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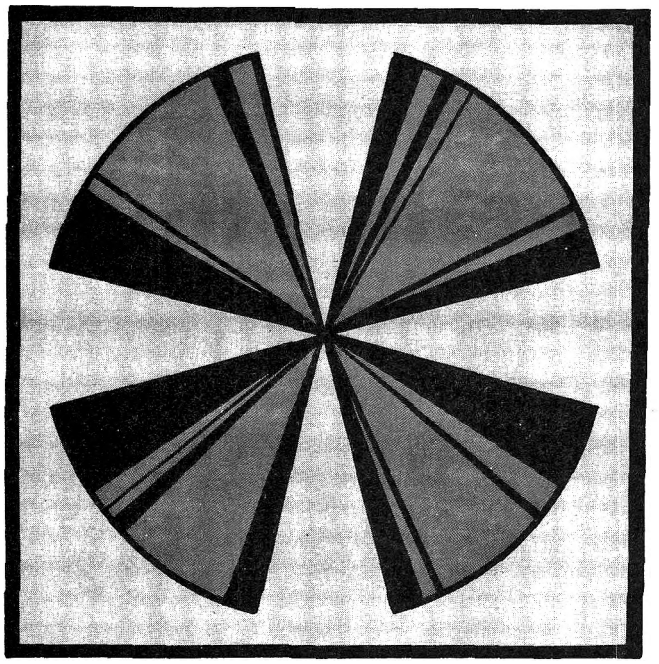

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VOLUME 40, NUMBER 12

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Synthesis of and Base-Induced Rearrangements in the 1,4-Diazabicyclo[4.1.0]hept-4-ene System

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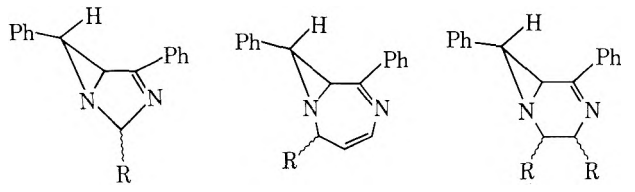
Received January 16, 1975

The synthesis and base-induced reactions of 2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-enes are described. These compounds are prepared from the reaction of *meso*- and *rac*-stilbenediamine with 1,3-diphenyl-2,3-dibromo-1-propanone. The assignment of stereochemistry about the ring system was made on the basis of the NMR spectra of the various structural isomers. The 1,4-diazabicyclo[4.1.0]hept-4-ene ring system was found to undergo an interesting set of reactions on treatment with base. The particular product formed was found to depend on both the initial stereochemistry of the ring system as well as on the experimental conditions used. The exo,exo isomer **4** gave 1-benzyl-2,3,5-triphenyldihydropyrazine (**10**) on treatment with potassium *tert*-butoxide. The other possible isomeric diazabicycloheptenes gave triphenylpyrazine when benzene was used as a solvent. When the reaction was carried out in *tert*-butyl alcohol, 2-benzyl-3,5,6-triphenylpyrazine (**7**), 2,3,5,7-tetraphenyl-1,4-diazacycloheptatriene (**13**), and 2,4,5,7-tetraphenyl-3,6-diazabicyclo[3.2.0]hepta-3,6-diene were isolated as the major products. The mechanistic pathways involved in the base-induced reactions are discussed.

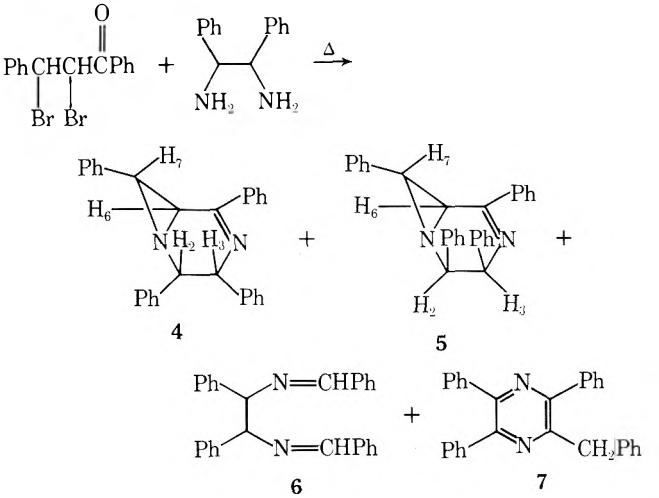
The synthesis and cycloaddition reactions of the 1,3-diazabicyclo[3.1.0]hex-3-ene (**1**) and 1,5-diazabicyclo[5.1.0]octa-3,5-diene (**2**) systems have previously been described.[2-4] The photo- and thermal reactions encountered with these fused aziridines were readily accounted for by carbon–carbon fission of the aziridine rings of **1** and **2** to form 1,3-dipolar intermediates (azomethine ylides).[2-4] The azomethine ylides were found to undergo 1,3-dipolar cycloaddition reactions with homo and hetero multiple bonds to give a variety of heterocyclic rings.[5-9] The formation of the azomethine ylides was envisioned as an electrocyclic process proceeding by either conrotatory or disrotatory ring opening.[10] In addition, both Heine's and our own research group have described some interesting rearrangements which occur when these systems were treated with base.[2,3] As part of our continuing interest in fused aziridines, we have extended our investigations to include the 1,4-diazabicyclo[4.1.0]hept-4-ene system (**3**). The present



1 **2** **3**

paper describes the synthesis of several 2,3-disubstituted 1,4-diazabicyclo[4.1.0]hept-4-enes and the unusual rearrangements that these systems undergo when treated with base.

Of the several possible methods to gain synthetic entry into the 1,4-diazabicyclo[4.1.0]hept-4-ene system,[11] the route involving the reaction of a dibromo ketone and a 1,2-diamine seemed most feasible. Heine and Henzel had previously demonstrated that 1-phenyl-2,3-dibromo-3-aryl-1-propanones underwent reaction with ethylenediamine and *o*-phenylenediamine to give the 1,4-diazabicyclo[4.1.0]hept-4-ene and 1,1a-dihydro-1,2-diarylazirino[1,2-*a*]quinoxaline rings.[12] When 1,3-diphenyl-2,3-dibromo-1-propanone was allowed to react with *meso*-stilbenediamine in an ethanolic solution containing triethylamine and small quantities of ammonium bromide, a mixture of four compounds was obtained. Fractional crystallization of the mixture resulted in the isolation of a crystalline solid, mp 160–161°, whose structure was assigned as (2α,3α,6α,7α)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (**4**) on



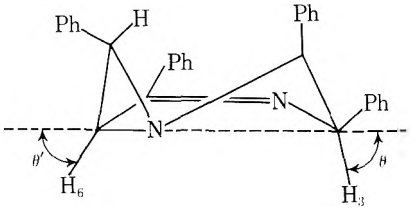
4 **5**

6 **7**

the basis of its spectral and analytical properties. The diazabicyclic **4** displayed a maximum at 252 nm (ε 17,000) in

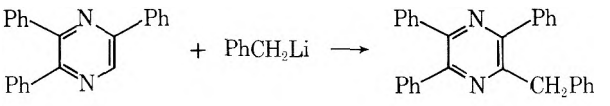
the ultraviolet region. Its NMR spectrum showed the two aziridinyl protons at τ 6.78 (H_6, d, J = 3.0 Hz) and 6.45 (H_7, d, J = 3.0 Hz), the two benzylic protons at 5.68 (H_2, d, J = 6.5 Hz) and 4.91 (H_3, d, J = 6.5 Hz), and the aromatic protons as a multiplet centered at τ 2.07–3.20. The spatial relationship of the phenyl groups was established experimentally by application of nuclear Overhauser effects.[13] Double irradiation of the signal at τ 5.68 or 4.91 gave evidence of a 17–25% intensity enhancement in the τ 6.45 peak. Accordingly, the tertiary benzylic hydrogens (H_2 and H_3) and the aziridinyl hydrogen (H_7) must be proximal, an observation which requires the spatial relationship embodied in the exo,exo isomer (**4**).

A small quantity of the isomeric (2α,3α,6β,7β)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (**5**), mp 146–147°, was also isolated from the reaction mixture. The yield of this material could be substantially improved if the reaction conditions were slightly altered. This was done by using chloroform as the solvent and carrying out the reaction at room temperature. Under these conditions a 40% yield of diazabicyclic **5** was obtained. The NMR spectrum of **5** consisted of a doublet of doublets at τ 6.84 (H_6, J = 3.0 and 1.5 Hz), a set of doublets at τ 6.45 (H_7, J = 3.0 Hz) and 4.98 (H_2, J = 5.5 Hz), and a doublet of doublets at τ 4.50 (H_3, J = 5.5 and 1.5 Hz) as well as a 20-proton multiplet at τ 2.50–3.10. Inspection of molecular models shows that protons H_3 and H_6 for this isomer are oriented in such a manner that homoallylic coupling across the C–N double bond should be at a maximum. Examples of homoallylic coupling across a C–C double bond have been observed previously and give rise to a coupling constant which ranges from 0.2 to 1.8 Hz.[14] The magnitude of homoallylic coupling is known to be dependent on the angles θ and θ' between the plane of the C=N double bond and the C_1–H_1 and C_4–H_4 bonds, respectively.[14] The coupling magnitude will be greatest when θ and θ' are 90° and will be at a minimum when the angles are at 0°. For diazabicycloheptene **5**, protons H_3 and H_6 are oriented in such a fashion that both θ and θ' are approximately 80° in the conformation shown below. The isomeric diazabicycloheptene **4** does not exist in



a conformation where both θ and θ' have the proper angle to allow for significant homoallylic coupling. On this basis, we can distinguish between the two isomeric diazabicycloheptenes. Spin decoupling of structure **5** was also carried out in order to verify the existence of the homoallylic coupling. When the doublet of doublets at τ 4.50 (H_3) was saturated with an external field, the doublet of doublets at τ 6.84 (H_6, J = 3.0 and 1.5 Hz) collapsed to a simple doublet (J = 3.0 Hz). Similarly, double irradiation of the signal at τ 6.84 resulted in the collapse of the double doublet at τ 4.50 to a simple doublet (J = 5.5 Hz). Accordingly, the tertiary benzylic hydrogen (H_3) and the aziridinyl hydrogen (H_6) must be homoallylically coupled, an observation which requires an endo orientation of the C_3 phenyl ring.

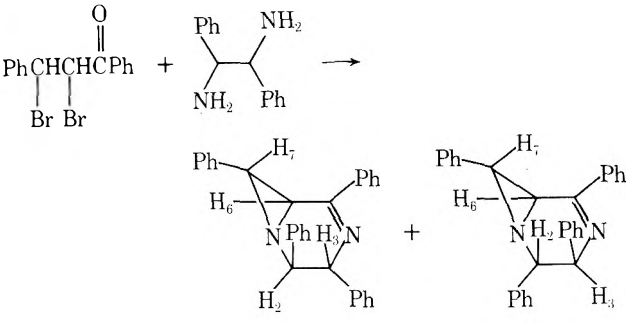
In addition to the two isomeric 1,4-diazabicyclo[4.1.0]heptenes (**4** and **5**), two additional compounds, **6** (19%) and **7** (5%), were also isolated from the reaction of *meso*-stilbenediamine with 1,4-diphenyl-2,3-dibromo-1-propanone. Structure **6** was identified as 1,3,4,6-tetraphenyl-2,5-diazahexa-1,5-diene, mp 166–167°, by comparison with an authentic sample prepared from the reaction of *meso*-stilbenediamine with benzaldehyde. Structure **7** was assigned as 2-benzyl-3,5,6-triphenylpyrazine, mp 141–142°, on the basis of its spectral properties: uv (95% ethanol) 326 nm (ϵ 15,800), 303 (ϵ 15,200), and 272 (ϵ 15,400); NMR ($CDCl_3$) τ 5.60 (s, 2 H) and 2.20–2.76 (m, 20 H); *m/e* 398 (M^+). This structure was unambiguously verified by comparison with an authentic sample of **7** which was prepared by treating triphenylpyrazine with benzyllithium according to the general procedure of Klein and Spoerri.[15]



7

A mechanistic rationale which accounts for the formation of **6** is based on the premise that benzaldehyde is produced in small quantities during the reaction.[16] Stilbenediamine will then condense with the generated benzaldehyde to produce compound **6**. The formation of diazabicycloheptenes **4** and **5** can be conveniently rationalized by a series of reactions which are analogous to those proposed to account for the formation of *N*-alkylaroylaziridines from the reaction of dibromochalcone with alkylamines.[17] A mechanism for the formation of 2-benzyl-3,5,6-triphenylpyrazine (**7**) will be put forth at a later point in this paper.

Treatment of 1,3-diphenyl-2,3-dibromo-1-propanone with *rac*-stilbenediamine proceeded in an analogous fashion and afforded a mixture of (2α,3β,6β,7β)- and (2α,3β,6α,7α)-2,3,5,7-tetraphenyl-1,4-diazabicyclo-[4.1.0]hept-4-ene (**8** and **9**). The mixture could be separated

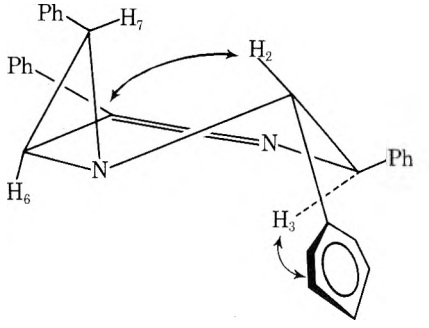


8 9

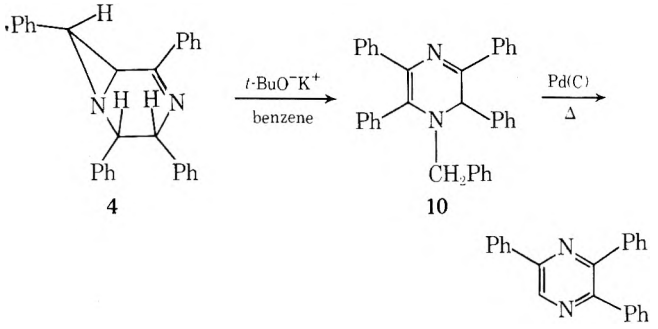
by silica gel chromatography using a 15% ether–85% cyclohexane mixture. The structure assigned to the first material obtained from the chromatography column was (2α,3β,6β,7β)-2,3,5,7-tetraphenyl-1,4-diazabicyclo-[4.1.0]hept-4-ene (**8**), mp 159–160°. The NMR spectrum of **8** shows proton H_2 as a doublet at τ 6.80 (J = 9.0 Hz). This unusually high field position can be attributed to anisotropic shielding of this proton by the neighboring phenyl ring. Proton H_3 also appears as a doublet (τ 5.42, J = 9.0 Hz) and is also located at a higher field position than the corresponding proton in structures **4** or **5**. This again can be attributed to the anisotropic shielding by the neighboring phenyl group. The two aziridinyl protons appear to be magnetically equivalent, since they both appear as a singlet at τ 7.10. This equivalence can be explained by the large upfield shift experienced by proton H_7 and is undoubtedly due to the anisotropic shielding by the C_2 phenyl ring. Proton H_6 is also shielded, but to a lesser extent by the C_3 phenyl ring.

The second fraction isolated from the chromatographic separation was assigned the structure of (2α,3β,6α,7α)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (**9**), mp 206°. The stereochemistry of this diazabicyclic system

follows from an analysis of its diagnostic NMR spectrum. The signal corresponding to proton H_2 in **9** appeared as a doublet at τ 6.40 (J = 10.0 Hz). The appearance of this proton (H_2) at a higher field relative to proton H_2 in **5** (τ 4.98) is consistent with the anisotropic shielding of this proton by the adjacent aziridine ring.[18] Proton H_3 also appears at high field as a broad doublet at τ 5.40 (J = 10.0 Hz). The high field position of H_3 can also be attributed to the shielding effect of the C_2 phenyl ring. Proton H_7 of structure **9** appears as a doublet at τ 6.04 (J = 2.0 Hz), and proton H_6 appears as a broad doublet at τ 6.60 (J = 2.0 Hz). The broad nature of the doublets assigned to protons H_3 and H_6 can be attributed to a long-range homoallylic coupling across the C–N double bond. Double irradiation of the signal at τ 5.40 resulted in the collapse of the τ 6.60 broad doublet to a clean doublet (J = 2.0 Hz). When the doublet at τ 6.04 was irradiated with an external field, the broad doublet at τ 6.60 collapsed to a broad singlet. These observations require that the stereochemistry of the phenyl ring at C_3 be located in the endo position. The most likely conformation of diazabicycloheptene **9** which accounts for the NMR data is that shown below.

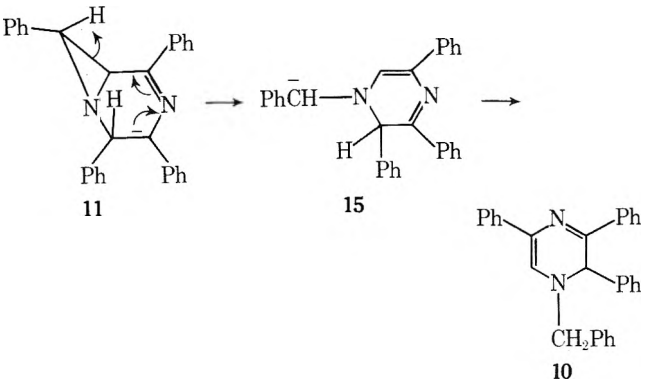


The 1,4-diazabicyclo[4.1.0]hept-4-ene ring system was found to undergo an interesting set of reactions on treatment with base. The particular product formed was found to depend on both the initial stereochemistry of the ring system as well as the experimental conditions used. Thus, treatment of diazabicycloheptene **4** with potassium *tert*-butoxide in benzene afforded a yellow solid, mp 128–129°, in good yield. This compound was assigned the structure of 1-benzyl-2,3,5-triphenyldihydropyrazine (**10**) on the basis

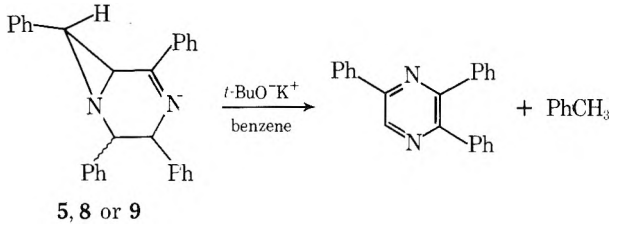


of its spectroscopic and chemical properties. The infrared spectrum of **10** showed an absorption band at 6.23 μ, characteristic of a C=N double bond. The NMR spectrum consisted of singlets at τ 4.54 (1 H) and 3.44 (1 H), an AB quartet centered at τ 5.55 (2 H, J = 14.0 Hz), and a multiplet located at τ 2.4–3.0 (20 H). The mass spectrum showed the molecular ion at m/e 400 and also exhibited a major peak at m/e 309 corresponding to the loss of a benzyl group. Chemical confirmation of this structure was obtained by dehydrogenation of **10** with palladium on charcoal to triphenylpyrazine.

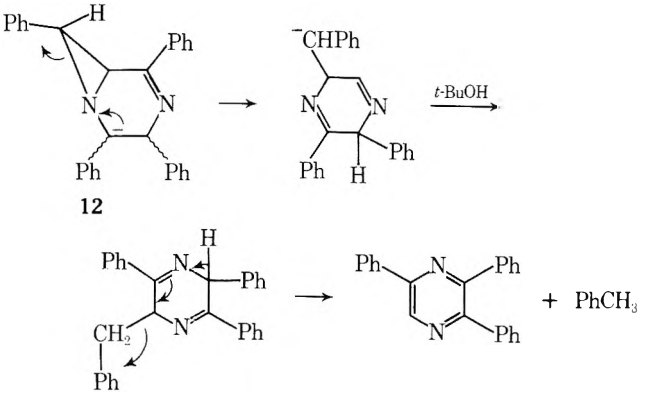
A mechanistic rationalization of the formation of **10** from the base treatment of **4** is based on the premise that the initially generated carbanion (**11**) induces carbon–carbon bond cleavage of the aziridine ring. This step is then followed by protonation to give the final product.



It is interesting to note that treatment of the isomeric 1,4-diazabicyclo[4.1.0]heptenes **5**, **8**, or **9** with potassium *tert*-butoxide, under conditions identical with those outlined above, did not produce any detectable quantities of 1-benzyl-2,3,5-triphenyldihydropyrazine (**10**). Instead, the two products formed were toluene and triphenylpyrazine.



A control experiment showed that dihydropyrazine **10** was stable under the reaction conditions. The absence of dihydropyrazine **10** from the base treatment of diazabicycloheptenes **5**, **8**, and **9** indicates that these isomers rearrange by a different pathway from that encountered with diazabicycloheptene **4**. The formation of triphenylpyrazine can be postulated to arise by carbon–nitrogen bond cleavage of the aziridine ring. The two reaction pathways differ primarily



in the site of proton removal. Inspection of molecular models shows that the C_2 proton in structure **4** is situated in a sterically congested environment and consequently removal of this proton by the bulky *tert*-butoxide is sterically hindered. Instead, proton loss occurs at C_3 to generate carbanion **11**. On the other hand, proton loss with the isomeric diazabicycloheptenes (**5**, **8**, and **9**) occurs on the more accessible C_2 carbon to generate anion **12**, which subsequently undergoes carbon–nitrogen ring opening.

When the base-induced reactions of diazabicycloheptenes **5**, **8**, or **9** were carried out at 60° in the presence of *tert*-butyl alcohol, three new products were formed. The

relative yields of these three new compounds were found to vary as a function of time. Careful examination of the product distribution showed that compounds **7** and **13** were formed shortly after the addition of base. After 3 hr, the yield of **13** began to decrease while compound **14** started to appear in the reaction mixture. When the reaction was carried out at room temperature, only compounds **7** and **13** could be detected. From these observations we conclude that **7** and **13** are products which result from two separate mechanistic pathways which are operating concurrently. Further experiments showed that **13** was converted to **14** in high yield when it was heated in benzene. Compound **13** was assigned the structure of 2,3,5,7-tetraphenyl-1,4-diazacyclohepta-1,3,5-triene, mp 152–154°, on the basis of its spectroscopic properties: ir (KBr) 6.22 μ; uv (95% ethanol) 263 nm (ϵ 26,600) and 335 (4800); NMR ($CDCl_3$) τ 5.52 (s, 1 H) and 1.8–2.9 (m, 21 H); *m/e* 398 (M^+), 308, 295 (base), 103, and 77. The structure of **14** was assigned as (1α,2β,5α)-2,4,5,7-tetraphenyl-3,6-diazabicyclo-[3.2.0]hepta-3,6-diene, mp 205–206°, on the basis of a mass spectrum parent peak at *m/e* 398, infrared absorptions at 6.23 and 6.59 μ, uv absorptions at 384 (ϵ 13,900) and 257 nm (31,000), and NMR signals at τ 7.78 (1 H, d, J = 11.0 Hz) and 4.50 (1 H, d, J = 11.0 Hz) as well as a 20-proton multiplet located at τ 1.9–2.9. The chemical shift of proton H_1 (τ 7.78) in **14** is similar in position to the corresponding proton of the carbocyclic analog (2,2,6-trimethylbicyclo-[3.2.0]hepta-3,6-diene) which has been reported to have a value of τ 7.30.[19] The position of proton H_2 (τ 4.50) in structure **14** is similar to the analogous proton in 2,5-diphenyl-Δ^1-pyrroline, which has been reported to absorb at τ 4.28.[20] The observed coupling constant for the two tertiary hydrogens in **14** (J = 11.0 Hz) can be accounted for if one assumes a cis vicinal relationship between protons H_1 and H_2.[21] The formation of **14** from the thermolysis of **13** corresponds to a 4π-electrocyclic ring closure.

The ring expansion of diazabicycloheptenes (**5**, **8**, or **9**) into diazacycloheptatriene **13** is envisaged to occur by removal of the proton at C_2 to give carbanion **12**, which undergoes a subsequent ring opening in one of two directions. One direction involves a cleavage of the exocyclic C–N bond of the aziridine ring to produce a dihydropyrazine which, in this case, is preferentially oxidized to the corresponding pyrazine rather than eliminating benzyl carbanion as had been observed in the absence of *tert*-butyl alcohol. This route would also account for the formation of the small amount of **7** formed from the reaction of dibromochalcone and *meso*-stilbenediamine in 95% ethanol. The other competitive path involves cleavage of the endocyclic C–N bond of the aziridine ring to generate carbanion **15**, which is subsequently oxidized to the final product (i.e., **13**). This path is closely related to the base-induced rearrangement of 2,4,6-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene to 2,4,6-triphenylpyrimidine.[2,3] Apparently, the presence of *tert*-butyl alcohol in the reaction mixture affects the reaction conditions in such a way that endocyclic C–N bond cleavage becomes competitive with exocyclic C–N ring cleavage. The reason for this is not apparent at this time and further work must be done before this point can be clarified. As expected, treatment of 1,4-diazabicycloheptene **4** with potassium *tert*-butoxide under similar reaction conditions gave no detectable quantities of structures **7**, **13**, or **14**. The only product isolated from this reaction was dihydropyrazine **10**. This result is consistent with the formation of a different carbanion (i.e., **11**) with this isomer as a consequence of the steric factors associated with proton removal.

Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 100 MHz using a Jeol MH-100 spectrometer.

Reaction of Dibromodihydrochalcone with *meso*-Stilbenediamine. A mixture containing 7.28 g of dibromodihydrochalcone, 4.16 g of *meso*-stilbenediamine,[22] 6 ml of triethylamine, and 100 mg of ammonium bromide in 230 ml of 95% ethanol was heated at reflux for 2 hr. The reaction mixture was cooled to 0° and a white solid precipitated out. Recrystallization of this material from 20% benzene–80% heptane gave 1.9 g (26%) of a white solid, mp 160–161°, whose structure was assigned as (2α,3α,6α,7α)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (**4**) on the basis of the following data.

Anal. Calcd for $C_{29}H_{24}N_2$: C, 86.96; H, 6.04; N, 7.00. Found: C, 87.04; H, 6.21; N, 7.04.

The infrared spectrum (KBr) showed absorption bands at 3.32, 6.20, 6.70, 6.90, 7.12, 7.98, 9.42, 9.70, 13.02, 13.20, 13.95, and 14.40 μ. The ultraviolet spectrum (95% ethanol) was characterized by a maximum at 252 nm (ϵ 17,000). The NMR spectrum ($CDCl_3$) showed doublets at τ 6.78 (1 H, J = 3.0 Hz), 6.45 (1 H, J = 3.0 Hz), 5.68 (1 H, J = 6.2 Hz), and 4.91 (1 H, J = 6.2 Hz) and a multiplet at τ 3.2–2.1 (20 H). The mass spectrum (70 eV) showed the molecular ion at *m/e* (rel intensity) 400 (1) and exhibited major peaks at 309 (27), 308 (85), 307 (25), 295 (84), 206 (53), 193 (63), 104 (100), and 91 (50).

The filtrate was evaporated to an oil and ether was added. Filtration of the ether slurry to remove triethylamine hydrobromide afforded an oil which was concentrated and crystallized from 95% ethanol to give 1.5 g (19%) of a white solid, mp 166–167°. The structure of this material was assigned as 1,3,4,6-tetraphenyl-2,5-diazahexa-1,5-diene (**6**) on the basis of the following data.

Anal. Calcd for $C_{28}H_{24}N_2$: C, 86.56; H, 6.23; N, 7.21. Found: C, 86.45; H, 6.35; N, 7.18.

The infrared spectrum (KBr) showed absorption bands at 3.32, 3.55, 6.18, 6.82, 6.90, 7.29, 9.20, 13.40, and 14.5 μ. The ultraviolet spectrum (95% ethanol) was characterized by a maximum at 252 nm (ϵ 34,300). The NMR spectrum ($CDCl_3$) showed a singlet at τ 5.28 (2 H) and a multiplet at τ 2.3–3.0 (20 H). The mass spectrum

(70 eV) showed the molecular ion at *m/e* (rel intensity) 388 (4) and a base peak at *m/e* 194.

An authentic sample of 1,3,4,6-tetraphenyl-2,5-diazahexa-1,5-diene (**6**) was prepared according to the procedure outlined below. A mixture containing 500 mg of *meso*-stilbenediamine and 550 mg of benzaldehyde in 25 ml of 95% ethanol was heated at reflux for 18 hr. Filtration of the solution afforded 850 mg of a white solid (82%). Recrystallization of this material from 95% ethanol gave a white solid, mp 166–167°, whose infrared spectrum was identical with that of a sample of **6** isolated from the reaction of dibromodihydrochalcone with *meso*-stilbenediamine. A mixture melting point of the two samples was undepressed at 166–167°.

Cooling the mother liquors from the reaction of dibromodihydrochalcone and *meso*-stilbenediamine deposited 2.1 g of a gummy solid which was chromatographed on a 2 × 55 cm Florisil column. The column was eluted with a 10% ethyl acetate–90% benzene mixture (200 ml) to afford 360 mg of a material which crystallized from 95% ethanol to give a white, crystalline solid, mp 141–142°. This material was assigned the structure of 2-benzyl-3,5,6-triphenylpyrazine (**7**) on the basis of the following data.

Anal. Calcd for $C_{29}H_{22}N_2$: C, 87.40; H, 5.57; N, 7.03. Found: C, 87.15; H, 5.66; N, 7.20.

The infrared spectrum (KBr) showed absorption bands at 6.69, 6.91, 7.21, 8.47, 8.75, 8.08, 9.20, 9.61, 9.71, 13.14, and 14.42 μ. The ultraviolet spectrum (95% ethanol) was characterized by maxima at 326 nm (ϵ 15,800), 303 (15,200), and 272 (15,400). The NMR spectrum ($CDCl_3$) showed a singlet at τ 5.60 (2 H) and a multiplet between τ 2.76 and 2.20 (20 H). The mass spectrum (70 eV) showed the molecular ion at *m/e* (rel intensity) 398 (100) and exhibited major peaks at *m/e* 295 (100), 191 (30), and 77 (22).

Structure **7** was further confirmed by an unequivocal synthesis. To a solution containing 0.003 mol of benzyllithium in 30 ml of dry ether was added 600 mg of triphenylpyrazine. The reaction mixture was allowed to stir at room temperature under a nitrogen atmosphere for 12 hr. The reaction mixture was then quenched with an aqueous solution of ammonium chloride and the ethereal layer was washed twice with water and dried over anhydrous magnesium sulfate. Concentration of the ether layer under reduced pressure gave a yellow oil which was subjected to preparative thick layer chromatography. The thick layer plate was developed with benzene and the band with R_f 0.44 was extracted with methylene chloride. Evaporation of the solvent left 210 mg of a white solid. Recrystallization of this material from 95% ethanol gave a white, crystalline solid, mp 141–142°. The infrared spectrum of this material was identical with that of a sample of **7** obtained from the reaction of dibromodihydrochalcone with *meso*-stilbenediamine. A mixture melting point of the two samples was undepressed at 141–142°.

The isomeric (2α,3α,6β,7β)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (**5**) could be isolated from the reaction of dibromodihydrochalcone with *meso*-stilbenediamine when chloroform was used as the solvent. A mixture containing 7.28 g of dibromodihydrochalcone, 4.16 g of *meso*-stilbenediamine, 6 ml of triethylamine, and 100 mg of ammonium bromide in 87 ml of chloroform was allowed to stand at room temperature for 7 days. At the end of this time the solution was washed four times with water and then dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give an amber oil. The oil was taken up in 50 ml of a 17% methylene chloride–83% methanol mixture and was allowed to stand for 2 days, at which time 3.05 g of a white solid precipitated. This material was identified as (2α,3α,6α,7α)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (**4**). The solution was filtered and the mother liquor was concentrated to give a yellow oil. Addition of 50 ml of methanol to this oil resulted in the precipitation of 2.3 g (33%) of a white solid which contained a 3:2 mixture of **4** and **5**. An 800-mg sample of the white solid was subjected to scanning liquid–liquid partition chromatography.[23] The optical density trace consisted of two major peaks. The first major component of the mixture contained 400 mg (51%) of a white solid which was recrystallized from 95% ethanol to give white needles, mp 146–147°. This material was assigned the structure of (2α,3α,6β,7β)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (**5**) on the basis of the following data.

Anal. Calcd for $C_{29}H_{24}N_2$: C, 86.96; H, 6.04; N, 7.00. Found: C, 86.91; H, 6.29; N, 6.94.

The infrared spectrum (KBr) shows absorption bands at 3.37, 6.17, 6.67, 6.89, 7.90, 9.38, 9.65, 12.20, 12.81, 12.95, 13.37, 13.70, and 14.40 μ. The ultraviolet spectrum (in 95% ethanol) was characterized by a maximum at 248 nm (ϵ 22,500). The NMR spectrum ($CDCl_3$) was characterized by a doublet of doublets at τ 6.84 (1 H, J = 1.5, 1.0 Hz), doublets at τ 6.45 (1 H, J = 3.0 Hz) and 4.98 (1 H, J = 5.5 Hz), a broad doublet at τ 4.50 (1 H, J = 5.5 Hz), and a multiplet between τ 3.1 and 2.0 (20 H).

Reaction of Dibromodihydrochalcone with *rac*-Stilbenediamine. A mixture containing 3.6 g of dibromodihydrochalcone, 2 g of *rac*-stilbenediamine,[24] 3 ml of triethylamine, 30 mg of ammonium bromide, and 100 ml of chloroform was allowed to stand at room temperature for 7 days. At the end of this time the solution was washed four times with water and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 2.4 g (65%) of a yellow oil. A 1.0-g sample of the oil was chromatographed on a 2 × 45 cm Brinkman silica gel 60 column. The column was eluted with a 15% ether–85% cyclohexane mixture at a flow rate of 3 ml/min. The first fraction collected was concentrated under reduced pressure to give 440 mg of a white solid. Recrystallization from 95% ethanol gave colorless prisms, mp 159–160°, whose structure was assigned as (2α,3β,6β,7β)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (**8**) on the basis of the following data.

