rates. Table III lists the results of these correlations. The correlation of reactivity with the relative total binding energy change is shown in Figure 1. The details of the procedure may be found in the Experimental Section. As can be seen from the results, the uncertainty associated with each relative rate is large. This is probably due

Table II. Relative Reactivities of Vinylarenes toward Thiophenol at 70.0 °C

Registry no.	Compd (Chart I)	Solvent	k_x/k_{std}[a]	$\Delta\Delta E_{total}$	$\Delta\Delta E_\pi$[b]	F[c]
98-83-9	Phenyl (III)	Benzene	0.91 ± 0.14[d]	0	0	0.7697
3710-23-4	2-Naph (V)	Benzene	2.5 ± 0.3	0.061	0.044	0.7691
58873-44-2	9-Phenanth (IX)	Benzene	1.8 ± 0.2	0.125	0.099	0.7748
1855-47-6	1-Naph (IV)	Benzene	3.6 ± 0.5	0.140	0.083	0.7716
58873-45-3	6-Chrys (XI)	Benzene	3.5 ± 0.2	0.142	0.118	0.7827
5668-69-9	2-Anth (VII)	Benzene	5.4 ± 1.2	0.167	0.131	0.7691
58873-46-4	1-Anth (VI)	Benzene	5.9 ± 1.5	0.209	0.143	0.7878
58873-47-5	1-Pyr (X)	Benzene	10.5 ± 3.5	0.234	0.098	0.7747
58873-48-6	9-Anth (VIII)	Benzene	1.6 ± 1.2	0.424	0.375	0.7785

[a] The standard olefin was *p*-methoxy-α-methylstyrene. [b] In electron volts. Changes relative to styrene. [c] Free valence at the terminal methylene position. [d] Average deviation.

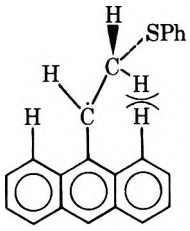
Table III. Correlations between the Reactivities of Vinylarenes and Calculated Quantities[a]

Quantity correlated	Slope	Corr coeff
Total energy change—overall	4.06 ± 0.08[b]	0.932
α-Naphthalene type compds	5.61 ± 0.08	0.944
β-Naphthalene type compds	4.45 ± 0.07	0.972
π-Energy change (SCF)	5.10 ± 0.15	0.730
π-Energy change (HMO)	2.53 ± 0.13	0.858
Total energy change—cation (see discussion)	0.69 ± 0.16	0.802
Free valence	16.7 ± 0.20	0.349

[a] Excluding data for 9-vinylanthracene. [b] Average deviation.

to the indirect method of analysis that was used to determine the rate ratio.

The results seem to indicate that 9-vinylanthracene is much less reactive than would be expected. Apparently, the steric interaction is again more severe in this case. No planar



XIII

structure is possible which will not show a large peri interaction. Le Fèvre et al. have determined that the angle between the plane of the vinyl group and the plane of the anthracene moiety is 60°.[23] Using this conformation to calculate the energies of the olefin and the radical gave a predicted energy change of −0.110 eV relative to styrene. This corresponds to a predicted reactivity that is much lower than is experimentally observed. Such a discrepancy may reflect either the error in the determination of the conformation of 9-vinylanthracene or that the greater dependence of the radical system upon delocalization may lead to a reduction in the deformation angle at the expense of increased nonbonded interactions which are not explicitly incorporated into the molecular orbital treatment.

As can be seen in Table III, the total energy change (relative to styrene) calculated by the variable bond length SCF procedure gives a better correlation than either the SCF π binding energy change alone or the HMO π binding energy. Such results seem to indicate the importance of the σ energy component, as well as the previously observed better correlation by the SCF-MO method over the HMO method.[17]

This correlation of reactivity with the energy difference between the intermediate and the olefin reactant seems to

$$\underset{\text{XIV}}{\text{ArCH}{=}\text{CH}_2\cdot\text{SPh}} \longleftrightarrow \underset{\text{XV}}{\text{ArCH}^{\cdot}{-}\text{CH}_2{-}\text{SPh}} \longleftrightarrow \underset{\text{XVI}}{\text{ArCH}^{+}{-}\overset{\cdot}{\text{C}}\text{H}_2{:}\text{SPh}^{-}}$$

imply a substantial amount of radical character (XV) in the transition state of the addition step. The poorer correlation of the reactivity with the energy difference between the olefin and an intermediate carbonium ion (XVII)[24] may reflect a

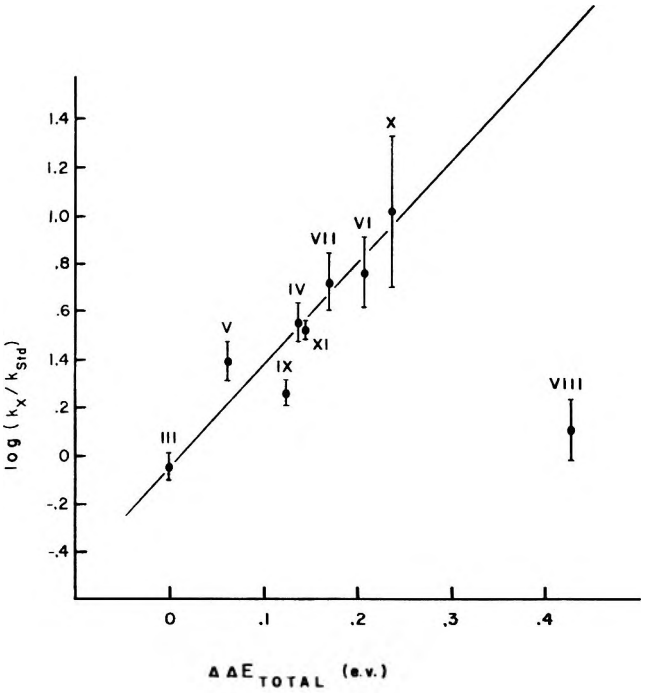


Figure 1. Correlation of log k_x/k_{std} and $\Delta\Delta E_{total}$ for the reaction of vinylarenes with thiophenol.

$$\text{Ar}{-}\underset{+}{\text{CH}}{-}\text{CH}_3$$

XVII

relatively small contribution by the charge-separated form (XVI). The very poor correlation with the free valence certainly is evidence for the lack of any significant stabilization of the transition state by the reactant-like contributing form (XIV). The same was found to be the case when other, appropriate ground-state parameters, such as bond orders or the atom–atom self-polarizability of the terminal carbon, were utilized.

These results indicate a smaller dependence of the rate upon the ability of the arene system to stabilize the transition state of the addition step than was observed earlier for the hydrogen atom abstraction by trichloromethyl radical.[17] This is reasonable in view of the relatively more facile nature of the addition compared to the abstraction process.

Experimental Section

Equipment. NMR spectra were run on either Varian HA-100 or EM-360 spectrometers. Gas–liquid chromatography was done using a Varian Aerograph Model 202B equipped with a thermal conductivity detector and a Sargent recorder with a disc integrator. A 12 ft × 0.25 in. aluminum column packed with 5% SE-30 on Chromosorb W (AW, DMCS) was used for all analyses. Indices of refraction were found using a Bausch and Lombe Abbé refractometer at the indicated temperatures. All melting points were determined on a Mel-Temp apparatus and are uncorrected.

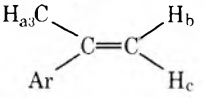
Materials. The purity of all materials, as determined by GLC and/or NMR, was greater than 95%. Reagent grade (Matheson Coleman and Bell) benzene was distilled at 80 °C and dried over sodium wire before use. Reagent grade (Matheson Coleman and Bell) *o*-dichlorobenzene was stored over Linde molecular sieve. No other

Table IV. Summary of Physical Properties and Overall Yields of the Isopropenylarenes[a]

Compd	Bp (Torr) or mp, °C	n_D^{temp}	Yield, %	Ref
1-Naph	bp 85–100 (1) [114–115 (5)]	1.6053^{25} (1.6137^{20})	78	25
2-Naph	mp 52–53 (56)		83	25
9-Phenan	bp 112–116 (0.05) [163 (20)]	(1.6765^{22})	24	27
9-Anth	mp 81–83 (85–86)		13	28

[a] Literature values in parentheses.

Table V. Summary of NMR Data for the Isopropenylarenes in Carbon Tetrachloride[a]



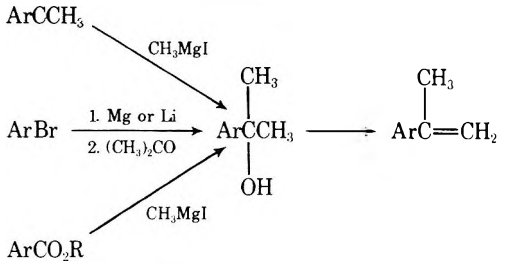
Compd	H_a[b]	H_b[b]	H_c[b]	$H_{aromatic}$
1-Naph	2.16	5.00	5.35	7.10–8.00
2-Naph	2.20	5.10	5.50	7.30–7.80
9-Phenan	2.15	5.10	5.30	7.00–8.50
9-Anth	2.30	5.20	5.70	7.20–8.30

[a] Experimental and calculated proton ratios agree within 5%. [b] Chemical shift from Me_4Si in δ (ppm).

purification was done prior to its use. Commercial α-methylstyrene (Aldrich) was used after distillation at 160–161 °C (760 Torr). Commercial 9-vinylanthracene (Pfaltz and Bauer) was used without further purification. Physical properties and the NMR spectrum can be found in Tables VI and VII, respectively.

All of the isopropenylarenes were prepared by way of an organometallic addition to a carbonyl compound followed by dehydration of the resulting 2-aryl-2-propanol (Scheme I). The 9-isopropenyl-

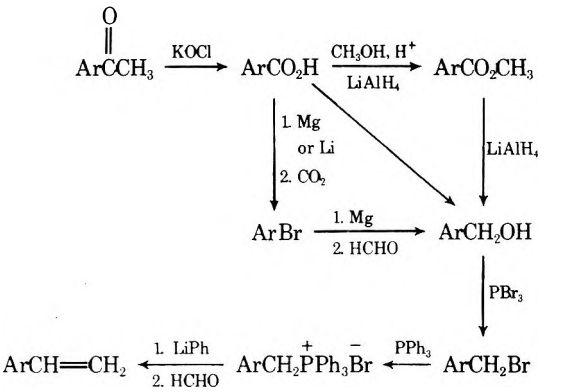
Scheme I



phenanthrene derivative was also prepared via a Wittig procedure starting with 9-acetylphenanthrene. Literature procedures were followed. See Table IV for a summary of the physical properties of the isopropenylarenes, as well as references to their syntheses. Table V contains a summary of the NMR data for these compounds.

Several of the vinylarenes (styrene, 1- and 2-vinylnaphthalene) were synthesized by a similar procedure. However, for many of these compounds, the final dehydration was accompanied by extensive polymerization of the product olefin. Thus, Scheme II was followed

Scheme II



with reasonable success. Literature procedures[29] were followed for all of the reactions except the final step. The preparation of the olefin was carried out by adding an equimolar amount of phenyllithium in ether to a suspension of the phosphonium bromide in tetrahydrofuran. Formaldehyde was then added. Workup then easily yielded pure olefin. Overall yields starting from the acid were on the order of 10–40%. Tables VI and VII summarize physical properties and NMR data, respectively.

Kinetics. The basic procedure has been described previously.[35] An isopropenylarene, 2-isopropenylnaphthalene, thiophenol, o-dichlorobenzene, and benzene were mixed in the ratio of 1:1:1:1:10, respectively. These solutions were then divided between eight Pyrex ampules, degassed, and sealed under low pressure nitrogen. Seven of these tubes were then heated at 70.0 °C, the eighth being retained as the reference sample. Thermal initiation proved to be adequate in this case, and up to 90% reaction occurred after 30 min. Analysis of the reaction mixtures was identical with the method employed in the earlier study.[15]

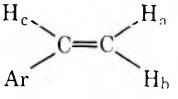
Mixtures containing a vinylarene, p-methoxy-α-methylstyrene, thiophenol, o-dichlorobenzene, and benzene in the approximate ratio

Table VI. Summary of Physical Properties and Overall Yields of Vinylarenes[a]

Compd	Bp (Torr) or mp, °C	n_D temp	Yield, %	Ref
Styrene	bp 100–110 (50) [145–146 (760)]	1.5430^{25} (1.5463^{20})	48	30
1-Naph	bp 79–80 (0.45) [115–116 (4)]	1.6411^{25} (1.6436^{20})	12	31
2-Naph	mp 64–66 (66)		26	32
1-Anth	mp 53–56 (58–61)		4.2	28
2-Anth	mp 185–189 (187–188)		4.7	28
9-Anth	mp 60–63 (64–67)			28
9-Phenanth	bp 140 (0.1) [194–197 (6)]		10	33
1-Pyr	mp 82–84 (87–89)		20	34
6-Chrys	mp 138–140		2.8	

[a] Literature values in parentheses.

Table VII. Summary of NMR Data for the Vinylarenes in Deuteriochloroform[a]



Registry no.	Compd	H_a[b]	H_b[b]	H_c[b,c]	H_{arom}[b]
100-42-5	Styrene	5.16 (J_{ab} = 1)	5.66 (J_{bc} = 18)	6.65 (J_{ac} = 10)	7.00–7.45
826-74-4	1-Naph	5.36 (J_{ab} = 1)	5.65 (J_{bc} = 18)	(J_{ac} = 10)	7.20–7.45
827-54-3	2-Naph	5.25 (J_{ab} = 1.5)	5.75 (J_{bc} = 18)	6.80 (J_{ac} = 10)	7.20–7.70
22584-39-0	1-Anth	5.41 (J_{ab} = 1.5)	5.74 (J_{bc} = 17)	(J_{ac} = 11)	7.10–8.67
2026-16-6	2-Anth	5.40 (J_{ab} = 0)	5.93 (J_{bc} = 17)	6.97 (J_{ac} = 11)	7.40–8.46
2444-68-0	9-Anth	6.00 (J_{ab} = 2)	5.63 (J_{bc} = 17)	(J_{ac} = 11)	7.33–8.50
14134-06-6	9-Phenanth	5.34 (J_{ab} = 2)	5.69 (J_{bc} = 16)	(J_{ac} = 11)	7.01–8.55
17088-21-0	1-Pyr	5.49 (J_{ab} = 2)	5.87 (J_{bc} = 17)	(J_{ac} = 11)	7.48–8.39
58873-49-7	6-Chrys	5.60 (J_{ab} = 2)	6.00 (J_{bc} = 16)	(J_{ac} = 11)	7.20–9.00

[a] Experimental and calculated proton ratios agree within 5%. [b] Chemical shift from Me_4Si in δ (ppm). Coupling constants in hertz in parentheses. [c] Often partially buried in the "aromatic" signal.

of 1:1:1:1:75 were prepared and divided among eight ampules as before. When the vinylarenes were 1-, 2-, or 9-vinylanthracene or 1-vinylpyrene, about 5 mol % benzoyl peroxide was added to seven of the ampules before sealing. This was done because the vinylanthracenes and 1-vinylpyrene all seemed to undergo photoinduced dimerization reactions. The other compounds were all initiated by light. One ampule was always reserved as a reference solution. Seven ampules were then allowed to react at 70.0 °C in a constant-temperature bath for times ranging from 10 to 40 h. From 15 to 80% of the vinylarenes reacted in this period. When photolytic initiation was used, a 275-W sun lamp was placed 10 cm above the tubes in the bath.

The usual calculations of the relative rates[35] were modified in the following manner. The areas of the olefins and thiophenol relative to the internal standard are calculated by

$$X = A/S \tag{12}$$

where X is a relative area, A is an actual measured area, and S is the area of the internal standard. Using the normal method of analysis, the rate ratio is given by

$$\frac{R_1}{R_2} = \frac{\ln\left[\frac{X_1^i}{X_1^f}\right]}{\ln\left[\frac{X_2^i}{X_2^f}\right]} \tag{13}$$

The subscripts refer to olefins 1 and 2 and the superscripts i and f denote unreacted and reacted samples, respectively. If olefin 1 is a vinylarene, the numerator may be calculated as follows

$$\frac{X_1^i}{X_1^f} = \frac{M_1}{M_1 - M_s \cdot \left[1 - \frac{X_s^f}{X_s^i}\right] + M_2 \cdot \left[1 - \frac{X_2^f}{X_2^i}\right]} \tag{14}$$

where the M's are the number of moles of each of the indicated species that were initially weighed out in the preparation of the reaction mixture. Subscripts refer to olefins 1 and 2 and to thiophenol S. Expression 14 is then substituted into eq 13 and the rate ratio is calculated as before.

Acknowledgment. We wish to thank the OSU Computing Center for their generous donation of the computer time necessary for carrying out this project.

Registry No.—Thiophenol, 108-98-5.

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Effect of Acetylene Structure on the Rates and Products of Addition of 4-Chlorobenzenesulfenyl Chloride†

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The rates and products of addition of 4-chlorobenzenesulfenyl chloride to acetylene and 12 alkyl-substituted derivatives have been determined in 1,1,2,2-tetrachloroethane at 25 °C. The effect of the alkyl groups on the rate of addition to 10 of the 13 alkynes can be correlated by means of the Taft equation: $\log k_2 = -4.47\Sigma\sigma^* + 1.64$. The three compounds that do not lie on the line contain *tert*-butyl substituents. Polar effects of the substituents on the rates are dominant and steric effects are important only for *tert*-butyl groups. The product regiochemistry, however, is determined by the steric bulk of the substituent. The results are consistent with a mechanism involving bridged thiirenium ion-like rate and product determining transition states.

The electrophilic addition of arenesulfenyl chlorides to alkynes has received much less attention than the analogous addition to alkenes. The majority of work on this subject has been concentrated on the addition to phenyl-substituted alkynes.[2-4] We now wish to present the results of a systematic study of the polar and steric effects of alkyl groups on the rate and products of addition of 4-chlorobenzenesulfenyl chloride to alkynes in 1,1,2,2-tetrachloroethane at 25 °C.

† Reactions of Sulfenyl Halides and Their Derivatives. 14. For part 13 see ref 1.

Results and Discussion

Effect of Alkyl Groups on the Rate of Addition. The rates of addition of 4-chlorobenzenesulfenyl chloride to acetylene (1) and 12 alkyl-substituted derivatives (2–13) were measured by following the disappearance of the 4-chloro-

Table I. Bimolecular Specific Rate Constants for the Addition of 4-Chlorobenzenesulfenyl Chloride to Alkynes in 1,1,2,2-Tetrachloroethane at 25 °C

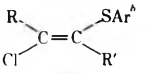
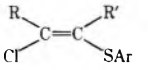
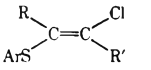
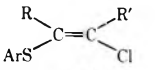
Registry no.	Alkyne	k_2, M^{-1} s^{-1}	k_{rel}
74-86-2	HC≡CH (1)	2.31 ± 0.02 × 10^{-3}	1.0
74-99-7	CH_3C≡CH (2)	0.424 ± 0.002	183
107-00-6	C_2H_5C≡CH (3)	0.993 ± 0.002	429
598-23-2	i-C_3H_7C≡CH (4)	1.52 ± 0.04	658
917-12-0	t-C_4H_9C≡CH (5)	1.02 ± 0.01	442
627-19-0	n-C_3H_7C≡CH (6)	0.912 ± 0.002	394
693-02-7	n-C_4H_9C≡CH (7)	0.961 ± 0.003	416
503-17-3	CH_3C≡CCH_3 (8)	75.9 ± 0.4	3.29 × 10^4
627-21-4	C_2H_5C≡CCH_3 (9)	132 ± 1	5.71 × 10^4
21020-27-9	i-C_3H_7C≡CCH_3 (10)	137 ± 1	5.93 × 10^4
999-78-0	t-C_4H_9C≡CCH_3 (11)	31.8 ± 0.1	1.38 × 10^4
928-49-4	C_2H_5C≡CC_2H_5 (12)	233 ± 1	1.00 × 10^5
17530-24-4	t-C_4H_9C≡C-t-C_4H_9 (13)	0.329 ± 0.003	142

Table II. Cumulative Effect of Methyl and Ethyl Groups on the Addition

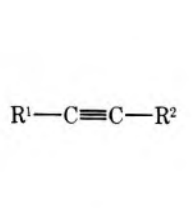
Methyl substituted series	k_{rel}	Ethyl substituted series	k_{rel}	k_{rel}[a]
HC≡CH	1.0	HC≡CH	1.0	1.0
HC≡CCH_3	183	HC≡CC_2H_5	429	274
CH_3C≡CCH_3	3.29 × 10^4 = $(181)^2$	C_2H_5C≡CC_2H_5	1.00 × 10^5 = $(316)^2$	2.08 × 10^4 = $(144)^2$

[a] Data taken from ref 7.