Anal. Calcd for $C_{29}H_{24}N_2$: C, 86.96; H, 6.04; N, 1.00. Found: C, 86.91; H, 6.22; N, 6.94.

The infrared spectrum (KBr) showed absorption bands at 6.14, 6.70, 6.91, 7.11, 7.50, 7.69, 8.00, 8.30, 8.46, 9.11, 9.29, 9.38, 9.65, 9.85, 10.58, 10.80, 11.50, 13.10, 13.40, and 14.40 μ. The ultraviolet spectrum (95% ethanol) was characterized by a maximum of 250 nm (ϵ 19,000). The NMR spectrum ($CDCl_3$) contained a broad singlet at τ 7.10 (2 H), doublets at τ 6.80 (1 H, J = 9 Hz) and 5.42 (1 H, J = 9 Hz), and a multiplet between τ 3.1 and 2.0 (20 H).

The second fraction obtained from the column consisted of 410 mg of a white solid. Recrystallization from 95% ethanol gave colorless needles, mp 206–207°. This material was assigned as (2α,3β,6α,7α)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (**9**) on the basis of the following data.

Anal. Calcd for $C_{29}H_{24}N_2$: C, 86.96; H, 6.04; N, 1.00. Found: C, 86.74; H, 6.17; N, 6.93.

The infrared spectrum (KBr) showed absorption bands at 6.17, 6.69, 6.89, 7.11, 7.94, 8.47, 9.22, 9.40, 9.68, 10.58, 10.79, 10.97, 11.49, 12.01, 13.10, 13.44, and 14.40 μ. The ultraviolet spectrum (in 95% ethanol) was characterized by a maximum of 247 nm (ϵ 19,400). The NMR spectrum ($CDCl_3$) contained doublets at τ 6.60 (1 H, J = 2 Hz), 6.40 (1 H, J = 10 Hz), 6.04 (1 H, J = 2 Hz), and 5.40 (1 H, J = 10 Hz) and a multiplet between τ 2.9 and 2.1 (20 H).

Treatment of (2α,3α,6α,7α)-2,3,5,7-Tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (4) with Potassium *tert*-Butoxide. A solution containing 170 mg of **4** and 540 mg of potassium *tert*-butoxide in 50 ml of benzene was allowed to stir at room temperature for 5 hr. The reaction mixture was quenched with water and the organic layer was subsequently washed with water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give 130 mg (76%) of a yellow oil. Recrystallization from 95% ethanol afforded yellow needles, mp 128–129°. The structure of this material was assigned as 1-benzyl-2,3,5-triphenyldihydropyrazine (**10**) on the basis of the following observations. The infrared spectrum (KBr) showed bands at 6.23, 6.78, 6.88, 7.02, 7.32, 7.45, 8.23, 8.62, 9.23, 9.68, 11.88, 13.00, 13.20, 13.40, 14.26, and 14.50 μ. The ultraviolet spectrum (in 95% ethanol) was characterized by maxima at 315 nm (ϵ 14,300), 258 (17,600), and 238 (18,000). The NMR spectrum ($CDCl_3$) contained singlets at τ 4.54 (1 H) and 3.44 (1 H), an AB quartet at τ 5.55 (2 H, J = 14.0 Hz), and a multiplet between τ 3.0 and 2.4 (20 H). The mass spectrum (70 eV) showed the molecular ion at *m/e* (rel intensity) 400 (16) and exhibited major peaks at *m/e* 309 (28), 308 (90), 307 (70), 295 (16), 102 (100), and 91 (96).

Anal. Calcd for $C_{29}H_{24}N_2$: C, 86.96; H, 6.04; N, 7.00. Found: C, 87.21; H, 5.85; N, 6.92.

Oxidation of 1-Benzyl-2,3,5-triphenyldihydropyrazine with Palladium on Carbon. A mixture containing 130 mg of **10** and 50 mg of 5% palladium on carbon in 50 ml of benzene was heated at reflux for 32 hr. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to leave behind a yellow oil. Recrystallization of the oil from methanol gave 87 mg (87%) of a crystalline solid, mp 154–155°. The infrared and NMR spectra of this material were identical in all respects with those of an authentic sample of triphenylpyrazine.[3] A mixture melting point was undepressed at 154–155°.

Treatment of (2α,3α,6β,7β)-2,3,5,7-Tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (5) with Potassium *tert*-Butoxide. A solution containing 35 mg of **5** and 270 mg of potassium *tert*-butox-

ide in 50 ml of benzene was allowed to stir at room temperature for 4 hr. At the end of this time the reaction mixture was quenched with water and the organic layer was washed with water and then dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give a yellow oil which was recrystallized from 95% ethanol to give 48 mg of a crystalline solid, mp 154–155°. The infrared spectrum of this material was identical in all respects with that of an authentic sample of triphenylpyrazine.[3] A mixture melting point was undepressed at 153–154°.

Treatment of (2α,3α,6β,7β)-2,3,5,7-Tetraphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene with Potassium *tert*-Butoxide in the Presence of *tert*-Butyl Alcohol. A solution containing 85 mg of **5**, 270 mg of potassium *tert*-butoxide, and 5 ml of *tert*-butyl alcohol in 50 ml of benzene was allowed to stir at room temperature for 1 hr. The reaction mixture was quenched with water and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a yellow oil. Recrystallization of this material from 95% ethanol afforded 55 mg (65%) of a yellow solid, mp 152–154°, whose structure was assigned as 2,3,5,7-tetraphenyl-1,4-diazacyclohepta-1,3,5-triene (**13**) on the basis of the following data. The infrared spectrum (KBr) showed absorption bands at 6.22, 6.40, 6.75, 6.91, 7.78, 9.45, 9.75, 12.90, 13.10, 13.60, and 14.40 μ. The ultraviolet spectrum (95% ethanol) was characterized by maxima at 263 nm (ε 26,600) and 335 (4800). The NMR spectrum ($CDCl_3$) contained a singlet at τ 5.52 (1 H) and a multiplet between τ 2.9 and 1.8 (21 H). The mass spectrum (70 eV) showed the molecular ion at *m/e* (rel intensity) 398 (31) and exhibited major peaks at *m/e* 308 (52), 295 (100), 103 (155), and 77 (90).

When the reaction mixture was allowed to stir for 4 hr, a second product was present as evidenced by thin layer analysis. Separation of the two products could be accomplished by preparative thick layer chromatography. The thick layer plate was developed using a 20% acetone–80% hexane solution and the lower band was extracted with methylene chloride. Evaporation of the solvent left 25 mg (25%) of a white residue which was recrystallized from 95% ethanol to give a white, crystalline solid, mp 141–142°. This material was assigned the structure of 2-benzyl-3,5,6-triphenylpyrazine (**7**). The infrared spectrum of this material was identical in all respects with that of a sample of **7** obtained from the reaction of triphenylpyrazine and benzyllithium. A mixture melting point of the two samples was undepressed at 149–150°.

Preparation of (1α,2β,5α)-2,4,5,7-Tetraphenyl-3,6-diazabicyclo[3.2.0]hepta-3,6-diene. A solution containing 600 mg of **13** in 200 ml of anhydrous benzene was heated at reflux for 4 hr. Evaporation of the solvent under reduced pressure left a yellow oil which was recrystallized from 95% ethanol to give 410 mg (68%) of a light yellow, crystalline material, mp 205.5–206.5°. This material was assigned as (1α,2β,5α)-2,4,5,7-tetraphenyl-3,6-diazabicyclo-[3.2.0]hepta-3,6-diene (**14**) on the basis of the following data.

Anal. Calcd for $C_{29}H_{22}N_2$: C, 87.40; H, 5.57; N, 7.03. Found: C, 86.99; H, 5.58; N, 6.92.

The infrared spectrum (KBr) showed absorption bands at 6.59, 6.68, 6.91, 6.95, 7.62, 8.08, 8.40, 9.31, 9.69, 10.09, 10.61, 12.60, 13.01, 14.05, and 14.45 μ. The ultraviolet spectrum (95% ethanol) was characterized by maxima at 348 nm (ε 13,900) and 257 (31,000). The NMR spectrum ($CDCl_3$) showed doublets at τ 7.78 (1 H, J = 11 Hz) and 4.50 (1 H, J = 11 Hz) and a multiplet between τ 2.9 and 1.9 (20 H). The mass spectrum (70 eV) showed the molecular ion at *m/e* (rel intensity) 398 (17) and exhibited major peaks at *m/e* 295 (100), 191 (19), 103 (82), and 77 (21).

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Registry No.—**4**, 54964-39-5; **5**, 54985-40-9; **6**, 3190-01-0; **7**, 54964-40-8; **8**, 54985-41-0; **9**, 54985-42-1; **10**, 54964-41-9; **13**, 54964-42-0; **14**, 54964-43-1; dibromodihydrochalcone, 611-91-6; *meso*-stilbenediamine, 951-87-1; benzyllithium, 766-04-1; triphenylpyrazine, 36476-77-4; *rac*-stilbenediamine, 16635-95-3; potassium *tert*-butoxide, 865-47-4.

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Nonbenzenoid Aromatic Systems. XI.[1] Synthesis and Buffered Acetolysis of 2-(2-Azulyl)ethyl Tosylate and Nosylate

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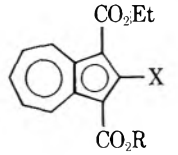
The synthesis of 2-(2-azulyl)ethanol (**1**-OH) was accomplished starting with methyl or ethyl 2-chloro-1-azulenecarboxylate (**6**) and involved nucleophilic substitution at C_2 with sodium methylcyanoacetate followed by lithium iodide ester halogenodealkylation with concomitant bisdecarboxylation to 2-azulylacetonitrile (**10**). Hydrolysis of **10** followed by diborane reduction of the acetic acid **11** gave **1**-OH. The kinetics of buffered acetolysis of **1**-OTs and **1**-ONs were determined. After one solvolytic $t_{1/2}$ **1**-OTs gave 51% **1**-OAc and 34% 2-vinylazulene (**12**). **12** was shown to arise by elimination from both **1**-OTs and **1**-OAc. Similarly **1**-ONs was found to yield 74% **1**-OAc and 11% **12** after one solvolytic $t_{1/2}$. Deuterium labeling with **1**-α,α-d_2-ONs established that the major component in k_{solv} of **1**-ONs is k_Δ with only a minor contribution from k_s, and that ion-pair return from the ethylene-2-azulenium ion–nosylate anion pair (**15**) is *not* occurring. These results are discussed in terms of the five nonequivalent azulene ring positions to which the β-ethanol side chain can be attached.

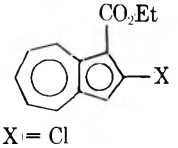
In 1971 we[2] reported preliminary results showing that the 1-azulyl substituent was a "super-participator" in β-arylethyl arenesulfonate solvolyses,[3] showing an acetolysis rate ratio of about 10^5 compared to 2-phenylethyl OTs for the k_Δ process at 25°. Our interest in the azulene ring as a participating aryl group also allows examination of the differences effected by attachment of the β-ethanol side chain to the five nonequivalent ring positions. Our results with 2-(6-azulyl)ethyl arenesulfonate buffered acetolysis showed it to behave solvolytically similar to derivatives of 2-phenylethanol in yielding an ethylenearenonium ion (k_Δ) with competitive elimination to 6-vinylazulene and solvent displacement (k_s).[4] 2-(4-Azulyl)ethyl arenesulfonates behaved similar to the 6 isomers except that the k_Δ process was believed to involve the ring 3 position in an Ar_3-5 mechanism.[4]

One of the reasons for entry into the chemistry of azulene was to determine the effects of the five nonequivalent ring positions in a number of reaction types.[5] In the reaction type of solvolysis of β-arylethyl derivatives, we now wish to report our results for 2-(2-azulyl)ethyl arenesulfonate buffered acetolysis.

Substrate Synthesis. The general Nozoe azulene synthesis was employed for the synthesis of 2-(2-azulyl)ethanol (**1**-OH). 2-Chlorotropone[6] was allowed to condense with 2 equiv of ethyl cyanoacetate with ethanolic sodium ethoxide to yield diethyl 2-amino-1,3-azulenedicarboxylate[8] (**2**) in average 70% yield. Diethyl 2-chloro-1,3-azulenedicarboxylate (**3**) was prepared from **2** by nitrous acid deamination in benzene and hydrogen chloride.[9] Sodium ethylcyanoacetate in ethanol effected nucleophilic displacement at C_2 of **3**, giving diethyl 2-(cyanoethoxycarbonylmethyl)-1,3-azulenedicarboxylate (**4**) in near-quantitative yield. However, considerable difficulties were found when we attempted to convert **4** to 2-azulylacetonitrile (**10**).



2, X = NH_2; R = C_2H_5
3, X = Cl; R = C_2H_5
4, X = $CH(CN)CO_2C_2H_5$; R = C_2H_5
5, X = Cl; R = H



6, X = Cl
7, X = $CH(CN)CO_2CH_3$
8, X = CH_2CN
9, X = $CH(CN)CH_3$

Half-hydrolysis of **3** afforded 2-chloro-3-carboethoxy-1-azuloic acid (**5**) in 66% yield. Thermal, low-pressure decarboxylation gave ethyl 2-chloro-1-azulenecarboxylate (**6**). Nucleophilic displacement at C_2 of **6** occurred with sodium methylcyanoacetate in refluxing dimethylformamide (DMF) to yield ethyl 2-(cyanomethoxycarbonylmethyl)-1-azulenecarboxylate (**7**). **7** was heated under reflux in DMF with lithium iodide (ester halogenodealkylation)[10] for 1.5 hr to yield an inseparable mixture (1:1.6 by NMR integration) of ethyl 2-cyanomethyl-1-azulenecarboxylate (**8**) and ethyl 2-(1-cyanoethyl)-1-azulenecarboxylate (**9**). The apparent origin of **9** was from methylation by liberated methyl iodide of the conjugate base of **8**. Addition of a small amount of acetic acid to a subsequent LiI–DMF halogenodealkylation of **7** gave a 75% yield of **8** free of any contamination by **9**.

When **8** was allowed to react with LiI–DMF–HOAc under nitrogen at reflux for 24 hr, the neutral fraction after work-up contained a small amount of acetonitrile **10** and unreacted **8**. This observation, together with the known faster ester halogenodealkylations of methyl esters compared to ethyl esters,[10] led us to consider the methyl ester corresponding to **6** as starting material. Since the reagents used in the nucleophilic substitution on **6** and the halogenodealkylation of **7** involved the same solvent and were compatible, these two reactions were combined and carried out consecutively in the same flask.

Starting with the methyl ester of **6**, nucleophilic substitution with sodium methylcyanoacetate for 1 hr in DMF under reflux was followed by addition of lithium iodide and a small amount of acetic acid and continued heating under reflux. After 11 hr the optimized yield of **10** was 68%. Using shorter ester halogenodealkylation reaction times afforded acidic products and lower yields of **10** while longer reaction times gave varying amounts of **10** and 2-methylazulene, a product probably arising from hydrolysis and decarboxylation of **10**.

Scheme I

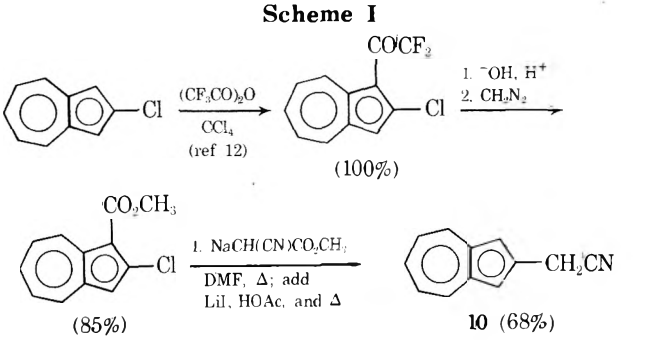


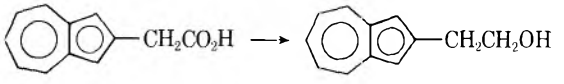
Table I
Buffered Acetolysis Kinetic Data for 2-(2-Azulyl)ethyl Tosylate and Nosylate

Compd	Temp, °C	$10^5 k$, sec^{-1}	Av $10^5 k$, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	k_{RONs}/k_{ROTs}
1-OTs	100.0	3.88 ± 0.003	3.92			
		3.96 ± 0.01				
1-ONs	80.0	4.96 ± 0.01	4.98	25.7	−5.8	
		5.00 ± 0.04				
	100.0	37.6 ± 0.2	37.5			9.6
		37.5 ± 0.2				
4-AzEtOTs[a]	100.0		1.23	21.4	−24.1	
4-AzEtONs[a]	100.0		2.17	24.0	−16.1	1.8
6-AzEtOTs[a]	100.0		1.09	23.2	−19.5	
6-AzEtONs[a]	100.0		3.55	23.4	−16.8	3.2
C_6H_5EtOTs[a]	100.0		0.41	24.2	−18.8	
C_6H_5EtONs[a]	100.0		4.66	24.3	−13.6	11.4
p-AnisylEtOTs[a]	100.0		22.2	24.1	−11.2	
p-AnisylEtONs[a]	100.0		293.	23.6	−7.3	13.2

[a] Reference 4.

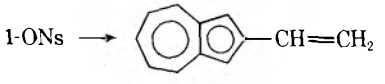
The above experimental results and the availability of quantities of 2-chloroazulene[9] previously prepared for a number of reasons led us to the sequence outlined in Scheme I.

Hydrolysis of **10** using conditions previously employed for hydrolysis of 1-azulylacetonitrile[13] gave 2-azulylacetic acid (**11**) in 89% yield. Diborane reduction of **11** gave 2-(2-azulyl)ethanol, which was purified as the acetate, 2-(2-azulyl)ethyl acetate (**1-OAc**), in 96% yield. The *p*-toluenesulfonate (tosylate) (**1-OTs**) and *p*-nitrobenzenesulfonate (nosylate) (**1-ONs**) esters were prepared by hydrolysis of **1-OAc** to **1-OH** and conversion to the arenesulfonates by standard procedures.[4] Using deuteriodiborane in the reduction of **11**, 1-α,α-d_2-OH was produced containing 1.84



11 **1-OH**

deuterium atoms in the α position of the side chain (multiple NMR integrations). Reaction of **1-ONs** with potassium hydroxide in EtOH–THF gave a 96% yield of 2-vinylazulene (**12**).



12

Discussion of Kinetic and Product Results from 1-OTs and 1-ONs. The buffered acetolyses of **1-OTs** and **1-ONs** were followed using the conductometric method[14] with the M-D Mini-Cell.[15] The rate constants and activation parameters for these and certain related compounds determined under these conditions are listed in Table I.

The buffered acetolysis of **1-OTs** was complicated by elimination to the 2-vinylazulene (**12**) both from **1-OTs** and the acetolysis product **1-OAc**. An acetolysis stability check on **1-OAc** at 100° for one acetolysis half-life of **1-OTs** gave 76.9% of recovered **1-OAc** and 6.2% of **12**. Assuming that the loss in material balance was due to instability of **12**, the amount of **12** produced from **1-OAc** in 1 half-life was 23.1%. The "1 half-life" preparative scale buffered acetolysis of **1-OTs** gave 52.8% recovered **1-OTs**, 24.1% (51% net) of **1-OAc**, and 15.8% (33.5% net) of **12**. Again assuming that **12** is partially destroyed (polymer) and that **1-OAc** was stable except toward elimination, the amount of **12** produced was 49% of the consumed **1-OTs**. While the ratio of acetate/olefin was larger than had been previously obtained from 2-(4-(**13**) and 2-(6-azulyl)ethyl OTs (**14**) buffered acetolyses,[4] it was evident that attempts to even determine k_{solv} of **1-OTs** let alone dissect it into the k_s and k_Δ components would be difficult.

Table II
Methylene Scrambling in Buffered Acetolysis of 1-α,α-d_2-ONs

	Run	Reaction time ($t_{1/2}$)	Proton content[a] C_α	C_β	% scramble of C_α and C_β[b]
2-$AzCH_2CD_2ONs$		0	0.18	1.99	
2-$AzCH_2CD_2ONs$	1	1	0.16	2.02	0.0
	2	1	0.16	2.03	0.0
2-$AzCH_2(D_2)$-$CH_2(D_2)OAc$	1	1	1.04	1.10	48.3
	2	1	1.04	1.13	47.5

[a] Calculated by multiple NMR integrations using dioxane or CH_2Cl_2 as an internal proton count standard. [b] Calculated using the equation $[(C_1 - X)/[(C_1 - X) + (C_2 - X)]] \cdot 100$ = % scramble, where C_1 and C_2 are the proton contents of recovered materials at C_α and C_β, respectively, and X is the original proton content at C_α of 1-α,α-d_2-ONs; 50% scramble represents the maximum possible.

The buffered acetolysis of **1-ONs** was then carried out with the hope that with the better leaving group (larger k's) and therefore shorter reaction times (smaller $t_{1/2}$) the contribution of k_{elim} could be reduced. The kinetic data for **1-ONs** are given in Table I and we see that a "normal" k_{RONs}/k_{ROTs} ratio is observed. An acetolysis stability check for **1-OAc** for 1 half-life of **1-ONs** at 100° gave 91.5% recovery of **1-OAc** and 3% of **12**. The "1 half-life" preparative buffered acetolysis of **1-ONs** at 100° afforded 54.3% recovered **1-ONs**, 33.9% (74.2% net) **1-OAc**, and 4.9% (10.7% net) **12**.

The substantial amounts of elimination from **1-OTs**, **1-ONs**, and **1-OAc** in buffered acetolysis, as well as from **13** and **14** and their nosylate and acetate esters, probably reflects the acidities of the C_β–H bonds in these substrates. In contrast, the preparative, buffered acetolysis of 2-(3-nitro-1-azulyl)ethyl OTs at 70° gives a quantitative yield of its acetate.[13] This is qualitatively seen in the HMO anion localization energies at these ring sites.[16] Since deuterium is not lost from the β-methylene of the side chain in the scrambling study with 1-α,α-d_2-ONs (see Table II), equilibrium formation of the C_β carbanion cannot be involved if the elimination is base ($^-$OAc) catalyzed.

At this point we decided not to concern ourselves with the precise values of the rate constants, k_{elim}, k_Δ, and k_s, in this system. However, the magnitude of the k_Δ/k_s ratio and the rate constant for ion-pair return, $(1 - F)k_\Delta{}^3$, would still

Table III
Comparative Processes in β-Azulylethyl Arenesulfonate Buffered Acetolyses[2,4]

Compd	% C_α-C_β scrambling in RONs[a]	% C_α-C_β scrambling in ROAc[a]	k_{rel}, 100° (RONs)	Amount of k_Δ in k_{solv} of RONs	Amount of k_{elim} in acetolysis of RONs
1-$AzCH_2CH_2OTs$	0[b]	50[b]	3.6×10^4 [f]	Exclusive[b]	None[b]
2-$AzCH_2CH_2ONs$	0[c]	48[c]	17	Major[c]	Minor[c]
4-$AzCH_2CH_2ONs$	0[d]	0[d]	1.0	[d,e]	Significant[d]
6-$AzCH_2CH_2ONs$	12[d]	10[d]	1.6	Minor[d]	Significant[d]

[a] From deuterium labeling results after $t_{1/2}$ for recovered RONs and product ROAc. [b] At 35° with ROTs. [c] At 100°. [d] At 120°. [e] Some amount of k_Δ(Ar_3-5) was probably present but was not observable in these experiments.[4] [f] This value uses the extrapolated k for the ROTs times a factor of 10 as the k_{RONs}/k_{ROTs} ratio.

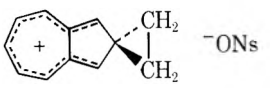
Table IV
HMO Cation Localization Energies[a]

Ring position	L_r, β units
1	1.924
2	2.362
4	2.551
5	2.341
6	2.930

[a] Reference 16.

be of interest in the comparisons of the five nonequivalent azulene ring positions to function in these processes. To this end, the buffered acetolysis of 1-α,α-d_2-ONs (prepared from 1-α,α-d_2-OH) was examined over 1 half-life of 1-ONs. Duplicate runs were made and analyses were performed by multiple integrations of the NMR spectra of the isolated products which are listed in Table II.

From the data in Table II we can see that the k_Δ process is the dominant pathway followed in k_{solv} of the buffered acetolysis of 1-ONs with only a minor contribution by solvent displacement, k_s. Also, ion-pair return $(1 - F)k_\Delta$ from the symmetric ethylene-2-azulenium ion pair (**15**) is not



15

observed, which requires that $F = 1$ for this system. Special salt effects have been established for several acetate salts in acetolyses.[17,18] That $F = 1$ for 1-ONs compared to $F = 0.76$ for 2-(*p*-anisyl)ethyl OTs under the same conditions at 95°[19] may be due primarily to the presence of nosylate vs. tosylate anions in the respective ion pairs.

The data in Table III compare the four β-azulylethyl arenesulfonates studied to date. While we have only very approximate values of k_Δ for the 2-(4- and 2-(6-azulyl)ethyl nosylates, we can see that the relative abilities of these four azulene ring positions to participate fall in the order 1 > 2 > 6 ~ 4. This is also the order of HMO cation localization energies for these positions[16] listed in Table IV. If this order is to be followed the HMO cation localization energies in Table IV predict that the as yet unknown 2-(5-azulyl)ethyl arenesulfonates should have k_{solv} very similar to that found in 2-ONs. Synthetic efforts are proceeding to test this prediction.

Experimental Section[19]

Diethyl 2-Amino-1,3-azulenedicarboxylate (2).[8] To 150 ml of absolute ethanol was added 5.00 g (0.217 g-atom) of sodium. After the evolution of hydrogen had ceased, 48.5 g (0.428 mol) of ethyl cyanoacetate was added to form a white suspension. To this stirred mixture was added dropwise at 0° 15.0 g (0.107 mol) of 2-chlorotropone[6] in 150 ml of ethanol, and the color changed immediately from white to orange. This mixture was allowed to stand at room temperature for 12 hr, and then was refrigerated for 24 hr. The orange mixture was filtered and the filter cake was washed with benzene. The filtrate and benzene wash solution were evaporated to dryness. The residue was partially dissolved in dichloromethane and filtered again. The filter cake was washed with benzene, and this wash solution combined with the dichloromethane filtrate was evaporated to dryness. The residue was dissolved in ethanol and placed in the refrigerator. Crystallization afforded 22.70 g (74%) of the title compound as orange crystals: mp 92–93° (lit.[8] mp 93–94°); ir (KBr) 2.82 (m, N–H), 2.93 (m, N–H), 6.02 μ (s, C=O); NMR ($CDCl_3$, internal TMS) τ 0.62–1.02 (m, $C_{4,8}$ ring H's, 2), 2.00–2.84 (m, 5), 5.52 (q, J = 7 Hz, $CO_2CH_2CH_3$, 4), and 8.52 (t, J = 7 Hz, $CO_2CH_2CH_3$, 6); λ_{max} (cyclohexane) 315 nm (log ε 4.68), 327 (4.80), 370 (3.83), 392 (3.85), and 456 (3.39).

Anal. Calcd for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.97. Found: C, 66.75; H, 6.05.

Diethyl 2-Chloro-1,3-azulenedicarboxylate (3).[8] Anhydrous HCl (bubbled through concentrated H_2SO_4) was bubbled into 300 ml of dry benzene containing 10.0 g (34.1 mmol) of **2** with ice cooling for 3 hr as red platelets precipitated. The dropwise addition over a 15-min duration of 4.55 g (39.0 mmol) of isoamyl nitrite to this suspension led to color changes from orange to green to blue and finally to red over an 18-hr period. The benzene solution was washed with four 150-ml portions of water and dried (Na_2SO_4), the solvent volume was reduced, and the residue was chromatographed on basic alumina. Elution with 1:1 carbon tetrachloride–benzene removed a diffuse, blue band, followed closely by a broad, red band. Benzene–dichloromethane (1:1) eluted a narrow, orange band and chloroform eluted a yellow band. Only the broad, red band was investigated which gave 10.00 g (96%) of the title compound. Crystallization from ethanol yielded red prisms: mp 75.0–76.0° (lit.[9] mp 77–78°); ir (KBr) 5.95 (s, C=O) and 9.55 μ (s, C–O); NMR (CCl_4, internal TMS) τ 0.25–0.62 (m, $C_{4,8}$ ring H's, 2), 2.07–2.60 (m, $C_{5,6,7}$ ring H's, 3), 5.52 (q, J = 7 Hz, $CO_2CH_2CH_3$, 4), and 8.53 (t, J = 7 Hz, $CO_2CH_2CH_3$, 6); λ_{max} (cyclohexane) 367 nm (log ε 4.26), 298 (4.61), 308 (4.69), 346 (3.75), 353 (3.78), 370 (3.61), 504 (2.67), and 525 (2.66).

Anal. Calcd for $C_{16}H_{15}O_4Cl$: C, 62.65; H, 4.93. Found: C, 63.00; H, 5.00.

Diethyl 2-(Cyanoethoxycarbonylmethyl)-1,3-azulenedicarboxylate (4).[9] To 10 ml of absolute ethanol was added 383 mg (16.65 mg-atom) of sodium. When the sodium had dissolved, 1.880 g (16.65 mmol) of ethyl cyanoacetate was added to form a white suspension. To this mixture, 1.278 g (4.17 mmol) of **3** was added. The mixture was heated under reflux for 1 hr, diluted with 50 ml of water, acidified with 6 *N* hydrochloric acid, and extracted with three 50-ml portions of ether. The combined ethereal extracts were dried ($MgSO_4$), the solvent volume was reduced, and the residue was chromatographed on basic alumina. Elution with ether developed a large, red band that afforded 1.520 g (95%) of the title compound. Crystallization from 1:1 ether–hexanes yielded small, red plates: mp 113.5–114.0° (lit.[9] mp 116–117°); ir (neat film) 4.52 (w, C≡N), 5.75 (s, C=O), 5.90 (s, C=O), and 9.70 μ (s, C–O); NMR ($CDCl_3$, internal TMS) τ 0.05–0.38 (m, $C_{4,8}$ ring H's, 2), 1.87–2.47 (m, $C_{5,6,7}$ ring H's, 3), 2.97 (s, $CHCNCO_2C_2H_5$, 1), 5.20–5.93 (m, $CO_2CH_2CH_3$, 6), and 8.33–9.88 (m, $CO_2CH_2CH_3$, 9); λ_{max} (cyclohexane) 273 nm (log ε 4.31), 294 (4.48), 304 (4.59), 338 (3.66), 367 (3.79), 511 (2.75), 538 (2.73), and 587 (2.35).

Anal. Calcd for $C_{21}H_{21}O_6N$: C, 65.78; H, 5.52. Found: C, 65.55; H, 5.65.

2-Chloro-3-carboethoxy-1-azuloic Acid (5).[9] To 760 mg (2.48 mmol) of **3** in 8 ml of ethanol was added 170 mg (3.0 mmol) of potassium hydroxide in 2 ml of water. This mixture was heated under reflux with stirring for 15 min, diluted with 100 ml of water, and extracted with four 100-ml portions of ether to remove unreacted **3**. These extracts were dried (Na_2SO_4), and the solvent volume was reduced to yield 240 mg of unreacted material. The aqueous layer was acidified with 10% hydrochloric acid and extracted with six 100-ml portions of ether. These extracts were dried (Na_2SO_4), and the solvent volume was reduced to yield 456 mg (66%, 97% net) of the title compound. Crystallization from methanol afforded pink

granules: mp 206–207° (sealed capillary) (lit.[9] mp 193° dec); ir (KBr) 5.95 (m, C=O), 6.05 (s, C=O), and 9.50 μ (m, C–O); NMR (DMSO-d_6, internal TMS) τ −3.12 (broad s, CO_2H, 1), 0.22–0.75 (m, $C_{4,8}$ ring H's, 2), 1.73–2.33 (m, $C_{5,6,7}$ ring H's, 3), 5.53 (q, J = 7 Hz, $CO_2CH_2CH_3$, 4), and 8.57 (t, J = 7 Hz, $CO_2CH_2CH_3$, 6); λ_{max} (95% ethanol) 270 nm (log ε 4.33), 295 (4.60), 302 (4.64), 350 (3.81), 366 (3.77), and 498 (2.75).

Anal. Calcd for $C_{14}H_{11}O_4Cl$: C, 60.33; H, 3.98. Found: C, 60.10; H, 4.00.

Ethyl 2-Chloro-1-azulenecarboxylate (6).[9] A sublimation tube containing 327 mg (1.17 mmol) of **5** was heated to 250° (200 Torr) for 3 hr. The red-violet oil that collected on the condenser was removed and chromatographed on basic alumina. Elution with hexanes afforded a violet band that gave 38 mg of 2-chloroazulene. Hexanes–dichloromethane (1:1) eluted a broad red-violet band that gave 220 mg (80%) of the title compound, a red-violet oil: ir (neat film) 5.92 (s, C=O) and 9.58 μ (s, C–O); NMR (CCl_4, internal TMS) τ 0.80–1.10 (m, C_8 ring H, 1), 1.77–2.10 (m, C_4 ring H, 1), 2.23–2.90 (m, $C_{5,6,7}$ ring H's, 3), 3.00 (s, C_3 ring H, 1), 5.58 (q, J = 7 Hz, $CO_2CH_2CH_3$, 4), and 8.57 (q, J = 7 Hz, $CO_2CH_2CH_3$, 6). For analysis a trinitrobenzene complex was prepared and crystallized from 1:1 ethyl acetate–hexanes to yield long, fine, yellow needles: mp 85.0–85.5°; λ_{max} (cyclohexane) 293 nm (log ε 4.76), 305 (4.79), 342 (3.87), 354 (3.93), 369 (3.62), 522 (2.62), 550 (2.59), and 595 (2.23).

Anal. Calcd for $C_{19}H_{14}O_8N_3Cl$: C, 50.96; H, 3.15. Found: C, 51.10; H, 3.30.

Ethyl 2-(Cyanomethoxycarbonylmethyl)-1-azulenecarboxylate (7). To 260 mg (5.8 mmol) of a 57% oil dispersion of sodium hydride in 10 ml of dry (distilled from BaO) DMF was added dropwise 2.0 ml of methyl cyanoacetate. After bubbles of hydrogen had ceased to be evolved, 212 mg (0.905 mmol) of **6** in 10 ml of dry DMF was added, and this mixture was heated for 1 hr at 150°. This mixture was cooled, diluted with 100 ml of water, and extracted with 50 ml of ether. The ethereal extract was discarded, and the aqueous layer was acidified with 5% hydrochloric acid and extracted with three 50-ml portions of ether. The combined ethereal extracts were washed with 100 ml of water and dried (Na_2SO_4), the solvent volume was reduced, and the residue was chromatographed on basic alumina. Benzene eluted a narrow, yellow band that was not investigated, and 9:1 chloroform–ethanol eluted a violet band that afforded 165 mg (61%) of the title compound. Crystallization from ethanol yielded violet crystals: mp 130–132°; ir (KBr) 5.70 (s, C=O), 5.98 (s, C=O), and 9.68 μ (s, C–O); NMR ($CDCl_3$, internal TMS) τ −0.03 to 0.57 (m, C_8 ring H, 1), 1.50–1.75 (m, C_4 ring H, 1), 2.02–2.82 (m, $C_{3,5,6,7}$ ring H's, 4), 4.15 (s, CH, 1), 5.67 (q, J = 7 Hz, $CO_2CH_2CH_3$, 2), 6.28 (s, CO_2CH_3, 3), and 8.67 (t, J = 7 Hz, $CO_2CH_2CH_3$, 3); λ_{max} (CH_2Cl_2) 290 nm (log ε 4.68), 302 (4.79), 338 (3.89), 347 (3.84)(sh), 365 (3.95), 528 (2.76), 550 (2.74)(sh), and 600 (2.37)(sh).

Anal. Calcd for $C_{17}H_{15}O_4N$: C, 68.67; H, 5.09; N, 4.71. Found: C, 68.37; H, 5.20; N, 4.55.

Ethyl 2-Cyanomethyl-1-azulenecarboxylate (8). To 100 mg (0.336 mmol) of **7** in 10 ml of dry (distilled from BaO) DMF was added 400 mg (2.35 mmol) of lithium iodide dihydrate[10] and 1.0 ml of acetic acid. This mixture was heated for 1 hr at 140°, cooled, diluted with 100 ml of water, and extracted with three 50-ml portions of ether. The combined ethereal extracts were washed with 100 ml of water and dried (Na_2SO_4), the solvent volume was reduced, and the residue was chromatographed on basic alumina. Dichloromethane–ether (1:1) eluted a red-violet band that afforded 60 mg (75%) of the title compound. Crystallization yielded violet crystals: mp 90–91°; ir (KBr) 5.92 (s, C=O) and 9.50 μ (C–O); NMR ($CDCl_3$, internal TMS) τ 0.37–0.63 (m, C_8 ring H, 1), 1.57–1.83 (m, C_4 ring H, 1), 2.03–2.83 (m, $C_{3,5,6,7}$ ring H's, 4), 5.58 and 5.70 (superimposed q, J = 7 Hz, and s, $CO_2CH_2CH_3$ and CH_2CN, 4), and 8.53 (t, J = 7 Hz, $CO_2CH_2CH_3$, 3); λ_{max} (CH_2Cl_2) 291 nm (log ε 4.76), 302 (4.77), 338 (3.77), 349 (3.77), 366 (3.89), 525 (2.69), 550 (2.65)(sh), and 600 (2.26)(sh).

A second reaction with the above conditions and without the addition of acetic acid was allowed to occur. An inseparable mixture of the title compound and ethyl 2-(1-cyanoethyl)-1-azulenecarboxylate (**9**) was obtained as identified by NMR spectroscopy.

2-Chloroazulene.[9] This was obtained by thermal decarboxylation of 2-chloro-1,3-azulenedicarboxylic acid.[9] From 500 mg (1.63 mmol) of diethyl 2-chloro-1,3-azulenedicarboxylate (**3**) after saponification the crude, dry diacid (410 mg, 100%) was heated in a large sublimer at 260° (200 Torr). Chromatography of the sublimate on basic alumina and hexanes elution gave 260 mg (98%) of the title compound. Crystallization from methanol gave violet needles: mp 90.0–90.5° (lit.[9] mp 91–92°); ir (CCl_4) no characteristic absorptions; NMR (CCl_4, internal TMS) τ 1.83–2.22 (m, $C_{4,8}$ ring H's, 2) and 2.42–3.20 (m, $C_{1,3,5,6,7}$ ring H's, 5); λ_{max} (cyclohexane) 276 nm (log ε 5.06), 285 (5.09), 303 (4.01), 330 (3.93), 344 (4.04), 357 (3.68), 551 (2.53), 592 (2.48), 615 (2.21), 635 (2.09), and 650 (2.10).

Anal. Calcd for $C_{10}H_7Cl$: C, 73.85; H, 4.34. Found: C, 74.00; H, 4.48.

2-Chloro-1-trifluoroacetylazulene. From the procedure of Anderson[12] for the trifluoroacetylation of azulene, 1.0 ml of trifluoroacetic anhydride was added to 780 mg (4.81 mmol) of 2-chloroazulene in 10 ml of carbon tetrachloride, and within 2 min the color changed from violet to red. This mixture was stirred for 3 hr, diluted with 50 ml of 5% aqueous sodium bicarbonate, and extracted into two 100-ml portions of ether. The combined ethereal extracts were washed with 100 ml of water and dried (Na_2SO_4), and the solvent volume was reduced. The residue was chromatographed on deactivated (3% water) basic alumina. Dichloromethane developed a single, broad, violet hand that was eluted with chloroform to afford 1.240 g (100%) of the title compound. Crystallization from ethanol afforded large, red plates: mp 88.0–88.5°; ir (KBr) 6.12 μ (s, C=O); NMR ($CDCl_3$, internal TMS) τ 0.43–0.77 (m, C_8 ring H, 1), 1.50–1.85 (m, C_4 ring H, 1), 1.87–2.67 (m, $C_{5,6,7}$ ring H's, 3), and 2.77 (s, C_3 ring H, 1); λ_{max} (CH_2Cl_2) 275 nm (log ε 4.44), 323 (4.61), 376 (4.15)(sh), 392 (4.13)(sh), and 495 (2.95).

Anal. Calcd for $C_{12}H_6F_3ClO$: C, 55.72; H, 2.34. Found: C, 55.55; H, 2.46.

Methyl 2-Chloro-1-azulenecarboxylate. To 1.900 g (7.35 mmol) of 2-chloro-1-trifluoroacetylazulene in 30 ml of ethanol was added 1.80 g (32.1 mmol) of potassium hydroxide in 30 ml of water. This mixture was heated under reflux for 1 hr as the color changed from red to violet, diluted with 100 ml of water, and extracted with 100 ml of ether. The ethereal extract was discarded and the aqueous portion was acidified with 5% hydrochloric acid. This acidified portion was extracted with five 200-ml portions of ethyl acetate and dried (Na_2SO_4) and the solvent volume was reduced to yield 1.440 g (95%) of crude 2-chloro-1-azuloic acid.

To 1.590 g (7.7 mmol) of crude 2-chloro-1-azuloic acid in 500 ml of ethyl acetate was added an excess of an ethereal diazomethane solution. This mixture was allowed to stand for 30 min, the solvent volume was reduced, and the residue was chromatographed on basic alumina. Benzene eluted a narrow, yellow band that was not investigated and a broad, red band that afforded 1.470 g (87%) of the title compound. Dichloromethane eluted a narrow, yellow-orange band that was not investigated. Crystallization from ethanol gave the product as fine, red needles: mp 86.0–86.5°; ir (KBr) 5.92 (s, C=O) and 9.55 μ (s, C–O); NMR ($CDCl_3$, internal TMS) τ 0.38–0.72 (m, C_8 ring H, 1), 1.57–1.87 (m, C_4 ring H, 1), 2.05–2.67 (m, $C_{5,6,7}$ ring H's, 3), 2.78 (s, C_3 ring H, 1), and 6.02 (s, CO_2CH_3, 3); λ_{max} (CH_2Cl_2) 294 nm (log ε 4.72), 304 (4.77), 340 (3.81), 350 (3.84), 366 (3.51), 515 (2.72), 538 (2.70)(sh), and 590 (2.28)(sh).

Anal. Calcd for $C_{12}H_9O_2Cl$: C, 65.32; H, 4.11. Found: C, 65.62; H, 3.97.

2-Azulylacetonitrile (10). To a suspension of 200 mg (4.75 mmol) of a 57% oil dispersion of sodium hydride in 10 ml of dry DMF (distilled from BaO) was added dropwise 600 mg (6.07 mmol) of methyl cyanoacetate. After bubbles of hydrogen had ceased to evolve, 420 mg (1.90 mmol) of methyl 2-chloro-1-azulenecarboxylate in 10 ml of dry DMF was added, and this mixture was heated at 140–150° for 1 hr. After this mixture was allowed to cool to room temperature, 2.0 ml of acetic acid and 3.40 g (20 mmol) of crushed lithium iodide dihydrate[10] were added. This mixture was heated to 140–150° under a dry, nitrogen atmosphere with stirring for 11 hr, diluted with 100 ml of water, and extracted with three 100-ml portions of ether. The combined extracts were washed with two 100-ml portions of water and dried (Na_2SO_4), the solvent volume was reduced, and the residue was chromatographed on basic alumina. A violet band eluted with 1:1 benzene–hexanes that afforded 50 mg (18%) of 2-methylazulene. Benzene eluted a narrow, yellow band that was not investigated and a broad, violet band that yielded 215 mg (68%) of the title compound. Crystallization from 1:1 ether–hexanes afforded violet crystals: mp 95.0–95.5°; ir (KBr) 4.44 μ (m, C≡N); NMR ($CDCl_3$, internal TMS) τ 1.62–1.90 (m, $C_{4,8}$ ring H's, 2), 1.97–3.03 (m, $C_{1,3,5,6,7}$ ring H's, 5), and 5.92 (s, CH_2CN, 2); λ_{max} (CH_2Cl_2) 276 nm (log ε 4.79), 283 (4.81), 300 (3.87)(sh), 326 (3.63), 340 (3.79), 560 (2.58), 595 (2.52), and 655 (2.11)(sh).

Anal. Calcd for $C_{12}H_9N$: C, 86.20; H, 5.42; N, 8.38. Found: C, 85.96; H, 5.35; N, 8.20.

2-Azulylacetic Acid (11). Forty milliliters of 50% aqueous ethanol and 1.350 g (24.1 mmol) of potassium hydroxide were heated

under a continuous, dry, oxygen-free, nitrogen sweep with stirring for 2 hr. To this mixture was added 280 mg (1.675 mmol) of **10** in 2.5 ml of THF. This mixture was heated under gentle reflux for 7 hr, diluted with 100 ml of water, and extracted with 50 ml of ether. The ethereal extract was discarded and the aqueous portion was acidified with 5% hydrochloric acid. The acidified layer was extracted with two 50-ml portions of ether. The ethereal extracts were combined and dried (Na_2SO_4), and the solvent volume was reduced to yield 295 mg (89%) of the title compound. Crystallization from 4:1 ether–hexanes afforded violet plates: mp 128–129°; ir (KBr) 5.90 μ (s, C=O); NMR ($CDCl_3$, internal TMS) τ −0.32 (broad s, CO_2H, 1), 1.67–1.93 (m, $C_{4,8}$ ring H's, 2), 2.47–3.17 (m, $C_{1,3,5,6,7}$ ring H's, 5) and 5.98 (s, CH_2CO_2H, 2); λ_{max} (CH_2Cl_2) 277 nm (log ϵ 4.79), 285 (4.83), 298 (3.73)(sh), 327 (3.60), 342 (3.73), 564 (2.53), 605 (2.48)(sh), and 660 (2.07)(sh); mass spectrum (70 eV, heated inlet) *m/e* (rel abundance) 186 ($M^{\cdot+}$, 8), 185 (58), 142 (76), 141 (100), and 115 (34).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.29; H, 5.49.

2-(2-Azulyl)ethyl Acetate (1-OAc). A mixture of 250 mg (1.26 mmol) of acid **11** and 366 mg (9.60 mmol) of $NaBH_4$ in 30 ml of dry THF was stirred at room temperature until hydrogen evolution ceased. To this mixture was added dropwise 5 ml of boron trifluoride etherate in 25 ml of dry THF over a period of 30 min. After 60 min of additional stirring, 10 ml of 10% hydrochloric acid was added dropwise and then the mixture was diluted with 100 ml of ether and 50 ml of water. The layers were separated and the extraction was repeated twice with 100-ml portions of ether. The combined ethereal extracts were washed with 100 ml of 5% aqueous sodium bicarbonate and 100 ml of water and dried (Na_2SO_4). The solvent volume was reduced and the residue was chromatographed with chloroform on basic alumina. A single, violet band eluted which was contaminated with impurity as determined by NMR.

This crude alcohol was stirred with 3 ml of dry pyridine and 1 ml of reagent grade acetic anhydride for 2 hr at 0°, protected from atmospheric moisture. This mixture was diluted with 100 ml of ice-cold 10% hydrochloric acid and 50 ml of ether. The layers were separated and the ethereal layer was washed with four 100-ml portions of 10% hydrochloric acid and one 100-ml portion of water. The ethereal layer was dried (Na_2SO_4), the solvent volume was reduced, and the residue was chromatographed on basic alumina with 1:1 carbon tetrachloride–dichloromethane. A single violet band eluted that afforded 260 mg (96%) of **1-OAc** as a violet oil: ir (neat film) 5.75 (s, C=O) and 9.60 μ (s, C–O); NMR (CCl_4, internal TMS) τ 1.75–2.03 (m, $C_{4,8}$ ring H's, 2), 2.33–3.17 (m, $C_{1,3,5,6,7}$ ring H's, 5), 5.60 (t, J = 6.5 Hz, CH_2CH_2OAc, 2), 6.73 (t, J = 6.5 Hz, CH_2CH_2OAc, 2) and 8.00 (s, O_2CCH_3, 3); mass spectrum (70 eV, heated inlet) *m/e* (rel abundance) 214 ($M^{\cdot+}$, 47), 155 (22), 154 (100), 153 (13), 141 (24), 115 (13), and 43 (34).

For analysis a 1,3,5-trinitrobenzene complex was prepared and crystallized from 1:1 ethyl acetate–hexanes to afford bronze-colored crystals: mp 80.5–81.0°; λ_{max} (CH_2Cl_2) 276 nm (log ϵ 4.75), 285 (4.82), 300 (3.73), 329 (3.55), 343 (3.69), 560 (2.47), 602 (2.42), and 665 (1.99)(sh).

Anal. Calcd for $C_{20}H_{17}O_8N_3$: C, 56.21; H, 4.01. Found: C, 56.06; H, 4.11.

2-(2-Azulyl)ethanol (1-OH). A mixture of 260 mg (1.21 mmol) of 1-OAc in 8 ml of ethanol and 500 mg (8.9 mmol) of potassium hydroxide in 2 ml of water was stirred at 0° for 1 hr. This mixture was diluted with 100 ml of ice-cold water and extracted with two 50-ml portions of ether. The combined ethereal layers were dried (Na_2SO_4), the solvent volume was reduced, and the residue was chromatographed on basic alumina. Dichloromethane developed a broad, blue band that was eluted with chloroform to afford 218 mg (98%) of the title compound. Crystallization from carbon tetrachloride yielded long, violet needles: mp 97.0–97.5°; ir (KBr) 3.06 (s, O–H) and 9.50 μ (s, C–O); NMR (CCl_4, internal TMS) τ 1.75–2.05 (m, $C_{4,8}$ ring H's, 2), 2.52–3.20 (m, $C_{1,3,5,6,7}$ ring H's, 5), 6.05 (t, J = 6 Hz, CH_2CH_2OH, 2), 6.87 (t, J = 6 Hz, CH_2CH_2OH, 2), and 8.57 (broad s, OH, 1); λ_{max} (CH_2Cl_2) 276 nm (log ϵ 4.76), 286 (4.83), 301 (3.73), 330 (3.61), 343 (3.70), 561 (2.47), 602 (2.41), and 660 (1.97)(sh); mass spectrum (70 eV, heated inlet) *m/e* (rel abundance) 172 ($M^{\cdot+}$, 79), 155 (30), 154 (22), 142 (37), 141 (100), 139 (21), 129 (76), 128 (18), and 115 (50).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.68; H, 7.03. Found: C, 83.40; H, 7.10.

2-(2-Azulyl)ethyl Tosylate (1-OTs). To 195 mg (1.13 mmol) of 1-OH in 3.0 ml of dry ether was added 232 mg (1.22 mmol) of sublimed tosyl chloride and 200 mg (3.58 mmol) of crushed potassium hydroxide. The mixture was allowed to stir at 0°, protected from atmospheric moisture, for 6 hr, and diluted with 100 ml of ether and 200 ml of ice-cold water. The layers were separated and the aqueous portion was extracted with a second 100 ml of ether. The combined ethereal extracts were washed twice with 100-ml portions of water and dried (Na_2SO_4), the solvent volume was reduced, and the residue was chromatographed on deactivated (6% water) basic alumina. Dichloromethane eluted a broad, violet band, followed by a narrow, violet band. The narrow, violet band yielded 15 mg of unreacted 1-OH. The broad, violet band afforded 340 mg (92%, 100% net) of the title compound, a violet oil that crystallized upon standing. Crystallization from ethyl acetate gave long, violet needles: mp 105.0–106.0°; ir (KBr) 7.38 (s, S–O) and 8.42 μ (s, S–O); NMR ($CDCl_3$, internal TMS) τ 1.67–2.08 (m, $C_{4,8}$ ring H's, 2), 2.13–3.09 (m, 9), 5.60 (t, J = 7 Hz, CH_2CH_2OTs, 2), 6.68 (t, J = 7 Hz, CH_2CH_2OTs, 2), and 7.62 (s, tosyl CH_3, 3); λ_{max} (CH_2Cl_2) 277 nm (log ϵ 4.69), 285 (4.76), 300 (3.73)(sh), 329 (3.54), 343 (3.66), 564 (2.46), 605 (2.40), and 660 (2.00)(sh); mass spectrum (70 eV, heated inlet) *m/e* (rel abundance) 326 ($M^{\cdot+}$, 0.6), 172 (86), 154 (24), 108 (20), 107 (30), 91 (62), and 45 (100).

Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.91; H, 5.56. Found: C, 69.91; H, 5.62.

2-(2-Azulyl)ethyl Nosylate (1-ONs). To 65 mg (0.378 mmol) of 1-OH in 3 ml of dry THF was added 17 mg of a 57% oil dispersion of sodium hydride. This mixture was allowed to stir overnight at room temperature as a violet precipitate separated. The mixture was cooled to 0° and 110 mg (0.40 mmol) of recrystallized *p*-nitrobenzenesulfonyl chloride was added. After 4 hr of stirring at 0°, 50 ml of ice-cold water and 50 ml of ether were added, the layers were separated, and the aqueous layer was extracted with two additional 50-ml portions of ether. The combined ethereal layers were washed with 100 ml of water and dried (Na_2SO_4), the solvent volume was reduced, and the residue was chromatographed on deactivated (3% water) basic alumina. Dichloromethane eluted a blue band and chloroform eluted a second blue band. The second band afforded 30 mg of unreacted alcohol, and the first band yielded 63 mg (47%, 87% net) of the title compound. Crystallization from 1:1 ethyl acetate–hexanes gave copper-colored prisms: mp 128.0–128.8°; ir (KBr) 7.32 (s, S–O), 7.42 (s, S–O), and 8.42 μ (s, S–O); NMR ($CDCl_3$, internal TMS) τ 1.70–3.07 (m, 11), 5.47 (t, J = 6.5 Hz, CH_2CH_2ONs, 2) and 6.67 (t, J = 6.5 Hz, CH_2CH_2ONs, 2); λ_{max} (CH_2Cl_2) 278 nm (log ϵ 4.70), 285 (4.73), 300 (4.08)(sh), 314 (3.87)(sh), 342 (3.66), 563 (2.49), 605 (2.44)(sh), and 665 (1.99)(sh).

Anal. Calcd for $C_{18}H_{15}NO_5S$: C, 60.49; H, 4.23. Found: C, 60.21; H, 4.13.

2-Vinylazulene (12). To 55 mg (0.142 mmol) of 1-ONs in 5 ml of absolute ethanol and 2 ml of THF was added at 0° under stirring 200 mg (3.58 mmol) of crushed potassium hydroxide. This mixture was stirred for 1 hr and diluted with 100 ml of ether and 100 ml of water. The layers were separated and the aqueous layer was extracted with a second 100-ml portion of ether. The combined, blue extracts were dried (Na_2SO_4), the solvent volume was reduced, and the residue was chromatographed with carbon tetrachloride on basic alumina. A single, blue band eluted that yielded 21 mg (96%) of the title compound. Crystallization from hexanes afforded blue plates: mp 104.5–106.0°; ir (KBr) 12.15 (s) and 13.78 μ (s); NMR ($CDCl_3$, internal TMS) τ 1.67–1.97 (m, $C_{4,8}$ ring H's, 2), 2.17–3.30 (m, 6), and 3.80–4.67 (m, 8 lines, 2); λ_{max} (cyclohexane) 281 nm (log ϵ 4.62), 291 (4.72), 302 (4.61), 319 (3.60), 334 (3.49), 349 (3.63), 364 (3.90), 374 (3.60), 382 (4.09), 580 (2.47), 600 (2.41), 613 (2.42), 626 (2.47), 645 (2.23)(sh), 664 (2.12), and 690 (2.21).

For analysis a trinitrobenzene complex was prepared and crystallized from ethanol–hexanes (1:1) to yield brown needles, mp 106.0–107.0°.

Anal. Calcd for $C_{18}H_{13}O_6N_3$: C, 58.86; H, 3.57. Found: C, 58.73; H, 3.72.

Kinetic Method. The method previously described[14,15] was used with some modifications. A Beckman differential reading thermometer, calibrated in 0.01°, was used, in conjunction with ASTM thermometers, to monitor temperature variations and to obtain the $10t_{1/2}$ point at a temperature representative of the points taken during the first 2 half-lives. The constant-temperature bath cover and perimeter were insulated to prevent heat loss. Temperature changes of ±0.002° were then detectable and could be approximated, and temperature variations were normally about ±0.003° during a typical solvolytic run. There was no observable change noted in the conductance readings between the $10t_{1/2}$ point and subsequent points when the readings were taken at the same temperature.

All kinetic runs were made with 1.0×10^{-3} *M* ROTs (RONs) and 1.2×10^{-3} *M* potassium acetate. Infinity ($10t_{1/2}$) titers of these solutions gave the following percent reaction: 1-OTs (100°), 94.2%; 1-ONs (80°), 97.3%; 1-ONs (100°), 97.8%.

All preparative scale buffered acetolyses were determined using 0.010 *M* ROTs and 0.012 *M* potassium acetate. The solutions were sealed in flasks and placed in the constant-temperature bath for the allotted time. After removal from the bath and quenching in ice–water, the contents were poured from the flasks into water and extracted with methylene chloride which was washed with water, 5% aqueous $NaHCO_3$, and water and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue then gave the products.

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Registry No.—1-OH, 54798-03-7; 1-OTs, 54798-04-8; 1-ONs, 54798-05-9; 1-OAc, 54798-06-0; 1-OAc 1,3,5-trinitrobenzene complex, 54798-07-1; **2**, 3806-02-8; **3**, 36044-40-3; **4**, 54832-62-1; **5**, 54798-08-2; **6**, 54522-71-3; **6** 1,3,5-trinitrobenzene complex, 54798-09-3; **7**, 54798-10-6; **8**, 54798-11-7; **10**, 54798-12-8; **11**, 54798-13-9; **12**, 53477-10-4; **12** 1,3,5-trinitrobenzene complex, 54798-14-0; ethyl cyanoacetate, 105-56-6; 2-chlorotropone, 3839-48-3; 2-chloroazulene, 36044-31-2; 2-chloro-1-trifluoroacetylazulene, 54798-15-1; methyl 2-chloro-1-azulenecarboxylate, 54798-16-2; 2-chloro-1-azuloic acid 54798-17-3; *p*-nitrobenzenesulfonyl chloride, 98-74-8; tosyl chloride, 98-59-9.

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(15) Available from R-M Research Products, Inc., Manhattan, Kans. 66502. The small (3 ml) working volume of this conductance cell and the ability to work at elevated temperatures with this cell[4,14] made these studies possible.
(16) E. Heilbronner in "Non-Benzenoid Aromatic Compounds", D. Ginsburg, Ed., Interscience, New York, N.Y., 1959, p 200.
(17) S. Winstein, P. E. Klinedinst, and G. C. Robinson, *J. Am. Chem. Soc.*, **83**, 885 (1961); E. F. Jenny and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958).
(18) Footnote 21 in ref 2.
(19) Melting points were determined on a Kofler hot stage and are uncorrected. Spectra were determined with commercial instruments (ir, Perkin-Elmer 137; NMR, Varian A-60 and T-60; uv–visible, Cary 11; mass, AEI-MS9). NMR spectral data are listed as centers except for multiplets, where the range of the signals is given.

Molecular Rearrangements. XII.[1a] Reactions of 2-Chlorobicyclo[2.2.1]hept-2-ene *exo*-Oxide and 2-Chlorobicyclo[2.2.2]oct-2-ene Oxide with Lithium Diethylamide

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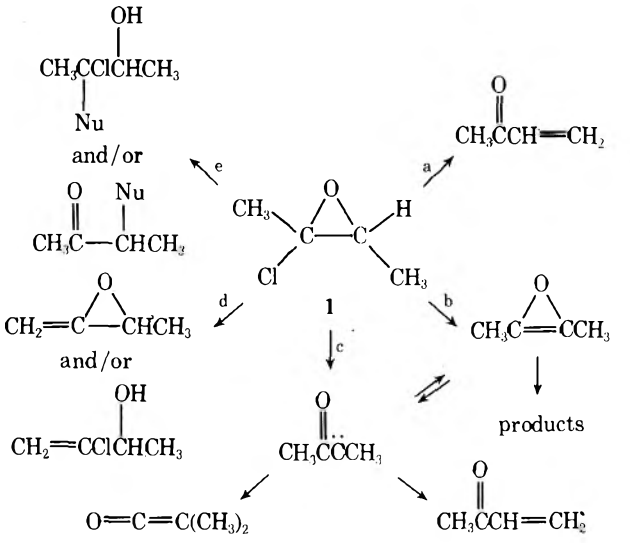
The reactions of two bicyclic α-chloro epoxides, 2-chlorobicyclo[2.2.1]hept-2-ene *exo*-oxide (**2**) and 2-chlorobicyclo[2.2.2]oct-2-ene oxide (**3**), with lithium diethylamide have been investigated. With **2**, refluxing benzene–ether and ether (0 to −15°) were examined as solvents while, with **3**, only refluxing benzene–ether was studied. From **2** the major product was tricyclo[2.2.1.$0^{2,6}$]heptan-3-one (**4**). The amount of the minor product, tricyclo[2.2.1.$0^{2,6}$]heptan-3-ol (**5**), was solvent and base concentration dependent. Using **2**-*3-d* in ether, no deuterium was found in **4** and none at C_3 of **5**. While the formation of **4** can be readily rationalized as involving transannular insertion by the α-keto carbene formed by α elimination at C_3 of **2**, the pathway **2** → **5** is unclear. From **3**, two major products, tricyclo[3.2.1.$0^{2,7}$]octan-6-one (**15**) and *N,N*-diethylbicyclo[2.2.1.]heptane-7-carboxamide (**16**), and two minor products, 3-chlorobicyclo[2.2.2]octan-2-one (**13**) and bicyclo[2.2.2]octanone (**14**), were isolated. Ketone **15** and amide **16** are believed derived from the α-keto carbene, **15** by transannular insertion and **16** by Wolff ring contraction, while ketones **13** and **14** probably arise via thermal rearrangement of **3**. These results are compared with those from other methods of generating the respective bicyclic α-keto carbenes or carbenoids. The site specificity in these conversions of bicyclic α-chloro epoxides **2** and **3** to tricyclic ketones **4** and **15**, respectively, may prove synthetically useful.

The reactions of strong bases with acyclic, cyclic, and bicyclic epoxides have been studied by a number of researchers,[2] notably Cope, Crandall, and Rickborn. The major types of processes observed were α elimination (yielding insertion and ketone products), β elimination, and nucleophilic epoxide ring opening. The extent of involvement of these processes was dependent on structural effects in both the epoxide and the base.

Our interests in the chemistry of α-chloro epoxides[1,3] led us to consider how the α-chloro substituent might effect the outcome of such strong base reactions. Using (*Z*)-2-chlorobutene oxide (**1**) as an example, the conceivable pathways are listed in Scheme I. Nouri-Bimorghi[4] reported that varying amounts of β elimination (pathway a) and nucleophilic epoxide ring opening (pathway e) were observed when three acyclic α-chloro epoxides were allowed to react

Scheme I

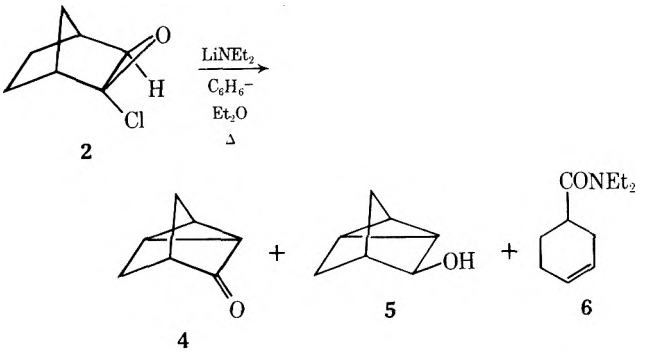


with phenyllithium. As expected, the extent of involvement of these pathways was dependent on the substrate structure.

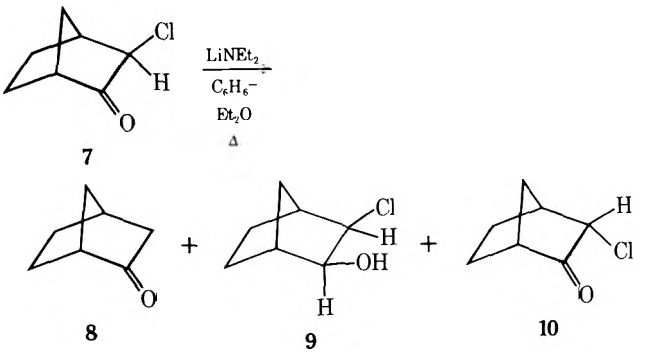
For the present study, we wished to limit the probable reaction pathways given in Scheme I to c, which would enable us to evaluate it as a method of accomplishing Wolff-type rearrangements via α-keto carbenes (or carbenoids). Such should be possible using certain bicyclic α-chloro epoxides where pathways a, b, d, and e should be disfavored, as should the eqilibrium shown between α-keto carbene and oxirene structures.[5] The α-chloro bicyclic epoxides chosen were 2-chlorobicyclo[2.2.1]hept-2-ene *exo*-oxide[1,6] (**2**) and 2-chlorobicyclo[2.2.2]oct-2-ene oxide[7] (**3**), since we had previously studied their neat, thermal, and certain catalyzed rearrangements, and Crandall[2f,j] had reported on lithium diethylamide reactions of the parent bicyclic epoxides.

Results and Discussion

When [2.2.1] α-chloro epoxide **2**[6] was heated under reflux in benzene–ether solution containing excess lithium diethylamide and diethylamine for 50 hr, the product (3.05 g from 4.35 g of **2**) was found to contain 84% tricyclo[2.2.1.$0^{2,6}$]heptan-3-one (**4**), 8% tricyclo[2.2.1.$0^{2,6}$]heptan-3-ol (**5**), 2% recovered **2**, and 2% of an amide tentatively identified as *N,N*-diethylcyclohex-3-enecarboxamide (**6**) along with four minor unidentified components (by GLC). Using cyclohexene–ether as solvent in this reaction gave essentially identical results.



To establish that **4** and **5** especially were primary products in the above reaction and not artifacts of thermal rearrangement of **2** → *exo*-chlorobicyclo[2.2.1]heptan-2-one[1,6] (**7**), **7** was treated under the reaction conditions. The product was shown to contain 63% bicyclo[2.2.1]heptan-2-one (**8**), 12% *exo*-3-chlorobicyclo[2.2.1]heptan-*exo*-2-ol (**9**), 11% **7**, and 14% *endo*-3-chlorobicyclo[2.2.1]heptan-2-one (**10**).



Since we had previously shown that **4** is reduced to a mixture of **4** and **5** under these reaction conditions (albeit under reflux for 4 days), the formation of **8** and **9** from **7** is rationalized by carbonyl reduction of **7** to **9** (or its C_2 epimer) followed by dehydrochlorination.