Table III. Kinetically Controlled Product Distribution for the Addition of 4-Chlorobenzenesulfenyl Chloride to Unsymmetrical Alkynes

		Product composition			
					
R	R′	E-M[a]	Z-M[a]	E-aM[a]	Z-aM[a]
CH_3	H (2)	14	0	86	0
C_2H_5	H (3)	10	0	90	0
i-Pr	H (4)	27	0	73	0
t-Bu	H (5)	0	0	100	0
n-C_3H_7	H (6)	16	0	84	0
n-C_4H_9	H (7)	20	0	80	0
CH_3	C_2H_5 (9)	60	0	40	0
CH_3	i-Pr (10)	48	0	52	0
CH_3	t-Bu (11)	12	5	76	7

[a] M = Markownikoff isomer is the one in which the chlorine is bonded to the carbon atom whose Taft inductive substituent constant, σ^*, is the more negative. [b] Ar = 4-ClC_6H_4.



	R^1	R^2		R^1	R^2
1	H	H	8	CH_3	CH_3
2	CH_3	H	9	CH_3	C_2H_5
3	C_2H_5	H	10	CH_3	i-C_3H_7
4	i-C_3H_7	H	11	CH_3	t-C_4H_9
5	t-C_4H_9	H	12	C_2H_5	C_2H_5
6	n-C_3H_7	H	13	t-C_4H_9	t-C_4H_9
7	n-C_4H_9	H			

benzenesulfenyl chloride absorption at 392.5 nm. The stopped-flow technique using a Durrum-Gibson spectrophotometer was used for all the compounds except acetylene, whose reaction was monitored by conventional techniques using a Cary 16 spectrophotometer. The additions were found to follow normal second-order kinetics, first order in both alkyne and sulfenyl halide to 80% completion of the reaction. The second-order rate constants are given in Table I.

From the rate data in Table I it is clear that the substitution of one hydrogen on acetylene by an alkyl group leads to a rate enhancement of several hundred. Replacement of both hydrogens leads to further rate enhancements. The rate constants follow the simple Taft correlation[5] as illustrated in Figure 1. Ten of the 13 points lie on a straight line whose equation is

$$\log k_2 = -4.47\sum\sigma^* + 1.64$$

The remaining three points, for compounds containing *tert*-butyl groups, lie off the line. Such a relationship implies that for methyl, ethyl, and isopropyl substituents, only their polar effects are important in the rate-determining transition state. Steric effects are important only when *tert*-butyl is a substituent. The fact that the point for di-*tert*-butylacetylene is way off the line further supports this view.

In accord with previous findings,[6] the rate of addition to alkynes is slower than to ethylenes. For the two series the rate difference is a maximum for the two parent compounds $k(CH_2$=$CH_2)/k(HC$≡$CH)$ = 2.82 × 10^5. As the hydrogens are progressively substituted by alkyl groups the ratio k_{al}/k_{ac} diminishes. Thus the effect of alkyl substituents is greater upon the rate of addition to alkynes than to alkenes. Such a result is inconsistent with a radical mechanism. Rather it is consistent with the different extent of p character in the carbon atoms of the two bridged ions formed in the addition to alkynes and alkenes. The amount of p character in the carbon atoms is less in the rate-determining transition state for the addition to alkynes. Consequently the carbons are more electronegative and make a greater demand upon the electron-donating alkyl substituents.

Table IV. Observed Carbon-13 Magnetic Resonance Parameters for the Adducts of 4-Chlorobenzenesulfenyl Chloride to Disubstituted Alkynes

Registry no.	Compd		Chemical shifts, δ, ppm[a]					Coupling constants, Hz		
			C_3	C_2	C_1	C_1'	C_2'	C_3'	J_{C_3H}	J_{C_2H}	$J_{C_2'H}$	$J_{C_3'H}$
58866-30-1	$CH_3C(Cl)=C(SAr)CH_3$	*E*		24.48	133.51	124.23	21.65			130.1	129.7	
58866-31-2		*Z*		23.40	133.98	125.69	19.69			129.7	126.6	
58866-32-3	$CH_3C(Cl)=C(SAr)CH_2CH_3$	*E*		24.70	133.63	129.86	27.95	12.09		130.0	130.0	128.5
58866-33-4		*Z*		21.33	134.45	129.88	24.34	12.13				
58866-34-5	$CH_3C(Cl)=C(SAr)CH(CH_3)_2$	*E*		25.23	132.44	133.77	32.65	21.86				
58866-35-6		*Z*		22.22	133.28	134.47	30.22	20.26				
58866-36-7	$CH_3C(Cl)=C(SAr)C(CH_3)_3$	*E*		26.36	133.09	136.05	36.31	30.78				
58866-37-8		*Z*		24.75			34.57	30.29				
58866-38-9	$CH_3CH_2C(Cl)=C(SAr)CH_3$	*E*	12.83	30.83	141.43	123.31	21.66		126.9	129.0	129.4	
58866-39-0		*Z*	12.45	29.94	143.10	125.18	19.28		128.8	128.6	129.4	
58866-40-3	$CH_3CH_2C(Cl)=C(SAr)CH_2CH_3$	*E*	12.84	30.96	141.60	129.66	27.83	12.13				
58866-41-4		*Z*	12.37	29.46	142.88	130.34	24.37	12.18				
58866-42-5	$(CH_3)_2CHC(Cl)=C(SAr)CH_3$	*E*	20.89	33.49	146.71	122.00	20.51					
58866-43-6		*Z*	21.23	31.38	148.15	125.04	18.55					
58866-44-7	$(CH_3)_3CC(Cl)=C(SAr)CH_3$	*E*	29.78	38.56	148.24	123.03	21.57					
58866-45-8		*Z*	29.65	36.34	149.32	123.21	18.58					

[a] Chloroform-*d* solution 45% w/v, internal Me_4Si.

Figure 1. Plot of log k_2 vs. $\Sigma\sigma^*$ for addition of 4-chlorobenzenesulfenyl chloride to alkynes.

The mechanism of the addition of arenesulfenyl chlorides to alkynes has been postulated[2] to involve a bridged rate-determining transition state leading to a thiirenium ion **14** (eq 1). Chloride attack at either ring carbon of **14** results in formation of the adduct (eq 2). The anti stereospecific and

(1)

14

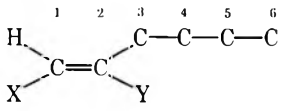
(2)

nonregiospecific addition is consistent with such a mechanism.[2,7] Recently the thiirenium ion **15** has been prepared in liquid SO_2 and its spectral properties have been reported.[8]

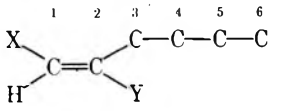
15

The data in Table I support this mechanism. The effect of progressively substituting the hydrogens on acetylene by methyl and ethyl is cumulative as shown in Table II. This indicates that the charge distribution is similar on both acetylenic carbon atoms in the rate-determining transition state, consistent with a bridged ion structure.

Table V. Observed Carbon-13 Magnetic Resonance Parameters for the Adducts of 4-Chlorobenzenesulfenyl Chloride to Terminal Alkynes



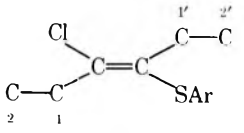
Z



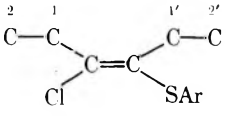
E

		Chemical shifts, δ, ppm					
		C_1	C_2	C_3	C_4	C_5	C_6
X = ArS Y = Cl							
$HC(SAr)=C(Cl)CH_3$	*E*	118.59 d	133.58 s	22.21 q			
$HC(SAr)=C(Cl)CH_2CH_3$	*E*	117.34 d	137.54 s	32.08 t	15.02 q		
$HC(SAr)=C(Cl)CH(CH_3)_2$	*E*	116.58 d	143.19 s	32.14 d	20.23 q		
$HC(SAr)=C(Cl)C(CH_3)_3$	*E*	115.37 d	148.29 s	39.78 s	31.28 q		
$HC(SAr)=C(Cl)(CH_2)_2CH_3$	*E*	116.54 d	139.62 s	37.45 t	27.38 t	14.02 q	
$HC(SAr)=C(Cl)(CH_2)_3CH_3$	*E*	116.48 d	140.24 s	36.34 t	26.88 t	22.31 t	13.88 q
X = Cl Y = SAr							
$HC(Cl)=C(SAr)CH_3$	*E*	119.56 d	129.53 s	18.30 q			
$HC(Cl)=C(SAr)CH_2CH_3$	*E*	119.32 d	130.67 s	29.38 t	14.21 t		
$HC(Cl)=C(SAr)CH(CH_3)_2$	*E*	119.17 d	131.56 s	31.29 d	20.47 q		
$HC(Cl)=C(SAr)C(CH_3)_3$	*E*	120.22 d	135.23 s	36.22 s	30.02 q		
$HC(Cl)=C(SAr)(CH_2)_2CH_3$	*E*	119.34 d	131.08 s	32.43 t	23.11 t	13.78 q	
$HC(Cl)=C(SAr)(CH_2)_3CH_3$	*E*	119.36 d	131.03 s	32.78 t	24.31 t	13.22 q	

Table VI. Observed Proton Magnetic Resonance Parameters for the Adducts of 4-Chlorobenzenesulfenyl Chloride to Disubstituted Alkynes



E



Z

		Chemical shifts, δ, ppm[a]				Coupling constants, Hz		
Compd		H_2	H_1	H_1'	H_2'	$J_{HCC=CCH}$	J_{12}	$J_{1'2'}$
$CH_3(Cl)=C(SAr)CH_3$	*E*		2.42 q	2.04 q		1.5		
	Z		2.21 q	1.82 q		1.0		
$CH_3C(Cl)=C(SAr)CH_2CH_3$	*E*		2.38 t	2.41 ct	1.03 t	1.2		7.0
	Z		2.19 t	2.28 qt	1.04 t	0.6		7.0
$CH_3C(Cl)=C(SAr)CH(CH_3)_2$	*E*		2.32 s	3.52 h'	1.00 d	≤0.4		6.5
	Z		2.15 s	3.42 h'	1.02 d			7.1
$CH_3C(Cl)=C(SAr)C(CH_3)_3$	*E*		2.47 s		1.38 s			
	Z		2.10 s		1.05 s			
$CH_3CH_2C(Cl)=C(SAr)CH_3$	*E*	1.12 t	2.80 qt	2.02 t		0.9	7.75	
	Z	1.15 t	2.50 qt	1.82 t		0.6	7.50	
$CH_3CH_2C(Cl)=C(SAr)CH_2CH_3$	*E*	1.12 t	2.80 q	2.40 q	1.04 t	≤0.7	7.50	7.50
	Z	1.16 t	2.48 q	2.21 q	1.08 t	0.6	7.21	7.26
$(CH_3)_2CHC(Cl)=C(SAr)CH_3$	*E*	1.11 d	3.50 h'	2.05 s		≤0.4	6.90	
	Z	1.15 d	3.67 h'	1.78 s			7.0	
$(CH_3)_3CC(Cl)=C(SAr)CH_3$	*E*	1.43 s		2.05 s				
	Z	1.18 s		1.74 s				

[a] Chloroform-*d* solution, 45% w/v, internal Me_4Si.

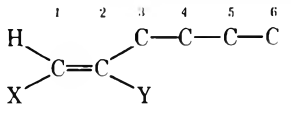
Effect of Alkyl Groups on Product Stereochemistry and Regiochemistry. The addition of arenesulfenyl chlorides to alkynes forms the 1:1 adducts in quantitative yield. No diadducts have ever been observed.[2-4] Previous work has established that the products of the reaction of arenesulfenyl chlorides and phenylacetylenes are formed by stereospecific anti and nonregiospecific addition. Similar results are found in this study based upon the nuclear magnetic resonance spectra of the products.

The kinetically controlled product distribution for the addition of 4-chlorobenzenesulfenyl chloride to the unsymmetrically substituted alkynes is given in Table III. The products of addition to the symmetrically substituted alkynes are those of anti stereospecific addition. No difference in product composition was observed in the presence or absence of oxygen and light.

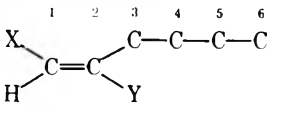
A catalytic amount of gaseous HCl was added to the reaction mixture of the addition to each unsymmetrical alkyne and it was observed that the ratio of Markownikoff to anti-Markownikoff products slowly changed over several weeks. In the absence of added HCl no isomerization was observed. These observations establish that the reaction products are formed under conditions of kinetic control. While HCl catalyzes the isomerization, it also causes decomposition of the products. This decomposition, while not serious initially, makes it impossible to establish the thermodynamically controlled product composition.

The percentage of each product was determined from the integrated area of nonoverlapping peaks in the proton spectrum (either 60 or 100 MHz) immediately after mixing. The products were identified by carbon-13 and proton magnetic resonance spectroscopy. The spectrum of each of the four

Table VII. Observed Proton Magnetic Resonance Parameters for the Adducts of 4-Chlorobenzenesulfenyl Chloride to Terminal Alkynes



Z



E

Registry no.			Chemical shifts, δ, ppm H_1	H_3	H_4	H_5	H_6
	X = ArS; Y = Cl						
58866-46-9	$HC(SAr)=C(Cl)CH_3$	E	6.24 q	2.23 d			
58866-47-0		Z	5.97 q	2.09 d			
58866-48-1	$HC(SAr)=C(Cl)CH_2CH_3$	E	6.23 t	2.39 dt	1.03 t		
58866-49-2		Z	5.99 t	2.16 dt	1.03 t		
58866-50-5	$HC(SAr)=C(Cl)CH(CH_3)_2$	E	6.20 s	3.32 h'	1.08 d		
58866-51-6	$HC(SAr)=C(Cl)C(CH_3)_3$	E	6.24 s		1.34 s		
58866-52-7	$HC(SAr)=C(Cl)(CH_2)_2CH_3$	E	6.22 s	2.4 m	1.5 m	1.00 t	
58866-53-8	$HC(SAr)=C(Cl)(CH_2)_3CH_3$	E	6.23 s	2.4 m	1.6 m	1.4 m	0.98 t
	X = Cl; Y = SAr						
58866-54-9	$HC(Cl)=C(SAr)CH_3$	E	6.31 q	1.95 d			
58866-55-0		Z	6.04 q	1.73 d			
58866-56-1	$HC(Cl)=C(SAr)CH_2CH_3$	E	6.26 t	2.41 dt	1.01 t		
58866-57 2		Z	6.04 t	2.31 dt	1.02 t		
58866-58-3	$HC(Cl)=C(SAr)CH(CH_3)_2$	E	6.11 s	3.29 h'	1.03 d		
58866-59-4	$HC(Cl)=C(SAr)C(CH_3)_3$	E	6.37 s		1.30 s		
58866-60-7	$HC(Cl)=C(SAr)(CH_2)_2CH_3$	E	6.20 s	2.4 m	1.5 m	0.99 t	
58866-61-8	$HC(Cl)=C(SAr)(CH_2)_3CH_3$	E	6.18 s	2.4 m	1.5 m	1.5 m	0.97 t

possible products which can be formed by the addition of 4-chlorobenzenesulfenyl chloride to an unsymmetrical alkyne was obtained in the following manner. The NMR spectrum of the reaction mixture was taken immediately after mixing. The reaction mixture was irradiated to isomerize the *E* to the *Z* isomers and the NMR spectrum was again recorded. Hydrogen chloride was added to a fresh reaction mixture to catalyze the Markownikoff to anti-Markownikoff rearrangement.

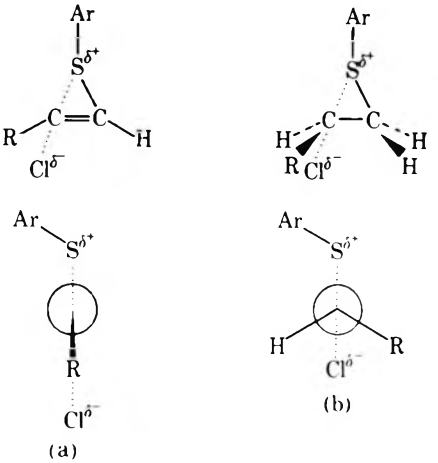
The assignment of peaks in the carbon-13 magnetic resonance spectrum for each regio- and stereoisomer is based upon two well-established relationships.[9] The carbon-13 chemical shifts of carbons attached to a carbon–carbon double bond appear at higher field for the *Z* than for the *E* isomer. Furthermore, the carbon-13 chemical shift for an olefinic carbon is at lower field when bonded to chlorine than to sulfur. Use of these two relationships permitted the assignments of the peaks of the adducts of unsymmetrical disubstituted and terminal alkynes in Tables IV and V, respectively.

Further confirmation of the product regio- and stereochemistry is obtained from their proton magnetic resonance spectra given in Tables VI and VII. The following relationships between adduct configuration and proton chemical shift have been previously observed.[10–13] In Table VI, (1) the chemical shift of protons vicinal to chlorine are observed at lower field relative to those vicinal to the arylthio group, (2) the chemical shifts of γ protons in the *Z* isomers are observed at higher field relative to those in the *E* isomer. These two observations serve to confirm the regio- and stereochemistry of the adducts formed by addition to the unsymmetrically disubstituted alkynes **9–11**.

The proton spectra are not as helpful in distinguishing between the isomers of the products of addition to the terminal alkynes. In Table VII, the same relationship exists between the chemical shifts of the γ protons and the *E* and *Z* configuration of the adducts. However, the position of the vinyl proton does not always follow the usual relationship between adjacent heteroatom electronegativity and chemical shift position. Fortunately, the carbon-13 spectra allow unambiguous determination of product regiochemistry.

The observation that the products of addition to terminal alkynes are predominantly those with anti-Markownikoff orientation clearly indicates that the alkyl groups exert a strong steric effect in the product-determining transition state. The effect of alkyl groups on product regiochemistry is generally more pronounced in the addition to alkynes than in the addition to similarly substituted alkenes.[1] Examination of the product-determining transition states for both reactions, illustrated in Chart I, provides an explanation. In the

Chart I



(a) (b)

product-determining transition state for addition to the alkynes (Chart Ia), the carbon of the substituent, the thiirenium ring, and the chloride ion all lie in the same plane. In contrast, the substituents on the thiiranium ion are above and below the plane containing the chloride ion and the thiiranium ring (Chart Ib). Consequently the steric hindrance between the entering chloride ion and the alkyl substituent is greater in the product-determining transition state for addition to alkynes than for ethylenes.

The regiochemistry of the products of addition to the unsymmetrically disubstituted alkynes is consistent with such steric control. Thus as the size of the substituent increases

from ethyl to isopropyl to *tert*-butyl, the amount of product with Markownikoff orientation decreases.

The addition to 4,4-dimethyl-2-pentyne forms small amounts of products with *Z*-Markownikoff and *Z*-anti-Markownikoff orientation. It is not yet clear if these products are the result of kinetic control or are the result of rapid isomerization of the major products of anti stereospecific addition.

Summary. The data presented clearly establish that alkyl groups have a different effect upon the rates than on the product composition of addition of 4-chlorobenzenesulfenyl chloride to alkynes. In the rate-determining transition state the effect of all of the alkyl groups, except *tert*-butyl, is predominantly polar. In the product-determining transition state, steric effects dominate.

Experimental Section

The alkynes were obtained commercially and their purity was verified by GLC and NMR.

4-Chlorobenzenesulfenyl chloride was prepared as previously described.[14]

1,1,2,2-Tetrachloroethane was purified as previously described.[14]

General Procedures. Ultraviolet Isomerization. A 2% solution of the *E* isomer, in benzene, was irradiated through Pyrex and copper sulfate filter for 40 h. The solvent was removed and the residue was dissolved in $CDCl_3$ and its proton and ^{13}C NMR spectrum recorded. The data are given in Tables IV–VII.

Acid-Catalyzed Isomerization. Anhydrous gaseous HCl was bubbled into a 1 M solution of the reaction mixture in benzene for approximately 1 min. Aliquots were taken from the solution, which was kept at room temperature. The solvent was removed, the residue was dissolved in $CDCl_3$, and its proton and ^{13}C NMR spectrum recorded. The data are given in Tables IV–VII. After several days the solutions began to darken and the NMR spectra indicated extensive decomposition.