Formation of amide **6** from **2** and lithium diethylamide can be considered to arise by attack of the base on the carbonyl of *exo*-2-chlorobicyclo[2.2.1]heptan-7-one, a major product in the neat, thermal rearrangement of **2**.[1,6] Generation of the amide group carbonyl, C_1–C_7 bond cleavage, and loss of chloride ion from C_2 would yield **6**.

In an effort to shorten the reaction time of **2** with lithium diethylamide, to obtain complete reaction, and to study the effect of solvents on this process, we examined several benzene–ether mixtures as well as ether as solvents. In short, the benzene–ether mixtures gave nonreproducible results.

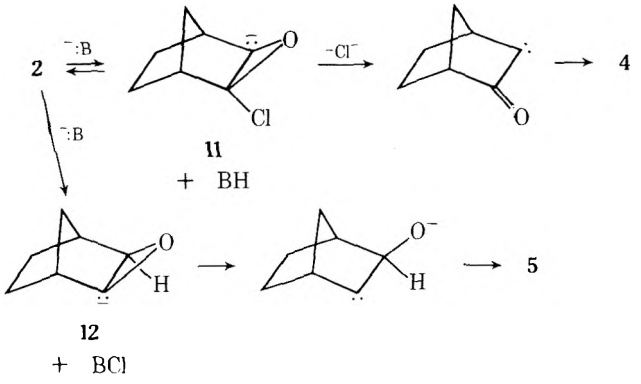
In refluxing either with 1.1 equiv of lithium diethylamide, the product derived from **2** was found to contain 10% **8**. Thus it appeared that thermal rearrangement of **2** → **7** followed by reduction was a competing process under these conditions. The amount of **8** could be lowered to <0.5% if 2 equiv of base was employed. Significantly, the **4**:**5** ratios from these two experiments were nearly the same, 2.85 and 3.00, respectiviely, suggesting that lithium diethylamide did not effect the **4** → **5** reduction in refluxing ether as had been observed in refluxing benzene–ether.

It was then found that reproducible yields, **4**:**5** product ratios, and complete conversion of **2** could be obtained in ether at reduced temperatures. The **4**:**5** product ratio was found to be 2.06 ± 0.05 with conditions ranging from 50% excess lithium diethylamide at −15° with a 30-min reaction time to that involving 300% excess base at 0° with 4.5-hr reaction time. Neither **8** nor **6** were observed in the product. It was inferred from the constant product ratio with large variations in base concentration and reaction time that **4** → **5** reduction by lithium diethylamide was unimportant under these reaction conditions.

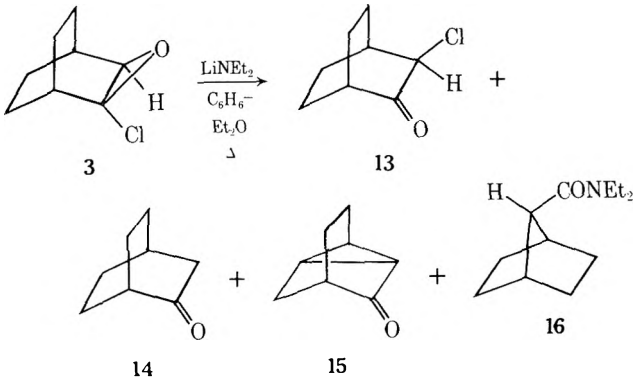
To decide how the products **4** and **5** were formed in this reaction, we prepared **2**-*3-d* containing 77% deuterium at C_3 (based on NMR spectral analysis). Reaction of **2**-*3-d* with 2.5 equiv of lithium diethylamide at −10 to 0° for 15 min as above gave after work-up and short-path distillation (analyses cited above carried out this way) the **4**:**5** ratio of 2.20. More careful solvent removal and redistillation gave the **4**:**5** ratio as 2.40 and a total yield, **4** + **5**, of 85%; a duplicate run gave the **4**:**5** ratio of 2.44 and a yield of 92%. Low-voltage (15 eV) mass spectral analysis showed 0 ± 2% excess deuterium in **4** from both experiments, while in **5** 2 ± 2% and 6 ± 2% excess deuterium was found. Multiple integrations of the NMR spectrum of **5** indicated no excess deuterium at C_3.

These results are in keeping with a mechanism of formation of **4** involving α elimination from C_3 and chloride ion

loss from C_2 of **2** followed by transannular insertion of the α-keto carbene at C_5. However, since simple reduction of **4** → **5** does *not* appear to occur under these conditions, the nature of the processes by which **5** is produced containing no deuterium at C_3 starting from **2-3-*d*** is not at all clear. One possibility is that the amine, ether solvent, or "some other species"[8] may be serving as a proton source in the equilibrium formation of anion **11**.[9] If reduction of the C_2–Cl bond in **2** by lithium diethylamide competes with carbene formation, anion **12** would be formed which could proceed to **5** by the mechanism shown by Crandall.[2f] Bicyclo[2.2.1]hept-2-ene *exo*-oxide might then be produced as an intermediate by protonation of **12**. Equilibrium between this epoxide and **12** would also account for further losses of deuterium at C_3 in **5**.

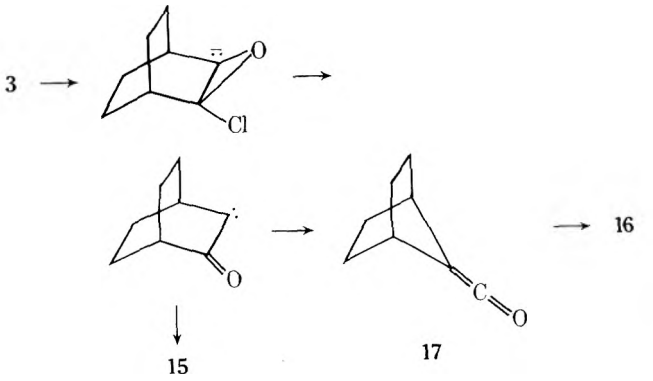


Turning our attention now to the reaction of lithium diethylamide and the [2.2.2] α-chloro epoxide **3** in benzene–ether, we find a somewhat different result. The product was shown to contain 8% unreacted **3**, 8% 3-chlorobicyclo[2.2.2]octan-2-one (**13**), 1% bicyclo[2.2.2]octanone (**14**), 52% tricyclo[3.2.1.$0^{2,7}$]octan-6-one (**15**), and 23% *N,N*-diethylbicyclo[2.2.1]heptane-7-carboxamide (**16**) along with five unidentified minor components.



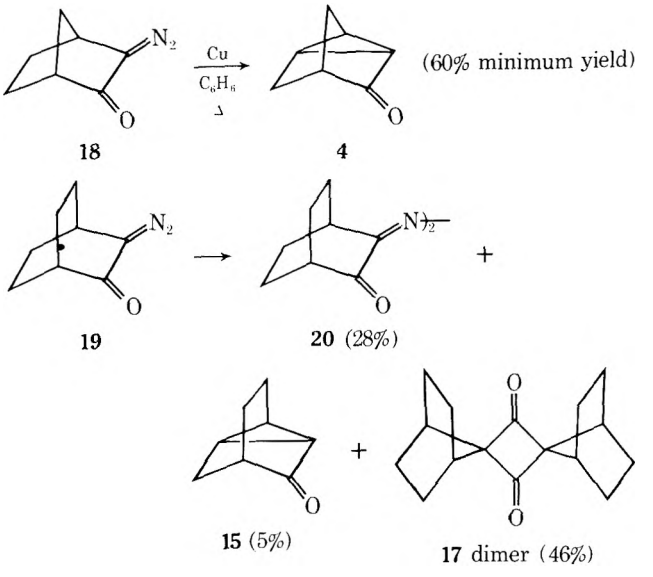
It appears that **13** and **14** are formed via thermal rearrangement of **3** leading to **13** as the primary product. Ketone **14** was shown to be the only product, although in low yield, when **13** was treated under the reaction conditions. The reaction of **3** with lithium diethylamide was not studied in ether, but from our experiences with **2** we suspect that formation of **13** and **14** can be greatly reduced, if not eliminated completely, by carrying out the reaction in ether at reduced temperatures.

Formation of ketone **15** and amide **16** indicates that in this system the α-keto carbene has two competitive reaction channels, one involving transannular C–H insertion (→ **15**) and the other Wolff ring contraction (→ **16**) via ketene **17**. From **3** we were not able to detect the presence of the tricyclic alcohol corresponding to the reduction of **15**, as had been observed from **2**; however, this alcohol may be one of the five minor unidentified components.



It is interesting to compare the above results with those reported by Yates and Crawford[10] for the copper-catalyzed reactions of 3-diazobicyclo[2.2.1]heptan-2-one (**18**) and 3-diazobicyclo[2.2.2]octanone (**19**). Their results carried out in refluxing benzene are given in Scheme II.

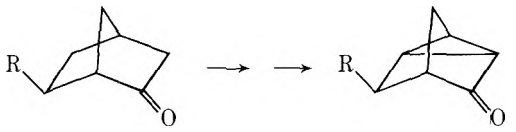
Scheme II



In the [2.2.1] series, the products from both **2** and **18** are quite similar considering that the reaction of lithium diethylamide and **2** appears to have an additional reaction channel leading to alcohol **5**. The predominate or exclusive product is ketone **4**, apparently arising by transannular C–H insertion by the carbene or carbenoid. Wolff ring contraction,[5] which is the major pathway in the photochemical decomposition of **18** in methanol,[11] is not observed in the strong base reaction of **2** or the copper-catalyzed decomposition of **18**.

Before comparing the results from **3** and **19** we must delete those products from processes unique to that particular substrate and reaction type. This then removes the production of **13** and **14** from **2** and azine **20** from **19**. Comparing the insertion:Wolff rearrangement ratios we have 0.11 (**15**:**17** dimer) from **19** and 2.26 (**15**:**16**) from **3**. These ratios show that there is a major difference in the nature of the product forming intermediates and/or the pathways by which the products are produced in these two reactions.

The sequence of reactions involved in the synthesis of α-chloro epoxides from the corresponding ketones combined with pathway c in Scheme I for the strong base reaction promises site specificity for generation of the α-keto carbene and its subsequent reactions, e.g., **21** → **22** conversion. This coupled with large insertion:Wolff rearrangement should make this sequence synthetically useful in certain circumstances. Such site specificity is not possible with



21 22

certain syntheses of α-diazo ketones using monoderivatization of α-diketones.[11]

Experimental Section[12]

Reaction of 2-Chlorobicyclo[2.2.1]heptene *exo*-Oxide (2)[6] with Lithium Diethylamide in Benzene–Ether. A solution of lithium diethylamide was prepared by treating a cold solution (ice bath) of 6.4 g (88 mmol, 9.0 ml) of diethylamine (distilled from barium oxide) in 25 ml of benzene (distilled from sodium) with 31.8 ml of 1.6 *M* (51 mmol) methyllithium in ether. After approximately 20 min, 4.35 g (30 mmol) of **2**[6] in 5 ml of benzene was added. The reaction mixture was heated under reflux for 50 hr, during which time a white precipitate formed and the color changed from colorless to light yellow. After cooling, the reaction mixture was decanted onto ice and extracted with chloroform, and the combined extracts were washed with saturated ammonium chloride and water. After drying ($MgSO_4$) the chloroform was removed by distillation and the residue was distilled through a short-path column (bath temperatures 60°, 0.2 mm), which gave 3.05 g of product. Analysis by GLC (12 ft × 0.25 in. 10% Carbowax 20M column) indicated the presence of seven components (integrated percent): 2% unreacted **2**, 84% **4**, 8% **5**, 2% of an amide tentatively identified as **6**, with the unknown components having integrals of 3, 1, <1, and <1%, respectively. Ketone **4** and alcohol **5**, mp 108–109.5° after sublimation (lit.[13] mp 108–109°), were identified by comparison of their NMR and ir spectra with those in the literature.[13,14]

The amide was GLC collected as a liquid and on the basis of the following spectral data was structurally assigned as *N,N*-diethylcyclohex-3-enecarboxamide (**6**): ir (neat) 6.09 μ (C=O, amide); NMR ($CDCl_3$, internal TMS) τ 4.33 (slightly broadened singlet, 2), 6.64 (q, J = 7 Hz, 4), 7.0–7.45 and 7.45–8.5 (m's, total ca. 7), and 8.9 (two overlapping t's, 6). The NMR chemical shifts at τ 4.33 (assigned as vinyl H's), 7.0–7.45 (assigned as C_1H), and 7.45–8.5 (assigned as C_2, C_5, and C_6 H's) are almost exactly those reported for cyclohex-3-enecarbonitrile;[15a] such are similarly reported for cyclohex-3-enecarboxaldehyde,[15b] cyclohex-3-enecarbonyl chloride,[15c] and methyl cyclohex-3-enecarboxylate.[15d] Likewise the coupling patterns observed in the multiplets at τ 7.0–7.45 and 7.45–8.5 are similar to those reported in the nitrile[15a] and acid chloride.[15c] The overlapping CH_3 triplets centered at τ 8.9 indicate that the NC_2H_5 groups are nonequivalent with one CH_3 group being shielded by the ring C=C.

Bicyclo[2.2.1]heptan-2-one-*3,3-d*$_2$. Using the method of Schaefer, Dagani, and Weinberg,[16] 15.4 g of bicyclo[2.2.1]heptan-2-one was deuterated with CF_3CO_2D to give 13.6 g (87%) of the product.

Anal. Calcd for $C_7H_8D_2O$: 20.00 atom % excess deuterium. Found: 19.6 atom % excess of deuterium by mass spectral analysis (17 eV).

2,2-Dichlorobicyclo[2.2.1]heptane-*3,3-d*$_2$. A solution of 19.0 g (170 mmol) of bicyclo[2.2.1]heptane-2-one-*3,3-d*$_2$ in 35 ml of dry methylene chloride was added dropwise over a period of 12 min to a stirred, cooled mixture of 52.0 g (250 mmol) of PCl_5 and 35 ml of PCl_3. The internal temperature was held at 10–12° during the addition. The mixture was stirred while being allowed to warm to 28° over a period of 1 hr. After stirring for an additional 5.5 hr at 28–29°, the mixture was cooled to 10°, poured onto 350 g of ice, and shaken continuously for 18 min. The layers were allowed to separate and the aqueous layer was extracted with three 15-ml portions of methylene chloride. The combined organic layers were washed with 50 ml of 5% sodium bicarbonate solution, dried (Na_2CO_3), redried ($MgSO_4$), and filtered. Most of the solvent was removed by distillation using a 13 mm × 30 cm Vigreux column. The product was distilled on a semimicro platinum spinning band column to give 24.2 g (85%) of the deuterated dichloride, bp 67–86° (17 mm). A forerun of 1.32 g (6%) of 2-chlorobicyclo[2.2.1]heptene-*3-d*, bp 53–59° (32 mm), was also obtained. NMR analysis indicated that it was pure chloroolefin with less than 2% H at C_3.

2-Chlorobicyclo[2.2.1]heptene-*3-d*. In a dry nitrogen atmosphere, a mixture of 23.3 g (139 mmol) of 2,2-dichlorobicyclo[2.2.1]heptane-*3,3-d*$_2$ dissolved in 45 ml of dry THF (distilled from $LiAlH_4$) was added to a solution of 31.0 g (276 mmol) of resublimed potassium *tert*-butoxide in 215 ml of dry THF. The mixture was heated under gentle reflux in a nitrogen atmosphere for 23.75 hr, poured into 250 ml of ice water, and extracted with five 100-ml portions of purified pentane. The combined organic layers were washed with three 100-ml portions of dilute brine, dried ($MgSO_4$), and filtered. The pentane was removed by distillation on a Vigreux column. The crude chloroolefin was distilled on a semimicro platinum spinning band column to yield 13.65 g (76%) of the product.[6] The integrated NMR spectrum showed that the deuterium content at C_3 was 77%.

Attempts to carry out this dehydrochlorination in *tert*-butyl alcohol[6] gave yields up to 84% but with deuterium contents of <50%.

2-Chlorobicyclo[2.2.1]heptene-*3-d* *exo*-Oxide(2-*3-d*). The published procedure was followed.[6] From 9.05 g of 2-chlorobicyclo[2.2.1]heptene-*3-d* (77% deuterium) and 16.8 g of *m*-chloroperbenzoic acid we obtained 7.69 g (76%) of 2-*3-d*. NMR spectral analysis indicated 77% excess deuterium at C_3.

Reaction of 2-Chlorobicyclo[2.2.1]heptene *exo*-Oxide (2) with Lithium Diethylamide in Ether. A 50-ml two-necked flask equipped with a magnetic stir bar, nitrogen inlet, and outlet was flamed out under a dry nitrogen sweep for 15 min. The outlet was closed with a rubber septum and the flask was cooled to −15°. Ether (freshly distilled from $LiAlH_4$) (10 ml) was injected by dry syringe, followed by 2.30 g (31.5 mmol) of diethylamine (distilled from barium oxide). A 1.57 *N* solution (18.8 ml, 29.5 mmol) of freshly prepared methyllithium in ether was injected by syringe over a period of 10 min with vigorous stirring at a bath temperature of −15 to −5°. The bath was cooled to −15°, and after 5 min a solution of 2.00 g (13.8 mmol) of 2 in 8 ml of dry ether was injected with stirring and cooling over a period of 8 min at a bath temperature of −15 to −10°. The flask was placed in an ice bath and the contents were stirred for 60 min. The mixture was poured onto 25 g of ice water and shaken, and the layers were allowed to separate. The aqueous layer was extracted with two 15-ml portions of ether. The combined ether extracts were washed with two 10-ml portions of water, dried (Na_2SO_4), redried ($MgSO_4$), and filtered. The entire solution was short-path distilled [25–95° (0.1 mm)]. GLC analysis of the distillate on a 6 ft × 0.25 in. 5% FFAP column showed only solvent, diethylamine, **4**, and **5** under conditions where unreacted **2**, **7**, or **8** would have been detected if present in amounts of 1% or greater. The solvent was removed by distillation on a 13 mm × 30 cm Vigreux column, yielding 1.920 g of light brown oil which was analyzed under the same GLC conditions. The mixture contained 69.7% of the bicyclic compounds in a **4**:**5** ratio of 2.13, corresponding to 0.911 g (63.3%) of **4** and 0.427 g (29.2%) of **5**. The identity of the bicyclic compounds was confirmed by chromatographic separation with methylene chloride on a basic, activity II alumina column, evaporation of the solvent, and comparison of the ir and NMR spectra with those in the literature.[13,14]

Similar treatments of **2** with 300% excess lithium diethylamide at 0° for 4.5 hr, 100% excess lithium diethylamide at 0° for 95 min, and 50% excess lithium diethylamide at −15° for 30 min gave **4**:**5** ratios of 2.09, 2.01, and 2.11, respectively, in the short-path distillates.

Several treatments of the α-chloro epoxide with less lithium diethylamide gave erratic results with varying amounts of unreacted starting material. Reaction at higher temperatures, especially in mixed benzene–ether solvent, gave up to 8% bicyclo[2.2.1]heptan-2-one (**8**) (identified spectrally and by GLC on a FFAP column) presumably arising by reduction of *exo*-3-chlorobicyclo[2.2.1]heptan-2-one (**10**), which is the major product of thermal rearrangement of **2**.[1,6]

Reaction of 2-Chlorobicyclo[2.2.1]heptene-*3-d* *exo*-Oxide (2-*3-d*) with Lithium Diethylamide in Ether. In the same manner as described above, a solution of 1.99 g (13.7 mmol) of 2-*3-d* (76.7% excess deuterium at C_3) in 8 ml of dry ether was injected with stirring and cooling over a period of 10 min at a bath temperature of −15 to −10° into a solution prepared from 10 ml of ether, 2.27 g (31.0 mmol) of diethylamine, and 18.8 ml (29.5 mmol) of a 1.57 *N* solution of methyllithium in ether. The flask was placed in an ice bath and the contents were stirred for 60 min and worked up as described previously. GLC analysis of the short-path distillate under the previously described conditions showed, in addition to solvent and diethylamine, **4** and **5** with a **4**:**5** ratio of 2.2. Concentration on a Vigreux column and redistillation gave 1.350 g of colorless oil which contained, in addition to 6.6% solvent and diethylamine, **4** and **5** in a ratio of 2.40, corresponding to 0.890 g (60.1% based on C_7H_8O) of **4** and 0.371 g (24.6% based on $C_7H_{10}O$) of **5**. Low-voltage mass spectral analysis of portions of the products pu-

rified by GLC on a 6 ft × 0.25 in. FFAP column indicated 0 ± 2% C_7H_7DO in **4** and 2 ± 2% C_7H_9DO in **5**. The integrated NMR spectrum indicated no excess deuterium at C_3 of **5** within the detection limits of the Varian T-60 NMR spectrometer.

A duplicate experiment using 2.28 g (31.2 mmol) of diethylamine, 18.8 ml (29.5 mmol) of methyllithium solution, and 2.02 g (13.90 mmol) of **2**-*3-d* gave 0.982 g (65.3%) of **4** and 0.401 g (26.2%) of **5** based on GLC analysis as above. Mass spectral analysis indicated 0 ± 2% C_7H_7DO and 6 ± 2% C_7H_9DO in **4** and **5**, respectively. The integrated NMR spectrum of **5** again showed no excess deuterium at C_3.

Reaction of Ketone 4 with Lithium Diethylamide. This reaction involved 108 mg (1.0 mmol) of **4**, 2.1 g (2.9 mmol) of diethylamine, 1.4 ml of 1.6 *M* (2.24 mmol) methyllithium in ether, and 10 ml of benzene in a dry, nitrogen atmosphere. The reaction mixture was heated under reflux for 4 days, poured into ice–water, extracted with ether, and dried ($MgSO_4$). The ether and benzene were removed in a short-path distillation, leaving 100 mg of product. GLC analysis on a 6 ft × 0.25 in. QF-1 column showed the presence of two components, **4** and **5**, in equal amounts.

Reaction of *exo*-3-Chlorobicyclo[2.2.1]heptan-2-one (7) with Lithium Diethylamide. A solution of 0.66 g (9.0 mmol) diethylamine in 10 ml of benzene (distilled from sodium) was cooled in an ice bath and treated with 3.13 ml of 1.6 *M* (5.0 mmol) methyllithium in ether under a nitrogen atmosphere. The reaction vessel had been previously flamed out under a nitrogen atmosphere. After 10 min, 434 mg (3 mmol) of **7** was injected with the immediate appearance of a blood-red color which turned brown after refluxing a few minutes. After heating under reflux for 24 hr, then cooling to room temperature, saturated, aqueous ammonium chloride was added to the reaction mixture and the organic layer separated. The aqueous phase was extracted with ether. The combined extracts were dried and the ether and benzene were removed for the most part by distillation (semimicro platinum spinning band column). GLC analysis on a 12 ft × 0.25 in. Carbowax 20M column showed this mixture to be composed of 63% **8**, 12% **9**, 11% **7**, and 14% **10**. GLC collection gave 170 mg of **8**, 15 mg of **9**, 11 mg of **7**, and 14 mg of **10**. Each component was identified by comparison of their GLC retention times and NMR spectra with those of known samples.

Reaction of 2-Chlorobicyclo[2.2.2]octene Oxide (3) with Lithium Diethylamide. An ice-cold solution of 3.5 g (48 mmol, 5 ml) of diethylamine in 25 ml of benzene was treated with 15 ml of 1.6 *M* (24 mmol) methyllithium in ether under a nitrogen atmosphere. After 20 min, 2.5 g (15.8 mmol) of **3** dissolved in 20 ml of benzene was added. After heating under reflux for 4 days the reaction mixture was worked up in the usual manner. The ether and benzene were removed in a short-path distillation, leaving 1.86 g of reaction product. GLC analysis on a 6 ft × 0.25 in. QF-1 column showed the presence of ten components. Those components identified by comparison of their GLC retention times and/or spectra with those of authentic samples were unreacted **3** (8%), **13** (8%), **14** (1%), and **15**[14a,17] (52%).

A fifth component isolated as a liquid by GLC collection was identified as the ring contraction product, *N,N*-diethylbicyclo[2.2.1]heptane-7-carboxamide (**16**): ir (neat) 6.1 μ (s, amide C=O); NMR (CCl_4, internal TMS) τ 6.63 (quartet, broadened, NCH_2–, 4) and 7.5–9.2 (m, peaks at τ 7.65, 8.07, 8.45, 8.55, 8.70, 8.81, and 8.9, 17 H); mass spectrum (70 eV) *m/e* (rel intensity) 195 (M^+·, 40), 141 (100), 100 (27), 95 (80), and 58 (36).

Anal. Calcd for $C_{12}H_{21}NO$: mol wt, 195.1623. Found: mol wt, 195.1626 (mass spectrally with a resolution of ca. 30,000).

Reaction of 3-Chlorobicyclo[2.2.2]octan-2-one (13) with Lithium Diethylamide. A cold solution (ice bath) of 0.66 g (9.0 mmol) of diethylamine in 10 ml of benzene was treated with 3.13 ml of 1.6 *M* (5.0 mmol) methyllithium in ether. After a few minutes 474 mg (3.0 mmol) of **13** was added and the mixture was heated to reflux. After 47 hr, GLC analysis indicated the presence of two components in the ratio of 52:48. Retention time comparisons with authentic samples showed that the first eluted component was **14** and the second component was **13**. The reaction was continued for a total of 108 hr. Saturated ammonium chloride was added to the reaction mixture extracted with ether. After drying the ether was distilled. A short-path distillation of the residue gave 187 mg of reaction product as a white solid and left a polymeric residue. Analysis by GLC on a 6 ft × 0.25 in. QF-1 column again showed only the presence of the same two components **13** and **14** but the **13**:**14** ratio had changed to 3. It thus appears that while **13** is converted to **14**, **14** is being destroyed in the reaction. Samples of **13** and **14** were GLC collected and their ir and NMR spectra were found to be identical with those of authentic samples.

Acknowledgments. The authors wish to thank the National Science Foundation (GP-7818, GP-10691) for support of this research and instrument grants for the NMR (A-60 and T-60) and mass spectrometers used in this study.

Registry No.—**2**, 16709-75-4; **2**-*3-d*, 54831-45-7; **3**, 23804-45-7; **4**, 695-05-6; **6**, 3811-07-8; **7**, 10464-71-8; **13**, 23804-48-0; **16**, 54798-00-4; lithium diethylamide, 816-43-3; bicyclo[2.2.1]heptan-2-one-*3,3-d*$_2$, 18153-61-2; 2,2-dichlorobicyclo[2.2.1]heptane-*3,3-d*$_2$, 54798-01-5; 2-chlorobicyclo[2.2.1]heptene-*3-d*, 54798-02-6.

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Strain in a Bicyclo[3.3.0]oct-1-ene. Preparation of 5,8-Dimethylbicyclo[3.3.0]oct-8-en-2-one and Related Compounds

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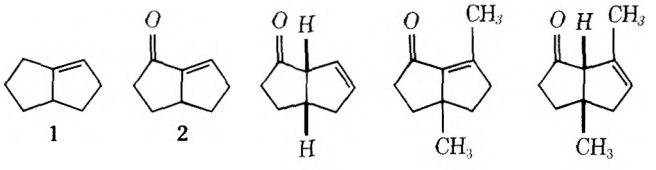
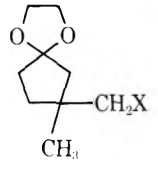
Pyrolysis of the acetylenic cyclopentanone **11** furnishes **4** and **13** in 94% yield. **4** is formed from secondary rearrangement of **13**; this reaction is reversible; and the equilibrium ratio at ~380° is 69:31 (**4**:**13**). Base-catalyzed enolization of **4** leads to equilibration with unconjugated isomer **5**; here the equilibrium ratio is 3:97 (**4**:**5**), corresponding to a free energy difference of ~2.4 kcal/mol in favor of **5**.

The presence of a double bond at the bridgehead in bicyclo[3.3.0]oct-1-ene (**1**) should introduce significant angle strain in the carbon skeleton. Very few compounds incorporating this feature have been described, however, and there is no information available concerning the relative stability of this strained system. The simple conjugated ketone **2**, for example, remains unknown, although its β,γ-unsaturated isomer **3** has been synthesized by at least three routes and has been exposed to conditions which presumably could have led to shift of the double bond into conjugation.[1] This suggests that ketones such as **2** cannot be approached synthetically by way of their β,γ isomers, and furthermore that they may well not survive exposure to acid or base, since these enolizing conditions could lead to deconjugation of the double bond. In the present report we describe preparation of an alkylated derivative of **2**, 5,8-dimethylbicyclo[3.3.0]oct-8-en-2-one (**4**),[2] along with observations on its base-catalyzed equilibration with the less strained β,γ isomer **5**.

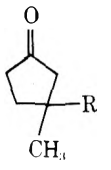


1 **2** **3** **4** **5**

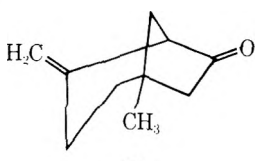
The synthetic sequence began with **6**, prepared as previously described by ketalization and hydride reduction of keto acid **7**.[3] Hydroxy ketal **6** was converted via tosylate **8**



6, X = OH
8, X = OTs
9, X = I
10, X = $CH_2C{\equiv}CSi(CH_3)_3$

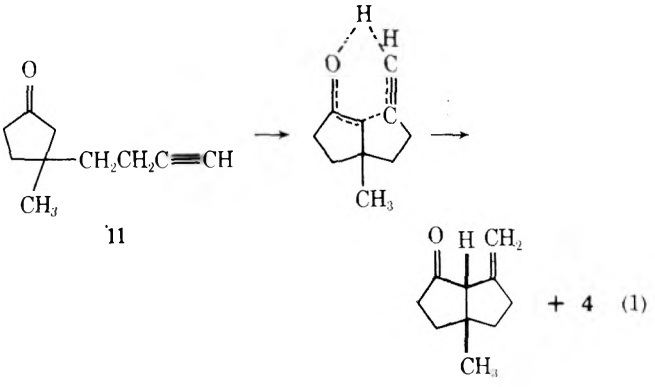


7, R = COOH
12, R = $CH_2CH_2CH_2CH_3$



14

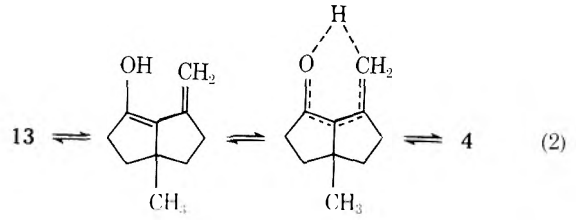
into the iodide **9**. This displacement of a neopentyl tosylate took place very efficiently (91% yield after distillation) using sodium iodide in warm hexamethylphosphoramide.[4] A second substitution at this hindered center occurred upon treatment of **9** in the same solvent with lithio-1-trimethylsilylpropyne[5] to form **10**. Earlier workers have commented on the particular effectiveness of hexamethylphosphoramide as solvent in neopentyl substitution reactions,[6] and our results here are in line with this experience. Exposure of **10** to aqueous ethanolic silver nitrate followed by potassium cyanide led to removal of both protecting groups and formation of ketone **11**. This treatment with silver(I) is a known[7] method for desilylation of protected acetylenes, and the changes involved in converting **10** into the intermediate silver acetylide render the aqueous alcoholic medium sufficiently acidic (apparent pH ~2) to permit concomitant acid hydrolysis of the ethylene ketal. The structure of **11** was confirmed by catalytic hydrogenation of the triple bond to furnish the corresponding butyl compound **12**. A comparison sample of **12** was available through conjugate addition of lithium dibutylcuprate[8] to 3-methyl-2-cyclopentenone. The acetylenic ketone **11** was then pyrolyzed in an evacuated sealed tube for 7 min at ~380° to furnish a mixture of bicyclic ketones **4** and **13** in 94% yield (eq 1).



11 **13** + **4** (1)

While thermal cyclization of various unsaturated ketones has been the subject of detailed study,[9] there are on record very few examples of this transformation leading to bicyclo[3.3.0]octanes,[10] or involving alkynes[11] rather than alkenes. Ketones **4** and **13** were separated by preparative vapor phase chromatography (VPC) and their structures assigned on the basis of spectroscopic data, subsequent reactions, and the following considerations.

The cis ring juncture of **13** is suggested by previous observations that related pyrolyses lead preferentially to cis-fused ring systems;[9] in models of **11** it is virtually impossible to achieve the geometry necessary for trans cyclization. This stereochemistry of **13** was confirmed chemically by transformations noted below. The direct product expected[9,10] from this intramolecular ene reaction of the enol of **11** was the exo methylene ketone **13**, since previous cyclization of appropriately substituted cyclopentanones had furnished none of the alternative bicyclo[3.2.1]octanes.[12] The presence of **4** in the thermolysis product can be accounted for by wall-catalyzed[11] enolization of **13**, followed by symmetry-allowed[13] [1,5] hydrogen shift in the enol,[14] as shown in eq 2. Indeed we were able to carry out this rearrange-

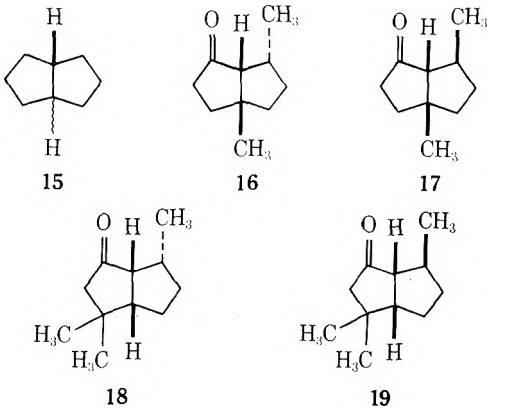


(2)

ment starting with purified **13**, and further to show that it is a reversible reaction. Thermolysis of either **4** or **13** at ~380° led to an equilibrium mixture containing these two isomers in the ratio 69:31 (**4**:**13**). Preparation of the strained skeleton of **4** was thus possible by this thermal route which permitted interconversion of **4** and **13** at a temperature sufficiently high to overcome what at room temperature presumably would be an unfavorable equilibrium. Furthermore, these thermal conditions quite specifically avoided in the final step the undesired presence of acid or base.

The expected sensitivity of **4** to enolizing conditions was confirmed. Exposure of the α,β-unsaturated ketone to potassium carbonate in aqueous alcohol at 80° led to smooth migration of the double bond out of conjugation and formation of **5**. At equilibrium the relative amounts of the two species are 3:97 (**4**:**5**). The equilibration was conveniently monitored spectroscopically, since the vestigial equilibrium concentration of **4** could be measured readily through its strong ultraviolet absorption at 261 nm (ϵ 8800). These measurements indicate that **4** is disfavored relative to **5** by about 2.4 kcal/mol. Since in **4** the double bond is both conjugated with the carbonyl group and also more highly substituted than in **5**, this energy difference must include some 2–3 kcal/mol stabilization for the disfavored isomer. With this fact taken into account, the estimated strain energy in **4** is approximately 5 kcal/mol, which appears quite reasonable. The corresponding difference, for example, between the cis and trans isomers of bicyclo[3.3.0]octane (**15**) as determined by calorimetry is 6.0 kcal/mol.[15]

This instability of trans-fused bicyclooctanes permits assignment of cis stereochemistry to **5**, since this β,γ-unsaturated ketone is formed under enolizing conditions. Catalytic hydrogenation of the double bond in either **5** or **13** gave rise to a mixture of the same two bicyclooctanones, **16** and **17**, and this correlation provides chemical evidence for the cis ring fusion in **13**. Addition of hydrogen to both **5** and **13** should be favored from the convex upper face of the molecule; on this basis the major hydrogenation product, which is the same in the two cases, is endo methyl ketone **16**. This stereochemical assignment is supported by NMR spectral comparisons between **16** and **17** and the previously described[16] ketones **18** and **19**. The doublet methyl signals in **16** and **17** appear at δ 1.00 and 1.12 ppm, respectively, while the corresponding resonances in **18** and **19** are at 1.0 and 1.11 ppm.[16]



Experimental Section

Materials and Equipment. All VPC was carried out using a Varian Aerograph Model A-90-P3 gas chromatograph with one of the following columns: A, 25% QF-1, 15 ft × 0.375 in.; B, 25% QF-1, 10 ft × 0.25 in.; C, 30% DEGS, 10 ft × 0.375 in.; D, 25% PDEAS, 50 ft × 0.25 in. All columns were prepared using 45/60 Chromosorb W in aluminum tubing. Uv spectra were obtained in 95% ethanol solutions with a Cary Model 14PM recording spectrophotometer. Ir and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian HR-220 (220 MHz) spectrometer. Mass spectra were obtained on a Du Pont 21-492 double-focusing mass spectrometer with a resolution of 10^4 and results were processed with an AEI DS-30 data system. Boiling points are uncorrected; solutions were dried over $MgSO_4$. Unless otherwise noted, products were obtained as colorless oils.

3-(3-Butynyl)-3-methylcyclopentanone (11). The preparation of hydroxy ketal **6** has been described previously.[3] An analytical sample was obtained by preparative VPC on column B (160°, 120 ml/min): ir 3620 (m), 3475 (br), 2940 (s), 2855 (m), 1338 (m), 1100 (s), 1018 (s), 940 cm^{-1} (m); NMR δ 3.81 (s, 4 H), 3.29 (s, 2 H), 2.30 (br s, 1 H), 1.88–1.31 (m, 6 H), 1.04 (s, 3 H).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.61; H, 9.40.

Unpurified **6** (6.76 g, 39.3 mmol) in pyridine (100 ml) was converted to the tosylate with *p*-toluenesulfonyl chloride (11.45 g, 60 mmol) at 0° for 20 hr. The reaction mixture was poured onto ice and extracted three times with ether. The combined organic extracts were washed several times with water and then brine. After drying and removal of solvent in vacuo, 17.38 g (96%) of a pale red oil was obtained. An ir spectrum of this material lacked hydroxyl absorption and contained sulfonate ester bands at 1168 and 1177 cm^{-1}. Without further purification, the tosylate (1.265 g, 3.88 mmol) was treated with sodium iodide (4.92 g, 32.8 mmol) in hexamethylphosphortriamide (20 ml) at 75° for 20 hr. The reaction mixture was poured onto ice and extracted three times with pentane. The combined pentane extracts were washed with water and brine and dried. After removal of solvent by distillation through a Vigreux column and bulb-to-bulb distillation (105°, 0.6 mm), 993 mg (91%) of an oil was obtained: ir 2955 (s), 2880 (m), 1375 (m), 1330 (s), 1095 (s), 1023 (m), 932 cm^{-1} (m); NMR δ 3.79 (s, 4 H), 3.25 (s, 2 H), 1.95–1.50 (m, 7 H), 1.18 (s, 3 H). This crude iodo ketal (7.90 g, 29.1 mmol) was treated with lithio-1-trimethylsilylpropyne (2 equiv) for 2 hr at −25° according to the procedure of Corey.[5] Distillation of the crude product gave two major fractions, which were analyzed by ir spectroscopy and VPC on column C (167°, 135 ml/min). The first fraction (2.15 g), bp 78–95° (0.6 mm), was predominantly unprotected acetylenic ketal; the second fraction (2.49 g), bp 120–125° (0.6 mm), consisted essentially of the fully protected acetylene (70% yield).

Removal of both protecting groups was accomplished by treating an ethanolic solution of the distilled product with an equivalent weight of silver nitrate in 80% aqueous ethanol; after stirring at room temperature for 15 min, the reaction mixture was heated to reflux and then allowed to cool. Aqueous potassium cyanide (5 equiv) was added and the mixture was stirred for 1 hr. After dilution with water and extractive work-up with pentane, bulb-to-bulb distillation (135°, 12 mm) gave highly pure acetylenic ketone **11**. Spectra were recorded on a sample further purified by preparative VPC on column C (170°, 135 ml/min): ir 3310 (s), 2955 (s), 2115 (w), 1748 (s), 1400 (m), 1375 (w), 1245 (m), 1150 cm^{-1} (m); NMR δ 2.24–1.63 (m, 11 H), 1.07 (s, 3 H); mass spectrum *m/e* 150.1054 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

Longer reaction times and/or higher temperatures in the alkylation step produced significant amounts of internal acetylene, 3-(2-butynyl)-3-methylcyclopentanone, after deketalization. Separation was achieved by preparative VPC: ir 2958 (m), 2925 (w), 1747 (s), 1400 (m), 1375 (w), 1150 cm^{-1} (m); NMR δ 2.27–1.61 (m, 11 H) with t, J = 2.5 Hz, at 1.77, 1.13 (s, 3 H); mass spectrum *m/e* 150.1043 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

3-Butyl-3-methylcyclopentanone (12). To a suspension of copper iodide (15.24 g, 80 mmol) in anhydrous ether (300 ml), magnetically stirred under a nitrogen atmosphere and cooled to −25°, was added butyllithium (80 ml of a 2 *M* solution, 160 mmol) at a rate such that the temperature of the reaction did not exceed −20°. After completion of the addition, the mixture was stirred at −20 to −25° for 15 min before 3-methylcyclopent-2-enone (7.68 g, 80 mmol) in ether (50 ml) was added dropwise. After 0.5 hr at −25°, the reaction mixture was warmed to −5° and then poured

with rapid stirring onto saturated aqueous ammonium chloride. The ethereal layer was separated and the aqueous phase was extracted twice with ether; the combined organic phases were washed with saturated ammonium chloride, water, and brine and dried. Ir analysis of the residue obtained after removal of solvent in vacuo indicated no remaining unsaturated ketone. Purification was accomplished by distillation, bp 81–83° (10 mm), and preparative VPC on column C: ir 2960 (s), 2940 (s), 2875 (m), 2870 (m), 1748 (s), 1465 (m), 1400 (m), 1375 (m), 1250 (w), 1165 (m), 1125 cm^{-1} (m); NMR δ 2.22–2.12 (m, 2 H), 1.93 (AB q, J = 17.5 Hz, 2 H), 1.82–1.14 (m, 8 H), 1.04 (s, 3 H), 0.92 (t, J = 6.5 Hz, 3 H); mass spectrum m/e 154.1367 (M^+, calcd for $C_{10}H_{18}O$, 154.1357).

Hydrogenation of 11. The keto acetylene **11** was hydrogenated in methanol over 5% Pd/C. The reaction mixture was filtered, diluted with water, and extracted with pentane. After removal of solvent, the product had an identical VPC retention time and ir spectrum with those of authentic **12**.

Pyrolysis of 11. In general, 75–100 mg of the acetylenic ketone was placed in a 20-ml tube which was cooled, evacuated, sealed, and heated at ~380° for 7–10 min. Under these conditions, no acetylene remained. From 515 mg of **11** pyrolyzed in a number of batches, 483 mg was obtained after bulb-to-bulb distillation (115°, 12 min). VPC analysis on column A (158°) indicated the formation of a 1:1 mixture of two products. Preparative VPC gave a sample of each. The first was **13**: uv λ_{max} 294 nm (ϵ 99); ir 3070 (w), 2945 (s), 2860 (m), 1745 (s), 1645 (w), 1450 (m), 1410 (m), 1375 (w), 1240 (m), 1115 (m), 890 cm^{-1} (s); NMR δ 5.03 (dd, J = 2.0, 2.0 Hz, 1 H), 4.90 (dd, J = 2.0, 2.0 Hz, 1 H), 2.47 (br, 1 H), 2.46–2.22 (m, 4 H), 1.86–1.54 (m, 4 H), 1.22 (s, 3 H); mass spectrum m/e 150.1061 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

The second was **4**: uv λ_{max} 261 nm (ϵ 8800); ir 2945 (s), 2850 (m), 2825 (w), 1712 (s), 1655 (s), 1440 (m), 1415 (m), 1375 (m), 1295 (m), 1240 (m), 1118 (m), 1000 cm^{-1} (m); NMR δ 3.00–2.81 (m, 1 H), 2.59–2.27 (m, 3 H), 2.19–1.55 (m, 4 H), 1.97 (m, 3 H), 1.16 (s, 3 H); mass spectrum m/e 150.1047 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

Resubmission of either product to the reaction conditions for 1 hr produced an equilibrium mixture of 69% **4** and 31% **13**.

Base-Catalyzed Equilibration of 4. The α,β-unsaturated ketone **4** was taken up in 0.01 M potassium carbonate dissolved in 75% aqueous methanol (~1 mg/ml) and the mixture was heated at a gentle reflux under a nitrogen atmosphere for 1 day. After addition of water and extraction with pentane, VPC analysis of the residue on column A indicated one major (>90%) new peak which was collected and identified as **5**: uv λ_{max} 304 nm (ϵ 179); ir 3035 (w), 2945 (s), 2855 (m), 2845 (m), 1742 (s), 1448 (m), 1410 (m), 1375 (m), 1240 (m), 1015 (w), 840 cm^{-1} (w); NMR δ 5.43 (br s, 1 H), 2.47 (br s, 1 H), 2.32–2.14 (m, 4 H), 1.94–1.64 (m, 2 H), 1.71 (m, 3 H), 1.24 (s, 3 H); mass spectrum m/e 150.1040 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

The equilibration of **4** and **5** was performed in 95% ethanol and followed spectrophotometrically at 261 nm. The equilibrium constant for the reaction **4** $\rightleftarrows$ **5** is K = 32.3.

Preparation of *endo*- and *exo*-5,8-Dimethyl-*cis*-bicyclo[3.3.0]octan-2-one (16 and 17). Hydrogenation of **13** in methanol with 5% Pd/C catalyst gave a 22:78 mixture of two products. These were separated by preparative VPC on column D. First eluted was the minor product **17**: ir 2945 (s), 2855 (m), 1741 (s), 1455 (m), 1410 (w), 1375 (m), 1045 cm^{-1} (w); NMR δ 2.31–1.34 (br m, 10 H), 1.22 (s, 3 H), 1.12 (d, J = 6.5 Hz, 3 H); mass spectrum m/e 152.1201 (M^+, calcd for $C_{10}H_{16}O$, 152.1200).

Second eluted was the major product **16**: ir 2945 (s), 2855 (m), 1740 (s), 1450 (w), 1410 (w), 1375 (w), 1255 (w), 1140 cm^{-1} (m); NMR δ 2.31–1.34 (br m, 10 H), 1.21 (s, 3 H), 1.00 (d, J = 6.5 Hz, 3 H); mass spectrum m/e 152.1209 (M^+, calcd for $C_{10}H_{16}O$, 152.1200).

Hydrogenation of **5** under the same conditions produced **16** and **17** in the ratio 67:33.

Acknowledgments. We thank Miss Luz Catan and Mrs. Vivian Montalban for technical assistance, Mr. S. T. Bella for microanalyses, and The Rockefeller University Mass Spectrometry Laboratory for mass spectra. The 220-MHz NMR spectra were obtained on an instrument at The Rockefeller University and operated by a consortium supported in part by NSF Grant GB-43257.

Registry No.—**1**, 694-73-5; **4**, 54931-37-2; **5**, 54931-38-3; **6**, 39859-28-4; **8**, 54931-39-4; **9**, 54931-40-7; **10**, 54931-41-8; **10** unprotected analog, 54931-42-9; **11**, 54931-43-0; **12**, 54931-44-1; **13**, 54931-45-2; **16**, 54931-46-3; **17**, 54931-47-4; 3-(2-butynyl)-3-methylcyclopentanone, 54931-48-5; 3-methylcyclopent-2-enone, 2758-18-1.

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Effect of Ring Size on the Thermal Rearrangements of Bicyclo[*n*.1.0]alka-1,*n*-dienes[1]

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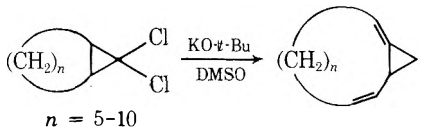
The bicyclo[*n*.1.0]alka-1,*n*-dienes (*n* = 5–10) have been synthesized and their thermal chemistry investigated. Products resulting from concerted sigmatropic processes or their structural equivalent in the form of biradicals where both carbon and hydrogen serve as the migrating group were observed, but the proportions of each were markedly controlled by ring size. When *n* = 5 spontaneous rearrangement (<25°) to 7-methylenebicyclo[4.1.0]-hept-2-ene (**3**) occurs. At higher temperatures this compound undergoes rearrangement to give two new hydrocarbons identified as 4-methylenebicyclo[3.2.0]hept-2-ene (**4**) and 1-vinyl-1,3-cyclohexadiene (**5**). When *n* = 6 and 7 the products are 3-methylene-1,4-cyclooctadiene (**9**) and 3-methylene-1,4-cyclononadiene (**12**), respectively. When *n* = 8 the starting diene is much more thermally stable and gives a 2:1 mixture of 4-methylenebicyclo-[5.3.0]dodec-2-ene (**16**) and 3-methylene-1,4-cyclodecadiene (**17**). The slower reaction rate is interpreted in terms of transannular nonbonded interactions within the ten-membered ring. Larger rings (*n* = 9 and 10) give 4-methylenebicyclo[6.1.0]undec-2-ene (**19**) and 4-methylenebicyclo[7.1.0]dodec-2-ene (**21**), respectively.

We have previously reported[3,4] the synthesis and thermolysis of the bicyclo[*n*.1.0]alka-1,*n*-dienes **1** and **2** (*n* = 5, 6). Since these two compounds exhibited very different thermal chemistry, it was of interest to investigate the effect of ring size on other accessible members of this family. In this paper we report more fully on compounds **1** and **2** and on four new bicyclo[*n*.1.0]alka-1,*n*-dienes where *n* = 7–10.

1 **2**

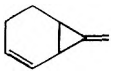
The bicyclo[*n*.1.0]alka-1,*n*-dienes were synthesized by treating the appropriate ω,ω-dichlorobicyclo[*n*.1.0]alkane with KO-*t*-Bu in DMSO[5] as shown by the general form of eq 1. For some of the larger rings the starting dichloride



n = 5–10 (1)

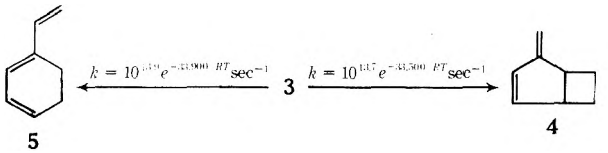
was a mixture of cis and trans isomers, but the stereochemistry is lost during the base-induced elimination–isomerization sequence.

Bicyclo[5.1.0]octa-1,5-diene (**1**) was not isolated from the synthetic scheme, but suffered a methylenecyclopropane rearrangement under the reaction conditions (15–25°) to give 7-methylenebicyclo[4.1.0]hept-2-ene (**3**), which was



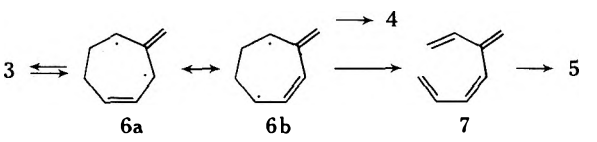
3

isolated in 50% yield. Thermolysis of **3** was carried out in the gas phase between 126.1 and 186.2°, using a diffusively stirred flow system with nitrogen as the carrier gas.[6] Two major thermolysis products were isolated and identified as 4-methylenebicyclo[3.2.0]hept-2-ene (**4**) and 1-vinyl-1,3-cyclohexadiene (**5**). They were produced in a 1.15 ± 0.05 ratio at all temperatures. The study of the thermolysis is outlined in eq 2. Both reactions followed a first-order



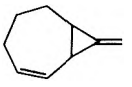
5 **4** (2)

Scheme I



course with the indicated rate constants. Scheme I conveniently accounts for both **4** and **5** from **3**. The formation of **4** suggests this diradical path, since a one-step thermally allowed 1,3-sigmatropic shift requires an inversion at the migrating carbon, leading to an unknown trans-fused ring system, and the 3,3-sigmatropic shift is impossible because of severe geometrical restraints. The formation of **5** from **3** is accounted for through the fission[7] of the "1,4" diradical **6** to the tetraene **7** followed by a facile cyclization to **5**.[8]

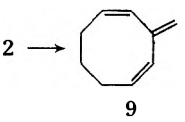
Bicyclo[6.1.0]nona-1,6-diene (**2**) was prepared from 9,9-dichlorobicyclo[6.1.0]nonane using the elimination–isomerization sequence illustrated in eq 1. The rearranged product analogous to **3**, compound **8**, was not detected, as shown



8

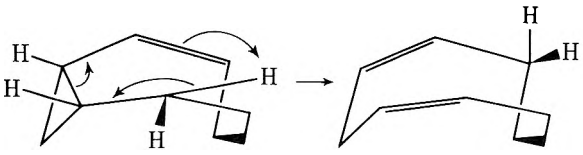
by the reduction to *cis*-bicyclo[6.1.0]nonane and the absence of a prominent ir band at ~11.3 μ (methylenecyclopropane). Presumably **2** is, by virtue of the larger ring size, less strained than **3**, accounting for the preparation of **2** and not **8**.

The thermolysis of **2** was studied in the liquid phase using DMF solvent and **2** was found to rearrange to 3-methylene-1,4-cyclooctadiene (**9**) by a first-order process, followed by NMR, giving $k = 10^{11}\, e^{-29{,}000/RT}\ \text{sec}^{-1}$ (eq 3).



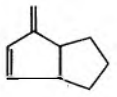
9 (3)

This rearrangement must involve a hydrogen migration. The marked contrast in the thermal chemistry of **1** and **2** is at first surprising. However, transannular interactions are well documented in C_8 rings[9] and similar, although less facile, rearrangements of related systems are well known[10] (eq 4). The strain energy associated with the methylenecyclopropane would be expected to accelerate **2** → **9**. In terms of conformation, compound **2** should be ideally disposed to form **9**, since labeling studies for the related systems[10] have



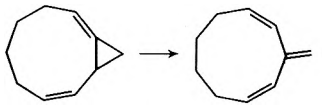
(4)

shown that the migrating hydrogen is trans to the cyclopropane ring. It may occur by the sequence **2** → **8** → **9**, or by a direct hydrogen shift in **8**. An argument against the intermediacy of 8 is that its expected rearrangement product,[4b] **10**, is undetected.



10

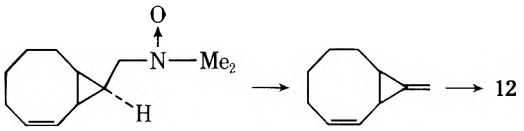
In strict analogy to eq 3 (**2** → **9**), bicyclo[7.1.0]deca-1,7-diene (**11**) rearranges exclusively to 3-methylene-1,4-cyclononadiene (**12**) (eq 5). This rearrangement is nearly com-



(5)

11 **12**

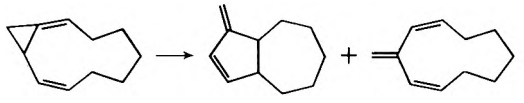
plete in 30 min at 110° or 3 hr at 80°. The formation of **12** was also observed by Radlick, Fenical, and Alford[11] in a closely related reaction. When they attempted to prepare 9-methylenebicyclo[6.1.0]nona-2-ene (**13**) by thermolysis of the hydrated amine oxide **14**, **12** was obtained, presumably via **13** (eq 6). Compounds **11** and **13** are related by a methylenecyclopropane rearrangement. Molecular models reveal that **11** probably exists in the cis-syn stereochemical form. This assures favorable conformation for direct hydrogen migration, although the same mechanistic uncertainties exist as discussed earlier for the rearrangement of **2**.



(6)

14 **13**

Unlike the other compounds in this series, bicyclo[8.1.0]undeca-1,8-diene (**15**) was found to undergo thermal reorganization by competing processes in which both carbon and hydrogen serve as the migrating atom. Thus, **15** rearranges slowly (16 hr at 140°) to give a 2:1 mixture (NMR) of 4-methylenebicyclo[5.3.0]deca-2-ene (**16**) and 3-methylenecyclodeca-1,4-diene (**17**) (eq 7).

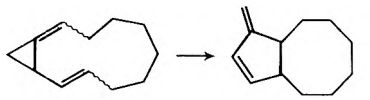


(7)

15 **16** **17**

The marked thermal stability of **15** in comparison to **2** and **11** is at first surprising, but can be reconciled on the basis of geometrical restraints in the ten-membered ring. Models indicate that the cis-syn stereochemical form of **15** is the more favorable one and the observation of a major GC peak suggests one isomer. Nevertheless, this compound is highly encumbered sterically and this probably serves to retard the rate of rearrangement.

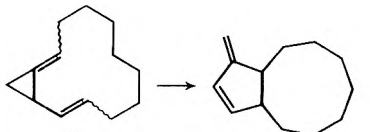
Larger rings give only rearrangement products resulting from sigmatropic processes involving carbon. Thus bicyclo[9.1.0]dodeca-1,9-diene (**18**) gives the cyclopentene **19** in nearly quantitative yield after refluxing in toluene at 105° for 4 hr (eq 8). A minor product, not identified, observed in the NMR spectrum of the crude product was shown to arise from thermal rearrangement of the product **19**.



(8)

18 **19**

Similarly, bicyclo[10.1.0]trideca-1,10-diene (**20**) yields only 4-methylenebicyclo[7.3.0]dodeca-2-ene (**21**) (eq 9).



(9)

20 **21**

The question of concertedness vs. diradicals for the alicyclic counterpart of eq 7–9 has been discussed in several recent papers.[4] Geometrical restraints within the starting hydrocarbons probably rule out concerted [3,3]-sigmatropic processes for the systems under study here. All of the products can be accounted for through the regiospecific closure of diradicals (**22** is not observed) or vinylcyclopropane rearrangement of intermediate **23**.

22 **23**

Experimental Section

General. Infrared spectra were recorded as liquid films on a Beckman IR-8 spectrometer. NMR spectra were recorded on Varian A-56/60A and Perkin-Elmer R-12 spectrometers in CCl_4 solution and results are expressed in parts per million downfield from internal TMS (δ). GLC analyses were carried out on Hewlett-Packard Model 700 and Aerograph Autoprep A-700 instruments with thermal conductivity detectors using a 3 ft × 0.125 in. 15% column packed with β,β'-oxydipropionitrile on Chromosorb P. All boiling points are uncorrected and were run using a short-path distillation head.

Materials. Cycloheptene and cyclododecene were supplied by Chemical Samples Co. and used without further purification. Cyclooctene was used as received from Matheson Coleman and Bell. Potassium *tert*-butoxide was supplied by MSA Research Corp. Dimethyl sulfoxide (Aldrich) was distilled from CaH_2 and stored over 4A molecular sieves prior to use. All other solvents were reagent grade and used as received.

Cyclononene, cyclododecene, and cycloundecene were prepared by reduction of the corresponding allenes with sodium in ammonia.[12] Precursor allenes were prepared by the general ring-expansion methods of Moore and Skattebøl[13] using cyclooctene as a starting point. *gem*-Dichlorocyclopropanes were prepared after Skell and Garner.[14]

7-Methylenebicyclo[4.1.0]hept-2-ene (3). The preparation of this compound from 8,8-dichlorobicyclo[5.1.0]octane is representative of the preparations outlined for the other bicyclo[n.1.0]alka-1,n-dienes. In a 250-ml three-necked flask equipped with a stirrer and nitrogen purging system was prepared a solution of 28.1 g (0.25 mol) of KO-*t*-Bu in 100 ml of dry dimethyl sulfoxide. 8,8-Dichlorobicyclo[5.1.0]octane (21.5 g, 0.12 mol) was added dropwise with stirring over a 30-min period. The mixture was then stirred for 1 hr followed by addition of water. The aqueous layer was extracted with pentane and dried over sodium sulfate. The solvent was then removed, leaving 6.36 g (0.06 mol, 50%) of crude **3**. Further purification was accomplished by distillation to give 5.34 g (42%) of **3**, bp 23° (0.22 mm). The identification of **3** rested on its spectra: prominent ir band at 11.28 μ (methylenecyclopropane); NMR signals at δ 0.9–2.2 (6 H) and 5.20–6.25 (4 H). ^{13}C NMR shows eight distinct signals, one unattached to hydrogen. The mass spectrum showed a parent molecular ion at *m/e* 106.

Bicyclo[6.1.0]nona-1,6-diene (2). Addition of 9,9-dichlorobicyclo[6.1.0]nonane (19.3 g, 0.1 mol) to a solution of 23.6 g (0.21 mol) of KO-*t*-Bu in 100 ml of dry DMSO produced 4.8 g of **2** (40%

yield). Reduction of **2** to bicyclo[6.1.0]nonane was found identical with the sodium in ammonia reduction product of the starting *gem*-dichlorocyclopropane. The NMR is consistent with the structure: δ 0.5–0.85 (1 H), 1.05–2.83 (8 H), 5.6 (m, 2 H), 5.89 (m, 1 H). The ^{13}C NMR shows nine signals, one for carbon not attached to hydrogen.

Bicyclo[7.1.0]deca-1,7-diene (11). Addition of 10,10-dichlorobicyclo[7.1.0]decane (11.0 g, 0.053 mol) to a solution of KO-*t*-Bu (12.4 g, 0.11 mol) in 50 ml of DMSO at 125–125° gave **12** in 42% yield: bp 28° (0.2 mm); ir 3040 w, 3010 s, 2980 s, 2950 s, 2920 s, 2880 s, 2840 m, 2830 m (C–H), 1640 m (C=C), 1440 s, 1330 w, 1270 w, 1225 w, 1075 w, 980 m, 925 m, 730 s, 705 cm^{-1} w; NMR δ 0.6–1.0 (m, 2 H), 1.1–2.9 (m, 9 H), 5.15–6.1 (m, 3 H).

Bicyclo[8.1.0]undeca-1,8-diene (15). Treatment of 6 g of 11,11-dichlorobicyclo [8.1.0]undecane with KO-*t*-Bu (6.2 g, 0.56 mol) in 25 ml of DMSO gave 2.9 g (72% yield) of **15:** bp 55–57° (1.3 mm); ir 3040 w, 3020 m, 2970 s, 2940 s. 2930 s, 2870 s, 2830 m (C–H), 1640 w (C=C), 1450 s, 1430 m, 1420 m, 1340 w, 1310 w, 1260 w, 1245 w, 1200 w, 1140 w, 1100 w, 1020 m, 908 s, 940 m, 840 m, 820 m, 790 m, 740 m, 720 m, 695 cm^{-1} m; NMR δ 0.65–2.9 (m, 13 H), 5.0–5.95 (m, 3 H).

Bicyclo[9.1.0]dodeca-1,9-diene (18). **18,** bp 68–70° (1.2 mm), was prepared in 69% yield by treating 12,12-dichlorobicyclo-[9.1.0]dodecane with a solution of 11.7 g (0.104 mol) of KO-*t*-Bu in 50 ml of DMSO: ir 3040 w, 3010 m, 3070 s, 3030 s, 2850 s (C–H), 1630 w (C=C), 1450 s, 1430 s, 1390 w, 1330 w, 1260 w, 1010 w, 980 w, 970 w, 960 w, 920 w, 830 w, 740 cm^{-1} m; NMR δ 0.8–1.75 (m, 11 H), 1.75–2.6 (m, 4 H), 4.9–5.9 (m, 3 H).

Bicyclo[10.1.0]trideca-1,10-diene (20). This compound was prepared in 94% yield (crude) as described previously.[5a] Distillation of the crude material gives the product, bp 83–85° (1.3 mm), in 75% yield. The crude material is nearly as pure as the distilled product.

Thermolysis of 7-Methylenebicyclo[4.1.0]hept-3-ene (3). Thermolysis of **3** was carried out in the gas phase using the flow system which has been described previously.[4b,6] Products **4** and **5** were obtained from the condensed effluent by preparative GLC using a 10 ft × 0.125 in. column packed with 15% FFAP on Chromosorb P. The uv of **4** shows the diene structure, λ_{max} 238 nm (ε 15,000); the proton NMR is well resolved, δ 1.5–2.7 (m, 4 H), 3.24 (m, 2 H), 4.62 (s, 1 H), 6.2 (s, 2 H). **5** is a known compound.[15] Its uv max absorption and NMR spectrum are indistinguishable from those kindly supplied by Dr. Ziegenbein. Kinetic measurements were carried out between 126.1 and 186.2° as described earlier for several related systems.[4b]

Thermolysis of Bicyclo[6.1.0]nona-1,6-diene (2). The thermolysis of **2** was carried out in DMF at 80–100°. The product **9** is shown by the λ_{max} 250 nm and the skeleton by reduction to methylcyclooctane with PtO_2 in ether. The NMR is too simple to allow a structure of lesser symmetry: δ 1.44 (m, 2 H), 2.55 (m, 4 H), 4.93 (s, 2 H), 5.33 (dt, 2 H, J = 11.5, 8.4 Hz), 6.24 (d, 2 H, J = 11.5 Hz).

Thermolysis of Bicyclo[7.1.0]deca-1,7-diene (11). A solution of **11** (0.5 g) was heated at 110° in 21 ml of toluene for 30 min, after which analysis by NMR showed nearly complete conversion to 3-methylene-1,4-cyclononadiene (**12**). In benzene (80°) it takes 3 hr. Identification of the very sensitive **13** rested on its NMR spectrum, which was identical with that reported.[11]

Thermolysis of Bicyclo[8.1.0]undeca-1,8-diene (15). A solution of **15** in xylene was heated at 140° for 16 hr. After this time ~90% of **15** was converted to a 2:1 mixture of 4-methylenebicyclo-[5.3.0]dec-2-ene (**16**) and 3-methylene-1,4-cyclodecadiene (**17**). No suitable GLC column and conditions were found to adequately separate the high-boiling, easily polymerized compounds. Column chromatography through 25% $AgNO_3$ on silica gel resulted in purification of **16,** but **17,** which was first to emerge from the column, could only be enriched. Compound **17** was readily identified by the very close resemblance of its NMR spectrum to that of **13.** The olefinic portion shows a narrow multiplet at δ 4.87 (2 H, $=CH_2$), doublet triplet at 5.30 (2 H, J = 11, 8.5 Hz), and a doublet triplet at 6.05 (2 H, J = 11, 1 Hz). Compound **16** shows NMR signals at δ 1.5–2.0 (m, 10 H), 2.65–3.1 (m, 2 H) 4.57 (s, 1 H), 4.8 (s, 1 H), and 5.65–6.1 (m, 2 H).

Thermolysis of Bicyclo[9.1.0]dodeca-1,9-diene (18). **18** was completely converted to 4-methylenebicyclo[6.3.0]undec-2-ene (**19**) by refluxing in xylene at 140° for 30 min or toluene for 3 hr at 119°. Column chromatography (25% $AgNO_3$ on silica gel) gave pure **19:** ir 3080 w, 3060 w, 2920 s, 2860 m (C–H), 1720 w (C=C), 1625 s ($C=CH_2$), 1460 s, 1535 m, 850 s, 790 cm^{-1} m; NMR δ 5.7–6.1 (m, 2 H), 4.65 (d, 2 H, J = 13 Hz), 2.45–3.0 (m, 2 H), 1.15–1.9 (m, 12 H).

Thermolysis of Bicyclo[10.1.0]trideca-1,10-diene (20). The rearrangement of **20** to **21** was complete after 4 hr in toluene reflux (110°): ir 3080 w, 3060 w, 2970 m, 2930 s, 2850 s (C–H), 1720 w (C=C), 1625 s ($C=CH_2$), 1460 s, 1435 s, 1340 w, 850 m, 780 cm^{-1} m; NMR δ 1.0–2.0 (m, 14 H), 2.45–3.0 (m, 2 H), 4.65–5.1 (m, 2 H), 4.7 (d, 2 H, J = 12 Hz, $C=CH_2$).