Kinetics. Solutions for kinetic runs were prepared in general by direct weighing. The initial concentration of 4-chlorobenzenesulfenyl chloride was in the range $1 \pm 0.1 \times 10^{-3}$ M. The kinetic runs were carried out under pseudo-first-order conditions with a 20–80 times excess concentration of alkyne. When the alkyne was a gas at room temperature, the gas was bubbled into a given quantity of solvent and its concentration was determined by titration with a standard solution of 4-chlorobenzenesulfenyl chloride. The end point was taken as the appearance of the characteristic yellow of the slight excess of sulfenyl chloride. After the kinetic runs, the alkyne concentration was redetermined. No loss of alkyne by evaporation was ever detected.

All kinetic runs except for acetylene were carried out on a Durrum-Gibson stopped-flow spectrophotometer as previously described.[14] Rates of addition to acetylene were measured under pseudo-first-order conditions using the same concentrations of substrates as for the stopped-flow measurements, on a Cary 16 spectrophotometer with an external recorder by means of standard procedures.

Product Compositions. A solution of 0.12 g (0.001 mol) of 4-chlorobenzenesulfenyl chloride in 5 ml of 1,1,2,2-tetrachloroethane (TCE) was added dropwise to a solution containing 0.001 mol of alkyne in 3 ml of TCE at room temperature. The solvent was evaporated in a stream of dry nitrogen to constant weight. The residue, which corresponded to a quantitative yield, was dissolved in $CDCl_3$ and analyzed by NMR.

Analytical samples were prepared by adding a solution of 0.12 g (0.001 mol) of 4-chlorobenzenesulfenyl chloride in 5 ml of methylene chloride to 0.001 mol of alkyne in 3 ml of methylene chloride at room temperature. The solvent was evaporated in a stream of dry nitrogen to constant weight. Attempts to purify the residue by GLC or distillation led to decomposition. Satisfactory elemental analysis for **1–5, 8–10, 12** for C, H, Cl (±0.4%) were obtained directly upon removal of the solvent.

Acknowledgment. Continued financial support from the National Research Council of Canada is gratefully acknowledged. A University of Toronto Special Open Fellowship (1973–1974) and an NRC Postgraduate Scholarship (1974–1976) to Dennis G. Garratt are also very much appreciated.

Registry No.—4-Chlorobenzenesulfenyl chloride, 933-01-7; 1,1,2,2-tetrachloroethane, 630-20-6.

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Halogenated Ketenes. 29. Further Studies on Mixed Dimerizations[1]

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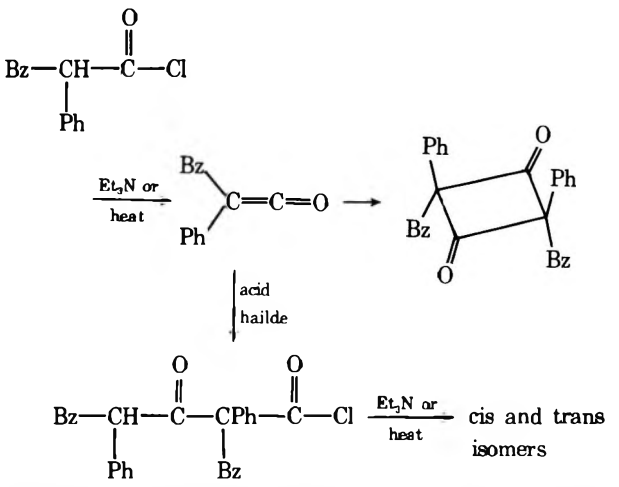
The mixed dimerizations of methylchloro- and *tert*-butylchloroketenes with methyl-*n*-propyl- and methylisopropylketenes resulted in equal amounts of the isomeric cyclobutanediones. *tert*-Butylketene codimerized with methylchloro-, methylbromo-, *tert*-butylchloro-, and *tert*-butylbromoketenes to yield only 2-oxetanone dimers. The β-keto acid chlorides prepared by the addition of α-chloropropionyl chloride and dichloroacetyl chloride to dimethylketene reacted with triethylamine to yield only the corresponding 2-oxetanones.

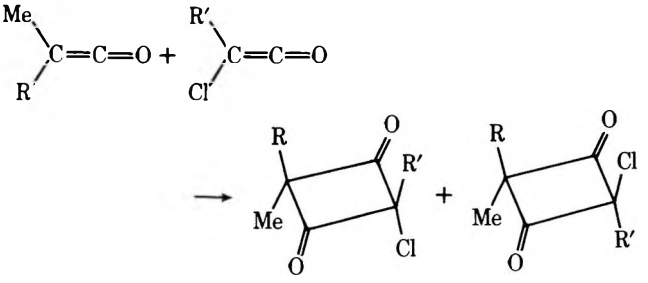
The dimerization of ketenes is regarded as a $[_\pi 2_s + _\pi 2_a]$ concerted process with a high negative entropy of activation and little solvent polarity dependence.[2] One of the ketene molecules participates as a $_\pi 2_s$ component, while the other acts in a normal $_\pi 2_a$ fashion, whereby the transition state involves an orthogonal approach of the reactant molecules.[3]

Dehmlow has recently reported that the thermal dimerization of some isolated unsymmetrical ketoketenes such as phenylmethyl-, benzylmethyl-, and benzylphenylketenes produced *cis*-cyclobutanediones. The same dimerization of benzylphenylketene by the dehydrochlorination of 2,3-diphenylpropanoyl chloride with either triethylamine or by heating above 230 °C produced both *cis*- and *trans*-cyclobutanediones. The proposed mechanism to produce the trans isomer was considered to be through the β-keto acid chloride, 2-benzyl-3-keto-2,4,5-triphenylpentanoyl chloride.[4]



We have previously reported on the mixed dimerizations of halogenated ketenes and nonhalogenated ketenes and would now like to describe some studies concerning the mechanism of formation of these unsymmetrical halogenated cyclobutanediones.[5] A fundamental question to consider was whether or not a concerted cycloaddition was occurring from the two respective ketenes as is the case for isolated ketoketenes or whether the ketenes did not dimerize but rather the cyclobutanediones were formed by the cyclization of an intermediate β-keto acid halide.

The codimerization of certain unsymmetrical dialkylketenes with some haloketenes yielded isomer diones in equal amounts as illustrated. These isomers were distinguished on



I, R = *n*-Pr; R′ = Me
II, R = *i*-Pr; R′ = Me
III, R = *n*-Pr; R′ = *t*-Bu

the basis of the NMR signal in the range of δ 1.48–1.60 for the protons of the methyl group cis to the chloro substituent and δ 1.28–1.36 for the methyl group trans to the chloro substituent (Table I).

Mixed dimerizations of isopropylmethylketene with isopropylchloro- and *tert*-butylchloroketenes were investigated and no evidence of dione or 2-oxetanone was detected. Apparently, the larger substituent retards the dimerization and polymerization predominates. Unfortunately, the stereochemistry in these systems was not as revealing as expected.

In hexane, *tert*-butylketene was generated by the triethylamine dehydrochlorination of 3,3-dimethylbutanoyl chloride. This ketene was unusually stable in the reaction mixture at room temperature, lasting for 2 or 3 days as evidenced by the infrared absorption at 2119 cm^{-1}. Attempts to isolate the ketene were unsuccessful owing to the equilibrium between the ketene and the acid halide and the polymerization of the ketene. Refluxing the reaction mixture for 3 days resulted in a 30% yield of the 2-oxetanone homodimer of *tert*-butylketene.

Codimerization of *tert*-butylketene with halogenated ketenes in situ yielded only 2-oxetanone dimers in moderate to poor yields. Two such 2-oxetanones are possible depending

Table I. Chemical Shifts (δ) of Methyl Protons of Cyclobutanediones

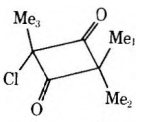
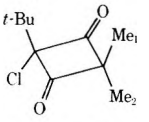
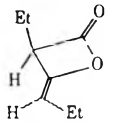
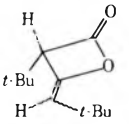
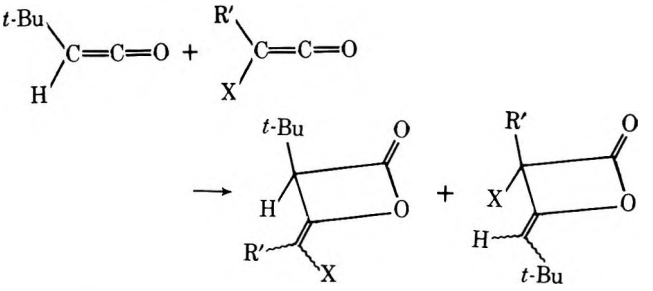
Compd	Me_1 (trans to Cl)	Me_2 (cis to Cl)	Me_3 (gem. to Cl)
	1.36	1.52	1.70
	1.28	1.60	
I	1.36	1.52	1.64, 1.72
II	1.27	1.46	1.60, 1.66
III	1.28	1.56	

Table II. Methyl and Proton Chemical Shifts (δ) of the 2-Oxetanones

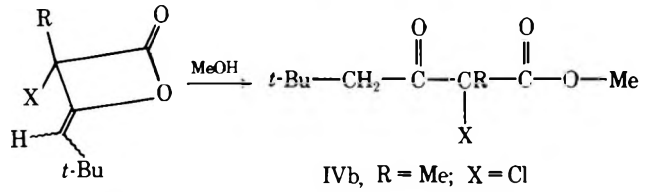
Compd	H(α)	H(vinyl)
	3.88	4.64
	3.74	4.64
IVa		4.84
VIa	3.86	
VIIa	3.80	

upon whether cycloaddition occurs across the carbon–oxygen double bond of the halogenated ketene or the *tert*-butylketene as illustrated. Only one 2-oxetanone was produced in each



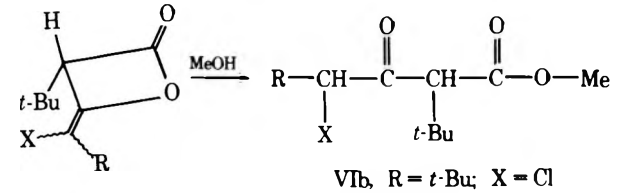
system, but the structure of the dimer was dependent upon the particular alkylhaloketene. The 2-oxetanone exhibited bands in the infrared at 1887–1900, 1828–1835 (C=O), and 1710–1742 cm^{-1} (C=C). The assignment of structure of the 2-oxetanone could be made on the basis of the α proton and the vinyl proton in the NMR. The α protons appeared in the range δ 3.80–3.86 and the vinyl protons in the range δ 4.80–4.85; a comparison of these values with the α proton and vinyl proton of the homodimers of ethyl- and *tert*-butylketenes allowed assignment to be made (Table II).

Methanolysis of the 2-oxetanones was used to confirm the NMR assignments. The distinction was made on the basis of the hydrogen in the NMR. Methyl 2-*tert*-butyl-3-keto-5,5-dimethylhexanoate was synthesized from the 2-oxetanone dimer of *tert*-butylketene with methanol for comparison purposes, and it was found that the γ hydrogen was revealed in the NMR at δ 2.30. Since the β-keto esters produced had values of 2.5 and 4.0, it was apparent that those with a chemical shift of δ 2.5 were derived from a 2-oxetanone which resulted from cycloaddition across the carbon–carbon double bond of the halogenated ketenes. Those β-keto esters with a



IVa, R = Me; X = Cl
Va, R = Et; X = Cl

IVb, R = Me; X = Cl
Vb, R = Et; X = Cl

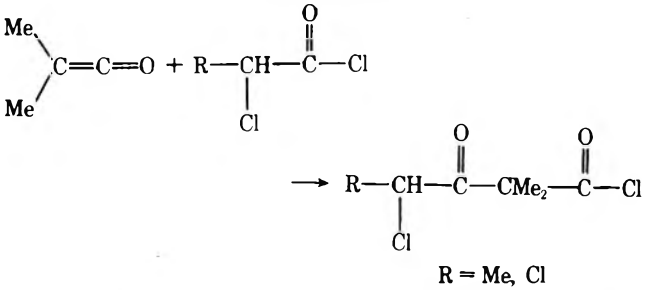


VIa, R = *t*-Bu; X = Cl
VIIa, R = *t*-Bu; X = Br

VIb, R = *t*-Bu; X = Cl
VIIb, R = *t*-Bu; X = Br

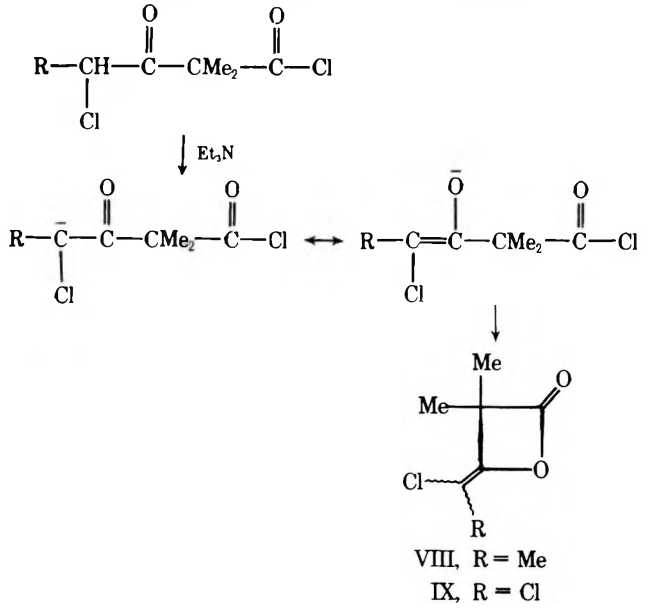
chemical shift of δ 4.0 were derived from the 2-oxetanone which resulted from cycloaddition across the carbon–carbon double bond of the *tert*-butylketene. It was found that for mixed dimerizations of *tert*-butylketene with methylchloro- or ethylchloroketenes, cycloaddition occurred only across the carbon–carbon double bond of the haloketenes. However, for *tert*-butylbromo- and *tert*-butylchloroketenes, cycloaddition occurred only across the carbon–carbon double bond of *tert*-butylketenes.

Since it is known that ketenes will react with acid halides to form β-keto acid halides and that these acid halides can cyclize to form cyclobutanediones, it seemed highly desirable to synthesize some β-keto acid halides. 4,4-Dichloro-3-keto-2,2-dimethylbutanoyl chloride and 4-chloro-3-keto-2,2-dimethylpentanoyl chloride were synthesized by the addition



R = Me, Cl

of dimethylketene to α-chloropropionyl chloride and dichloroacetyl chloride, respectively.[6] These β-keto acid chlorides



VIII, R = Me
IX, R = Cl

were treated separately with triethylamine in benzene under the same conditions as the mixed dimerizations. The 2-oxetanones were produced in both cases with no evidence of the dione dimer. The two 2-oxetanones were characterized by infrared, NMR, mass spectroscopy, and elemental analysis. Apparently, triethylamine abstracts the γ hydrogen to form an enolate anion which can then undergo an intramolecular nucleophilic displacement to form the 2-oxetanone.

Several attempts to synthesize the β-keto acid halide from dimethylketene and 2-chloro-3,3-dimethylbutanoyl chloride were unsuccessful. Also, attempts to isolate the β-keto acid chloride from the reaction mixture of equal molar amounts of α-chloropropionyl chloride, isobutyryl chloride, and triethylamine in benzene resulted in formation of only the α-chlorovinyl ester and the mixed dimer. No evidence of the β-keto acid chloride could be found. Furthermore, the addition of α-chloropropionyl chloride to a solution of *n*-propylmethylketene and triethylamine in benzene resulted in only the formation of the α-chlorovinyl ester and the mixed dimer. No evidence of any β-keto acid chloride could be found.

The dimerization of *tert*-butylketene with methylchloro- or ethylchloroketene resulted in the formation of a 2-oxetanone (IVa and Va) which is the result of cycloaddition across the carbon–carbon double bond of the halogenated ketene. The formation of these 2-oxetanones from the corresponding β-keto acid halide is very unlikely because it would require the haloketene adding to 3,3-dimethylbutanoyl chloride. This is quite unlikely for steric reasons but more importantly because acid halides normally require activation to add to ketenes. Conversely, this aldoketene with *tert*-butylchloro- or *tert*-butylbromoketene formed the 2-oxetanone (VIa and VIIa) whereby the addition occurred across the carbon–carbon double bond of *tert*-butylketene. An examination of the orthogonal [2 + 2] process with molecular models reveals a prohibitive steric interaction between the large *tert*-butyl groups in going from the orthogonal state to the 2-oxetanone. However, the formation of the necessary β-keto acid halides seems quite likely. Consequently, the most likely route to the 2-oxetanone mixed dimer is through the β-keto acid halide intermediate. The mixed dimerizations of *tert*-butylketene appear to be quite sensitive to steric effects, but the [2 + 2] process seems more sensitive than the β-keto acid halide pathway.

Since it is known that 2-oxetanone dimers of ketenes can isomerize to the 1,3-cyclobutanedione dimers, and vice versa, it seemed necessary to demonstrate whether isomerization of any kind was occurring in the reaction mixtures. The 2-oxetanone dimers of the *tert*-butylketene with *tert*-butylchloro- or methylchloroketenes in benzene containing triethylamine, upon refluxing for 24 h, underwent no change. Likewise, the dione dimer of methylchloroketene and *n*-propylmethylketene upon refluxing in benzene containing triethylamine revealed no change. Also, the dimerization was run both with a stoichiometric amount of triethylamine and with an excess of amine. The results were the same in both cases; only 2-oxetanone dimer was produced. Furthermore, the 2-oxetanone dimers in heptane or hexane containing a catalytic amount of sodium methoxide, upon refluxing for 24 h, underwent no change. Consequently, it is concluded that no isomerization occurred under the reaction conditions, and the results obtained actually represent the cycloaddition results.

In conclusion studies with alkylhaloketenes and dialkylketenes revealed only mixed dimers with the dione structure which are believed to be the result of cycloaddition of the two different ketenes. These mixed dimerizations are sensitive to steric effects, as no dimers were obtained when the substituents on the ketenes were bulky such as isopropyl and *tert*-butyl. Conversely, studies with the aldoketene, *tert*-butyl-

ketene, yielded only 2-oxetanone mixed dimers with the alkylhaloketenes with no evidence of the diones. Two different β-keto acid halides were prepared and shown to undergo conversion to the corresponding 2-oxetanones upon treatment with triethylamine. Consequently, it seems that even in the mixed dimerizations, if the two ketenes are ketoketenes the resultant dimers will be of the dione structure, and if one of the ketenes is an aldoketene, then only the 2-oxetanone is produced.

Experimental Section

^{1}H NMR spectra were recorded on a Jeolco PS-100 NMR spectrometer employing tetramethylsilane as an internal standard and CCl_4 as the solvent. All solvents and triethylamine were dried by distillation from sodium. VPC was performed on an F & M Scientific Model 700 gas chromatograph with 10 ft × 0.25 in. columns packed with 10% SE-30 and Carbowax 20M on an acid-washed Chromosorb W (80.000). Dimethylketene was prepared by the pyrolysis of tetramethylcyclobutanedione. The β-keto acid halides were prepared as previously described.[6]

General Procedure for Mixed Dimerizations. To a refluxing solution of 0.1 mol of α-halo acid chloride and 0.1 mol of 2-methylpentanoyl chloride, 2,3-dimethylbutanoyl chloride, or 3,3-dimethylbutanoyl chloride in 150 ml of benzene was added dropwise with stirring 0.25 mol of triethylamine in 20 ml of benzene. The reaction mixture was stirred for 8 h to 2 days and the salt removed by filtration, and then the filtrate was concentrated under vacuum and vacuum distilled.

2-Chloro-2,4-dimethyl-4-*n*-propyl-1,3-cyclobutanedione (I). The mixed dimer of methylchloroketene and *n*-propylmethylketene was obtained after refluxing for 1.5 days in a 57% yield at bp 42–45 °C (0.05 mm); ir 1761 cm^{-1} (C=O); NMR a multiplet centered at δ 1.60 out of which there were four singlets at 1.36, 1.52, 1.64, and 1.72.

Anal. Calcd for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90; Cl, 18.83. Found: C, 57.23; H, 6.87; Cl, 18.62.

2-Chloro-2,4-dimethyl-4-isopropyl-1,3-cyclobutanedione (II). The reaction mixture was refluxed for 2 days and afforded a 42% yield of the mixed dimer of methylchloroketene and isopropylmethylketene: bp 47–50 °C (0.8 mm); ir 1754 cm^{-1} (C=O); NMR four singlets at δ 1.27, 1.46, 1.60, and 1.66 and a multiplet at δ 2.40; mass spectrum parent peak at *m/e* 188.