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Registry No.—**2,** 36398-97-7; **3,** 36398-96-6; **4,** 36399-02-7; **5,** 1192-86-5; **9,** 36399-01-6; **11,** 54643-82-2; **12,** 28569-70-2; **15,** 54643-83-3; **16,** 54643-84-4; **17,** 54643-85-5; **18,** 54643-86-6; **19,** 54643-87-7; **20,** 54643-88-8; **21,** 54643-89-9; 8,8-dichlorobicyclo[5.1.0]octane, 6498-42-6; 9,9-dichlorobicyclo[6.1.0]nonane, 6498-44-8; 10,10-dichlorobicyclo[7.1.0]decane, 52512-01-3; 11,11-dichlorobicyclo[8.1.0]undecane, 54643-90-2; 12,12-dichlorobicyclo-[9.1.0]dodecane, 54643-91-3.

References and Notes

(1) Presented in part at the Southwest Regional Meeting of the American Chemical Society, San Antonio, Tex., 1971.
(2) (a) Alfred P. Sloan Foundation Fellow, 1973–1975. (b) Taken in part from the M.S. Thesis of B. A. Baker, Rice University, 1973. (c) National Science Foundation Predoctoral Fellow.
(3) For a preliminary account, see W. E. Billups, K. H. Leavell, W. Y. Chow, and E. S. Lewis, *J. Am. Chem. Soc.*, **94,** 1770 (1972).
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Relative Stereochemistry of Multistriatin (2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane)

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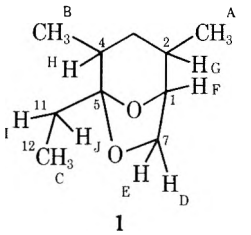
The stereochemical assignments for the C-2 and C-4 methyl groups in the four isomers of multistriatin (2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane, 1α–1δ) were determined on the basis of chemical and spectrometric data. The stereospecific addition of *cis*-2-buten-1-ol to 2-methyl-1-penten-3-one (3) to give 1α and 1γ, and a similar addition of *trans*-2-buten-1-ol to 3 to give 1δ established the relative stereochemistry at C-2. Assignment of the C-2 and C-4 methyl group signals in the NMR spectra based on deuterium-labeled 1α–1δ and comparisons of chemical shift data led to the assignment of the relative stereochemistry at C-4. These assignments were supported by acid-catalyzed equilibration of 1α and 1γ and of 1β and 1δ. α-Multistriatin (1α) is one of the three essential components of the aggregation pheromone of the European elm bark beetle.

The bicyclic ketal α-multistriatin is one of three essential components of an aggregation pheromone for the European elm bark beetle, *Scolytus multistriatus* (Marsham), which is the principal vector of Dutch elm disease in the United States. In earlier work[1] we established the gross structure of multistriatin (1) and demonstrated that a mixture of α-multistriatin, 4-methyl-3-heptanol, and α-cubebene elicits aggregating behavior similar to that observed in the mass attack of *S. multistriatus* on beetle-infested elm trees.



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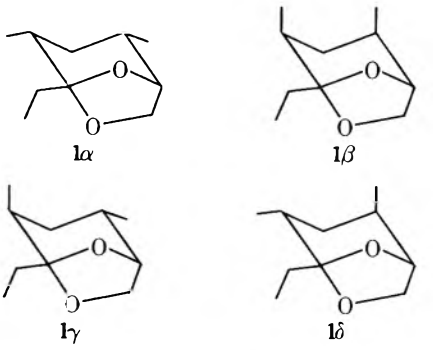
This pheromone was isolated from the air surrounding virgin female beetles boring in American elm (*Ulmus americana*) logs and is a potentially useful agent for monitoring and controlling beetle populations. The isolation procedure yielded two isomers of multistriatin, the biologically active α isomer (1α) and the inactive β form (1β). In addition to the two naturally occurring forms, two additional isomers, γ (1γ) and δ (1δ), are possible.

As part of a continuing study of the relationship between molecular structure and biological activity, we investigated the relative stereochemistry of the four multistriatin isomers, and in this report we provide evidence for the structural assignments of 1α–1δ.

The previously reported nonstereospecific synthesis of multistriatin gave four isomers (1α:1β:1γ:1δ 34:1:7:58) on GLC fractionation.[1] These isomers are characterized by



1α 1β 1γ 1δ

their MS, ir, and NMR spectra and by their gas chromatographic properties. The MS data for 1α–1δ exhibit no significant qualitative variations and only minor quantitative differences. Similarly, the ir data for 1α–1δ exhibit only minor variations at characteristic absorptions associated with CH, CC, and CO stretching frequencies. The four NMR spectra summarized in Tables I and II all show downfield signals for the three protons H_D, H_E, and H_F, a six-proton methylene envelope, and upfield signals for the three methyl groups. As shown in Figure 1, the isomer pair 1α,1γ clearly differs from the 1β,1δ pair in the patterns observed for the C-7 methylene protons, H_D and H_E. In the 1α and 1γ spectra, the two protons appear as two separate signals at approximately 3.7 (H_D) and 3.9 (H_E) ppm, respectively, whereas in 1β and 1δ both signals are observed at 3.9 ppm.

A stereospecific synthetic approach to the multistriatin isomers provided direct chemical evidence for the stereochemistry at C-2 relative to the bicyclic ketal ring system. The thermal addition of α,β-unsaturated aldehydes and ketones to α,β-unsaturated alcohols has been used as a one-

Table I
NMR Chemical Shifts (δ) for Multistriatin Isomers

Isomer	Multistriatin protons, chemical shifts[a] A	B	C	D	E	F
1α	0.81 (3 H, d)	0.81 (3 H, d)	0.94 (3 H, t)	3.68 (1 H, ddd)	3.89 (1 H, dd)	4.20 (1 H, m)
1β	1.24 (3 H, d)	1.10 (3 H, d)	0.93 (3 H, t)	3.85 (2 H, m)		4.26 (1 H, m)
1γ	0.80 (3 H, d)	1.01 (3 H, d)	0.92 (3 H, t)	3.65 (1 H, ddd)	3.94 (1 H, d)	4.19 (1 H, m)
1δ	1.15 (3 H, d)	0.81 (3 H, d)	0.94 (3 H, t)	3.85 (2 H, m)		4.22 (1 H, m)

[a] d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, m = multiplet.

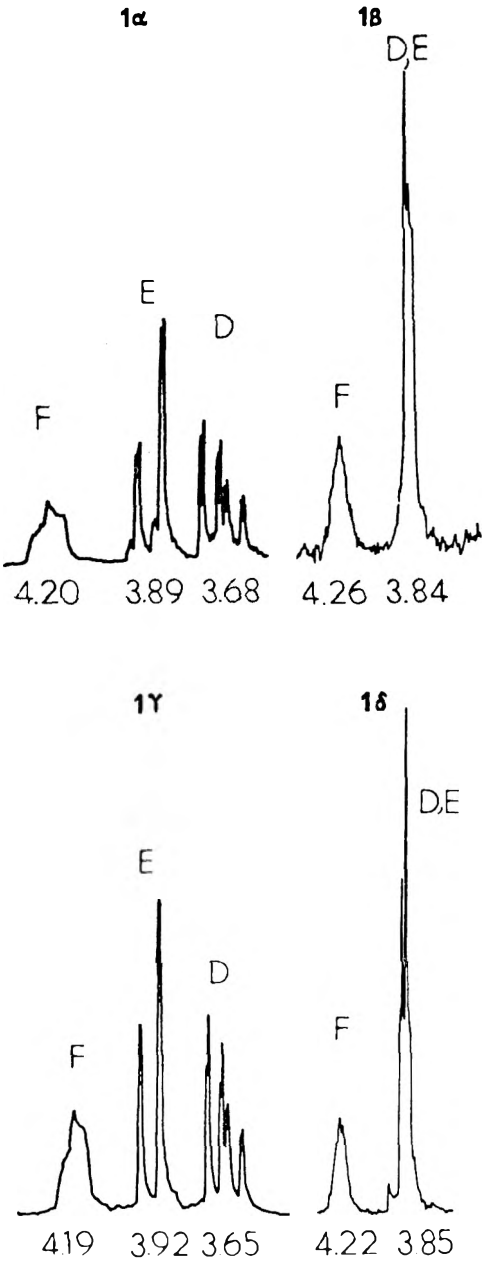
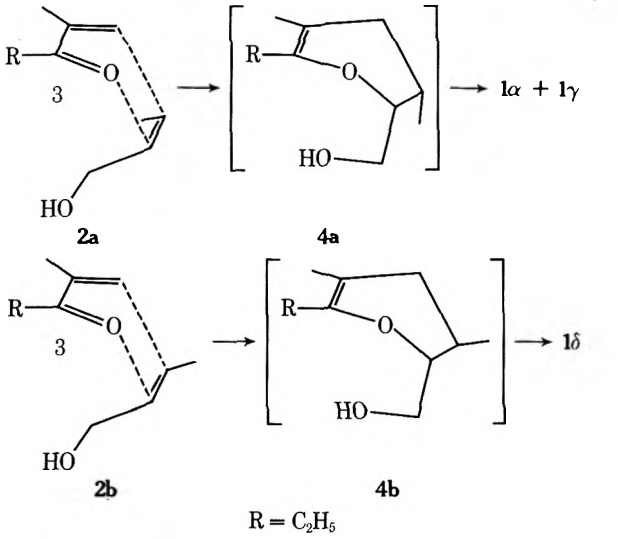


Figure 1. NMR spectra of protons D, E, and F for 1α, 1β, 1γ, and 1δ.

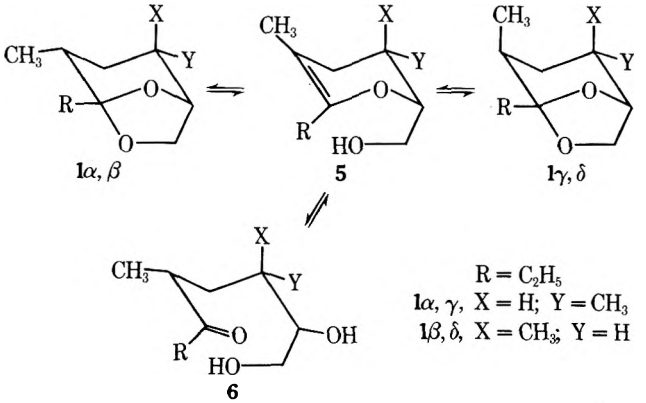
step synthesis of the dioxabicyclo[3.2.1]octane ring system.[2-4] We adopted a similar approach by adding 2-buten-1-ol (2) to 2-methyl-1-penten-3-one (3). Toluene solutions of the cis isomer (**2a**) and 3 and of the trans isomer (**2b**) and 3 were each heated to 270–290°, and the distribution of 1α–1δ was determined by preparative GLC, NMR, ir, and MS analysis. The results clearly showed that the addition of the cis alcohol (**2a**) to 3 gave 1α and 1γ (2:1) with the virtual exclusion of the 1β, 1δ isomer pair. However, when **2a** was replaced with the trans alcohol (**2b**), 1δ was formed with only trace quantities of 1α, 1γ, or 1β.

A one-step cycloaddition of **2a** or **2b** to 3 to give a dihydropyran intermediate (**4a** or **4b**) with subsequent ketal formation explains the stereospecificity observed in the formation of the multistriatin isomers and is consistent with previous findings associated with this type of reaction.[5,6] The stereospecific cycloaddition of **2a** to 3 should



give **4a**, and under the reaction conditions, ring closure would lead to products 1α and 1γ. Thus the C-2 methyl groups in 1α and 1γ must exist in the endo configuration. Similarly, the addition of **2b** to 3 would yield the 1β,1γ isomer pair, and the C-2 methyl groups would have the exo configuration. The failure to isolate 1β from the reaction mixture is probably related to the relative instability of this isomer.

Acid-catalyzed hydrolysis of the ketal to the keto glycol **6** via the dihydropyran intermediate **5** epimerizes the C-4 asymmetric center, leaving the configuration of C-2 unchanged. The result is that isomers with the same relative



configuration at C-2 are interconverted, whereas those with different configurations at C-2 are not. On equilibration in dilute phosphoric acid, GLC-purified isomer 1α yielded a 80:20 mixture of 1α and 1γ, but no 1β or 1γ; under the same conditions, pure isomer 1γ gave an identical equilibrium mixture. Similarly, equilibrating either 1β or 1γ yielded

Table II
NMR Coupling Constants for Multistriatin Isomers (Hz)

Isomer	J_{AG}	J_{BH}	$J_{CI,CJ}$	J_{DE}	J_{DF}	J_{EF}	J_{GD}
1α	7.0	7.0	7.0	7.0	5.0	0.8	0.8
1β	7.0	7.0	7.0	7.0[a]	5.0[a]	0.0[a]	0.0[a]
1γ	6.6	6.8	7.0	7.2	5.0	0.0	0.8
1δ	7.0	7.0	7.0	7.0[a]	5.0[a]	0.0[a]	0.0[a]

[a] Calculated.

a 95:5 mixture of 1γ and 1β with no 1α or 1γ. If C-4 is epimerized during the equilibration step, then isomers 1α and 1γ have one configuration at C-2, and 1β and 1δ have the opposite configuration at C-2.

The assumption that enolization occurred on C-4 and C-11 was verified by D–H exchange data. In the D–H exchange experiments, the equilibrating conditions were reproduced with D_3PO_4, and the mass spectrum of each isomer was recorded. In the NMR spectra, D–H exchange was accompanied by collapse to singlets of the C-12 methyl group triplet and *one* of the doublets associated with the C-2 and C-4 methyl groups. In the mass spectra, a molecular ion peak at *m/e* 173 and peaks at *m/e* 130 and 59, which were assigned to P − CH_3CDCH_2 and $CH_3CD_2CO^+$, respectively, point to the incorporation of one D atom at C-4 and two at C-11.

The differences in isomer ratios for the 1α,1γ pair and the 1β,1δ pair lend additional evidence for the stereochemical assignments. If we assume that the pyran ring exists primarily in the chair conformation, the C-2 endo methyl group is equatorial, with the C-4 group either axial or equatorial in the 1α,1γ isomer pair. In this case, both the equatorial–equatorial and the equatorial–axial isomers are relatively unhindered, and the 1α:1γ isomer ratios of 4:1 in equilibration and 2:1 in the stereospecific synthesis are consistent with these assignments. When the C-2 methyl group is exo as in the 1β,1δ isomer pair, the two methyl groups must exist either in a relatively unhindered axial–equatorial configuration or in the hindered axial–axial configuration. In the exo,exo isomer, the 1–3 axial–axial interaction could force the pyran ring into a boat conformation; however, the exo,exo isomer in either conformation should be significantly less stable than the exo,endo isomer. This difference in isomer stability is reflected in the 1:20 ratio observed on equilibration for the 1β,1δ isomers and the failure to observe 1β in the stereospecific synthesis. This evidence supports the assignment of the endo configuration at C-2 in 1α and 1γ and the exo configuration at C-2 for 1β and 1δ and also leads to the prediction that in 1β the methyl group is exo at C-4 and the corresponding C-4 methyl group in 1δ is endo.

An examination of the NMR shift data for the four isomers provides additional evidence for the assignments of the relative stereochemistry in the multistriatin isomers. Attention was focused on the two upfield doublets assigned to the C-2 and C-4 methyl groups, H_A and H_B, respectively. The signals for the two methyl groups could be distinguished by comparing spectra for the 4,11,11-trideuteriomultistriatin isomers in which the C-2 methyl group (H_A) appears as a doublet and the C-4 methyl group (H_B) and C-12 protons (H_C) give singlets. As shown in Table I, the exo C-2 methyl groups in 1β and 1δ and the C-4 exo methyl group in 1β exhibit chemical shifts of 1.15, 1.24, and 1.10 ppm, respectively, whereas the endo C-2 methyl groups in 1α and 1γ and the endo C-4 group in 1δ have shift values of 0.81, 0.80, and 0.81 ppm, respectively. The result of this comparison is that in all cases where the methyl group configuration is known or has been predicted, the endo methyl group signals are 0.29–0.44 ppm upfield from the exo methyl group signals. The pattern appears to be maintained in the case of the C-4 asymmetric center in the 1α,1γ pair in which the methyl group is endo in one isomer and exo in the other. Since the chemical shift for H_B is 0.81 ppm in 1α and 1.01 ppm in 1γ, the C-4 methyl group is assigned the endo configuration in 1α and the exo configuration in 1γ.

Interpretation of the observed splitting patterns for H_D and H_E was assisted by the use of spin–spin simulation experiments. As shown in Figure 1, the 1α,1γ pattern for protons H_D, H_E, and H_F exhibits an overall ABX form with a very small H_E–H_F coupling due to the dihedral angle of approximately 90° between these two protons.[7] The additional 0.8-Hz splitting in the H_D signal could be the result of long-range coupling between H_D and H_G.[8] This hypothesis was tested by simulating the H_D, H_E, H_F portion of the spectrum for 1α with chemical shift data from Table I, coupling constants from Table II, and a chemical shift value of 1.50 ppm for H_G. The simulated pattern for protons H_D and H_E agreed with the observed signals with respect to line position and relative line intensity. A second spin–spin simulation experiment demonstrated that the departure of the H_D, H_E pattern in 1β and 1δ from the pattern observed in the 1α,1γ isomer pair results from two factors. The coupling constants and chemical shift values for isomers 1α and 1γ were used as starting values for the 1β,1δ simulated spectra. When the chemical shift for H_D was increased by increments from 3.68 to 3.94 ppm the resulting spectra all contained more lines than the observed 1β,1δ spectra. When the J_{DG} value was changed from 0.8 to 0 Hz and the procedure repeated, the simulated spectrum duplicated the observed H_D, H_E pattern at an H_D value of 3.90 ppm. Thus, the observed differences in the H_D, H_E signals for the 1α,1γ and the 1β,1δ isomer pairs appear to result from a change in the J_{DG} value and in the chemical shift for H_D rather than from changes in the coupling of H_D, H_E, and H_F. This evidence indicates that the ring system conformation about C-1 and C-7 is relatively unchanged in the four isomers. Also the presence of long-range coupling in 1α,1γ and the absence of similar coupling in 1β,1δ provides spectral evidence for the relative configuration of the C-2 methyl group. The observed 0.8-Hz splitting in the H_D signal of 1α and 1γ could be the result of four-bond "W" coupling between H_D and H_G when the C-2 methyl group is in the endo configuration; and, conversely, this coupling would not be present in 1β and 1δ when the C-2 methyl group is exo.

The relative stereochemistry of the multistriatin isomers with respect to the C-2 and C-4 methyl groups can now be summarized as follows: 1α, 2 endo, 4 endo; 1β, 2 exo, 4 exo; 1γ, 2 endo, 4 exo; 1δ, 2 exo, 4 endo. Recent experiments have demonstrated that the naturally occurring 1α is optically active, and studies are currently in progress to establish the absolute configuration of carbons 2 and 4 in 1α and to measure the biological activity of the geometric isomers of multistriatin.

Experimental Section

Mass spectra were recorded on an Hitachi RMU-6E; the ir spectra in carbon tetrachloride solution on a Perkin-Elmer 621; and the Fourier transform ^1H NMR spectra in deuteriochloroform solution on a Varian XL-100 (unless otherwise indicated) as δ values with tetramethylsilane as an internal reference. The determination of coupling constants was assisted by the Varian 994029-B spin–spin simulation program and the 620 L computer. Preparative GLC was performed on a Varian Aerograph Series 2700 with glass columns containing 5% SE-30 on 60/80 DMCS Chromosorb G (10 mm × 3.6 m, He 100 ml/min, 140°), 5% Carbowax 20M on 60/80 DMCS Chromosorb G (6 mm × 6 m, He 60 ml/min), and 20% FFAP on 45/60 DMCS Chromosorb W (10 mm × 9.6 m, He 100 ml/min, 175°).

Nonstereospecific Synthesis of 1α–1δ. Compounds 1α–1δ were synthesized according to the method of Pearce et al.[1] The distillate (81–84°, 22 mm) was fractionated by GLC on Carbowax 20M at 140°, and four completely resolved peaks corresponding to 1δ, 1α, 1γ, and 1β with retention times of 14.4, 15.3, 16.5, and 18.0 min and relative areas of 58:34:7:1 were collected for ir, MS, and NMR analysis. The NMR data are summarized in Tables I and II, and a partial listing of the MS and ir data is as follows.

1α: MS *m/e* (rel intensity) 57 (100), 128 (9), 170 (4, M^+); ir 2960, 2930, 2880, 1455, 1375, 1358, 1172, 1122, 1030, 913, 894 cm^{-1}.

1β: MS m/e (rel intensity) 57 (100), 128 (10), 170 (5, M^+); ir 2980, 2950, 2890, 1465, 1380, 1360, 1235, 1060, 915, 910 cm^{-1}.

1γ: MS m/e (rel intensity) 57 (100), 128 (9), 170 (4, M^+); ir 3000, 2980, 2930, 1460, 1380, 1180, 1165, 1045, 1035, 1025, 905 cm^{-1}.

1δ: MS m/e (rel intensity) 57 (100), 128 (10), 170 (5, M^+); ir 2970, 2940, 2890, 1460, 1380, 1050, 915, 895 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.32; H, 10.49.

Equilibration of 1α–1δ. A GLC-purified sample of 1α (1 mg) was refluxed in a mixture of 0.5 ml of 1 M phosphoric acid and 0.5 ml of tetrahydrofuran (THF) for 48 hr. The solution was saturated with sodium chloride, and the THF layer was removed, dried with anhydrous sodium carbonate, and fractionated by GLC as previously described. Reaction products were identified by GLC retention times and ir spectra of the GLC fractions. This procedure was repeated for 1β, 1γ, and 1δ.

D–H Exchange in 1α–1δ. The reaction product of the nonstereospecific synthesis (50 mg) was refluxed in a mixture of 2.5 ml of 1 M deuteriophosphoric acid and 2.5 ml of THF for 48 hr. The reaction product was separated by preparative GLC, and the mass spectra of the individual fractions with retention times corresponding to 1α–1δ were recorded. Each compound gave characteristic MS peaks at m/e 59, 130, and 173. To obtain 1β in sufficient quantities for NMR experiments, the ketal mixture (1 g) was refluxed for 3 days in 5 ml of 1 M deuteriophosphoric acid and 5 ml of THF, and the reaction product was fractionated on the FFAP column with retention times of 35.6, 41.6, 44.0, and 47.6 min for 1δ, 1α, 1γ, and 1β, respectively.

NMR Spectra of Trideuterio-1α–1δ. The NMR spectra were recorded for each of the deuterium-labeled isomers 1α–1δ; however, in 1α the signals at 1.0 ± 0.2 were not clearly resolved. The spectrum of 1α in carbon tetrachloride solution was subsequently recorded in the presence of freshly sublimed d_{27}-tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-2,5-octanedione)europium(III). Spectra were recorded at 1α concentrations of 0.18, 0.12, 0.06, and 0.05 *M* with a constant shift reagent concentration of 0.006 *M*. At a 1α concentration of 0.06 *M*, all lines in the region of interest were clearly resolved.

Preparation of *cis*-2-Buten-1-ol (2a). The semihydrogenation of 2-butyn-1-ol (10 g) was performed in a Parr hydrogenation apparatus at 1–7 lb and 27° with methanol (260 ml) as the solvent and 5% palladium on barium sulfate (260 mg) poisoned with synthetic quinolone (260 mg) as the catalyst.[9,10] Distillation of the product gave **2a** (7.1 g, 71%): bp 56° (40 mm); NMR 1.95 (3 H, dd), 4.22 (2 H, m), 5.74 ppm (2 H, m), recorded on a Varian A-60. GLC analysis of the reduction products on Carbowax 20M at 120° gave resolved peaks for the cis and trans isomers **2a** and **2b** and on the basis of peak areas indicated a cis/trans ratio of 98:2.

Preparation of 2-Methyl-1-penten-3-one (3). A solution of paraformaldehyde (80 g, 2.6 mol), dimethylamine hydrochloride (224 g, 2.6 mol), and 3-pentanone (210 g, 2 mol) was refluxed for 3 hr in 400 ml of ethanol (95%) with 5 ml of hydrochloric acid.[11] Neutralization with potassium carbonate (450 g) followed by workup and subsequent methylation with methyl iodide (284 g, 2 mol) gave 480 g of a white quaternary ammonium salt. The salt was dissolved in 1 l. of water and stirred with 200 ml of ethyl ether and 200 ml of 4.3 *M* potassium hydroxide for 2 hr at room temperature.[12] The ether layer was replaced with a fresh 200-ml portion, and a second 200-ml aliquot of potassium hydroxide solution was added. Stirring was continued for an additional 2 hr and the ether was removed. The water was extracted twice with additional 200-ml portions of ether, and the combined extracts were dried over calcium sulfate. The ether was evaporated, and the product was distilled twice through a Vigreux column, yield 93.4 g (56%) of **3**: bp 37–38° (30 mm); NMR 1.10 (3 H, t), 1.88 (3 H, s), 2.70 (2 H, q), 5.74 (1 H, m), 5.94 ppm (1 H, d).

Stereospecific Synthesis of Multistriatin (1α and 1γ). A solution of **3** (6.8 g, 70 mmol), **2a** (5.8 g, 70 mmol), and 75 mg of hydroquinone in 7.5 ml of toluene was heated at 270–290° for 48 hr. The thermal additions were performed at autogenous pressure in glass tubes (6 mm × 60 cm, filled to ⅓ capacity), which were sealed under nitrogen and rocked continuously during the reaction. Vacuum distillation of the reaction product in a micro short path apparatus yielded three fractions; A, 30–55° (bath temperature) (1 mm); B, 80–100° (0.6 mm); and C, 80–100° (0.1 mm). GLC analysis on Carbowax 20M and NMR spectra of major components indicated that A contained toluene and **2a** (80% recovered), B contained a mixture of ketal isomers, and C contained only small amounts of the ketal isomers. Preparative GLC of fraction B on SE-30 gave a cluster of peaks between 17.6 and 25.6 min, which were collected and rechromatographed on Carbowax 20M at 140° for analytical determinations or on FFAP for large-scale purification. Peaks corresponding to 1α–1δ were collected, if present, and their identities verified by MS, NMR, and ir spectra. The purification sequence gave fractions corresponding to 1α and 1γ (2:1) with a total yield of 580 mg (5%). Yields of 1β and 1δ were less than 5% of the 1α + 1δ yield.

Stereospecific Synthesis of Multistriatin (1δ). The preceding procedure was repeated with **2a** being replaced with *trans*-2-buten-1-ol (**2b**). The purification scheme gave a major fraction (570 mg, 5%) with chromatographic and spectrometric properties corresponding to 1δ. Fractions corresponding to 1α, 1γ, and 1β were less than 5% of the 1δ yield.

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Registry No.—1α, 54815-06-4; 1β, 54832-20-1; 1γ, 54832-21-2; 1δ, 54832-22-3; **2a**, 4088-60-2; **2b**, 504-61-0; **3**, 25044-01-3; 2-butyn-1-ol, 764-01-2; 3-pentanone, 96-22-0.

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A Study of the Response of Bullvalenylcarbinyl *p*-Anisoate to Solvolysis and of Bullvalenyldiazomethane to Thermal Activation

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Cyanobullvalene has been prepared and transformed into bullvalenylcarboxaldehyde and carbinol. Upon treatment with bases under a variety of conditions, the tosylhydrazone was converted into bullvalenyldiazomethane, which was found to undergo intramolecular cyclization to afford the isomeric pyrazole more rapidly than loss of nitrogen. No evidence could be gained for intervention of the carbene. During attempts to convert the carbinol into its tosylate (**3b**), rearrangement to isomeric alcohol **13** occurred. This same compound arose as the exclusive solvolysis product of the *p*-anisoate derivative (**3c**) and mechanistic rationalization for its formation is given. The valence tautomers of **3b** and **3c** which are capable of leading directly to **13** are seen to be positionally isomeric with that of aldehyde **2** which accounts for acid-promoted rearrangement of the latter exclusively into **7** and **8**. This is taken to mean that bond reorganization of carbonium ion intermediates in the bullvalenyl series can be initiated from different valence isomers, a phenomenon which probably is highly dependent upon the nature of the carbocation center and its method of generation.

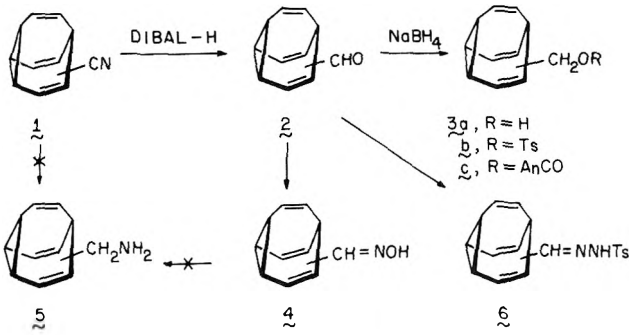
Subsequent to the synthesis of bullvalene[2-5] and the experimental realization of Doering's prediction[6] that this hydrocarbon enjoys an unparalleled capacity for rapid and reversible Cope rearrangement which scrambles completely (via 1,209,600 possible isoenergetic valence isomers!) the constituent cyclopropyl, vinyl, and bridgehead carbon atoms, a good deal of attention has been accorded the preparation of substituted bullvalenes.[7,8] The majority of this effort is due to Schröder and Oth, whose main purpose has been to elucidate the capability of a given group to partition itself by means of the available valence tautomerism channels between the several widely differing chemical environments.[9] These studies point up the uniquely distinctive property of the individual carbon atoms in bullvalene, viz., that they are subject to ready interconversion between four sites of nonidentical chemical character.

Several years ago, we developed an interest in investigating the capability of bullvalene and semibullvalene to function as neighboring groups in a wide range of chemical reactions. The specific question posed was: were a $-CH_2^+$, $-CH:$, $-N_2^+$, or other reactive functionality to be generated adjacent to a ring carbon atom of such highly fluxional molecules, would subsequent reaction occur from an sp^3 (bridgehead), $sp^{2.25}$ (cyclopropyl), or sp^2 (olefinic) hybridized state?[10] Several investigations involving nonfluxional dibenzosemibullvalene derivatives as model compounds have already been completed.[11] In this paper, we wish to delineate our more recent attempts to elucidate the chemical reactivity of of the bullvalenylcarbinyl cation and bullvalenylcarbene systems.[12]

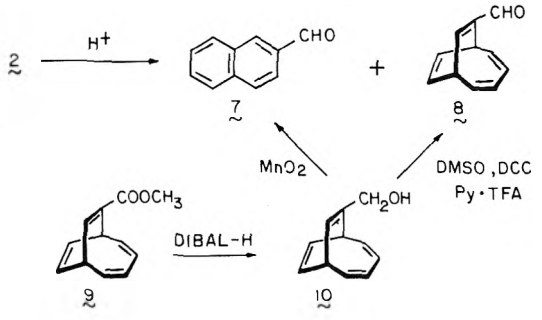
Results and Discussion

Reaction of bromobullvalene with sodium dicyanocuprate[13] in refluxing dimethylformamide solution conveniently afforded the unrearranged cyano derivative **1** in 80% yield. At 108°, the ^1H NMR spectrum ($CDCl_3$) of **1** comprised only a coalesced singlet ($W_{1/2}$ = 7.5 Hz) appearing at δ 4.45. Cooling to −35° sufficed to reveal the expected three sets of signals: a doublet at δ 6.76 (1 H) due to the vinyl proton β to cyano together with multiplets centered at δ 5.97 (4 H) and 2.56 (4 H) arising from the olefinic and cyclopropyl-aliphatic protons, respectively. Reduction of **1** with 1 equiv of diisobutylaluminum hybride (DIBAL-H) gave aldehyde **2** (67%), subsequent reduction of which with ethanolic sodium borohydride led to the desired alcohol **3a** (83%).[14]

Attempts to reduce **1** or oxime **4** with lithium aluminum hydride resulted in the generation of complex product mixtures. Examination of their ^1H NMR spectra showed clearly that the bullvalene ring system was no longer intact. No evidence was found for the formation of amine **5**. Comparable difficulties were encountered during lithium aluminum hydride reduction of **2**.



Aldehyde **2** was seen to be very prone to acid-catalyzed rearrangement. When exposed to a solution of *p*-toluenesulfonic acid in benzene at room temperature for 12 hr, **2** underwent conversion exclusively to 2-naphthaldehyde (**7**).



At shorter exposure times (1 hr), a mixture of **7** and **8** (72:28) was obtained, which proved to be inseparable by standard chromatographic techniques. The product ratio was determined by relative integration of the aldehydic proton absorptions in the ^1H NMR spectrum. The 2,4-dinitrophenylhydrazones of these aldehydes did prove separable by fractional crystallization. That derived from **8** was shown to be identical with a sample prepared from authentic aldehyde, synthetic entry to which was gained from the known ester **9**.[15] Reduction of **9** with 2 equiv of DIBAL-H followed by oxidation under Moffatt conditions gave **8**. Treatment of **9** with but 1 equiv of DIBAL-H at low temperature gave rise to a mixture of **9** and **10**. Upon oxidation

Table I
LIS ^{1}H NMR Data for 13 (δ, 60 MHz, $CDCl_3$)

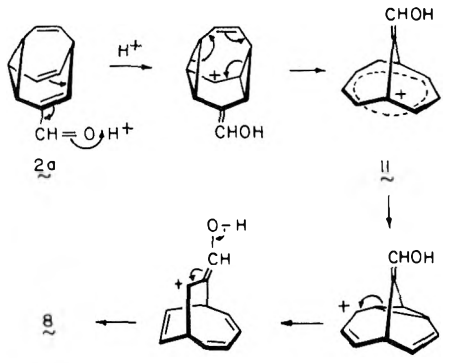
Mol % Eu(fod)$_3$	H_1	H_2	H_3	H_4, H_7	H_8, H_{10}	H_6	H_6'	H_5	H_9
0	*a*	4.12	*a*	*a*	*a*	4.80	5.00	*a*	*a*
9.9	*a*	*a*	*a*	*a*	*a*	5.13	5.38	4.12	*a*
19.4	*a*	10.00	9.52	7.58	6.78	5.38	5.70	4.70	8.63
28.9	9.07	12.73	11.27	8.47	7.22	5.68	6.05	5.32	9.83
39.2	*a*	15.25	12.85	9.08	7.58	5.95	6.35	5.87	10.80
48.5	11.90	17.10	13.92	9.95	7.83	6.13	6.55	6.23	11.62
59.6	12.90	18.85	14.75	9.90	8.07	6.27	6.72	6.50	12.15

[a] Not individually discernible owing to peak overlap.