Anal. Calcd for $C_9H_{13}ClO_2$: C, 57.29; H, 6.70. Found: C, 57.52; H, 6.92.

2-Chloro-2-*tert*-butyl-4-methyl-4-*n*-propyl-1,3-cyclobutanedione (III). The mixed dimer of *tert*-butylchloroketene and *n*-propylmethylketene was obtained after refluxing for 2 days in a 48% yield: bp 64–65 °C (0.25 mm); ir 1754 cm^{-1} (C=O); NMR δ 0.95 (m), 1.15 (s, 9 H), 1.28 (s), and 1.56 (s) out of multiplet, 1.85; mass spectrum parent peak at *m/e* 230.

Anal. Calcd for $C_{12}H_{19}ClO_2$: C, 62.47; H, 8.24; Cl, 15.40. Found: C, 62.67; H, 8.69; Cl, 15.99.

3-Chloro-3-methyl-4-(2,2-dimethylpropylidene)-2-oxetanone (IVa). The mixed dimer of *tert*-butylketene and methylchloroketene was isolated after refluxing for 8 h (32% yield): bp 45–48 °C (0.08 mm); ir, 1887, 1818 (C=O), and 1724 cm^{-1} (C=C); NMR δ 1.18 (s, 9 H), 1.88 (s, 3 H), and 4.84 (s, 1 H).

Anal. Calcd for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90; Cl, 18.83. Found: C, 56.72; H, 6.91; Cl, 18.74.

3-Chloro-3-ethyl-4-(2,2-dimethylpropylidene)-2-oxetanone (Va). The mixed dimer of *tert*-butylketene and ethylchloroketene was obtained by refluxing for 24 h (10% yield). This compound was characterized by ir at 1887, 1773 (C=O), and 1724 cm^{-1} (C=C) and conversion to the methyl keto ester (Vb).

3-*tert*-Butyl-4-(1-chloro-2,2-dimethylpropylidine)-2-oxetanone (VIa). The mixed dimer of *tert*-butylketene and *tert*-butylchlorotene was obtained by refluxing for 2 days (20% yield): bp 54–57 °C (0.1 mm); ir 1923–1852 (broad, C=O) and 1695 cm^{-1} (C=C); NMR δ 1.16 (s, 9 H), 1.32 (s, 9 H), and 3.86 (s, 1 H). This compound was further characterized by conversion to the methyl keto ester (VIb).

3-*tert*-Butyl-4-(1-bromo-2,2-dimethylpropylidene)-2-oxetanone (VIIa). This cycloadduct of *tert*-butylketene and *tert*-butylbromoketene was obtained after refluxing for 2 days (10% yield): bp 77–80 °C (0.15 mm); ir, 1908, 1852 (C=O), and 1681 cm^{-1} (C=C); NMR δ 1.23 (s, 9 H), 1.32 (s, 9 H), and 3.80 (s, 1 H).

Anal. Calcd for $C_{12}H_{19}BrO_2$: C, 52.36; H, 6.91; Br, 29.09. Found: C, 52.10; H, 7.19; Br, 29.14.

General Procedures for Methanolysis of 2-Oxetanones. Methanolysis of the 2-oxetanones from the mixed dimerizations of halogenated ketenes and *tert*-butylketene was accomplished by refluxing for 6–8 h in methanol to give a quantitative yield of the β-keto esters. The esters revealed bands in the ir at 1748 and 1718 cm^{-1} (C=O).

Methyl 2-Chloro-3-keto-2,5,5,-trimethylhexanoate (IVb). The 2-oxetanone derived from *tert*-butylketene and methylchloroketene (IVa) upon methanolysis distilled at 47–50 °C (0.25 mm): NMR δ 1.06 (s, 9 H), 1.52 (s, 3 H), 2.50 (2 s, 2 H), and 3.78 (s, 3 H).

Methyl 2-Chloro-2-ethyl-3-keto-5,5-dimethylhexanoate (Vb). The 2-oxetanone from ethylchloroketene and *tert*-butylketene (Va) gave the methyl ester at bp 65 °C (0.05 mm); NMR δ 0.96 (t) and 1.02 (s) total of 12 H, 2.28 (q, 2 H), 2.50 (2 s, 2 H), and 3.78 (s, 3 H).

Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10; Cl, 15.14. Found: C, 55.92; H, 8.24; Cl, 15.03.

Methyl 2-*tert*-Butyl-4-chloro-3-keto-5,5-dimethylhexanoate (VIb). This methyl keto ester was derived from the 2-oxetanone from *tert*-butylketene and *tert*-butylchloroketene (VIa) and was obtained at 58–60 °C (0.05 mm): NMR δ 1.10 (s, 18 H), 3.64 (s, 1 H), 3.70 (s, 3 H), and 4.0 (s, 1 H); mass spectrum parent peak at *m/e* 262.

Anal. Calcd for $C_{13}H_{23}ClO_3$: Cl, 13.52. Found: Cl, 13.35.

Methyl 4-Bromo-2-*tert*-butyl-3-keto-5,5-dimethylhexanoate (VIIb). This ester was derived from the 2-oxetanone from *tert*-butylketene and *tert*-butylbromoketene (VIIa) and was obtained at 60–65 °C (0.025 mm): NMR δ 1.08 (s, 9 H), 1.12 (s, 9 H), 3.68 (s) and 3.70 (s) total of 4 H, and 4.04 (s, 1 H); mass spectrum parent peak at *m/e* 274.

General Procedure for the Dehydrochlorination of β-Keto Acid Chlorides. To 0.06 mol of triethylamine in 20 ml of benzene was added 0.03 mol of β-keto acid chloride (4-chloro-3-keto-2,2-dimethylpentanoyl chloride or 4,4-dichloro-3-keto-2,2-dimethylbutanoyl chloride) in 5 ml of benzene. After the addition, the reaction mixture was refluxed for about 5 h. The amine salt was removed by filtration and washed with benzene. The solvent was removed by evaporation and the residue vacuum distilled.

3,3-Dimethyl-4-(1-chloroethylidene)-2-oxetanone (VIII). This compound appeared to undergo some decomposition during the distillation. The crude product was characterized by ir, 1887, 1818 (C=O), and 1754 cm^{-1} (C=C); NMR δ 1.48 (so, 6 H) and 2.02 (s, 3 H); mass spectrum parent peak at *m/e* 160.

3,3-Dimethyl-4-(dichloromethylene)-2-oxetanone (IX). This 2-oxetanone was distilled at 37–39 °C (0.24 mm): ir 1890, 1818 (C=O), and 1695 cm^{-1} (C=C); NMR δ 1.52 (s); mass spectrum parent peak at *m/e* 180.

Anal. Calcd for $C_6H_6Cl_2O_2$: C, 39.78; H, 3.31; Cl, 39.23. Found: C, 39.85; H, 3.42; Cl, 38.95.

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.—*trans*-I, 59005-14-0; *cis*-I, 59005-15-1; *trans*-II, 59005-16-2; *cis*-II, 59005-17-3; *trans*-III, 59005-18-4; *cis*-III, 59005-19-5; IVa, 59005-20-8; IVb, 59005-21-9; Va, 59005-22-0; Vb, 59005-23-1; VIa, 59005-24-2; VIb, 59005-25-3; VIIa, 59005-26-4; VIIb, 59005-27-5; VIII, 59005-28-6; IX, 59005-29-7; methylchloroketene, 13363-86-5; propylmethylketene, 29336-29-6; isopropylmethylketene, 59005-30-0; *tert*-butylchloroketene, 52920-17-9; *tert*-butylketene, 59005-31-1; ethylchloroketene, 29264-44-6; *tert*-butylbromoketene, 29264-48-0.

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β Scission of Acyl Radicals in the Radical Decomposition of Various α-Hydroperoxy Ketones[1]

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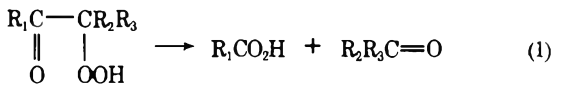
Thermolysis of α-hydroperoxy ketones ($R_1COCR_2R_3OOH$, **1**) at 130 or 250 °C was shown to give mainly carboxylic acids (R_1CO_2H) and ketones ($R_2R_3C{=}O$). Diketones (R_1COCOR_2) accompanied as a minor product (2–20% yield) when $R_3 = ArCH_2$. The redox reaction of $PhCOCPhR_3OOH$ with Fe^{2+} in aqueous MeOH at 25 °C afforded benzil (PhCOCOPh, ~20%) together with ketones ($PhR_3C{=}O$, 80–100%). The addition of $FeCl_3$ to this system afforded R_1CO_2Me (40–65%) and R_3Cl (0–18%) additionally. These results suggest a competitive scission of acyl and benzyl radicals from α-acylalkoxy radical $R_1COCR_2R_3O\cdot$ (**2**). The ligand transfer from $FeCl_3$ leading to R_3Cl and R_1CO_2Me is an evidence for the intermediacy of $R_3\cdot$ and $R_1\dot{C}{=}O$ (e.g., $R_1\dot{C}{=}O \rightarrow R_1COCl \rightarrow R_1CO_2Me$). The product ratios give the order of β scission of radicals from **2** at 25 and 250 °C: $i\text{-Pr}\dot{C}{=}O > Me\dot{C}{=}O > Ph\dot{C}{=}O \gg PhCH_2\cdot$. The scission of benzyl radicals showed a substituent effect of ρ (with σ^+) = −1.11 (70% MeOH, 25 °C) and −0.54 (vapor phase, 250 °C).

α-Hydroperoxy ketones (**1**) are intermediates in the autoxidative cleavage of ketones to carboxylic acids and carbonyl



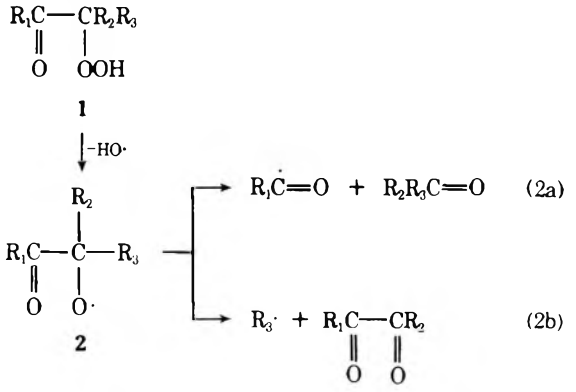
$$R_1C(=O)CR_2R_3(OOH) \longrightarrow R_1CO_2H + R_2R_3C{=}O \qquad (1)$$

1

compounds.[2] The decomposition of **1** in alkaline media has been shown to proceed mainly via an acyclic C=O addition mechanism[3a] rather than a cyclic dioxetane mechanism.[3b] On the other hand, the thermal decomposition of **1** proceeds homolytically,[4] but is complicated because of competitive acid-catalyzed heterolysis.[4a,5] Our previous report[6] described the thermal and redox decomposition of two typical peroxides, **1a** and **1c**, to proceed via the O–O homolysis followed by a facile scission of benzoyl radical. Here, we extend the study to various types of **1** to see the structural effects on the β scission of acyl radicals.

Results and Discussion

α-Hydroperoxy ketones (**1**) were decomposed under three conditions: (1) vapor phase thermolysis (thermolysis GLC) at 250 °C; (2) thermolysis in chlorobenzene at 130 °C; (3) redox reaction with $FeSO_4$ or $FeSO_4$–$FeCl_3$ in 70% MeOH at 25 °C. In every case, the decomposition of **1** affords products which suggest a formation of α-acylalkoxy radical (**2**) followed by the β scission of acyl (eq 2a) or alkyl radical (eq 2b) as reported previously.[6]



$$R_1C(=O)CR_2R_3(OOH) \xrightarrow{-HO\cdot} R_1C(=O)C(R_2)(R_3)(O\cdot) \longrightarrow R_1\dot{C}{=}O + R_2R_3C{=}O \qquad (2a)$$

2

$$\longrightarrow R_3\cdot + R_1C(=O)CR_2(=O) \qquad (2b)$$

Thermolysis GLC. A small amount (~4 μl) of a 0.01 M benzene solution of **1** was injected into GLC (injection temperature 250 °C, carrier gas N_2) and products were analyzed. Since the solvent vaporizes immediately after the injection, the decomposition of **1** occurs practically in vapor phase.[7] Similar results were obtained with the injection temperature of 180 or 290 °C.

Major products are ketone and carboxylic acid as shown in Table I. Peroxides with R_1 = Ph afford 4–16% yields of biphenyl and peroxides with $R_3 = ArCH_2$ give diketones in 2–22% yields. Interestingly, the yields of α-hydroxy ketones were quite poor (<2%).

The yield of biphenyl was not changed by a tenfold increase of the amount of **1a** in benzene, but reduced to zero when toluene or alcohols were used in place of benzene. In the case of toluene, there appeared typical products from the hydrogen abstraction of methyl, i.e., bibenzyl and benzyl alcohol. Hence, biphenyl is formed by a radical pathway:

$$Ph\dot{C}{=}O \xrightarrow{-CO} Ph\cdot \xrightarrow{PhH} Ph_2 \qquad (3)$$

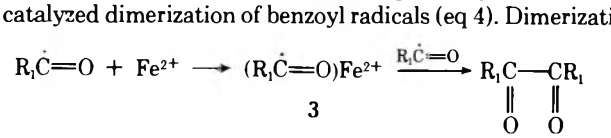
The same reaction of $Ph\dot{C}{=}O$ is known in liquid phase.[8]

The formation of diketone via eq 2b was observed only when $R_3 = ArCH_2$. An alternative pathway via the dimerization of acyl radicals is excluded by the fact that benzil was not detected even by a tenfold increase of the amount of **1a**.

Thermal Decomposition in Chlorobenzene. Thermal decomposition in chlorobenzene at 130 °C afforded a similar result to that of the thermolysis GLC. Benzil was formed only with $R_3 = ArCH_2$ and α-hydroxy ketones were obtained in a yield less than 5% (Table II). The decomposition in chlorobenzene is much faster than that in xylene, which seems to be a typical solvent effect for radical decomposition.[9] However, the homolysis cannot always be a main reaction, since an alternative acid-catalyzed decomposition of **1** is also probable.[5,10]

Redox Reaction. When **1** with R_1 = Ph was reduced by ferrous ion in 70% aqueous MeOH at 25 °C, benzil (~20%) was accompanied by ketones $R_2R_3C{=}O$ (80–100%) (Table III). α-Hydroxy ketones were also a minor product (<1%). In contrast, the reduction of cumene hydroperoxide afforded cumyl alcohol as a main product (Table III), and similar results were reported for other hydroperoxides.[11]

The formation of benzil proceeds probably via the Fe^{2+}-catalyzed dimerization of benzoyl radicals (eq 4). Dimerization



$$R_1\dot{C}{=}O + Fe^{2+} \longrightarrow (R_1\dot{C}{=}O)Fe^{2+} \xrightarrow{R_1\dot{C}=O} R_1C(=O)CR_1(=O) \qquad (4)$$

3

of $R_1\dot{C}{=}O$ is apparent, since **1a** and **1b** gave benzil and *p,p'*-dimethoxybenzil, respectively, and since their yields were almost reduced to zero by the addition of $FeCl_3$ (Table IV). The assumption of a metastable complex **3** is based on the fact that the yield of benzil was constant even when **1** was dropped

Table I. Pyrolysis GLC (250 °C) of α-Hydroperoxy Ketones (1)[a]

	$R_1C(=O)CR_2R_3$				Products, %[a]				
	R_1	R_2	R_3	Solvent	$R_2R_3C{=}O$	R_1CO_2H	Ph_2	R_1COCOR_2	Others
1a	Ph	Ph	Ph	PhH	98	78	5	0	
				PhMe[b]	99	79	0	0	$(PhCH_2)_2$, 7%; $PhCH_2OH$, 7%; PhCHO, 17%
1b	*p*-MeOPh	Ph	Ph	PhH	100	*c*	0	0	
1c	Ph	Ph	$PhCH_2$[d]	PhH	95	80	6	5.4	
1d	Ph	Ph	*p*-ClPhCH$_2$	PhH	90	74	4	4.2	
1e	Ph	Ph	*p*-MePhCH$_2$	MeOH	62	*c*	0	5.0	
1f	Ph	Ph	*p*-MeOPhCH$_2$	PhH	55	68	5	7.9	
1g	Ph	Ph	PhCH(Et)	MeOH	87	*c*	0	21.8	PhCH(Et)OH, 5.7%; α-HO ketone,[e] 2%
1h	Ph	Ph	*i*-Pr	PhH	69	*c*	16	0	
1i	Me	Ph	$PhCH_2$	MeOH	71	*c*	0	1.7	α-HO ketone,[e] 2%
1j	*i*-Pr	Ph	$PhCH_2$	MeOH	74	*c*	0	6.3	α-HO ketone,[e] 1%

[a] Ca. 4 μl of a 0.01 M solution was injected into GLC (injection temperature 250 °C, column temperature 80–250 °C, carrier gas nitrogen). Ph = C_6H_5 or C_6H_4. Yields are averages of two to six runs. [b] Data from ref 6. [c] Not determined. [d] Yields were the same when tenfold of the solution was injected. [e] The corresponding α-hydroxy ketone.

very slowly or added in one portion in an open flask. Since the reaction of hydroperoxides with ferrous ion is very fast[12] and completed within 1 min, the yield of benzil, without assuming the intermediacy of **3**, should be decreased by the slow dropping in air, which was not the case. A similar complex has been isolated or suggested for other radicals.[13]

The formation of acyl radical (eq 2a) was confirmed by the redox reaction of **1** with $FeSO_4$–$FeCl_3$ (Table IV). The presence of $FeCl_3$ reduced the benzil formation and instead produced methyl benzoate probably via a sequence

$$R_1\dot{C}{=}O \xrightarrow{FeCl_3} R_1COCl \xrightarrow{MeOH} R_1CO_2Me \qquad (5)$$

The β scission of benzyl radicals (eq 2b) when $R_3 = ArCH_2$ was likewise ascertained by a ligand transfer reaction:

$$R_3\cdot \xrightarrow{FeCl_3} R_3Cl \qquad (6)$$

The ligand transfer of halogen to a carbon radical is well known.[14]

Mechanism. A main reaction for the thermolysis of **1** can be written as a radical sequence as follows:

$$R_1C(=O)CR_2R_3 \longrightarrow R_1C(=O)CR_2R_3 + HO\cdot \qquad (7)$$

(**1** → **2**)

$$\mathbf{2} \longrightarrow R_1\dot{C}{=}O + R_2R_3C{=}O \qquad (8)$$

$$R_1\dot{C}{=}O + \mathbf{1} \longrightarrow R_1CO_2H + \mathbf{2} \qquad (9)$$

This radical chain decomposition mechanism is based on the following facts: (1) much faster decomposition in chlorobenzene than that in xylene or toluene.[9] (2) The high quantum yield of 2–4 observed for the photolysis of **1a** or **1c**.[10] (3) Trapping of $R_1\dot{C}{=}O$ by $FeCl_3$ (eq 5). (4) Formation of high yields of R_1CO_2H. A very low yield of α-ketol shows that the β scission of **2** (eq 8) is much faster than the hydrogen abstraction from solvent, etc. The major products, ketone and carboxylic acid, can be explained by the chain sequence (eq 8 and 9). Reaction 9 is an induced decomposition (SH2 reaction on O–O) of **1** with acyl radical. The induced decomposition of hydroperoxides[15] and the SH2 reaction of $Ph\dot{C}{=}O$ with peroxide[16] are known.

A minor reaction for the thermolysis of **1** is eq 10 and 11 in place of eq 8 and 9.

$$\mathbf{2} \longrightarrow R_3\cdot + R_1C(=O)CR_2 \qquad (10)$$

$$R_3\cdot + \mathbf{1} \longrightarrow R_3OH + \mathbf{2} \qquad (11)$$

This propagation is operative only when R_3 = benzyls, R_3OH being detectable (6%) for the case of **1g**. Radical $R_3\cdot$ is also trapped by $FeCl_3$ (eq 6).

The redox reaction of **1** with Fe^{2+} seems to be the same as the well-known process for other hydroperoxides.[17]

$$\mathbf{1} + Fe^{2+} \longrightarrow \mathbf{2} + (HO\cdot)Fe^{3+} \qquad (12)$$

This is followed by the competitive reactions, 8 and 10, and then by a ligand transfer reactions 4, 5, and 6.

β-Scission Reaction. The β scission of *tert*-alkoxy radicals has been established[11,18] and previous reports include the information on the scission of halomethyl,[18a,h] alkoxymethyl,[18h,i] alkoxycarbonyl,[18h,i] and acyl radicals.[19] The present results of low-yield formation of α-ketols (mostly <1%) shows that β scission reactions 8 and/or 10 are over 100-fold faster than the hydrogen abstraction of **2** from the solvent. The relative β-scission reactivities can be obtained

Table II. Thermal Decomposition of 1 in Chlorobenzene at 130 °C for 2 h[a]

Peroxide	Atmosphere	Products, %[b] R_1CO_2H	$R_2R_3C{=}O$	$R_1C(=O)CR_2R_3(OH)$	$PhC(=O)CPh(=O)$	Others[c]
1a	Air	92	99	<1	0	
1a	N_2	76	99	<1	0	
1c	Air	80	71	4.6	1.1	$(PhCH_2)_2$, 1.4%
1c	N_2	82	74	1.8	1.7	$(PhCH_2)_2$, 1.2%
1f	N_2	85	54	4.2	1.3	
1d	N_2	88	67	1.5	0	
1h	N_2	94	99	<1	0	

[a] Reaction with [1] = 0.01 M. [b] Determined by GLC. [c] The other minor products (<1%) were not determined.

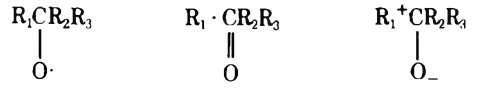
Table III. Reaction of 1 with Fe^{2+} in 70% MeOH at 25 °C[a]

Peroxide	Products, %[b] $R_2R_3C{=}O$	$R_1C(=O)CR_1(=O)$	$R_1C(=O)CR_2R_3(OH)$
1a	95	17[c]	<1
1b	92	17[c]	<1
1c	81	20[c]	<1
1h	100	21[c]	1.3
1i	102	[d]	<1
1j	104	[e]	<1
$PhCMe_2OOH$[f]	12[g]		69[h]

[a] Reaction with [1] = 0.01 M and $[FeSO_4]$ = 0.1 M under air. [b] Determined by GLC after extraction with $CHCl_3$. R_1CO_2H was not determined. [c] According to eq 4, this value should be duplicated. [d] Biacetyl was not determined. Another diketone MeCOCOPh was produced in 0.79% yield. [e] Diketone *i*-PrCOCOPh of 0.36% yield was detected. [f] Cumene hydroperoxide. [g] Acetophenone. [h] Cumyl alcohol.

from the product ratios (Table V). The scission of acyl radicals is much faster than that of benzyl or *tert*-butyl radical, the latter being the fastest one thus far known.[18d] There is not a large difference between the relative scissions in 70% MeOH at 25 °C or in vapor phase at 250 °C.

Polar effect in the β scission has been established and its transition state may be written as **4a–c**.[18d,e]



4a **4b** **4c**

Acyl radicals are σ radicals and stabilized by the resonance with lone pair electrons of carbonyl oxygen.[20] The observed order of *i*-PrĊ=O > MeC=O > PhC=O reflects probably the polar effect, i.e., the order of electron-releasing power (see **4c**). The lowest reactivity of PhĊ=O among the acyl radicals is comprehensible since the radical is not stabilized by the resonance with phenyl.[20] The fast scission of acyl radicals is rational in view of the stability of acyl radicals and their easy formation from aldehydes.[21,22] Moreover, the scission of acyl radical would be facilitated by the polar contribution such as **4c** (R_1 = acyl), since acyl cations are stable carbonium ions[23] and acyl radicals have a nucleophilic character.[20b,24]

Finally, the relative scission of substituted benzyl radicals was obtained from product ratios (Table VB) and correlated with σ^+ to give a negative ρ value. This effect is also explicable by the resonance contribution of **4c** for the β scission. The ρ value of −1.11 in 70% MeOH at 25 °C agrees well with the value of −1.04 from hypochlorite decomposition in CCl_4 at 25 °C.[18d]

Experimental Section

Materials. Starting ketones for **1d,e,f** were obtained from deoxybenzoin and the corresponding benzyl chlorides by the literature method.[25] A starting ketone for **1h** was synthesized by method B in our previous report.[3a] Starting ketones for **1i,j** were obtained by the reaction of *t*-BuOK, $R_1COCH_2R_2$, and $PhCH_2Cl$ (molar ratio of 1:1:1) in DMF–*t*-BuOH (3:1) at 20–30 °C under N_2.

The preparation of α-hydroperoxy ketones, **1a–c**, was described previously.[3a] Peroxides **1d,e,f,h,i,j** were synthesized by method I[3a] and crystallized from benzene–petroleum ether in 12–67% yields, melting points (purity by iodometry) being 153–156 (100%), 148–150 (98%), 147–148 (99%), 75–80 (99%), 104–107 (99%), and 125.5–126.0 °C (98%), respectively. Ir spectra (Nujol mull) of these peroxides show an absorption at ~3300 (OOH) and at ~1700 cm^{-1} (C=O). Also NMR spectra satisfied the formation of α-hydroperoxy ketones. For example, NMR spectra (CCl_4) for **1i** are as follows: δ 2.10 (s, 3 H, CH_3), 3.30 (d, J = 15 Hz), and 3.67 (d, J = 15 Hz) (each 1 H, asymmetric $PhCH_2$), 6.7–7.2 (broad, 10 H, two Ph), 8.30 (s, 1 H, OOH). Peroxide **1g** was obtained according to the literature method,[26] mp 147–148 °C (100% pure; lit.[26] mp 152–153 °C).

Decomposition and Product Analysis. Products were identified and determined in comparison with an authentic sample by GLC with three different columns (1 m): (1) Apiezon grease L, 15% on Celite 545; (2) PEG 20M, 2% on Chamelite CK; (3) PEG succinate, 13% on Chromosorb. Propiophenone or biphenyl were used as an internal standard.

Pyrolysis GLC was done by injecting ca. 4 μl of a 0.01 M solution of 1 (injection temperature 250 °C, carrier gas N_2, column temperature

Table IV. Reaction of 1 with $FeSO_4$–$FeCl_3$ in 70% Aqueous MeOH at 25 °C[a]

Peroxide	R_3 in 1	$R_1\dot{C}{=}O{\sim}$ R_1CO_2Me	$R_2R_3C{=}O$	$R_3\cdot{\sim}$ R_3Cl	R_1COCOR_2	R_3Cl[b] $R_2R_3C{=}O$
1a	Ph	60.6	100	0	2[c]	0.00
1d	*p*-$ClPhCH_2$	52.8	74.1	3.1	2.7	0.042
1c[d]	$PhCH_2$	54.9	81.7	4.9	3.9	0.060
1e	*p*-$MePhCH_2$	65.5	74.9	8.3	7.9	0.110
1f	*p*-$MeOPhCH_2$	40.6	51.8	16.8	22.3	0.41
1g	PhCH(Et)	55.0	70.6	18.2	27.9	0.258
1i	$PhCH_2$	[e]	103	2.0	2.05	0.019
1j	$PhCH_2$	[e]	99.5	1.3	1.2	0.013

[a] Reaction with [1] = 0.01 M, $[FeSO_4]$ = 0.1 M, and $[FeCl_3]$ = 0.05 M under air. Ph = C_6H_5 or C_6H_4. [b] Relative rate of scission of $R_3\cdot$ vs. that of $R_1\dot{C}{=}O$ (see eq 2a, 2b, and 6). [c] Benzil was formed by dimerization of PhC=O (eq 4). β-Elimination of Ph· from 2 did not occur, since **1b** (R_1 = *p*-MeOPh) did not produce *p*-methoxybenzil. [d] Data from ref 6. [e] Not determined.

Table V. Relative Reactivity of β Scission of Acyl and Benzil Radicals from 2

Radicals[a]	Relative rate of β scission: 70% MeOH (25 °C)[b]	Relative rate of β scission: Vapor phase (250 °C)[c]
A. Scission of Various Radicals		
i-PrĊ=O	78.1	263
MeĊ=O	51.5	41.8
PhĊ=O	16.7	17.5
PhĊHEt	4.3	4.4
$PhCH_2$·	(1.00)	(1.00)
B. Substituent Effect in Benzyl Radicals		
p-$ClPhCH_2$·	0.70	0.82
$PhCH_2$·	(1.00)	(1.00)
p-$MePhCH_2$·	1.83	1.44
p-$MeOPhCH_2$·	6.90	2.51
ρ (σ^+)	−1.11 (r = 0.997)	−0.54 (r = 0.999)
ρ (σ)	−1.81 (r = 0.897)	−0.91 (r = 0.926)

[a] Ph = C_6H_5 or C_6H_4. [b] Determined from product ratios of $R_3Cl/R_2R_3C{=}O$ in Table IV. [c] Determined from the ratios of $R_1COCOR_2/R_2R_1C{=}O$ in Table I.

80–250 °C). Since the solvent is vaporized immediately after the injection, the decomposition of **1** occurs practically in vapor phase (N_2 gas). Products were determined in situ by the usual GLC method.

Thermolysis of **1** in chlorobenzene was performed, after air was replaced with N_2, at 130 °C for 2 h and products were determined by GLC.

Redox reaction of **1** with Fe^{2+} was instantaneously completed when a methanolic solution of **1** (0.02 M, 5 ml) was added to a mixture of MeOH (2 ml), aqueous $FeSO_4$, and $FeCl_3$ (total 3 ml) at 25 °C. Products were analyzed by GLC after the extraction with $CHCl_3$.

Registry No.—**1a**, 57196-77-7; **1b**, 57272-35-2; **1c**, 57196-78-8; **1d**, 58966-95-3; **1e**, 58966-96-4; **1f**, 58966-97-5; **1g**, 7492-76-4; **1h**, 58966-98-6; **1i**, 58966-99-7; **1j**, 58967-00-3.

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Kinetic Salt Effects on the Hydrolysis of Benzaldehyde Dimethyl Acetal[1,2]

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The rates of acid-catalyzed hydrolysis of benzaldehyde dimethyl acetal in water at 25 °C show linear responses to the molar concentrations of neutral electrolytes. For the alkali metal perchlorates the rates follow the form $k = k_0 + b$[salt] in the range of 0–0.1 M salt. At about 0.1 M salt the slopes decrease but again are linear to at least 2 M salt. The rate enhancement shows specific cation effects and in the order $Li^+ < Na^+ < K^+ < NH_4^+$. The effect depends upon charge density of the cation since the kinetic salt slope correlates linearly with the cube of the ionic radius. Similar effects are seen for the alkaline-earth perchlorates and the rates increase in the order $Mg^{2+} < Ca^{2+} < Sr^{2+}$. Interestingly barium does not fit with these salts but does fit with the alkali metal perchlorates. There is also a specific anion effect and for the sodium salts the rates increase in the order $NO_3^- < Cl^- < Br^- < ClO_4^-$. Again the effect is one of charge density and the kinetic salt slope correlates linearly with the pK_b of the anion.

The hydrolysis of acetals has occupied a central position in the history of chemical kinetics and mechanism studies.[3,4] One of the problems of acetal hydrolysis which continues to be studied is the nature of the transition state and how it is affected by various environmental factors.[4] A critical environmental factor which is not understood is the rate of acceleration produced by the presence of neutral electrolytes.

Early studies in the literature report finding linear relationships between rate constants and salt concentration for acetal hydrolyses[5,6] and for sucrose hydrolysis.[7,8] More recent studies[9-11] report that neutral salts have a linear relationship for the logarithm of the rate constants and the concentration of the salt for the acetal hydrolysis. Reasons for the dramatic differences in these results have not been discussed to our knowledge.

Recently we reported that dimethyl acetal formation for para-substituted benzaldehydes in 95% methanol–5% water has a linear rate response to the molar concentration of sodium perchlorate.[12] The rates follow the general form

$$k_{H_3^+O} = k_0 + b[\text{salt}] \quad (1)$$

For the benzaldehydes studied, the rates are more sensitive to salt concentration the greater is the electron donating capability of the para substituent. Because it was possible that the effects observed were due to a methanol–water–salt interaction rather than a salt–reactant interaction, we extended our salt study to the hydrolysis of benzaldehyde dimethyl acetal in water. For this system we observed a specific cation effect for the alkali metal perchlorates with the rates of hydrolysis following eq 1 and the slopes increasing in the order $Li^+ < Na^+ < K^+$. Inasmuch as these studies in water were restricted to salt concentrations of less than 0.1 M one could not be completely sure that the rate effects observed to be linear in salt concentration with k might not be treated equally as well by a ln k vs. salt concentration over a wider range of concentrations. For that reason we expanded our study to concentrations as high as 2 M for alkali metal perchlorates and to include alkaline-earth metal perchlorates. We have also studied specific anion effects with sodium salts.

Experimental Section[13]

Benzaldehyde Dimethyl Acetal. This acetal was prepared from benzaldehyde and trimethyl orthoformate as previously described,[14] bp 68–69 °C (5 Torr), $n^{25}D$ 1.4910.

Salt Solutions. The reagent grade salts used in this study were purified by three recrystallizations from water and dried in a vacuum oven for 2 days. The dried salts were analyzed for residual water content by the Karl Fischer method and stored in a desiccator. All of the salts except $LiClO_4$, $Mg(ClO_4)_2 \cdot 6H_2O$, and $Ca(ClO_4)_2$ contained significantly less than 0.1% water and were used as pure. For the salts containing more than 0.1% water the weight of salt was corrected to ensure the proper molarity of salt solution. Solubilities permitting, salt solutions of 0.1, 1.0, 2.0, and 4.0 M were prepared in volumetric flasks. These salt solutions were diluted to give the necessary final salt concentration for the kinetic runs. The pH of each aqueous salt solution was checked at several concentrations between 0.01 and 0.2 M to ensure the absence of excess acid or base in the salts.

Catalyst Solution. This solution was prepared by adding 1 ml (pipet) of concentrated perchloric acid to 1 l. of distilled water and diluted to give a solution of 10^{-3}–10^{-4} M $HClO_4$. This solution was used in the kinetic runs.

Measurement of Rates. The rate at which benzaldehyde appeared was followed at 281 nm with a Beckman DU spectrophotometer. The special cell holder and temperature regulation system has been described in detail.[14,15]

Into each of three 50-ml volumetric flasks there was added 4 ml (pipet) of the perchloric acid solution and sufficient salt solution to give the correct salt molarity after final dilution. One of the flasks was diluted to the mark with water and part of the solution placed in the reference cell of the spectrophotometer. The other two flasks were thermally equilibrated in the constant temperature bath. A solution of benzaldehyde dimethyl acetal was prepared (about 5×10^{-3} M) in water and 5 ml of this solution was added to the reaction flask which was then diluted to the mark and a portion transferred to a cell compartment of the spectrophotometer. Absorbance readings were taken to at least 60% reaction and the infinite absorbance reading after at least 10 half-lives. In all cases the value of A_∞ agreed within 1% or better with the calculated value based upon 100% hydrolysis of the amount of added acetal. After the first run was started a second acetal solution was prepared and a duplicate kinetic run made. Quadruplicate runs were made in all cases.

For kinetic salt studies made in methanol–water[12] the rates were sufficiently slow that we could use about 10^{-3} M perchloric acid and obtain reproducible kinetics using $[H_3^+O] = [HClO_4]$. When the solvent was changed to water the rates were over an order of magnitude greater than in methanol–water. To have adequate operating time for accurate analytical measurements the concentration of the acid was reduced by a factor of about 10 and for these cases we could not obtain reproducible kinetics because of uncertainties in the concentration of perchloric acid. For this reason a pH meter was used to obtain the hydronium ion concentration and this enabled us to obtain reproducible kinetics.

pH Measurements. At the completion of each kinetic run the pH of the reference solution and of the two reaction solutions were measured. All pH values were measured with a Corning Model 10 pH meter equipped with an Orion double junction electrode, Model 90-02-00, and an Orion glass electrode, Model 91-01-00. The solution for the inner chamber of the reference electrode was Orion filling solution 90-00-02. The outer chamber was filled with a 10% solution of ammonium nitrate which was changed daily. The pH meter was standardized before each series of measurements with a buffer solution of pH 4.00 (Coleman certified buffer tablets). The electrodes were washed to remove buffer, excess water was removed, and the pH was measured for the solutions. In all cases the pH values were stable within 1–2 min and remained stable for 1 h or longer.

The influence of salts on the pH values was checked by measurements of pH of standard acid solutions to which various amounts of salts had been added. These results are shown in Tables I and II.

Table I. Perchloric Acid–Sodium Perchlorate Concentrations and pH[a]

$[HClO_2]$	$[NaClO_4]$	pH calcd	pH obsd
1.043×10^{-2}	0.000	1.98	2.05
1.043×10^{-2}	1.100	1.98	1.95
1.043×10^{-3}	0.000	2.98	2.99
1.043×10^{-3}	1.100	2.98	2.95
1.043×10^{-4}	0.000	3.98	3.98
1.043×10^{-4}	1.100	3.98	3.99

[a] All readings are averages of duplicate values.

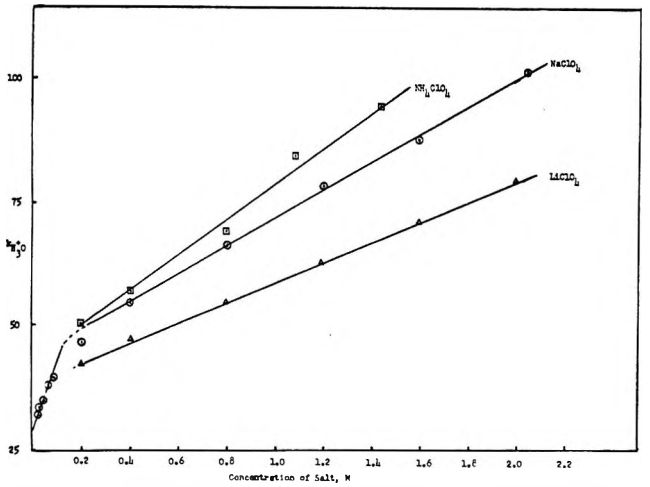


Figure 1. Linear plots of rate constants, $k_{H_3O^+}$, vs. salt concentration of NH_4ClO_4, $NaClO_4$, and $LiClO_4$ for the hydrolysis of benzaldehyde dimethyl acetal in water at 25.39 °C. The lines were fitted by least squares.

Results and Discussion

The rate of acid-catalyzed hydrolysis of benzaldehyde dimethyl acetal in water at 25.39 °C is markedly influenced by neutral electrolytes. The rate law in the absence of salt is $k_{obsd} = k_{H_3O^+}[H_3O^+]$. All rate constants reported in the presence of salt have been corrected for $[H_3O^+]$ as determined with a pH meter. The rate constants were reproducible to about ±1% or better.

The results obtained for the alkali metal salts are summarized in Table III. The alkali metal and ammonium perchlorate results are shown on the left side of the table and the results for sodium chloride, sodium bromide, and sodium nitrate on the right side of the table.

As we reported earlier,[12] the rate constants show a linear response to salt molarity for $KClO_4$, $NaClO_4$, and $LiClO_4$ and this study has now been expanded to include NH_4ClO_4, NaCl, NaBr, and $NaNO_3$. These salt effects are described by eq 1 for the salt concentration in the range of from zero to about 0.1 M. The slope, b, is specific for each salt and is a direct measure of the rate acceleration produced by that salt. These slope values are given for each salt in Table III along with the intercept and the normalized slope of $q = b/k_0$.

In the salt concentration of about 0.1 M the rate constant–salt concentration slopes undergo a marked decrease but again are linear to at least 2 M salt following the expression

$$k'_{H_3O} = k'_0 + b'[\text{salt}] \qquad (2)$$

which is of the same form as eq 1. These values of b' again are specific for each salt as are the q' values. The values of $k_{H_3O^+}$, b', k'_0, and q' are summarized in Table III.

Figure 1 shows a plot of k_{H_3O} vs. [salt] for sodium perchlorate over the entire concentration range and for lithium perchlorate and ammonium perchlorate for the higher concentration range only. These are representative results and the other salts show equally good linear plots.