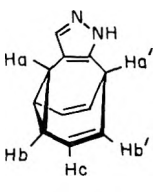
of **10** with manganese dioxide, 2-naphthaldehyde was obtained.

An interesting feature of this acid-catalyzed rearrangement is that only one each of the possible bicyclo[4.2.2]decatetraene carboxaldehydes and naphthaldehydes are produced. This can be concisely rationalized in terms of reaction through valence isomer **2a**, protonation of which leads initially to bishomotropylium ion **11**[16] (Scheme I). The isomerization of **8** to 9,10-dihydro-2-naphthaldehyde[5a] and subsequent air oxidation would give **7**. Significantly, were protonation of the other three valence tautomers of **2** to operate and bond reorganization of a comparable type to follow, exclusive access to **7** and **8** would not likely be gained.

Scheme I



Synthesis of tosylhydrazone **6** could be realized successfully by heating an ethanol solution containing equimolar quantities of **2** and tosylhydrazine on a steam bath for 20 min in the absence of acid. Upon cooling, **6** crystallizes from solution and can be isolated in 44% yield. Decomposition of **6** in glyme or ethylene glycol using *n*-butyllithium or sodium alkoxide as base resulted in the formation of a single compound in 34–42% yield. The same product was isolated from pyrolysis of the sodium salt of **6**. Its mass spectrum shows a parent ion at *m/e* 170 which corresponds to a molecular formula of $C_{11}H_{10}N_2$. In addition, the ^{1}H NMR spectrum clearly shows the presence of a homotropilidene structure,[17] and the ir spectrum contains an >NH absorption. In light of these data and ample precedent for conversion of vinyl diazo compounds to pyrazoles,[18] the substance was formulated as **12**.

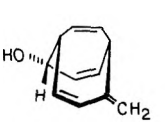


12

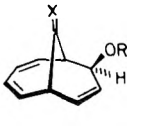
Combustion analysis of **12** indicated it to contain water of crystallization to the extent of one molecule of water per three molecules of the pyrazole. This was confirmed by Fourier transform ^{1}H NMR analysis at 90 MHz of a portion of the analytical sample. At the low concentration level of the sample the one >NH proton and the water of crystallization appeared at the same chemical shift as H_a, $H_{a'}$, H_b, and $H_{b'}$ resulting in a total area of 7.47 relative to protons H_c (2.00). This comprises a surplus of 0.47 proton attributable to the water of crystallization (calcd 0.67). When deuterium oxide was added, the relative areas changed to 5.70:2.00.

No evidence was gained for generation of the desired bullvalenylcarbene species even when recourse was made to low-temperature photochemical methods.

Attempts to prepare tosylate **3b** by stepwise addition of *n*-butyllithium and *p*-toluenesulfonyl chloride to alcohol **3a** led instead to isolation of a new alcohol, shown by mass spectrometry to be isomeric with **3a**. ^{1}H NMR analysis indicated the presence of six olefinic protons (m centered at δ 6.0), an exo methylene group (d, J = 2.0 Hz, at 5.00 and d, J = 2.0 Hz, at 4.78), a proton α to the hydroxyl group (m, 4.11), two bridgehead protons (m, 3.32), and the OH functionality (br s, 1.98). A lanthanide-induced shift study of this new alcohol showed clearly that the exo methylene is fixed so as to be distant from the hydroxyl group (see Table I and Figure 1). These data eliminate **14a** as a possiblity. In addition, little similarity is seen between the features of this LIS study and the one described by Willcott for **14b**.[19] On the other hand, structure **13** is fully consistent with



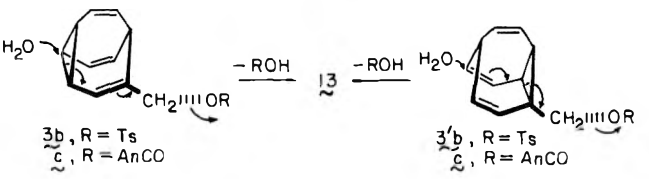
13



14a, R = H, X = CH_2
b, R = CH_3, X = H_2

these data and its formation is easily rationalized at the mechanistic level. Thus, attack by water as depicted in Scheme II during ionization of **3b** or **3'b**, probably under control by steric and electronic factors, affords **13** directly. Since water was precluded during tosylate formation, the solvolysis likely occurred during isolation (preparative TLC was utilized).

Scheme II



3b, R = Ts
c, R = AnCO
3'b, R = Ts
c, R = AnCO

Hydrolysis of the *p*-anisoate **3c** in 70:30 (v/v) acetone–water at 125° (sealed tube) for 24 hr also gave **13** (85% yield based upon recovered **3c**) as the only product.

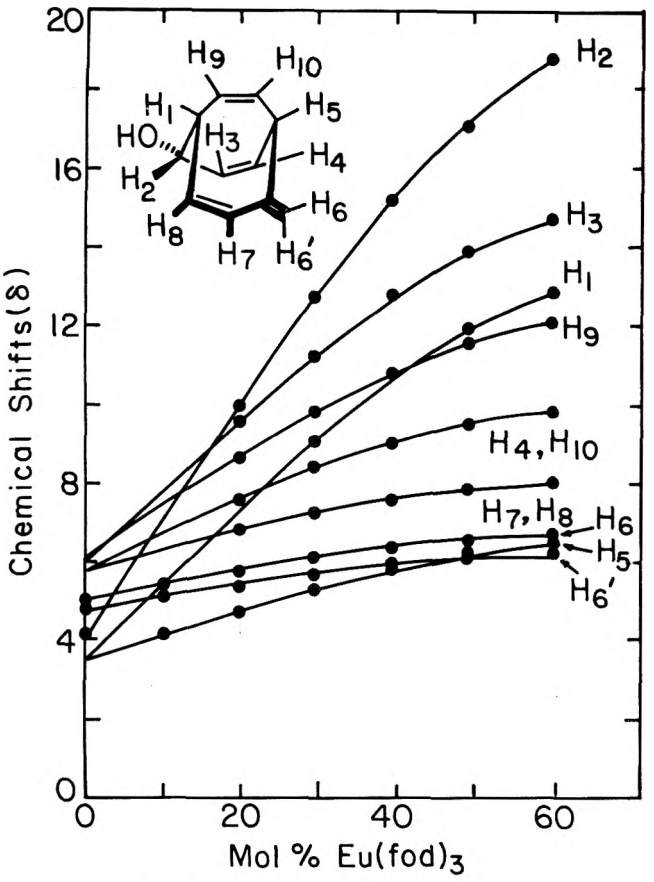


Figure 1. Plot of chemical shift vs. mol % Eu(fod)$_3$ for **13**.

Our finding of high levels of contrasting selectivity in the acid-catalyzed rearrangement of **2** and in the solvolysis of **3b** and **3c** permits us to suggest that rearrangement reactions of potential carbonium ion centers on the bullvalene backbone, e.g., **15** and **16**, appear capable of initiation from

15 **16**

different valence tautomeric forms. We propose that the ultimate course taken will likely depend upon the nature of the cationic center, its method of generation, and to some extent the timing of the transition state along the reaction coordinate. That several pathways are open is not surprising; what is now needed is additional experimental information that would assist in formulating on an a priori basis the mechanistically most favorable reaction channel available to a new bullvalene derivative.

Experimental Section

Proton magnetic resonance spectra were obtained with Varian A-60A and Jeolco MH-100 spectrometers; apparent splittings are given in all cases. Infrared spectra were determined with Perkin-Elmer Model 137 and 467 instruments. Mass spectra were recorded on an AEI-MS9 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Preparative VPC work was done on a Varian Aerograph A90-P3 instrument equipped with a thermal conductivity detector.

Cyanobullvalene (1). A mixture of 4.36 g (20.5 mmol) of bromobullvalene,[7b] 1.01 g (20.5 mmol) of sodium cyanide, 1.84 g (20.5 mmol) of cuprous cyanide, and 200 ml of freshly distilled dry dimethylformamide was refluxed under nitrogen for 8 hr. The reaction mixture gradually turned brown and then black. After cooling to room temperature, the black solution was transferred to a separatory funnel with 500 ml of 10 *N* sodium cyanide solution and 500 ml of ether. The ether layer was washed with water (2 × 1000 ml) and brine (1 × 1000 ml), dried over magnesium sulfate, filtered, and evaporated in vacuo. The resulting yellow oil was purified by column chromatography on silica gel (elution with 25% ether–hexane). The colorless oil so obtained was crystallized from 4 ml of ethanol at −30° to give 2.62 g (82%) of **1**: mp 60–60.5°; ν_{max} (KBr) 2190 cm^{-1}; δ_{TMS} ($CDCl_3$) (−35°) 6.76 (d, 1 H, olefinic β to CN), 5.97 (m, 4 H, olefinic), and 2.56 (m, 4 H, cyclopropyl and aliphatic); δ_{TMS} ($CDCl_3$) (108°) 4.45 (s, $W_{1/2}$ = 7.5 Hz).

Anal. Calcd for $C_{11}H_9N$: C, 85.13; H, 5.85. Found: C, 85.27; H, 6.16.

Bullvalenylcarboxaldehyde (2). A solution of 1.00 g (6.44 mmol) of **1** in 50 ml of dry benzene was stirred magnetically at room temperature and 5.6 ml of 26% diisobutylaluminum hydride in hexane (1.1 equiv) was added via syringe. The temperature of the reaction mixture was raised to 40° using a warm water bath and stirring was maintained for 0.5 hr. The solution was cooled in ice and residual active hydride was quenched by careful addition of 2.0 ml of methanol followed by 2.0 ml of water. After being stirred for 1 hr, the mixture was filtered through a pad of Celite and the filtrate was dried over magnesium sulfate, filtered, and evaporated in vacuo to yield an orange oil. This material crystallized slowly from benzene–hexane to give 0.678 g (67%) of **2** as a yellowish solid: mp 153–159°; ν_{max} (KBr) 2830, 1629, 1610 cm^{-1}; δ_{TMS} ($CDCl_3$) 9.05 (s, 1H, –CHO) and 4.50 (very br, 9 H).

Bullvalenylcarboxaldehyde Oxime (4). To 0.50 g (7.2 mmol) of hydroxylamine hydrochloride dissolved in 3 ml of water was added 2 ml of 10% sodium hydroxide solution followed by 100 mg (0.63 mmol) of **2** and 5 ml of ethanol. The mixture was heated on a steam bath for 15 min. The solid which was initially present quickly dissolved upon warming. Subsequent cooling deposited a pale green solid which was collected by suction filtration, taken up in hot ethanol, and treated with Norit. To the filtrate was added 5 ml of water and the total volume was reduced to 10 ml on a steam bath. Slow cooling yielded 98 mg (85%) of **4** as white needles: mp 184–185° (from ethanol); ν_{max} (KBr) 3230, 1620, 1290, 972, 953, 938, and 824 cm^{-1}; δ_{TMS} [$(CD_3)_2$ CO] 7.41 (s, 1 H, >CH=N–), 4.38 (very br, 9 H), and 2.78 (br s, 1 H, hydroxyl).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.02; H, 6.44; N, 7.82.

Bullvalenylcarbinol (3a). A mixture of 510 mg (3.22 mmol) of **2**, 200 mg (5.0 mmol) of sodium hydroxide, and 1.46 g (38.3 mmol) of sodium borohydride in 50 ml of ethanol was stirred for 24 hr at room temperature and then added to 500 ml of water and 100 ml of ether. The ether layer was separated, washed with water and brine, and dried over magnesium sulfate. After removal of the ether in vacuo, the resulting yellow oil was chromatographed on silica gel (elution with 50% ether–hexane) to give 428 mg (83%) of **3a** as a pale yellow oil. The analytical sample was obtained by preparative VPC at 170° (6 ft × 0.25 in. 5% SF-96 on Chromosorb G): ν_{max} (KBr) 3320 and 1015 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.35 (very br, 9 H), 4.02 (s, 2 H, methylene), and 1.88 (br, s, 1 H, hydroxyl).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.32; H, 7.73.

Bullvalenylcarboxaldehyde Tosylhydrazone (6). A mixture of 316 mg (2.00 mmol) of **2** and 372 mg (2.00 mmol) of tosylhydrazine in 10 ml of ethanol was heated on a steam bath for 20 min. The hot solution was filtered and allowed to cool to room temperature. The tosylhydrazone crystallized as pale yellow needles. After further cooling at −30°, the needles were collected to give 290 mg (44%) of **6**: mp 151° dec; ν_{max} (KBr) 1355, 1328, 1300, and 1160 cm^{-1}; δ_{TMS} ($CDCl_3$) 7.52 (m, 6 H, aromatic, >CH=N–, and >NH), 4.50 (very br, 9 H), and 2.40 (s, 3 H, methyl).

Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.61; H, 5.61; N, 8.47.

Acid-Catalyzed Rearrangement of 2. To 6.3 ml of a solution of *p*-toluenesulfonic acid in benzene (1.0 mmol/ml) was added 50 mg (0.63 mmol) of **2** and the mixture was stirred at room temperature for 12 hr. Addition of the solution to water (30 ml) and extraction with ether (10 ml), followed by washing of the organic layer with water and saturated sodium bicarbonate solution, drying over sodium sulfate, and removal of solvent in vacuo gave 29 mg (58%) of 2-naphthaldehyde (**7**). This product was identified by ^{1}H NMR comparison with a known sample, and by means of its 2,4-DNP derivative, mp 269–270.5° (lit.[20] mp 270°).

When the duration of reaction was limited to 1 hr, a mixture of two aldehydes was detected by ^{1}H NMR after the above work-up; these were determined to be **7** and **8** in a ratio of 72:28 as determined by the relative areas of their aldehyde absorptions in the ^{1}H NMR spectrum, 31 mg (62%).

Use of *p*-toluenesulfonic acid-d_1 gave identical results and showed no deuterium incorporation. These two aldehydes could not be separated by TLC and although separation could be achieved on a gas chromatograph equipped with an SF-96 (10%) column at 155°, the collected material that should have corresponded to **8** was found on a preparative scale to still be contaminated with **7**. Rearrangement was apparently also taking place in the exit port.

Reduction and Oxidation of 9. To an ice-cold solution of 100 mg (0.53 mmol) of **9**[15] in 5 ml of dry ether under argon was added via syringe 0.92 ml (1.17 mmol) of diisobutylaluminum hydride (26% by weight, 1.27 mmol/ml) in hexane. This clear solution was stirred at 0° for 1 hr, then treated with 0.5 ml of methanol and 0.5 ml of water. After 1 hr, the aluminum salts were removed by filtration through Celite and the gel was washed with three 20-ml portions of ether. The combined filtrates were dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on a short Florisil column (elution with 20% ether–carbon tetrachloride) to give **10** as a clear oil: δ_{TMS} ($CDCl_3$) 5.25–6.20 (m, 7 H, olefinic), 3.91 (s, 2 H, methylene), 2.85–3.43 (m, 2 H, bridgehead), and 2.88 (br, s, 1 H, hydroxyl). This oil was transferred to a 10-ml flask and 1 ml of dry dimethyl sulfoxide, 1 ml of dry benzene, 358 mg (1.74 mmol) of dicyclohexylcarbodiimide, 60 μl (0.74 mmol) of pyridine, and 30 μl (0.40 mmol) of trifluoroacetic acid were added. This solution was stirred magnetically for 24 hr at room temperature, at which point it was poured into 15 ml of ether to which was added 240 mg (2.67 mmol) of oxalic acid in 6 ml of methanol. After an additional 30 min, water (10 ml) was introduced, and the organic layer was separated and washed sequentially with water and saturated sodium carbonate solution, dried over sodium sulfate, and evaporated in vacuo. Thin layer chromatography showed that incomplete oxidation had taken place. Elution with 25% ether–hexane showed a minor component (i.e., **8**) and a major one (**10**). Isolation of **8** by preparative TLC gave 9 mg (11% from **9**) which was spectroscopically identical with **8** obtained from acid-catalyzed rearrangement of **2**. The 2,4-dinitrophenylhydrazine derivatives of **8** prepared by the two routes were also identical by infrared and TLC.

Oxidation of **10** with manganese dioxide gave 2-naphthaldehyde (**7**).

Pyrolysis of the Sodium Salt of Bullvalenylcarboxaldehyde Tosylhydrazone (6). A stirred solution of 163 mg (0.50 mmol) of **6** in 2 ml of dichloromethane (which had been stored over sodium hydroxide pellets) was treated with 21 mg (1 molar equiv) of 47% sodium hydride suspension. Gas evolution started immediately and ceased after 3 min. The solvent was removed in vacuo and the pyrolysis apparatus was assembled. The system consisted of the reaction flask, a bent adaptor leading into a straight vacuum adaptor, and a receiver. When a vacuum of 0.01 mmHg had been attained, the apparatus was lowered such that the reaction flask became immersed in a salt bath preheated at 200° and the receiver was cooled in a Dry Ice–isopropyl alcohol bath. Within a few seconds bubbling was noted in the reaction flask and deposition of a yellow oil was seen in the cooler portions of the bent adaptor. No change in the pumping speed was noted, indicating that no nitrogen was being evolved. After approximately 2 min, activity was no longer evident in the reaction flask, and a gray solid remained. The yellow oil crystallized upon scratching. After preparative thick layer chromatography, there was isolated 34 mg of the pyrazole **12** as a white solid: mp 83–87°; ν_{max} (KBr) 3360 and 3180 cm^{-1}; δ_{TMS} ($CDCl_3$) 7.35 (s, 1 H, >CH=N–), 5.80 (m, 2 H, olefinic), 4.10 (m, 4 H, olefinic = cyclopropyl), 3.27 (t, J = 8.5 Hz, 1 H, cyclopropyl = aliphatic), and 3.05 (t, J = 8.5 Hz, 1 H, cyclopropyl = aliphatic); calcd for $C_{11}H_{10}N_2$ m/e 170.0844, found 170.0847.

Anal. Calcd for $(C_{11}H_{10}N_2)_3 \cdot H_2O$: C, 74.97; H, 6.10. Found: C, 74.65; H, 6.27.

Base-Induced Decomposition of 6. To a stirred solution of 3 equiv of the base in 5 ml of dry solvent under nitrogen was added 1 equiv of **6** in one portion. This mixture was then heated in a 125° oil bath for 10 min. The only observable change was a darkening of the reaction mixture. This was then cooled in ice and rinsed into a separatory funnel with 80 ml of water and 25 ml of ether. The ether layer was washed with water, dried over sodium sulfate, filtered, and evaporated in vacuo. The resulting oil was chromatographed on a short column of silica gel (elution with 75% ether–hexane). The only isolated product was the pyrazole **12** (Table II).

Bullvalenylmethyl *p*-Anisoate (3c). To a solution of 158 mg (0.99 mmol) of **3a** in 3 ml of 2,6-lutidine was added 171 mg (1.00 mmol) of *p*-anisoyl chloride in 2 ml of 2,6-lutidine. A precipitate formed immediately and the mixture was placed in the refrigerator for 18 hr. The orange reaction mixture was added to 40 g of ice and water and the precipitate was collected by suction filtration, washed with 30 ml of cold water, and dried in air. Preparative TLC (elution with 75% ether–petroleum ether) yielded 151 mg (52%) of **3c** as an off-white solid. The second component was identified as *p*-anisoyl anhydride. Recrystallization from hexane gave pure **3c** as white prisms: mp 85–86°; ν_{max} (KBr) 1720, 1610, 1275, 1260, 1710, and 1110 cm^{-1}; δ_{TMS} ($CDCl_3$) 7.92 and 6.83 (AA'BB', 4 H, aromatic), 4.59 (s, 2 H, methylene), 4.30 (very br, 9 H), and 3.80 (s, 3 H, methoxyl).

Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.45; H, 6.23.

Table II
Decomposition of Bullvalenylcarboxaldehyde Tosylhydrazone (6)

Mmol of **6**	Solvent	Base	% yield of **12**
0.80	Diglyme	*n*-BuLi	37
0.46	Ethylene glycol	*n*-BuLi	33
0.86	Diglyme	$NaOCH_3$	42

Solvolysis of 3c. A 0.375-in. glass tube was charged with 107 mg (0.36 mmol) of **3c** and 1.0 ml of 70:30 (v/v) acetone–water and sealed 20 cm from the bottom under vacuum while being cooled in a Dry Ice–isopropyl alcohol bath. The sealed tube was allowed to warm to room temperature, then totally immersed in an air bath at 125°. After 10 min the tube was removed and inverted a few times to dissolve the molten ester at the bottom. The tube was subsequently replaced and heated for 24 hr. After cooling in a Dry Ice–isopropyl alcohol bath the tube was opened and the yellowish reaction mixture was added to 40 ml of water and extracted with ether (2 × 20 ml). The combined ether layers were washed with water (30 ml) and saturated sodium carbonate solution (30 ml), dried over sodium sulfate, and evaporated in vacuo to yield a yellow oil which upon preparative TLC purification was separated into its two components: R_f 0.73, 24 mg. Recovered **3c**: R_f 1.40, 38 mg. Rearranged alcohol **13** (85% based on recovered **3c**), white needles: mp 77–77.5° (from pentane); ν_{max} (neat) 3380 and 1015 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.00 (m, 6 H, olefinic), 5.00 (d, J = 2.0 Hz, 1 H, exo methylene), 4.78 (d, J = 2.0 Hz, 1 H, exo methylene), 4.11 (m, 1 H, >CHO), 3.32 (m, 2 H, bridgehead), and 1.98 (br s, 1 H, hydroxyl); calcd m/e 160.0888; found, 160.0890.

Attempted Preparation of 3b. To a magnetically stirred solution of 212 mg (1.32 mmol) of **3a** in 5.0 ml of dry tetrahydrofuran under nitrogen at 0° was added 0.63 ml (1 equiv) of 2.10 *M* *n*-butyllithium. The clear solution yellowed upon addition of the *n*-butyllithium; no other change was noted after 0.5 hr. To this was added 250 mg (1.32 mmol) of *p*-toluenesulfonyl chloride. After 0.5 hr, solvent was removed in vacuo, 2 ml of dichloromethane was added, and the resulting suspension was filtered. Only one spot was seen by TLC (R_f 0.81, 50% ether–hexane). Isolation by preparative TLC gave **13** (52 mg, 24%).

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Registry No.—**1**, 54934-08-6; **2**, 54934-09-7; **3a**, 54934-10-0; **3c**, 54934-11-1; **4**, 54934-12-2; **6**, 54934-13-3; **7**, 66-99-9; **9**, 20061-12-5; **10**, 54934-15-5; **12**, 54934-16-6; **13**, 54934-17-7; bromobullvalene, 27576-96-1; sodium cyanide, 143-33-9; cuprous cyanide, 544-92-3; tosylhydrazine, 1576-35-8; *p*-anisoyl chloride, 100-07-2; bullvalenyldiazomethane, 54934-14-4.

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N^3,O^4-Ethylene-1-methyluracilium Methanesulfonate. A Uracil-Derived Heteronuclear Stabilized Cation[1]

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The preparation and properties of N^3,O^4-ethylene-1-methyluracilium methanesulfonate, a heteronuclear stabilized cation, and its interconversions with 3-(β-methanesulfonyloxyethyl)-1-methyluracil were studied. The former was shown to have three sites for reactions with nucleophilic reagents: the β carbon of the ethylene moiety and C-4 and C-6 of the pyrimidine ring. Products resulting from attack at the β position were observed with DMSO, water, alcohols, benzoate, chloride, diethylamine, and pyridine. A strong rate dependence on solvent was noted with chloride ions. Products resulting from attack at C-4 were observed with water, hydroxide, alcohols, alkoxide, and isopropylamine. Diethylamine was the only reagent which led to a product resulting from attack at C-6 of the cation. Oxygen-18 experiments verified the sites at which the uracilium salt reacted with hydroxide and water. Although the N^3,O^4-ethylene-1-methyluracilium cation bears a net positive charge, deuterium exchange reactions were not observed. Mechanisms are proposed to account for the products of the various reactions which were investigated.

N^3,O^4-Ethylene-1-methyluracilium mesylate (**1**, Scheme I) was isolated during the course of the synthesis of 3-(β-mesyloxyethyl)-1-methyluracil[2] (**2**). This uracilium salt is an exceptionally stable member of the class of compounds referred to as heteronuclear stabilized cations.[3,4] Two examples of resonance-stabilized cations having the pyrimidine nucleus have been observed, but only in solution.[5]

Delocalization of the positive charge over several atoms of cation **1** enhances stability and provides multiple sites for chemical reactions. Furthermore, one of its resonance structures is analogous to that postulated as a rationalization for the carbanion mechanism of H-6 exchange in pyrimidines.[6]

In most cases where salts of heteronuclear stabilized cations have been isolated, the anions have been nonnucleophilic species such as ClO_4^-, BF_4^-, or SbF_6^-. By contrast, the anionic portion of salt **1** is sufficiently nucleophilic under certain circumstances to enable the salt to revert to its covalent isomer.

Results and Discussion

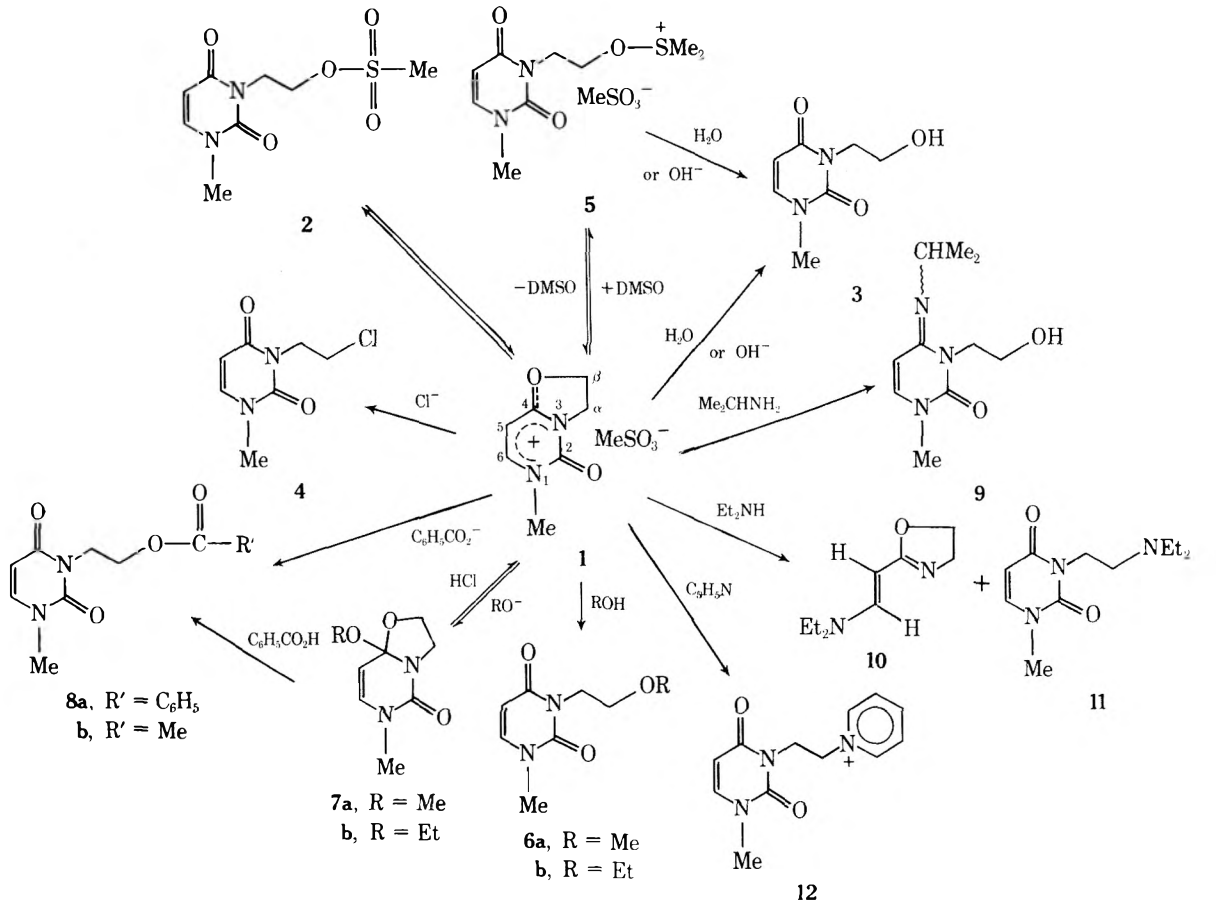
3-(β-Hydroxyethyl)-1-methyluracil (**3**) was obtained in high yield by a three-step synthesis starting with 2,4-diethoxypyrimidine.[7] Mesylation of **3** gave a 90% yield of ester **2** and a small amount of 3-(β-chloroethyl)-1-methyluracil (**4**). The structure assigned to **2** is supported by the ultraviolet absorption spectrum, which is essentially identical with that of **3**[8] and of 1,3-dimethyluracil.[9] The infrared spectrum of compound **2** is that of a typical 1,3-disubstituted uracil: ν (C_2=O) 1700, ν (C_4=O) 1660, ν (C=C) 1620 cm^{-1} and absorptions due to uracil nucleus vibrations at 1415–1440 and 1450–1490 cm^{-1}.[10] In fact, the infrared spectra of all of the compounds (**2**, **3**, **4**, **6**, **8**, **11**, and **12**) which have the uracil nucleus exhibit these characteristic absorption bands. In general, these compounds also absorb in regions characteristic of the functional groups which are substituents on the N-3 ethyl side chain; e.g., compound **2** absorbs at 1185 and 1345 cm^{-1}.[11] The ^{1}H NMR resonances of H-5, H-6, and NCH_3 in ester **2** are essentially the same as those in **3**, while the methylene resonances are shifted downfield, as expected. The resonance due to the protons in the methanesulfonyl group is in the same region as that of other methanesulfonate esters.[12] The ester was soluble and relatively stable in nonpolar solvents (e.g., chloroform, ethyl acetate, and acetone) and it migrated like a covalent compound in thin layer chromatography on silica gel.

Table I
Ultraviolet Absorption Spectra

Compd	95% EtOH		0.1 N HCl		0.1 N NaOH	
	λ_{max}	λ_{min}	λ_{max}	λ_{min}	λ_{max}	λ_{min}
1	290 (9.9)[a,b]	247 (0.7)[b]	288 (9.8)	245 (0.9)		
	202 (11.5)[b]					
2[c]	267 (7.2)	232 (2.0)				
	207 (7.0)					
3	267 (8.3)	234 (1.8)	267 (8.3)	235 (1.3)	267 (8.3)	236 (1.7)
	207 (7.9)					
4	267 (8.6)	234 (1.6)	267 (8.4)	234 (1.3)	267 (8.6)	236 (1.8)
	207 (8.4)					
5[d]	270 (7.3)					
6a	267 (8.3)	230 (1.9)	267 (8.3)	235 (1.7)	267 (8.3)	237 (2.2)
	206 (8.4)					
7b[e]	235 (6.5)	226 (6.3)				
8a	267 (9.2)	247 (5.4)	267 (9.3)	250 (6.2)	267 (9.2)	245 (4.8)
	228 (14.0)	212 (11.5)	230 (13.1)	214 (10.8)		
8b	266 (8.5)	233 (1.7)	267 (8.5)	235 (1.6)	267 (8.5)	237 (2.3)
	206 (8.4)					
9	285 (7.8)	250 (2.4)	292 (13.1)	255 (2.8)	285 (7.8)	254 (3.0)
	225 (10.8)	206 (6.7)				
10	287 (25.6)	240 (1.8)	296 (38.0)	245 (0.05)	285 (19.5)	238 (0.4)
11	267 (8.4)	224 (2.1)	268 (9.1)	234 (1.6)	267 (8.7)	239 (2.5)
12	261 (11.4)	265 sh (11.0)	261 (11.0)	265 sh (10.7)	260 (11.4)	266 sh (11.0)
	207 (12.4)	237 (3.5)		235 (2.5)		237 (3.5)

[a] λ in nanometers, $\epsilon \times 10^{-3}$ in parentheses. [b] MeCN. [c] Absolute EtOH. [d] DMSO. These data are for an equilibrium mixture of 1, 2, and 5. The molar extinction coefficient is corrected for the content of 1 and 2. [e] Absolute EtOH. The molar extinction coefficients are calculated on the assumption of quantitative conversion of 1 to 7.