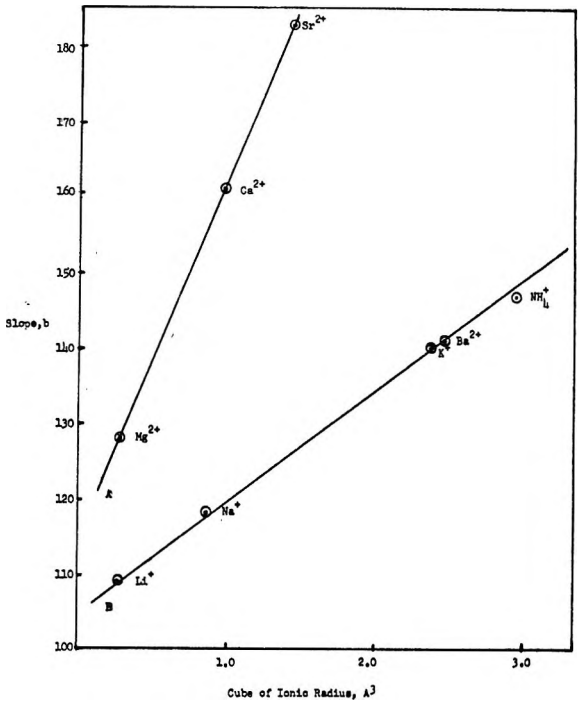


Figure 2. Kinetic salt effect slope vs. the cube of the cation radius for the hydrolysis of benzaldehyde dimethyl acetal in water at 25 °C. All salts were perchlorates and the catalyst was perchloric acid. Line A is for the alkaline earth metal perchlorates and line B is for the alkali metal perchlorates. The lines were placed by least squares.

For the perchlorate salts, the rates increase in the order $Li^+ < Na^+ < K^+ < NH_4^+$ for both concentration ranges. The effect appears to be one of charge density of the cation since plots of the slope terms vs. the cube of the ionic radii are linear and for the lower concentration ranges this result is shown as line B, Figure 2. For the univalent cations, all of the values fall on a single line which also includes Ba^{2+}. The cation having the largest volume or the lowest charge density exerts the greatest accelerating effect on the rate.

On the other hand, for a series of sodium salts with various anions the rates increase in the order $NO_3^- < Cl^- < Br^- < ClO_4^-$. Again it appears to be a charge density effect as a simple relationship exists between the slope terms and pK_b of the anions. For the lower salt range a plot has been made for $q(b/k_0)$ and pK_b of the anions and is shown as line A of Figure 3. The data covers about 8 orders of magnitude in pK_b and extrapolate to near zero over an additional 16 orders of magnitude. We have shown that this remarkable and simple linear free energy plot for the kinetic salt effect for the hydrolysis of benzaldehyde dimethyl acetal is applicable also to the data of Bronsted and Grove[5] for the hydrolysis of dimethyl acetal. This correlation is line B of Figure 3.

The results for the alkaline earth metal perchlorates are summarized in Table IV. Again these salts follow the catalytic salt expression, eq 1, as for the alkali metal salts with a change in slope at about 0.1 M and then follow eq 2. The slopes, b, for these salts are plotted against the cube of the ionic radii as line A in Figure 2. The values for Mg^{2+}, Ca^{2+}, and Sr^{2+} conform to a straight line but the Ba^{2+} value is significantly off the line. The Ba^{2+} value is on the line for the alkali metal perchlorates, a fact for which we have no rational explanation.

We are convinced that the salt effects reported here are real and are not artifacts of our experimental procedure. However, if the effects are real then there are certain conflicts of our

Table II. Influence of Concentration of Salt on pH of Perchloric Acid Solutions[a]

Calcd pH 2.84		Calcd pH 3.98		Calcd pH 3.98		Calcd pH 3.98	
$[NaClO_4]$	pH obsd	$[NaClO_4]$	pH obsd	[NaCl]	pH obsd	$[Ca(ClO_4)_2]$	pH obsd
0.00	2.85	0.00	3.98	0.00	4.00	0.00	4.03
0.010	2.85	0.498	4.01	0.0125	4.02	0.0190	4.05
0.030	2.86	0.900	3.99	0.0482	4.03	0.0610	4.08
0.050	2.86	1.200	3.97	0.288	3.99	0.0998	4.08
0.080	2.85	1.499	3.99	0.480	3.91	0.200	4.11
0.167	2.86			0.715	3.86	0.500	4.10
0.300	2.84						
0.500	2.81						
1.000	2.76						

[a] All readings are averages of duplicate values.

Table III. Influence of Concentration on the Rate of Hydrolysis of Benzaldehyde Dimethyl Acetal[a]

	$k_{H_3^+O}$,[b] M^{-1} s^{-1} for						
Salt molarity	$LiClO_4$	$NaClO_4$	$KClO_4$	NH_4ClO_4	NaCl	NaBr	$NaNO_3$
			A. Lower Salt Concentration				
0.00	29.5	29.5	29.5	29.5	29.5	29.5	29.5
0.008		31.7[d]					
0.02	30.7	32.8	32.9	33.1	31.7	31.9[d]	30.9
0.04	33.8	34.1	36.5	36.4	33.8	33.9	33.4
0.06		37.8		39.0	35.6	36.7	35.2
0.08	38.0	39.4	40.8	41.2[c]	37.8	38.6	36.1
Slope b	109.3	118.3	140.2	148.8	102.0	114.2	87.1
Intercept k_0	29.2	29.5	30.0	30.0	29.6	29.5	29.5
$q = b/k_0$	3.75	4.01	4.67	4.86	3.45	3.87	2.96
			B. Higher Salt Concentration				
0.20	41.0	45.6[c]		49.4	41.7[c]	41.6	
0.40	46.9[c]	54.3		55.5	43.5	43.5	
0.80	54.2	66.2[c]		67.9	52.0	54.8	
1.08				83.6			
1.20	62.1	78.0[c]			56.5	61.4	
1.44				93.8			
1.60	70.6[c]	87.4			60.5	68.2	
2.00	78.9	99.3			69.2[c]	79.3[c]	
Slope b'	20.6	29.5		36.9	14.9	20.0	
Intercept k'_0	37.7	41.8		41.1	38.6	38.0	
$q' = b'/k_0'$	0.55	0.71	010.90	0.39	0.53		

[a] The hydrolysis was conducted in water at 25.39 °C with $\simeq 10^{-5}$ M perchloric acid catalyst. All values of acidity were determined by pH meter. Each value reported is the average of quadruplicate results except where noted. All values are least-squares values. [b] This value is the hydrolytic rate constant corrected to 1 M H_3^+O based upon the measured pH value. [c] Average of triplicate results. [d] Average of duplicate results.

results with those obtained by the regular approaches to salt effects, particularly for kinetic studies of the hydrolysis of acetals.

Most workers use the prepared concentrations of acid as the values for the hydronium ion concentration and then presume that all salt effects are rationalized by the Debye–Huckel correction to the activity coefficients of the reactants and transition state. For concentrations of acids of 10^{-3} M or greater one can reliably prepare standard solutions but we were unable to do so for 10^{-5} M acid solutions as indicated by nonreproducible rate constants. For this reason pH measurements were used to obtain the concentrations of hydronium ion and by which reproducible rate constants were obtained. As one expects, the presence of neutral salt may affect the measured pH values. However, there are also salt effects on the activity coefficients of the reactants and the transition state as well as salt effects on the dielectric constant. By using a measured pH one may obtain a close approximation to $a_{H_3^+O}$ and thus at least one complication due to salt effects is minimized.

For our work the values of the pH which were used in the rate experiments were not compared to known values of the acid concentration (unmeasured). Subsequent to completion of the kinetic studies we attempted a calibration of our pH scale as a function of salt concentration and acid concentration.[16] The values of the pH which were calculated and those which were measured were identical within experimental error for dilute perchloric acid having neutral salts at 0.2–0.3 M or lower (see Table II). It is only for significant concentrations of acid (10^{-3} M or greater) that we observed a decrease in pH with increasing salt concentration but then only at higher salt concentrations (0.3 M or higher; see Tables I and II). Inasmuch as all of our rate measurements were made in aqueous acid with a hydronium ion concentration of from about 1×10^{-5} to 8×10^{-5} M, the measured hydronium ion concentrations are likely very close to the actual values for even the highest salt concentrations used. However, even if the salt does in any case increase the acidity of the solution, the pH meter sees the increase and this effect is corrected for in the rate expression.

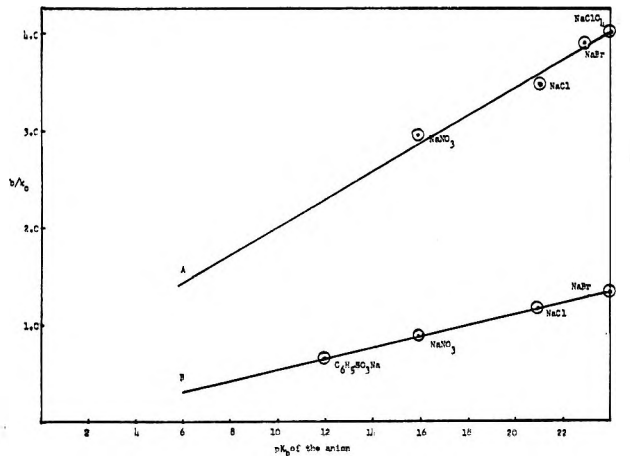


Figure 3. The influence of the basicity of anion of the salt on the rate of the acid-catalyzed hydrolysis of acetals in water at 25 °C. Line A is the data of this work for the hydrolysis of benzaldehyde dimethyl acetal. Line B is the data of Bronsted and Grove[5] for the hydrolysis of acetaldehyde dimethyl acetal. The lines were placed by least squares.

We find it necessary to use a double junction electrode for pH measurements above about 0.3–0.4 M salt.[17] For perchlorate salts this is imperative because of precipitation of $KClO_4$ at the junctions (from KCl in the reference electrode) but even for other salt solutions the double junction electrode works much better. Without the double junction electrode, the pH readings were erratic and nonreproducible for several hours even with the solutions protected from the atmosphere. We also find it necessary to recrystallize the salts (even the highest quality, reagent grade salts) because acid or base impurities can change the acidity of the reaction solutions, particularly since our acid catalyst is used at a very low concentration ($\sim 10^{-5}$ M). Failure to purify the salt magnifies the rate enhancement or inhibition depending upon whether the salt contains a trace of excess acid or base.

Studies by others on cation effects often report a reverse effect for the alkali metal salts to what we have observed (some see $K^+ < Na^+ < Li^+$ while we see $Li^+ < Na^+ < K^+$). In those cases where we have found such a reverse order from ours, the authors used a strong mineral acid at a significant concentration (0.1–1.0 M). The relatively high concentration of mineral acid is a significant electrolyte concentration to which is added the concentration of the neutral electrolyte. Thus the interaction of the mixed electrolyte may influence the ordering of the cation effect.

Our analyses of some recent data[10,11] show that their results are accommodated by some salts giving nicely linear plots for ln k vs. [salt] but not all. This same effect is observed for earlier results in the literature.[6–8] The work of Bronsted and Grove[5] for the hydrolysis of dimethyl acetal in the presence of salts is nicely correlated by a k vs. [salt] relationship.

It appears to us that there is no theoretical basis upon which to apply kinetic salt effects to reactions of this type (acetal hydrolysis) in water. The evidence calling to question the validity of the Debye–Huckel–Bronsted approach for the rationalization of specific salt effects is substantial,[18] at least for electrolytes used at real concentrations. Most workers who study salt effects on ion–molecular reactions use the Bronsted equation in spite of the fact that it predicts no salt effect for such systems ($Z_A Z_B = 0$). Furthermore, the equation is applied for salt concentrations far beyond its theoretical range which can be no more than about 0.1 M salt based upon the Debye–Huckel approximation. One of the more confusing aspects of work which attempts to interpret ion–molecule reactions by the Bronsted equation is that they usually observe specific salt effects for ln k vs. [salt] yet the Bronsted equation predicts nonspecific effects.[18] Finally, we would note that change in slope of the k vs. [salt] plots at about 0.1 M salt appears to be an unreported effect. We do not think the effect is one of a fundamental change in the properties of the solution since we know of no solvent–electrolyte effects which undergo maxima or minima at about 0.1 M salt. At this point we have no experimental or theoretical leads to explain the effect which we have seen for every salt studied (except for $KClO_4$, which was limited by its low solubility).

Table IV. Influence of Concentration of Alkaline I arth Perchlorates on the Rate of Hydrolysis of Benzaldehyde Dimethyl Acetal[a]

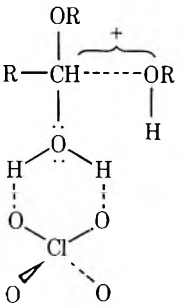
Salt molarity	k_2,[b] M^{-1} s^{-1} for $Mg(ClO_4)_2$	$Ca(ClO_4)_2$	$Ba(ClO_4)_2$	$Sr(ClO_4)_2$
	A. Lower Salt Concentration			
0.00	29.5	29.5	29.5	29.5
0.01		34.6		
0.02	34.5	37.0	34.8	35.0[d]
0.04	35.8	40.1	37.9	39.4[d]
0.06	38.2[c]			41.2[d]
0.08	40.5	44.1	41.6	44.3[d]
0.10		48.1		49.2[d]
Slope b	128.0	161.5	141.1	183.1
Intercept k_0	30.6	32.2	30.9	30.6
$q = b/k_0$	4.2	5.0	4.6	6.0
	B. Higher Salt Concentration			
0.12		49.8		
0.16		51.9		
0.20	44.5		49.1[d]	
0.40	51.7	59.4	56.3	
0.60	55.8[d]	69.5	65.3	
0.80	63.6[c]	78.6	77.1	
Slope b'	30.6	41.7	46.5	
Intercept k_0'	38.6	44.5	38.7	
$q' = b'/k'_0$	0.79	0.94	1.20	

[a] The hydrolysis was conducted in water at 25.39 °C with $\sim 10^{-4}$ M perchloric acid catalyst. All values of acidity were determined by a pH meter. Each value reported is the average k of quadruplicate least-squares results except where noted. All values are least-squares values. [b] These values are the hydrolytic rate constants corrected to 1 M $H_3{}^+O$ based upon the measured pH value. [c] Average of triplicate results. [d] Average of duplicate results.

The kinetic salt effects we observed are specific and cannot be interpreted simply in terms of activity coefficient changes.[18,19] The effects consistently fit eq 1 which is exactly of the form Winstein[20] found and exploited for the solvolyses of arenesulfonates in less polar solvents such as acetic acid. We do not believe that Perrin's model[21] is applicable to these acetal systems since his model assumes ion pairs for less polar solvents and requires the Debye–Huckel limitation of very dilute solutions. While the effects of salts on the kinetics of neutral molecule reactions are not understood, there are reports of their existence from the earliest days of organized chemistry to the present time.[22] Mechanism studies other than those due to Winstein's works on solvolyses have not properly taken neutral electrolytes into account.

One can readily postulate models to rationalize the specification and anion effects which are observed. For example, one could propose a direct interaction of the anion with the transition state. In this way the anion stabilizes the transition state while the cation as a counterion offsets the anion effect. However, one probably should not consider the ion effect to operate with unhydrated species and for this reason the

suggestion made by Olson and Tong[19] is attractive. Their proposal is that the anion serves to orient water molecules toward the positively charged transition state as well as serving to stabilize the developing transition state. An example could be



and this model can be used to explain very well the observed rate effects based on charge densities of the anion and the countercation. This explanation would require a direct involvement of the solvent in the transition state for acetal hydrolysis. All independent criteria developed for this system indicate that the solvent is not involved in the transition state,[4] but by no means has a final answer been found to this question. We do not at this time strongly advocate such a model since the explanation is essentially ad hoc in nature and is not quantitatively related to the fundamental properties of the solution or the solvent. We will not dwell upon this aspect of the results for this reason and because we are convinced that a great deal of experimental work must be performed for this and other systems as well as learning more about dielectric constants–salt effects[23] before one can hope to develop a sound theory for kinetic salt effects.

Registry No.—Benzaldehyde dimethyl acetal, 1125-88-8; $LiClO_4$, 7791-03-9; $NaClO_4$, 7601-89-0; $KClO_4$, 7778-74-7; NH_4ClO_4, 7790-98-9; NaCl, 7647-14-5; NaBr, 7647-15-6; $NaNO_3$, 7631-99-4; $Mg(ClO_4)_2$, 10034-81-8; $Ca(ClO_4)_2$, 13477-36-6; $Ba(ClO_4)_2$, 13465-95-7; $Sr(ClO_4)_2$, 13450-97-0.

Supplementary Material Available. Tables of rate data (5 pages). These tables list the salt, its concentration, the value of $(H_3{}^+O)$ as measured by pH meter, and the rate constant for each determination. Ordering information is given on any current masthead page.

References and Notes

(1) Grateful acknowledgment is given to Furman University for fellowships in support of this work and to the National Science Foundation for partial support through the URP program.
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Notes

Kinetic Salt Effects and Substituent Effects on Rates of Dimethyl Acetal Formation for Benzaldehydes[1]

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We recently reported[3] the effects of para substituents on rates and equilibria for benzaldehyde–benzaldehyde dimethyl acetal interconversions. In that study, which was made in 95% methanol–5% water, a substantial kinetic salt effect was observed. If one compares reactivities for the hydrolysis of a series of acetals (or for the formation of the acetals from the aldehydes) at some given salt concentration, it is not obvious that the rate variations observed can be attributed uniquely to the substituents. Part of the relative change in rate is due to the substituent change and part is due to kinetic salt effects. The interrelationship between these effects has not been established and must be understood before one can be sure of interpretations for structural studies.

We have studied the kinetics of dimethyl acetal formation for para-substituted benzaldehydes at 25.39 °C in 95% methanol–5% water in the presence of various amounts of sodium perchlorate. The catalyst was perchloric acid used at about 10^{-4} M. These results are reported along with a preliminary study of the influence of alkali metal perchlorates on the hydrolysis of benzaldehyde dimethyl acetal in water at 25.39 °C.

Experimental Section

Preparation and Purification of Reagents. Methanol (Union Carbide Chemicals Co.) was purified in 3-l. batches by the method of Lund and Bjerrum.[4] Each batch was distilled on a 1.5 × 45 cm protruded metal packed column until the transmittance was 97% or better against a specially purified sample of water at 256 nm. In all cases the water content (Karl Fischer) was less than 0.01% and was usually 0.005% or less.

95% Methanol–5% Water was prepared in kilogram lots by taring a 2-l. flask on a solution balance (±0.2 g) and adding 950 g of spectral grade methanol and 50.00 ml (pipet) of spectral grade water (distilled and deionized).

Salt Solutions. The $LiClO_4$, $NaClO_4$, and $KClO_4$ (G. Frederick Smith Co.) were recrystallized from water three times and dried at 120 °C for 1–2 days. Samples were analyzed for residual water content by the Karl Fischer method and the weights of salt needed for 0.1 M solutions corrected for the water contents. The pH of each batch of purified salt was measured as a function of concentration in water and found not to change from that of water.

Perchloric acid solution was prepared by adding 2–3 ml of concentrated perchloric acid (J. T. Baker) to about 500 ml of 95% methanol–5% water. The acid solution was standardized by titration with aqueous KOH solution (phenolphthalein end point.) The acid and base solutions were standardized biweekly. A similar procedure was used for perchloric acid in water.

Aldehydes. Benzaldehyde (J. T. Baker), *p*-tolualdehyde, furfural, and *p*-anisaldehyde (Columbia Organic Chemicals Co.) were each washed three times with 5% sodium bicarbonate and once with water, dried over sodium sulfate and distilled under vacuum. The aldehydes were collected in melting point capillary tubes and sealed under vacuum for reasons, and by the procedure, described previously.[3] The weighed, sealed tubes were crushed under the surface of the solvent in a volumetric flask. The flask was filled to the mark with solvent. The aldehyde solution was diluted for the kinetic runs and to check the extinction coefficients. Repeated preparations of the solutions by the sealed tube method throughout this work gave extinction coefficients which varied by less than ±1%. *p*-Bromobenzaldehyde was purified by recrystallization from hexane and then vacuum sublimed.

Rate Measurements. The rates at which the aldehydes disappeared were followed by measuring the carbonyl absorptions with a Beckman DU spectrophotometer as a function of time. The details of the system used and the operational method have been described.[3]

The first-order rate constants were calculated for the equilibration

$$\mathrm{RCHO} + 2\mathrm{CH_3OH} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{RCH}(\mathrm{OCH_3})_2 + \mathrm{H_2O} \qquad (1)$$

by means of standard expressions modified for our analytical system. For a reversible first-order process for acetal formation corrected for hydronium ion concentrations (using $[H_3{}^+O] = [HClO_4]$)

$$k_1 = \frac{-(\text{slope})(A_0 - A_\infty)}{60A_0[H_3{}^+O]}\ \mathrm{M^{-1}\ s^{-1}} \qquad (2)$$

with slope = $\ln(A - A_\infty)$ vs. time (min); A, A_0, and A_∞ are the measured absorptions at time t, at zero time, and at infinite time, re-

Table I. Kinetic Salt Effects on the Formation of Benzaldehyde Dimethyl Acetals[a]

Aldehyde (registry no.)	$[HClO_4]$[b]	$[NaClO_4]$[b]	k_1,[c] $M^{-1}\ s^{-1}$	Slope,[d] b	Intercept,[d] k_0	q[e]
p-Anisaldehyde (123-11-5)	7.286×10^{-5}	0.010	6.05 ± 0.25	14.65	5.88	2.49
		0.050	6.58 ± 0.07			
		0.070	6.91 ± 0.33			
		0.100	7.35 ± 0.07			
p-Tolualdehyde (104-87-0)	1.626×10^{-4}	0.010	3.71 ± 0.01	9.74	3.58	2.72
		0.050	3.97 ± 0.02			
		0.070	4.31 ± 0.10			
		0.100	4.61 ± 0.09			
Benzaldehyde (100-52-7)	2.689×10^{-4}	0.010	1.42 ± 0.02	3.61	1.39	2.60
		0.050	1.53 ± 0.01			
		0.064	1.62 ± 0.01			
		0.100	1.76 ± 0.02			
p-Bromobenzaldehyde (1122-91-4)	3.627×10^{-4}	0.010	0.500 ± 0.009	1.30	0.489	2.60
		0.050	0.555 ± 0.003			
		0.070	0.578 ± 0.001			
		0.100	0.621 ± 0.008			

[a] Rates determined in 95% methanol–5% water at 25.39 °C by following spectrophotometrically the disappearance of the carbonyl group at λ_{max} in the uv. [b] Concentration in mol $l.^{-1}$. [c] k_1 is the rate constant for acetal formation corrected for $[H_3{}^+O] = [HClO_4]$. [d] The salt effect follows the expression $k_{H_3{}^+O} = k_0 + b[\text{salt}]$ and the values given here are least-squares terms. [e] $q = b/k_0$.

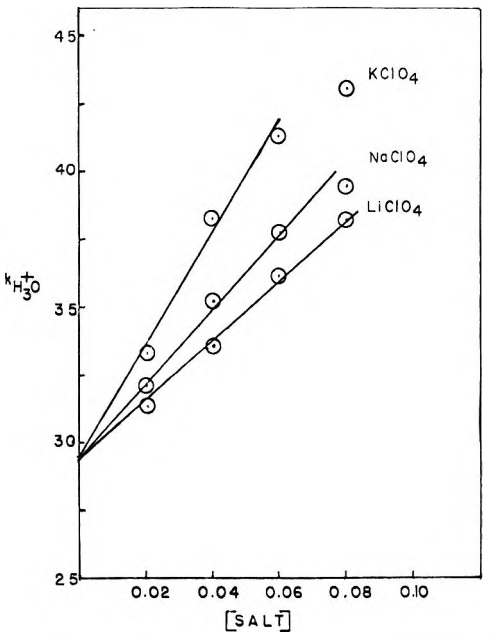

Figure 1. Plot of $k_{H_3O^+}$ vs. concentration of salt for $LiClO_4$, $NaClO_4$, and $KClO_4$ for the hydrolysis of benzaldehyde dimethyl acetal in water at 25.39 °C. The lines were placed by least squares.

spectively.[3] All rate constants were calculated by the method of least squares. One may also calculate the reverse rate constants, k_2, from this same data if desired,[3] but these values are not reported.

Results and Discussion

The influence of the concentration of sodium perchlorate (0.0–0.10 M) has been studied on the rates of formation of the dimethyl acetals of *p*-anisaldehyde, *p*-tolualdehyde, benzaldehyde, and *p*-bromobenzaldehyde. The reactions were conducted in 95% methanol–5% water at 25.39 °C with perchloric acid catalyst. The results are summarized in Table I. The kinetic salt effect is summarized by the expression

$$k_{H^+O} = k_0 + b[\text{salt}] \quad (3)$$

We have reported[3] that the rates of acetal formation increase as the electron-donating capability of the para substituents increase. Paralleling this rate–structure effect is the kinetic salt effect which the slope term, b, represents. The values of b given in Table I are seen to increase as the electon-donating capability of the para substituent increases. It is apparent that the methoxy group has a much greater slope than the bromo group and presumably the slope would be zero for a substituent having a zero rate.

Given the form of the kinetic salt effect for this reaction, are the relative rates for various substituents the same as long as the rates are measured at the same salt concentration? The results show a positive answer to this question. This fact may be seen by taking ratios of the rate expressions (eq 3) for various substituents. The results show an average q value of 2.60 and represent the slope of a line obtained by plotting the b terms vs. the intercepts for the para-substituted benzaldehydes. On this basis one may be confident of interpretations of relative rates for substituents providing they are made at the same electrolyte concentration.

Most results of kinetic salt studies of this type have been performed in water and usually the data have been treated by a log k vs. [salt].[5,6] It seemed possible that the effects we observed reflected a methanol–water–salt interaction rather than a reactant–salt interaction. Because of this possibility and because we had observed what to us seemed to be a specific salt effect in methanol–water we extended this study to the hydrolysis of benzaldehyde dimethyl acetal in water. The reaction was conducted at 25.39 °C with perchloric acid catalyst ($\sim 10^{-5}$ M) used with various amounts of lithium, sodium, or potassium perchlorates.

The preliminary results of the hydrolysis reaction in water are summarized in Figure 1. The plots of k_{H_3O} vs. salt concentration are satisfactorily linear with corrections coefficients of $r = 0.986$ for $KClO_4$, $r = 0.995$ for $NaClO_4$, and $r = 0.997$ for $LiClO_4$. The kinetic salt effect increases in the order Li < Na < K. These results show that the salt effect observed for acetal hydrolysis in water is of the same kind as we observed for acetal formation in methanol–water.

The 0.08 M salt values for $KClO_4$ and $NaClO_4$ are considerably off the line (although these values were included in the least-squares correlations). This deviation occurs because of a significant change in slope which is observed at about 0.1 M salt for all salts studied to date. The salt effects observed are ion specific and while the results presented demonstrate specific cation effects, specific anion effects have also been observed. Details of this kinetic salt effect for acetal hydrolysis in water are to be reported in more detail. We would note only that the results are of the same form Winstein has observed for the solvolysis of arenesulfonates.[7]

Registry No.—$LiClO_4$, 7791-03-9; $NaClO_4$, 7601-89-0; $KClO_4$, 7778-74-7; benzaldehyde dimethyl acetal, 1125-88-8.

References and Notes

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Acidity Constants of Some 5-Substituted 3-Furoic Acids[1]

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A great number of examples of the application of Hammett's equation to series of reactions of several aromatic heterocyclic systems are found in the literature.[2] In the furanic system, in particular, owing to the difficulty found in the synthesis of β-substituted derivatives, the use of this equation has been restricted almost exclusively to those systems in which the relation between the substituent R and the reacting side chain Y is of the 5-R-2-Y type.

In order to extend the observation made on the transmission of the substituent's effect to the "nonconjugated" 5-R-3-Y relationship in the furanic system, a series of 5-substituted 3-furoic acids were prepared and their pK_a values were determined and correlated with the corresponding Hammett substituent constants.

Experimental Section

The ^1H NMR spectra were determined on a Varian T-60 instrument using Me_4Si as an internal reference. The ir spectra were recorded using a Perkin-Elmer 337 spectrophotometer. All melting and boiling points are uncorrected.

Table I. ^{1}H NMR Chemical Shifts[a] and Coupling Constants of 5-Substituted 3-Furoic Acids

Registry no.	Compd	Solvent	δ, ppm, and multiplicity H2	H4	H5	CO_2H	J, Hz
488-93-7	Unsubstituted[b]	$CDCl_3$	8.13 (q)	6.80 (t)	7.47 (q)	10.67 (s)	J_{45} = 1.9; J_{25} = 1.6; J_{24} = 0.8
4282-28-4	5-CO_2H	$(CD_3)_2CO$	8.38 (d)	7.45 (d)		8.97 (s)	J_{24} = 0.9
58832-36-3	5-Br	$CDCl_3$	8.07 (d)	6.71 (d)		9.87 (s)	J_{24} = 1.2
770-07-0	5-NO_2	$(CD_3)_2CO$	8.47 (d)	7.72 (d)		10.90 (s)	J_{24} = 1.1

[a] From internal Me_4Si. [b] Reported[8] δ 8.12, 6.78, 7.45, 11.60 ppm.

Table IV. Apparent Ionization Constants, pK_a', and Thermodynamic Ionization Constants, pK_a, at 25.0 ± 0.1 °C of 5-Substituted 3-Furoic Acids in Water Solution

Compd	I_m	pK_a'	s[a]	−log γ_i	pK_a
3-Furoic acid	0.005	3.99[b]	0.01	0.04	4.03
5-Bromo-3-furoic acid	0.005	3.64	0.01	0.04	3.68
5-Nitro-3-furoic acid	0.005	3.04	0.01	0.04	3.08
2,5-Furandicarboxylic acid					
2 position	0.006	2.65	0.01	0.041	2.69
4 position	0.020	3.96	0.01	0.056	4.13

[a] Standard deviation. [b] Reported[17] 3.95.

2,4-Furandicarboxylic acid was prepared through the following sequence of reactions. Coumalic acid was prepared from malic acid.[3] The coumalic acid was converted into coumalyl chloride according to Fried and Elderfield's procedure,[4] using the modification proposed by Wiley and Knabeschuh.[5] The coumalyl chloride was converted into methyl coumalate.[5] The methyl coumalate was converted into methyl bromocoumalate[6] and then into 2,4-furandicarboxylic acid.[6] Ir spectrum (KBr) showed peaks at 1694 (ν_{CO}), 1586 and 1563 (ν_{ring}), 1155 (β_{CH}), 870 (β_{ring}), and 765 cm^{-1} (δ_{CH}).

3-Furoic acid was prepared from 2,4-furandicarboxylic acid by Reichstein and Zschokke's method.[7] Ir spectrum (KBr) showed peaks at 1670 (ν_{CO}), 1564 and 1510 (ν_{ring}), 1155 (β_{CH}), 876 (β_{ring}), and 750 cm^{-1} (δ_{CH}).

5-Bromo-3-furoic acid was prepared by the following method. 3-Furoic acid (2.38 g, 0.02 mol) was added to a solution of 6.4 g (0.02 mol) of pyridinium hydrobromide perbromide[8] in 10 ml of acetic acid. The reaction mixture was heated to 40–45 °C during 2 h, while the hydrogen bromide formed was swept by a stream of nitrogen. Next, the solvent was evaporated under reduced pressure, and the remaining solid was suspended in water, filtered, dried, and sublimated under reduced pressure to give a 55% yield of a product with mp 138–139 °C (reported[6] 130 °C). Ir spectrum (KBr) showed peaks at 1670 (ν_{CO}), 155 and 1510 (ν_{ring}), 1130 (β_{CH}), 854 (β_{ring}), and 755 cm^{-1} (γ_{CH}).

5-Nitro-3-furoic acid was prepared as described below. Nitric acid (70%), 9 g (0.10 mol), was added during a 2-min period to 60 ml of acetic anhydride, the temperature being held at 30–35 °C. The solution was then chilled to −15 °C, after which were added 2 drops of concentrated sulfuric acid and 5.6 g (0.05 mol) of 5-furoic acid. The temperature of the solution was allowed to rise to 0 °C and the solution was stirred at this temperature for 15 min. Water was added and the solution was stirred until the hydrolysis of the acetic anhydride was complete, then extracted with ether. The ethereal solution was washed with water and dried, and the ether removed by distillation. The residual oil mixed with an equal volume of pyridine (violent reaction), cooled, acidified with a 50% hydrochloric acid solution, and extracted with ether. The ethereal solution was washed with water and dried, and the ether evaporated. The remaining solid was recrystallized from water, giving a 60% yield of a product of mp 136–137 °C (reported[6] 138 °C). Ir spectrum (KBr) showed peaks at 1670 (ν_{CO}), 880 (β_{ring}), and 761 cm^{-1} (δ_{CH}).

All the substances prepared were characterized by ^{1}H NMR (Table I).

pK_a Determinations. The apparent acidity constants, pK_a', of 3-furoic acid, 5-bromo-3-furoic acid, and 5-nitro-3-furoic acid were measured at 25.0 ± 0.1 °C, in water, by sequential titration of 5.0 × 10^{-4} mol of the acids dissolved in 47.5 ml of ion-free water, with 10 amounts of 0.1000 M carbonate-free potassium hydroxide solution each 0.1 equiv. After each addition the pH was measured with a Methron Herissau Compensator E 388 pH meter, equipped with a combined glass electrode, with silver–silver chloride internal reference, in an apparatus as described by Albert and Serjeant.[9] The instrument was calibrated against standard buffer solution at pH 2.00 and 6.00. The standardization of the instrument was rechecked after each determination, and in no case was the drift greater than 0.02 pH units. The temperature drifts during measurements were less than 0.1 °C. The apparente pK_a' values (Table II, supplementary material) were obtained from eq 1

$$pK_a' = pH + \log \frac{C_{AH} - a_{H^+}}{C_{A^-} + a_{H^+}} \quad (1)$$

where C_{AH} and C_{A^-} are the stoichiometric concentration of the acid and its conjugated base, respectively.

The apparent acidity constant, pK_a', of 2,4-furandicarboxylic acid was measured at 25.0 ± 0.1 °C, in water, by sequential titration of 5.0 × 10^{-4} mol of the acid dissolved in 42.5 ml of ion-free water, with 20 amounts of 0.1000 M carbonate-free potassium hydroxide solution, each 0.05 equiv. The pH measurements were performed as above. The apparent pK_a' was obtained with the application of the Noyes method[10]

$$K'_{a1} = \frac{Y_1Z_1 - Y_2Z_1}{X_1Z_2 - X_2Z_1} \text{ and } K'_{a2} = \frac{X_1Z_2 - X_2Z_1}{Y_1Z_2 - Y_2Z_1} \quad (2)$$

where $X = a_{H^+}(B - C + a_{H^+})$, $Y = 2C - (B + a_{H^+})$, $Z = (a_{H^+})^2(B + a_{H^+})$; C is the total concentration of the acid being titrated; B is the concentration of the alkali added.

For readings obtained with less than 1 equiv of the titrant the corresponding values are X_1, Y_1, and Z_1, whereas X_2, Y_2, and Z_2 refer to readings obtained with more than 1 equiv of titrant. Pairs of readings were selected symmetrically from either side of the midpoint (Table III, supplementary material).

Results and Discussion

The apparent acidity constants, pK_a', of 3-furoic acid, 5-bromo-3-furoic acid, 5-nitro-3-furoic acid, and 2,4-furandicarboxylic acid were determined at 25.0 ± 0.1 °C, in aqueous solution, by potentiometric titration, using the technique described by Albert and Serjeant.[9]

The pK_a' values shown in Table IV were calculated using nine points of the titration curve, between the limit of 10 and 90% of ionization. Equation 1 was employed in the calculation of the pK_a' values of the monobasic acids.

As was expected, the application of this calculation method to the data obtained from the titration of the dibasic acid did not yield good results, since the difference between the pK_a' values of the ionizing group is smaller than 2.7 pH units, thus

causing the titration of one group to begin before that of the other group has been completed. Quite satisfactory results were obtained by applying the Noyes method[10] for separation of the overlapping pK_a' values (see Table IV). Since 2-furoic acid (pK_a = 3.12[11]) is stronger than 3-furoic acid (pK_a = 3.99[11]), we attributed the determined pK_a' = 2.65 to carboxyl group in position 2, and the pK_a' = 3.96 to the carboxyl group in position 4 of the 2,4-furandicarboxylic acid.

The thermodynamic pK_a for the 3-furoic acid, 5-bromo-3-furoic acid, and 5-nitro-3-furoic acid and the stronger group of the dibasic acid were calculated from the equation

$$pK_a = pK_a' - \log \gamma_i \quad (3)$$

and using the Debye–Hückel limiting law to define the activity coefficient, γ_i, and the value of the ionic strength at the midpoint of the titration. The thermodynamic pK_a becomes pK_a' + 0.04 (see Table IV).

The thermodynamic pK_a of the weaker group of the 2,4-furandicarboxylic acid was calculated from the equation

$$pK_a = pK_a' - 3 \log \gamma_i \quad (4)$$

The activity coefficient was calculated from the equation

$$-\log \gamma_i = \frac{A\sqrt{I_m}}{1 - Ba_i\sqrt{I_m}} \quad (5)$$

Using the values of the constants A and B,[12] the value of the ionic size parameter,[13] and the value of the ionic strength of the solution, I_m, at the semineutralization, the thermodynamic pK_a becomes pK'_{a2} + 0.17 (see Table IV).

We have correlated, by multiple linear regression analysis,[14] the acidity constants values of the 5-substituted 3-furoic acids to the corresponding substituent constants values σ_m and σ_p, employing values determined by McDaniel and Brown.[15]

With the σ_m values the slope ρ of the regression line is 1.25 and the correlation coefficient is 0.983; with the σ_p values ρ is 1.28 and the correlation coefficient is 0.990. It is noteworthy that 5-substituted 3-furoic acids correlate well with both meta and para substituent constants.

The ratio between the value of ρ obtained and the corresponding values for the benzene system agrees with those found for the 2-R-5-Y system[2,16] and reinforces the conclusion that the transmission of the substituent's effect is greater in the furan ring than in the benzene ring.

Supplementary Material Available. Tables II and III that report full determination of the apparent acidity constant data for the 5-substituted 3-furoic acids (2 pages). Ordering information is given on any current masthead page.

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A Convenient Synthesis of *N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine

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In peptide synthesis, especially using the solid-phase method, *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine has proved to be a useful intermediate to incorporate serine into a synthetic peptide.[1] Although several methods are currently available for the preparation of the *O*-benzyl derivative, they are laborious and not profitable for commercial exploitation. *O*-Benzyl-DL-serine was prepared by Okawa[2] via bromination of methyl acrylate. Resolution into the L isomer was achieved by hydrolysis of the *N*-acetyl derivative with the acylase.[3] In addition, *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine was prepared by Hruby and Ehler[4] via benzylation of *N-tert*-butyloxycarbonyl-L-serine in sodium–liquid ammonia at −30 °C. Isolation of the desired product was performed by use of column chromatography. This paper is concerned with the development of a more convenient synthetic method starting from L-serine.

N-tert-Butyloxycarbonyl-*O*-benzyl-L-serine was obtained directly from the readily available *N-tert*-butyloxycarbonyl-L-serine by treatment of the latter compound, in dimethylformamide at room temperature, with 2 molar equiv of sodium hydride and 1 molar equiv of benzyl bromide. Purified *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine was obtained in 57% yield as its cyclohexylammonium salt after recrystallization from ethyl acetate. The method described here is suitable for large-scale preparation because of its high efficiency, procedural simplicity, and mildness of reaction conditions.

When the same procedure was applied to the preparation of the *O*-benzyl-L-threonine derivative, the yield of the compound was low as revealed by thin layer chromatography. By use of column chromatography *N-tert*-butyloxycarbonyl-*O*-benzyl-L-threonine was isolated in 14% yield.

Experimental Section[5]

***N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine Cyclohexylammonium salt.** To a solution of *N-tert*-butyloxycarbonyl-L-serine[6] (2.05 g, 10 mmol) in dimethylformamide (50 ml) was added sodium hydride (65%) (820 mg, 22 mmol) at 0 °C. After the evolution of hydrogen gas ceased, the freshly distilled benzyl bromide (1.88 g, 11 mmol) was added to the solution. The reaction mixture was stirred at 25–30 °C for 5 h to give a clear solution. The solvent was then removed under reduced pressure below 40 °C. The residue was dissolved in water (50 ml) and the solution was extracted with ether (two 20-ml portions). The aqueous phase was acidified to pH 3.5 with 3 N HCl, and extracted with ethyl acetate (five 20-ml portions). The combined organic layers were washed with water and dried over magnesium sulfate. The ethyl acetate was removed under reduced pressure to give a colorless oil. The oil was then dissolved in ether (30 ml) and cyclohexylamine (0.9 g) was added to the solution. A precipitate formed and was collected by filtration. The solid was washed well with ether. Recrystallization from ethyl acetate yielded the title compound (2.2 g, 57%): mp 159–160 °C; $[\alpha]^{25}D$ +29.0° (c 1, methanol) [authentic sample prepared by the known method,[6] mp 159–160 °C; $[\alpha]^{25}D$ +29.8° (c 1, methanol)].

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_6H_{13}N$: C, 63.93; H, 8.69; N, 7.10. Found: C, 63.76; H, 8.54; N, 6.89.

Optical Purity of *O*-Benzyl-L-serine. One gram of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine prepared by the above procedure was dissolved in 2 N HCl–AcOH (5 ml). After 1 h at room temperature, the solvent was evaporated under reduced pressure below 35 °C to yield crystals. The crystals showed the same optical rotations as a sample of *O*-benzyl-L-serine hydrochloride prepared by the method previously reported,[3] $[\alpha]^{25}D$ +7.4° (c 2, 1 N HCl).

Registry No.—*N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine cyclohexylammonium salt, 30200-52-3; *N-tert*-butyloxycarbonyl-L-serine, 3262-72-4; benzyl bromide, 100-39-0; *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine, 23680-31-1.

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(3) K. Okawa, *Bull. Chem. Soc. Jpn.*, **29**, 486 (1956).
(4) V. J. Hruby and K. W. Ehler, *J. Org. Chem.*, **35**, 1690 (1970).
(5) All melting points are uncorrected. Thin layer chromatography was performed on silica gel plates (Merck) using chloroform–methanol–acetic acid (95:5:3).
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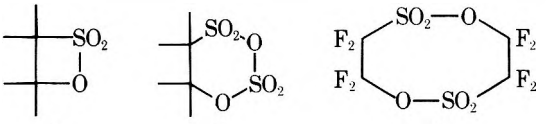
A Novel Reaction of Sulfur Trioxide with Fluoro Olefins

B. E. Smart

Contribution No. 2355 from the Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

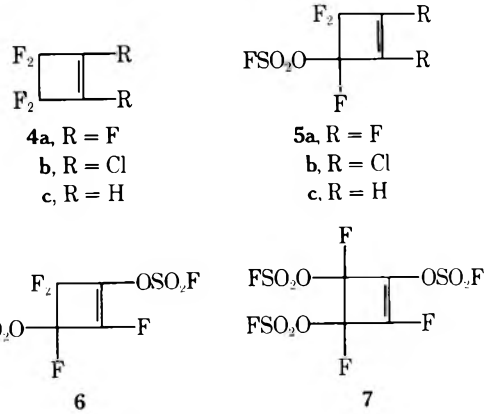
Received February 20, 1976

It is well known that sulfur trioxide reacts with fluoro olefins to normally give stable β-sultones (**1**) and β-disultones (**2**).[1] Tetrafluoroethylene is reported to also give the unusual eight-membered ring heterocycle **3.** In some cases, the β-sultone products rearrange to alkenyl fluorosulfates (–C=C–OSO_2F) under the reaction conditions. Polyfluorocyclobutenes are reported here to react in a novel manner with sulfur trioxide to give a new class of products, 3-(fluorosulfato)polyfluorocyclobutenes.



1 **2** **3**

Hexafluorocyclobutene (**4a**) reacts slowly with sulfur trioxide at room temperature and reacts rapidly at 100 °C to give a mixture of 63% **5a,** 32% **6,** and 5% **7** (65% conversion, 91% yield). At 100 °C, **4a** reacts with 2 equiv of sulfur trioxide to give 34% **5a,** 50% **6,** and 16% **7.** Similarly at 100 °C, **4b** gives **5b.** 3,3,4,4-Tetrafluorocyclobutene (**4c**) reacts exothermally with sulfur trioxide at room temperature to give **5c** in 74% yield. There are no appreciable sultone products or 1-cycloalkenyl fluorosulfate monoadducts detected in these reactions.



4a, R = F
b, R = Cl
c, R = H

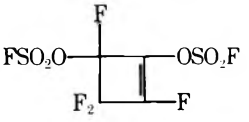
5a, R = F
b, R = Cl
c, R = H

6 **7**

In contrast with **4a** and **4b,** the acyclic analogue octafluoro-2-butene, $CF_3CF{=}CFCF_3$, does not react appreciably with sulfur trioxide at 100 °C,[2] and 2,3-dichlorohexafluoro-2-butene, $CF_3CCl{=}CClCF_3$, is reported to give the β-sultone.[3]

The structures of the reaction products are readily established by ir and NMR analyses. The comparable carbon–carbon double bond vibrational stretching frequencies in **4a–c** and **5a–c** confirm the double bond substitution pattern: **5a** (1792 cm^{-1}), **4a** (1799 cm^{-1}), **5b** (1629 cm^{-1}), **4b** (1620 cm^{-1}), **5c** (1561 cm^{-1}), **4c** (1560 cm^{-1}). The double bond stretching frequencies in **6** and **7** appear at 1762 and 1765 cm^{-1}, respectively, which are comparable to the stretching frequency in 1-methoxypentafluorocyclobutene (1765 cm^{-1}). The NMR spectra of **5a–c** are also consistent with the assigned structures (see Experimental Section).

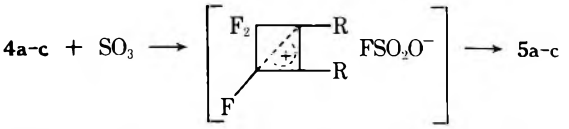
For the 2:1 adduct, it is not obvious whether **6** or **8** is the correct structure. The NMR spectrum of this adduct was



8

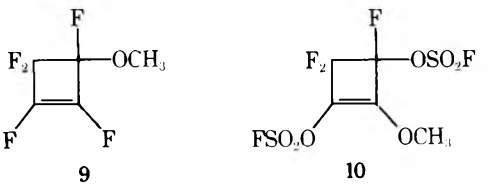
analyzed with computer assistance to obtain the F–F couplings (see Experimental Section). The vinyl fluorine cross couples with the nonequivalent geminal fluorines by 14.4 and 15.2 Hz, while it couples with an adjacent fluorine by 4.4 Hz. When compared with model fluorinated cyclobutenes, the observed couplings are consistent only with structure **6.**[4]

The initial step in the reaction of sulfur trioxide with olefins is normally an electrophilic attack by sulfur trioxide on the double bond to give an intermediate π complex which rearranges to a zwitterionic intermediate ($^+C–C–OSO_2^-$). Depending upon the fluoro olefin and the reaction conditions, this intermediate usually collapses directly to β-sultone product (**1**) or reacts with an additional 1 equiv of sulfur trioxide, followed by collapse to β-disultone (**2**). For the cyclobutenes **4a–c,** a competitive pathway which involves sulfur trioxide attack on an allylic fluorine to generate an intermediate cyclobutenyl fluorosulfate ion pair is suggested.



In contrast with acyclic alkenyl cations where charge is delocalized only by classical allyl resonance, cyclobutenyl cations can be further stabilized by 1,3-π overlap.[5] This may in part contribute to the increased reactivity of **4a** over its acyclic analogue, octafluoro-2-butene. Similarly, the potential allyl cation generated by attack of sulfur trioxide on an allylic fluorine in 2,3-dichlorohexafluoro-2-butene is less stable than the corresponding cyclobutenyl cation generated from **4b;** therefore, sulfur trioxide preferentially adds to the double bond in the acyclic alkene to give normal β-sultone product.

The cyclobutenyl fluorosulfates **5** are useful alkylating agents. For example, methanolysis of **5a** gives **9** in 80% yield, the only known practical route to this compound.[6] Methanolysis of **6** gives a modest yield (40%) of **10.**

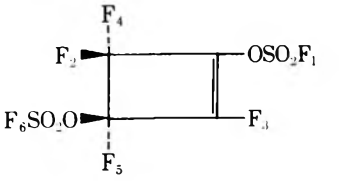


9 **10**

Experimental Section

All NMR spectra were recorded on a Varian Associates XL-100 spectrometer. The ^1H NMR spectra are referenced to internal tetramethylsilane and the ^{19}F NMR spectra are referenced to internal

Table I



	F_1	F_2	F_3	F_4	F_5	F_6
ϕ, ppm	+44.70	−113.14	−113.29	−115.92	−121.26	+48.21

Couplings

Fx,y	J, Hz	Fx,y	J, Hz
1,2	1.5	3,4	14.4
1,3	3.6	3,5	4.4
1,4	1.4	3,6	1.0
2,3	15.2	4,5	−11.8
2,4	188.8	4,6	0.7
2,5	27.4	5,6	9.8
2,6	3.4	1,5; 1,6	0.0

trichlorofluoromethane. Infrared spectra were recorded on a Perkin-Elmer 467 spectrophotometer. Baker and Adams stabilized sulfur trioxide (Sulfan) was employed. All boiling points are uncorrected.

3-(Fluorosulfato)-1,2,3,4,4-pentafluorocyclobutene (5a), 1,3-Bis(fluorosulfato)-2,3,4,4-tetrafluorocyclobutene (6), and 1,2,3-Tris(fluorosulfato)-2,3,4,4-trifluorocyclobutene (7). Two 250-ml Carius tubes, one charged with 60 g (0.37 mol) of hexafluorocyclobutene (**4a**) and 24 g (0.30 mol) of sulfur trioxide and the other charged with 63 g (0.39 mol) of **4a** and 0.30 mol of sulfur trioxide, were heated on a steam bath for 16 h. The tubes were opened, and the contents were combined and distilled to give 59.5 g of **4a** and 53 g of **5a**: bp 49–50 °C (150 mm); ir (neat) 1792 cm^{-1} (C=C); NMR (CCl_4) ϕ +47.6 (d of d of m, 1, J = 9.8, 3.1 Hz), −115.4, −118.2 (AB m of m, 2, J_{AB} = 189 Hz), −121.6 (complex m, 1), −125.7 (complex m, 1), −126.2 (complex m, 1).

Further distillation gave 37.7 g of **6**: bp 79–80 °C (50 mm), ir (neat) 1762 cm^{-1} (C=C), and 6.8 g of **7**, bp 85–88 °C (11 mm), ir (neat) 1765 cm^{-1} (C=C).[7]

Anal. Calcd for $C_4F_6O_3S$ (**5a**): C, 19.84; F, 47.08; S, 13.24. Found: C, 19.75; F, 47.06; S, 13.29. Calcd for $C_4F_6O_6S_2$ (**6**): C, 14.91; F, 35.38; S, 19.90. Found: C, 14.80; F, 35.28; S, 20.12. Calcd for $C_4F_6O_9S_3$ (**7**): C, 11.94; F, 28.34; S, 23.91. Found: C, 12.26; F, 28.57; S, 23.95.

Similarly, 0.1 mol of **4a** and 0.1 mol of sulfur trioxide at 100 °C for 2 h gave a mixture of 68% **5a** and 32% **6** (65% conversion, 91% yield).

The NMR spectral parameters for **6** are given in Table I.[8]

3-(Fluorosulfato)-1,2-dichloro-3,4,4-trifluorocyclobutene (5b). A mixture of 19.5 g (0.10 mol) of **4b** and 0.1 mol of sulfur trioxide in a Carius tube was heated on a steam bath for 14 h. The product mixture was fractionated to give 12.2 g of **5b**: bp 77–78 °C (80 mm); ir (neat) 1629 cm^{-1} (C=C); NMR (CCl_4) ϕ +48.6 (d of d, 1, J = 10, 4.5 Hz), −112.9, −115.5 (AB m of m, 2, J_{AB} = 190 Hz; A, d of d, J = 22, 4.5 Hz; B, d, J = 9 Hz), −120.4 (d of t, 2, J = 22, 9 Hz).

Anal. Calcd for $C_4Cl_2F_4O_3S$: C, 17.47; F, 27.63; S, 11.66. Found: C, 16.69; F, 26.83; S, 11.91.

3-(Fluorosulfato)-3,4,4-trifluorocyclobutene (5c). Neat **4c** (12.6 g, 0.10 mol) was treated dropwise with 0.1 mol of sulfur trioxide (exotherm to ca. 40 °C). After stirring for 2 h the mixture was fractionated to give 15.3 g of **5c**: bp 62–63 °C (50 mm); ir (neat) 1561 cm^{-1} (very weak C=C); Raman 1561 cm^{-1} (intense); NMR (CCl_4), ^1H δ 6.90, 6.94 (complex AB m of m, 2, J_{AB} = 3.4 Hz), ^{19}F ϕ + 46.9 (d of d, 1, J_{FF} = 9.8, 2 Hz), −107.5, −119.7 (complex AB m of m, 2, J_{AB} = 198 Hz; A, d of d of m, J_{FF} = 25, 2 Hz; B, d of m, J_{FF} = 6.2 Hz), −112.8 (complex m, 1, J_{FF} = 25, 9.8, 6.2 Hz).

Anal. Calcd for $C_4H_2F_4O_4S$: C, 23.31; H, 0.98; F, 36.88. Found: C, 23.76; H, 1.03; F, 36.87.

3-Methoxy-1,2,3,4,4-pentafluorocyclobutene (9). A solution of 12.1 g (0.05 mol) of **5a** in 50 ml of methanol was refluxed for 30 min. The reaction mixture was carefully fractionated to give 7.0 g (80%) of **9**: bp 45–46 °C; ir (neat) 1785 cm^{-1} (C=C); NMR (CCl_4), ^1H δ 3.63 (d, $J \simeq 1$ Hz), ^{19}F ϕ −118.5, −120.3 (AB m of m, 2, J_{AB} = 188 Hz), −129.3 to −128.4 (complex m, 2), −135.3 (complex m, 1).

Anal. Calcd for $C_5H_3F_5O$: F, 34.50. Found: F, 34.61.

1,3-Bis(fluorosulfato)-2-methoxy-3,4,4-trifluorocyclobutene (10). To 50 ml of methanol chilled in an ice bath was added dropwise 16.1 g (0.05 mol) of **6**. After slowly warming to room temperature, the reaction mixture was quenched in 100 ml of cold water. The organic layer was taken up in methylene dichloride, washed with water and saturated sodium chloride, and dried ($MgSO_4$) and fractionated to give 6.3 g (40%) of **10**: bp 60 °C (1 mm); ir (neat) 1740 cm^{-1} (C=C); NMR (CCl_4), ^1H δ 4.20 (s). ^{19}F ϕ +48.3 (d of d, 1, J = 8.8, 5 Hz), +42.0 (t, 1, J = 5 Hz), −108.9, −111.5 (AB m of m, 2, J_{AB} = 188 Hz; A, d of t, J = 22, 5 Hz; B, d of d, J = 11, 5 Hz), −123.0 (d of d of d, 1, J = 22, 11, 8.8 Hz).

Anal. Calcd for $C_5H_3F_5O_7S_2$: C, 18.87; H, 0.95; F, 29.87. Found: C, 18.59; H, 1.16; F, 29.77.

Registry No.—**4a**, 697-11-0; **4b**, 377-93-5; **4c**, 2714-38-7; **5a**, 59034-67-2; **5b**, 59034-68-3; **5c**, 59034-69-4; **6**, 59034-70-7; *cis*-**7**, 59034-71-8; *trans*-**7**, 59034-72-9; **9**, 59034-73-0; **10**, 59034-74-1; sulfur trioxide, 14265-45-3.

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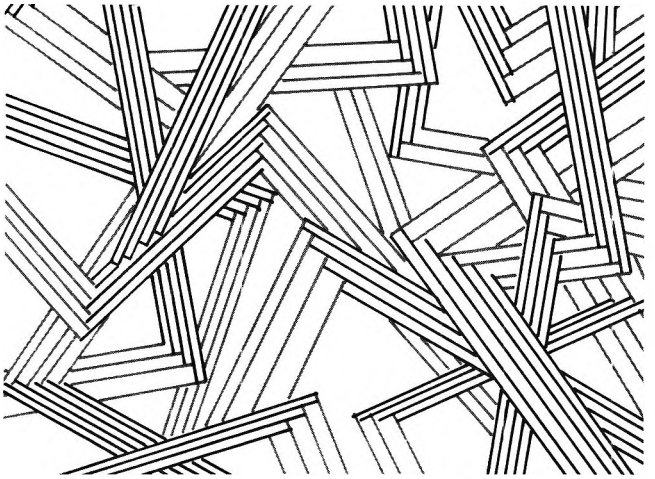
(1) See I. L. Knunyants and G. A. Sokolski, *Angew. Chem., Int. Ed. Engl.*, **11**, 583 (1972), and references cited therein for a review of sulfur trioxide additions to fluoro olefins.
(2) C. G. Krespan, unpublished results.
(3) Y. H. Kwei, *Acta Chim. Sinica*, **26**, 330 (1957).
(4) Vinyl and allyl fluorine cross couplings are typically 16–19 Hz, while vinyl and adjacent allyl couplings are 4–8 Hz; see K. Jones and E. F. Mooney, *Annu. Rep. NMR Spectrosc.*, **4**, 414 (1971).
(5) See G. A. Olah et al., *J. Am. Chem. Soc.*, **97**, 3489 (1975), and references cited therein for a discussion of 1,3 interactions in cyclobutenyl cations.
(6) Hexafluorocyclobutene reacts with methoxide ion to give 1-methoxypentafluorocyclobutene and 1,2-dimethoxytetrafluorocyclobutene but only a trace of **9**; see J. D. Park, R. J. McMurtry, and J. H. Adams, *Fluorine Chem. Rev.*, **2**, 60–61 (1968).
(7) The NMR spectrum of **7** is exceedingly complex and indicates a mixture of cis and trans isomers. The absence of typical 180–200 Hz geminal fluorine couplings rules out the possible 1,3,3-tris(fluorosulfato)-2,4,4-trifluorocyclobutene product.
(8) This molecule was analyzed as a six-spin ABCDMX system using a LAOCOON III program. The agreement between the observed and calculated spectra is within 0.1 Hz. The solution is unique and the negative sign for J_{45} is correct. The estimated uncertainties in the chemical shifts and coupling constants are 0.001 ppm and 0.1 Hz, respectively. The assistance of Dr. G. S. Reddy is gratefully acknowledged for this analysis.



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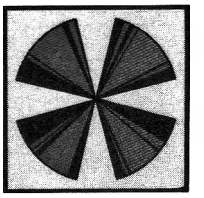

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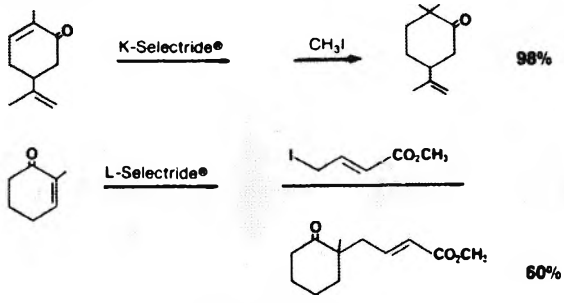

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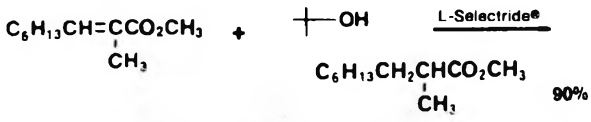
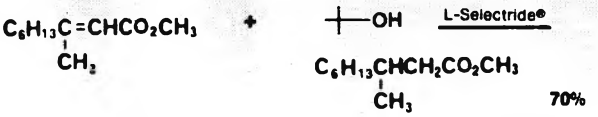
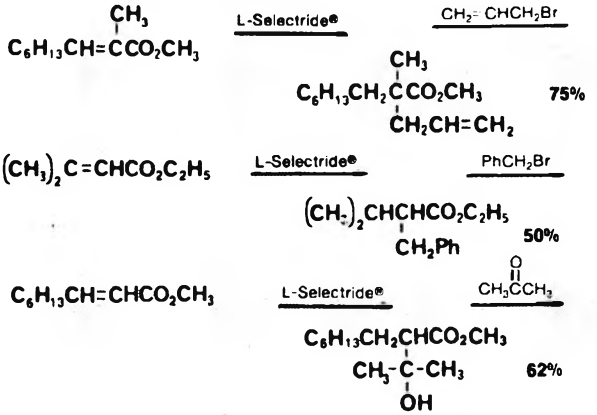




Alkylation of these **Selectride**-produced ester-enolates is possible and is of obvious synthetic potential.[3]



This new alkylation process based on **Selectride**-generated ester-enolates gives results comparable to the reaction involving low temperature metallation of saturated esters using lithium dialkylamides.

Selectride reagents have been accepted as useful stereoselective reducing agents for cyclic ketones.[4] The present development by Professor Ganem emphasizes the versatility of these reagents. Thus, the **Selectrides** should now find further usage as reagents for carbon-carbon bond formation *via* reductive alkylations.

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2) E.J. Corey, K.B. Becker, and R.K. Varma, *J. Amer. Chem. Soc.*, **94**, 8616 (1972).
3) J.M. Fortunato and B. Ganem, *J. Org. Chem.*, **41**, 2194 (1976).
4) For two recent applications, see J.A. Marshall and R.H. Ellison, *J. Org. Chem.*, **40**, 2070 (1975); G. Stork and M. Isobe, *J. Amer. Chem. Soc.*, **97**, 4745 (1975).

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