Scheme I



The ester 2 was unstable at room temperature, both neat and in solution in polar solvents such as water or alcohol.[2] It rearranged readily to a new compound (1), whose salt-like nature soon became evident. Electrophoresis in acetate buffer, pH 4.6,[13] demonstrated that the uv-absorbing moiety of 1 was positively charged. The salt-like nature of 1

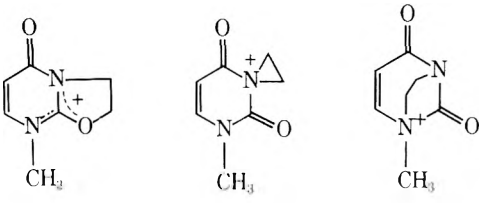
Table II
^{1}H NMR Spectra[a]

Compd	Solvent	H-6 (d)	H-5 (d)	$J_{5,6}$	$C_\alpha H_2$–$C_\beta H_2$[b]		$J_{\alpha,\beta}$	NMe (s)	Other
1	DMSO-d_6	8.83	6.83	8	5.20	4.40	9.5	3.59	2.32 (s, 3, $CH_3SO_3^-$)
	D_2O	8.60	6.65	8	5.32	4.57		3.69	2.79 (s, 3, $CH_3SO_3^-$)
	CF_3COOH	8.45	6.55	8	5.37	4.68		3.80	3.15 (s, 3, $CH_3SO_3^-$)[c]
2	DMSO-d_6	7.70	5.68	8	4.35	4.18	6	3.30	3.13 (s, 3, CH_3SO_3)
	D_2O	7.62	5.87	8	4.58	4.32		3.40	3.17 (s, 3, CH_3SO_3)
	$CDCl_3$	7.18	5.89	8	4.46	4.35		3.40	3.02 (s, 3, CH_3SO_3)
3	DMSO-d_6	7.65	5.65	8	3.92	3.48	6	3.28	4.68 (broad, 1, OH)
	$CDCl_3$	7.17	5.75	8	4.22	3.90		3.40	3.87 (broad, 1, OH)
4	$CDCl_3$	7.22	5.82	8	4.15	3.71		3.37	
5	DMSO-h_6	7.75	5.72	8	4.48	4.17	6	3.33	2.32 (s, 3, $CH_3SO_3^-$), 3.30 [s, 6, $(CH_3)_2S$]
6a	DMSO-d_6	7.66	5.64	8	4.00	3.47	6	3.23 or 3.29	3.29 or 3.23 (s, 3, CH_3O)
	$CDCl_3$	7.19	5.72	8	4.19	3.64		3.40 or 3.38	3.38 or 3.40 (s, 3, CH_3O)
7b	DMSO-d_6	6.60	5.11	8	3.97			3.05	3.26 (q, 2, J_{Et} = 7, CH_3CH_2O), 1.07 (t, 3, J_{Et} = 7, CH_3CH_2O)
	$CDCl_3$	6.34	5.12	8	4.08			3.17	3.35 (q, 2, J_{Et} = 7, CH_3CH_2O), 1.16 (t, 3, J_{Et} = 7, CH_3CH_2O)
8a	$CDCl_3$	7.13	5.68	8	4.38	4.54	6	3.34	8.00 and 7.43 (m, 5, aromatic protons)
8b	$CDCl_3$	7.20	5.72	8	4.28			3.40	3.61 (s, 3, CH_3CO)
9	$CDCl_3$	6.75	5.75	8	4.28	3.83	4.5	3.30	5.17 (m, 1, OH), 3.57 [septet, 1, $J_{i\text{-}Pr}$ = 6.5, $NCH(CH_3)_2$], 1.14 [d, 6, $J_{i\text{-}Pr}$ = 6.5, $(CH_3)_2CHN$]
10[d]	$CDCl_3$	7.17	4.70	13.5	4.19	3.82	9		3.17 (q, 4, J_{Et} = 7.5, CH_3CH_2N), 1.15 (t, 6, J_{Et} = 7.5, CH_3CH_2N)
11	$CDCl_3$	7.21	5.68	8	4.05	2.70		3.39	2.61 (q, 4, J_{Et} = 7, CH_3CH_2N), 1.04 (t, 6, J_{Et} = 7, CH_3CH_2N),
12[e]	D_2O	7.60	5.77	8	4.88	4.62	5	3.35	8.58 and 8.88 (m, 5, aromatic protons), 2.80 (s, 3, $CH_3SO_3^-$)

[a] Chemical shifts are in parts per million from TMS or DSS; multiplicity is in parentheses; coupling constants are in hertz; integration is correct for assignments. [b] The definite assignment of the α and β protons can be made only in the case of 3, where hydroxyl coupling is observed. The others could be interchanged. The spectra of these protons consists of a set of multiplets which are symmetrical and can best be described as an A_2B_2 pattern. The A_2B_2 pattern fits best for those structures in which the ethylene group is part of a ring. However, even in the nonring compounds, the spectra are not complex enough to be AA'BB' systems. Therefore, the chemical shifts given are for the approximate position of the highest line in the multiplet, assumed to be line 4. The coupling constant $J_{\alpha\beta}$ is one-half the difference between lines 2 and 7. See J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Oxford, 1965, pp 347–351. [c] The methyl protons of CH_3SO_3H in CF_3COOH have δ 3.25 ppm. [d] The numbering system used for designating the atoms in 1 was retained for the purpose of simplification and ease of comparison. [e] See ref 2.

also was evident on thin layer chromatography on silica gel and by its insolubility in nonpolar solvents and solubility in polar solvents. Confirmation of the structure was provided by spectroscopic data. The cation has a λ_{max} at 290 nm, as contrasted with a λ_{max} of 267 nm for the ester **2**, indicating an extended conjugated system. Analogous resonant cations[5] also exhibit long-wavelength maxima. The infrared spectrum of **1** in the region 1600–1800 cm^{-1} differs considerably from that of a typical 1,3-disubstituted uracil. The major changes are the absence of an absorption at ca. 1660 cm^{-1}, corresponding to ν (C_4=O), and the appearance of a band at 1605 cm^{-1}, corresponding to the structural element $-O-C^+=NCH_3$.[14] The absorption due to ν (C=C) is still unchanged at 1619 cm^{-1} and that corresponding to ν (C_2=O) has shifted to 1751 cm^{-1}. The ^{1}H NMR absorptions of the cation portion of the salt are shifted to lower field relative to the corresponding resonances of the mesyl ester **2**, as expected for a positively charged species. The mesyl resonance is shifted upfield to δ 2.32, a value corresponding to that of mesylate anion.[15] Finally, the reaction of **4** with silver tetrafluoroborate in acetonitrile[3b] produces the same cation **1**.

Alternative positively charged cyclic structures for cation **1** include the following.



13 **14** **15**

Crystal structure data for uracil and 1-methyluracil show that the bond between C-4 and O-4 is longer than the one between C-2 and O-2,[16] and therefore compound **1** is a more likely product than **13**. In fact, of the four structures illustrated for the uracilium cation (**1**, **13**, **14**,[17] and **15**), the one in Scheme I is the most resonance stabilized; the positive charge in it is more delocalized than in the others. This argument in support of the assigned structure is analogous to the explanation given for the stability of the cation derived by monoprotonation of uracil on O-4 relative to the one derived by protonation on O-2.[18] Finally, structures **13**, **14**, and **15** are inconsistent with the uv, ^{1}H NMR, and chemical data.

Although the cation **1** was prepared by the thermolysis of **2**, the two compounds were found to be interconvertible.

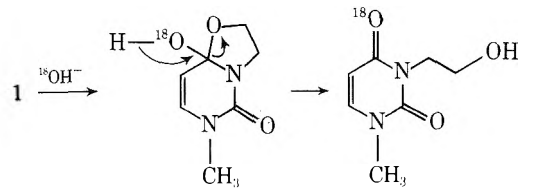
When the cation was heated in the solid probe of the mass spectrometer, only the mass spectrum of **2** was observed. Further, in contrast to the behavior of **2** in polar solvents (vide supra), **1** on solution in acetonitrile at room temperature equilibrated to a mixture containing **2** and **1**. The reaction, **2** to **1**, is merely an intramolecular nucleophilic substitution of the mesylate anion by the oxygen atom on C-4, while the reverse is an SN2 reaction of mesylate anion at the β carbon atom of the ethylene moiety. The former resembles the conversion of 5-(2-methanesulfonyloxyethyl)-uracil to 2*H*,3*H*,5(7)*H*-furano[2,3]pyrimidin-6-one.[5b]

The earlier expectation that there would be multiple reaction sites in cation **1** was borne out by further study of its behavior toward a variety of reagents. The ester **2** and salt **1** both reacted with DMSO at room temperature to give an equilibrium mixture containing 21% **2**, 16% **1**, and 63% of a new cation to which we assign the structure of a dimethylsulfoxonium salt (**5**). Equilibrium was reached in about 4 hr from the salt and 20 hr from the ester (^{1}H NMR). On evaporation of the DMSO solution, **5** reverted to **1**. This regeneration of **1** on evaporation of the DMSO was confirmed by means of both ^{1}H NMR and uv spectroscopy. Compound **3** was obtained quantitatively on the addition of water or a catalytic amount of aqueous sodium hydroxide to the DMSO solution of the equilibrium mixture.

Although **5** could not be isolated, the ^{1}H NMR data in DMSO support the suggested structure. The chemical shifts assigned to **5** have values similar to those of the mesyl ester **2**, except for the resonance due to the mesyl group. This is in the same position as in mesylate anion. In addition, a new six-proton singlet is observed at δ 3.30.[19] The changes in the uv spectrum which take place on solution of **1** in DMSO also support the proposed structure.

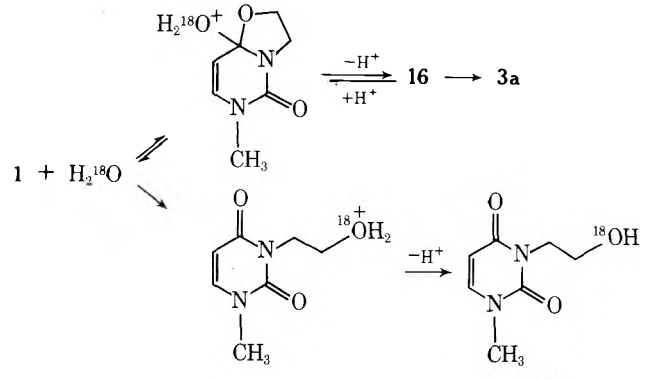
The cation **1** was stable at low pH values, but it reacted rapidly in alkaline solutions to give **3**. When **1** was treated with $Na^{18}OH$ in $H_2{}^{18}O$, the labeled **3** contained all of the ^{18}O in the C-4 carbonyl group. The solvolysis in $H_2{}^{18}O$ yielded **3** containing only one atom of ^{18}O; one-half the molecules of **3** were labeled in O-4 and the other half were labeled in the β-OH group.[20]

The results with $Na^{18}OH$ are best explained by a mechanism such as shown.



16 3a

A mechanism for the aqueous solvolysis which explains the observed distribution of the ^{18}O label is as follows.



3b

As the reaction progresses, the medium becomes more acidic. The equilibria between **1** and **16** shift in favor of **1** and thus suppress incorporation of ^{18}O in the C-4 carbonyl. Substitution in the β position, to give **3b**, then becomes more important.

In agreement with the $Na^{18}OH$ experiment, cation **1** reacted with alcoholic alkoxide solutions[21] to form an addition compound (**7**), behavior analogous to the mode of formation of the dimethyl acetal of dimethylformamide, $(CH_3)_2NCH(OCH_3)_2$.[22] Formation of **7** was instantaneous and quantitative. Spectroscopic evidence confirmed the structure assigned to the product resulting from the addition of ethoxide at C-4. The uv maximum of **7b** is at 235 nm (ϵ 6500), in agreement with values reported for 2-oxo-4,4,6-trimethyl-1,2,3,4-tetrahydropyrimidine and its N-3 methyl derivative.[23] The ^{1}H NMR spectrum has resonances for both H-5 and H-6, with J = 8 Hz, shifted upfield relative to the corresponding resonances in **2**, **3**, **4**, and **6**, as expected.[24] Absorptions corresponding to the ethoxyl group also are present.

Chemical evidence supporting the structure assigned to **7** includes the fact that it reverted immediately and quantitatively to the uracilium cation **1** when an alcoholic solution of it was acidified with a strong acid, such as hydrochloric acid. On the other hand, addition of benzoic acid to an alcoholic solution of **7** resulted in the formation of 3-(β-benzoxyethyl)-1-methyluracil (**8a**) in 80% yield. The first step in both of these reactions involves protonation of **7**, followed by loss of ROH to give cation **1**. In the case of benzoic acid, the benzoate ion then reacts further with this cation, a reaction similar in character to the reaction of benzoic acid with the dimethyl acetal of dimethylformamide.[25] The fact that ethyl benzoate was not formed indicates that the cyclic cation is more stable than the alternative acyclic one. Reaction of uracilium ion **1** with sodium benzoate in DMF gave rise to the same ester, **8a**.

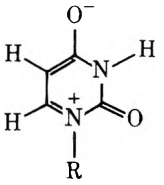
Methanol slowly solvolyzed **1** to 3-(β-methoxyethyl)-1-methyluracil (**6a**), whose structure is evident from the spectral data. The formation of this product was not surprising in view of the results of the $H_2{}^{18}O$ experiment. The analogy between hydrolysis and alcoholysis of **1** is reinforced by another experiment. On solution of **1** in absolute ethanol, 20–25% of it was converted to **7b**. This observation is in accord with the series of reactions proposed above for the aqueous solvolysis.

As implied previously, the uracilium ion **1** is quite stable in aqueous hydrochloric acid. In acetonitrile, however, **1** reacted rapidly with lithium or tetraethylammonium chloride to form the β chloride **4**. That the rate enhancement is solvent dependent was demonstrated by the reaction of **1** with aqueous hydrochloric acid in acetonitrile, again a fast reaction compared to aqueous hydrochloric acid itself.[26] This marked difference in rates could be due to little or no pairing of **1** with chloride ion in water compared to acetonitrile and/or to the fact that chloride ion is much less solvated in acetonitrile than in aqueous solution.

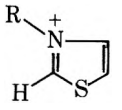
As in ordinary water, at room temperature the uracilium cation **1** was solvolyzed slowly (10% in 3 hr) in D_2O to **3**. No deuterium exchange at C-5 or C-6 of either the starting material or the product was observed. Even in 0.5 *N* sodium deuteroxide no exchange was observed at these positions during the conversion of **1** to **3**. In methanol-*O*-*d*–methoxide, the C-4 adduct **7a** formed instantly. On removal of the methanol-*O*-*d* by distillation, the adduct was converted to **3**. This product also did not contain deuterium.

These results appear surprising at first. Rabi and Fox[6b] have provided support for the suggestion that H-6 exchange in various uracil derivatives takes place through the

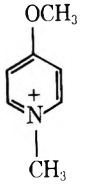
intermediacy of a C-6 carbanion. A resonance structure such as shown presumably accounts for the acidity of H-6



in these systems.[6a] The uracilium cation **1**, with a net positive charge, might have been expected to have a more acidic H-6 than a species with a net charge of zero. Breslow, in thiamine analogs of the type shown, has found exchange of



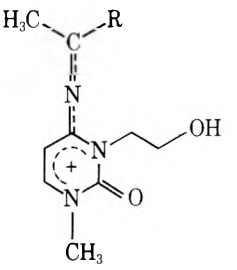
the C-2 hydrogen to occur in D_2O at room temperature in a few hours.[27] Beak et al. have reported that some pyridinium salts, such as shown, exchange C-2 and C-6 hydrogen



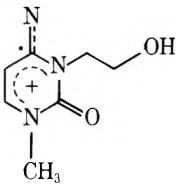
atoms in methoxide–methanol-*O*-*d* in 15 min at room temperature.[28] The uracilium cation, instead, preferentially reacts with hydroxide and methoxide ions at C-4 to give electrically neutral products. The D_2O reaction, on the other hand, demonstrates that the C-6 hydrogen in **1** is not as acidic as the C-2 hydrogen of thiamine analogs.

Reaction of **1** with 1 equiv of tetramethylammonium hydroxide pentahydrate in DMSO-d_6 gave **3** containing ca. 15% deuterium at C-6 and less than 5% at C-5. A similar experiment with **3** led to 50% degradation of starting material,[9,29] but recovered **3** contained 100% deuterium at C-6 and 67% at C-5. The exchange observed with **1** occurred in all likelihood after conversion to **3**.

The reactions of the cyclic salt **1** with amines led to products which were markedly dependent on whether the amine was primary, secondary, or tertiary. Isopropylamine gave solely the product resulting from attack at C-4, 3-(β-hydroxyethyl)-1-methyl-N^4-isopropylcytosine (**9**). Spectroscopic data are the basis for the structure assigned to this compound. Comparison of the uv spectral characteristics of **9** with the values for N^3,N^4-bis(β-hydroxyethyl)-1-methylcytosine,[30] 1,3-dimethylcytosine,[31] and 3-methylcytidine[5a] show substantial agreement. These compounds exist in the N^4-imino, rather than amino, forms. Further, an important characteristic of the infrared spectra of cytosine derivatives which have a double bond between C-4 and its exocyclic nitrogen has been noted by Brown et al. Such compounds have two absorption bands in the region 1650–1700 cm^{-1}. By contrast, compounds having a single bond between these two atoms have only a single absorption in this region.[32] Compound **9** also has two absorption bands in this region. The ^1H NMR and mass spectra also are in agreement with the assigned structure for **9**. Although a peak corresponding to the molecular ion was not found in the latter spectrum, the three ions of *m/e* 210, 196, and 168 lend further support to this structure. These may be represented by the resonance-stabilized structures below.

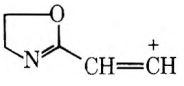


R = H, *m/e* 196
R = CH_3, *m/e* 210

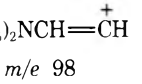


m/e 168

Diethylamine plus **1** afforded three uv-absorbing bases: 61% of *trans*-2-(β-diethylaminoethyl)-Δ^2-oxazoline (**10**); 27% of 3-(β-diethylaminoethyl)-1-methyluracil (**11**); and 12% of a compound to which the structure shown is tentatively assigned.[33] In addition, *N*,*N*-diethyl-*N'*-methylurea was isolated from the reaction mixture in 62% yield. The uv data for **10** agree with that of dienamines derived from α,β-unsaturated ketones.[34] The similarity in the wavelengths of the maxima and minima of the uv spectra of **9** and **10**, and their variation with changes in solvent, is corroborative structural evidence, since the chromophore in both of these is the structural element N—C=C—C=N. The infrared spectrum of **10** is also in agreement with the spectra reported for 2-methyl- and 2-ethyl-Δ^2-oxazoline[35] and with a characteristic frequency (1647–1652 cm^{-1}) reported for 2-aryl-Δ^2-oxazolines.[36] The ^1H NMR data lend added support to the structure given for **10**; in particular, the data demonstrate that the compound has the trans configuration. The mass spectrum is in agreement with the assigned structure too. The principal ions observed are the molecular ion and two other ions which are of structural significance. These may be represented as shown.

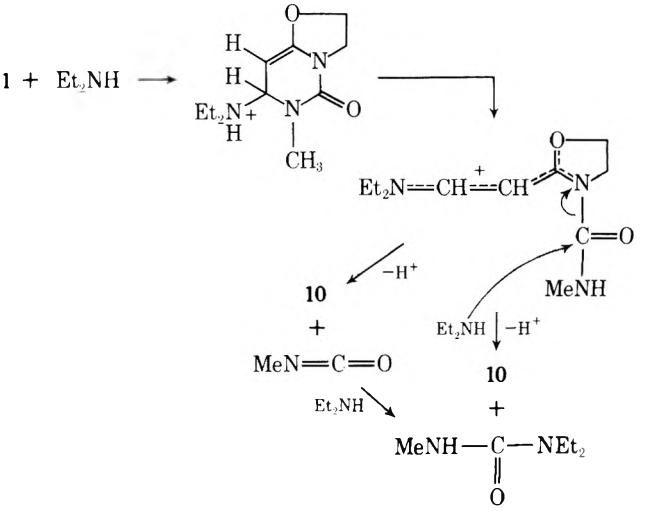


m/e 96



m/e 98

The reaction leading to **10**, the only clear-cut example of C-6 addition, involves initial attack of diethylamine at C-6 followed by ring opening between N-1 and C-6. Next, two pathways may lead to the final products. A similar reaction



has been observed with 3-methyl-4-thiouracil and dimethylamine, but it required much more drastic conditions (155°, 60 hr).[37]

The uracilium salt **1**, when dissolved in pyridine, was converted to [β-(1-methyluracil-3)ethyl]pyridinium mesylate (**12**). The basis for the assignment of structures to **11** and **12** is evident from the spectral data.

The uracilium cation **1** appears to be the first resonance-stabilized cation which has been demonstrated to have more than two reactive centers toward nucleophiles, i.e., C-4, C-6, and the β position. For this reason, if no other, its chemistry is more complex than that of the numerous heteronuclear stabilized cations which have been described in the literature.[3] The β-substitution products can be formed in two ways: direct attack at the β position or attack at C-4 followed by expulsion of the β-hydroxyethyl group. The β products are undoubtedly the most stable final products, since the α,β-conjugated system is regenerated in them. In only one case (diethylamine) the product results from attack at C-6. The absence of C-6 adducts with other nucleophiles is probably due to the fact that they would contain a ketene-*N,O*-acetal group. It has been reported that this functional group is extremely susceptible to nucleophilic attack.[14] By analogy, were C-6 adducts of cation **1** to be formed, they would be rapidly converted by further reaction with nucleophiles to C-4 addition products.

The nucleophiles which were examined fall into two groups: those which are electrically neutral and those which are anions. Both groups are each to be further divided into two subgroups. With one of these, whether electrically neutral or negatively charged, the bond initially formed at C-4 or C-6 is preserved in the final product. With the other subgroup, the final product is the result of nucleophilic substitution on the β carbon. The electrically neutral reagents which fall in the first subgroup mentioned are water, alcohols, isopropylamine, and diethylamine; those in the second are DMSO, pyridine and, once again, water and alcohols. With the latter, the equilibria involving the formation of an adduct from **1** and the nucleophile presumably is not favored. Instead, a relatively slow nucleophilic attack at the β position predominates. Of the anionic reagents, the first subgroup consists of hydroxide and alkoxide ions; the second includes mesylate, benzoate, and chloride ions. The first step in these anionic reactions takes advantage of coulombic attraction to form an ion pair which is then converted to a covalent adduct at C-4. The interaction of **1** with alkoxide is the only reaction in which the initial product was stable enough to be detected. The hydroxide ion adduct loses a proton and regains a conjugated carbonyl group. The others undergo an intramolecular conversion to the β-substituted product. These steps are analogous to those reported for the conversion of 2-methyl-*cis*-4,5-tetramethylene-1,3-dioxolenium cation by means of acetate to *cis*-1,2-acetoxycyclohexane.[38]

It is of interest to compare the chemistry of the uracilium cation **1** with the oxazolinium cations of Tomalia and Paige.[3b] By analogy with the results of these authors, solvolysis of cation **1** would involve initial attack of the nucleophile at C-4 and eventual cleavage of the bond between C-4 and N-3. No examples of this type of behavior were found. A further comparison of cation **1** with the *N,O*-trimethylenephthalimidium cation (**17**) of Hünig[3a] is desirable too. The principal differences between cations **1** and **17** lie in their solvolytic behavior. Cation **1** is converted by alcohols to **6**, whereas if its behavior paralleled that of **17** the product would have been **3**. In addition, the ^{18}O experiments with cation **1** clearly demonstrate that its reaction with water leads to a mixture of **3** labeled at O-4 and **3** labeled at the β-OH group, in contrast to the prediction of Hünig. The reaction of a secondary amine, diethylamine, with cation **1** also is quite different in character from the reaction of piperidine with **17**. Both amines form adducts with the respective cations, but since diethylamine is more sterically hindered than piperidine, and an alternative position is available in **1** for adduct formation, the diethylamine adds to C-6 rather than C-4. The initial adduct from piperidine and **17** loses a proton to form a stable product, while the adduct from diethylamine and **1** undergoes much more complex transformations to yield a stable end product. The behavior of pyridine and halide ion toward **1** is analogous to that observed by Hünig for their reactions with **17**.

Experimental Section

^1H NMR spectra were obtained on a Varian A-60 spectrometer at room temperature using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standards. A Cary 14, a Beckman DU, and a Perkin-Elmer 457 grating infrared spectrophotometer were used to obtain uv and ir spectra. Mass spectra were obtained on a Varian M-66 mass spectrometer at an ionizing potential of 70 eV, an ionizing current of 30 μA, and a resolution of ca. 2200, and with perfluorokerosene as a standard.

VPC was done on a 24 × 0.25 in. o.d. aluminum column packed with 1% SE-30 (Applied Science Laboratories, State College, Pa.) on Anakrom AS, 40–50 mesh (Analabs, North Haven, Conn.). Column temperatures ranged from 110 to 155° with He flow rates of 85–100 ml/min. Thin layer chromatography was performed on Analtech silica gel G thin layer plates containing fluorescent indicator (Analtech, Inc., Newark, Del.). Preparative chromatography (dry column) was performed on silica gel Woelm (Waters Associates, Inc., Framingham, Mass.).

Uv and ^1H NMR data for compounds **1**–**12** are summarized in Tables I and II, respectively. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Melting points are uncorrected.

3-(β-Hydroxyethyl)-1-methyluracil (3). 2,4-Diethoxypyrimidine, prepared from uracil via the dichloride,[39] was methylated with methyl iodide and hydrolyzed to give 1-methyluracil.[7a] 1-Methyluracil (6.33 g, 50.2 mmol), ethylene carbonate (4.8 g, 57.1 mmol), and potassium carbonate (100 mg, 0.72 mmol) were heated to reflux in dimethylformamide for 75 min.[7b] The reaction mixture was cooled to room temperature and evaporated in vacuo. The residue, crystallized from absolute EtOH, afforded 8.16 g (95%) of **3**: mp 138.5–140° (lit.[40] mp 136.5–138.5°); TLC, AcOEt; ir ($CHCl_3$) 3450 (m), 3000 (m), 1710 (s), 1660 (s), 1635 (s), 1455 (s), 1435 (m), 1390 (m), 1360 (w), 1335 (m), 1210 (m), 1155 (w), 1120 (w), 1015 (w), and 965 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 140 (22), 139 (14), 128 (13), 127 (100), 84 (27), 83 (31), and 82 (58).

3-(β-Mesyloxyethyl)-1-methyluracil (2). All materials were thoroughly dried and cooled to 0–10°. All operations were carried out in this temperature range. Compound **3** (1.7 g, 10 mmol) was dissolved in 100 ml of MeCN plus 6 ml (43.2 mmol) of triethylamine in a three-necked flask fitted with addition funnel, drying tube, and thermometer. Mesyl chloride (2 ml, 25.8 mmol) in 25 ml of MeCN was added slowly to the stirred reaction mixture. It is important to keep the temperature below 10°. The reaction mixture was stirred for an additional 30 min and then filtered to remove triethylamine hydrochloride. The filtrate was concentrated in vacuo to a thick oil. AcOEt was added and the solution was filtered again to remove triethylamine hydrochloride. The filtrate was evaporated in vacuo to a small volume and 2 g of silica gel was added. This mixture next was added to a column containing 25 g of silica gel and then was eluted with AcOEt. Fractions (3 ml) 12–14 contained 0.45 g of **2** plus **4** and 15–57 contained 2.24 g (91%) of **2**. The latter crystallized on evaporation of solvent. It appeared to soften at 48°, became liquid at 53°, then resolidified and melted at 105–112°. Crystalline samples liquefied when stored at room temperature overnight, but were stable for at least 30 days if stored below 10°: ir ($CHCl_3$) 1715 (s), 1665 (s), 1645 (sh), 1450 (m), 1435 (w), 1385 (m), 1355 (m), 1345 (s), 1185 (s), 1135 (w), 1078 (w), 1000 (m) and 965 cm^{-1} (m).

Ester **2** dissolved unchanged (^1H NMR) in $CDCl_3$, acetone-d_6, and pyridine-d_5.

3-(β-Chloroethyl)-1-methyluracil (4). The fractions from two

preparations of 2 (from 16.9 mmol of 3) which contained 4 were combined and chromatographed on 21 g of silica gel with AcOEt as eluent. Fractions (3 ml) 3–6 contained a single component weighing 220 mg (7%). Crystallization from MeOH–Et_2O afforded 160 mg of 4: mp 93–94.5°; ir ($CHCl_3$) 3000 (w), 1702 (s), 1665 (s), 1638 (m), 1450 (s), 1439 (m), 1390 (m), 1370 (w), 1348 (m), 1321 (w), and 1000 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 190 (28), 188 (85), 153 (100), 139 (22), 127 (20), 126 (94), 84 (46), 83 (31), and 82 (60).

Anal. Calcd for $C_7H_9N_2O_2Cl$: C, 44.57; H, 4.81; N, 14.85; Cl, 18.79. Found: C, 44.50; H, 4.59; N, 14.81; Cl, 18.79.

N^3,O^4-Ethylene-1-methyluracilium Mesylate (1). The ester 2 (1.115 g) was heated in vacuo at 81° for 4 hr. The compound melted and bubbled at approximately 70–73° and then solidified. The solid was broken up and washed with 3 × 5 ml of dry MeCN and dried in vacuo at 60–65° to afford 0.780 g of product (70%): mp 122.5–125°; ir (MeCN) 1751 (s), 1619 (s) and 1605 cm^{-1} (s); mass spectrum[41] *m/e* (rel intensity) 248 (10) ($M\cdot^+$), 170 (14), 169 (100) ($M\cdot^+ - CH_3SO_2$), 153 (18), 152 (6), 151 (11), 139 (34), 127 (14), 126 (15), 96 (6), 84 (49), 83 (23), 82 (51), 79 (17), and 70 (6).

Anal. Calcd for $C_8H_{12}N_2O_5S$: C, 38.72; H, 4.87; N, 11.29; S, 12.89. Found: C, 38.50; H, 5.08; N, 11.20; S, 13.05.

Salt 1 was soluble in H_2O and DMSO (vide infra). It dissolved unchanged in DMF and CF_3CO_2H; it was slightly soluble in MeCN and EtOH; and it was insoluble in $CHCl_3$ and AcOEt. On electrophoresis at pH 4.6 (paper, 0.05 *M* acetate buffer) 1 migrated 4 cm toward the cathode, whereas 3 did not move at all.

Although the filtrate contained 1 and 2 (TLC, AcOEt; R_f of 1 0), attempts to recover more 1 from it were unsuccessful. The reason for this became apparent when pure 1 (19.70 mg, 7.95 × 10^{-2} mmol) was dissolved in 25 ml of MeCN. An aliquot of this solution, diluted with more MeCN, had λ_{max} 290 nm. After 4 hr at room temperature, the optical density at 290 nm had decreased and a shoulder appeared at 267 nm. This spectrum remained constant and represented 64% of 1 and 36% of 2. After 24 hr another aliquot was removed and diluted with 0.1 *N* HCl. The λ_{max} of this solution slowly reached a constant absorbance at 288 nm, corresponding to complete regeneration of 1. The finite equilibrium between 1 and 2 also was evident from an ir spectrum in MeCN. In addition to the bands characteristic of 1, there were strong absorptions at 1716, 1668, and 1655 cm^{-1} (sh) corresponding to 2.

Reaction of 4 with Silver Tetrafluoroborate. Compound 4 (178 mg, 0.94 mmol) was dissolved in 4 ml of MeCN and anhydrous $AgBF_4$ (0.6 g, 3.0 mmol) was added. After 3 days the absorbance at 290 nm corresponded to a 75% yield of the cation of 1. TLC of the reaction mixture in AcOEt showed a spot at the origin and a spot with the same R_f as starting material. The solution was filtered and concentrated in vacuo. The crude residue, recrystallized from MeCN–1,2-dichloroethane, afforded 132 mg (59%) of the tetrafluoroborate of the cation of 1: mp 156–159°; ir (MeCN) 1751 (s), 1621 (s), and 1606 cm^{-1} (s); ^1H NMR (D_2O) δ 8.59 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 6.62 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 5.30 and 4.59 (m, 4, NCH_2CH_2O), and 3.68 (s, 3, NCH_3). The sample turned dark on standing, an indication of contamination by silver ion.

***O*-[β-(1-Methyluracil-3)ethyl]-*S*-dimethylsulfoxonium Mesylate (5).** Attempts to obtain the ^1H NMR spectra of the mesyl ester 2 and the cyclic cation 1 in DMSO-d_6 indicated that both were transformed to a third product. Starting with 2, equilibrium was reached in ca. 20 hr; with 1 it took ca. 5 hr. At equilibrium the ^1H NMR spectrum showed the new compound 5 to be 63% of the total, 2 21%, and 1 16%. In an attempt to prepare and isolate 5, a sample of 1 (255 mg) was dissolved in 2 ml of DMSO-h_6 with gentle warming. The λ_{max} of an aliquot of this solution in absolute EtOH had shifted from 290 to 265 nm, suggesting conversion to 5. The solvent was evaporated in vacuo and a ^1H NMR spectrum of a portion of the residue was obtained in DMSO-d_6. This spectrum was identical with that obtained by dissolving 1 in DMSO-d_6, i.e., no dimethylsulfoxonium absorption was observed. Spectra in CF_3CO_2H and D_2O of other portions of the residue confirmed that 5 had reverted to 1 on evaporation of the DMSO. When 1 was dissolved in DMSO-h_6, the ^1H NMR spectrum showed a new line for the dimethylsulfoxonium group at 3.30 ppm. The uv spectrum of an equilibrated solution of 1 in DMSO had λ_{max} 270 nm (ϵ ~7300).[42] Evaporation of this solution, followed by dissolution of the residue in absolute EtOH, showed increased absorbance at 290 nm, the λ_{max} of 1, further confirming reversal of formation of 5 on removal of DMSO.

Addition of D_2O or NaOD to equilibrated DMSO-d_6 solutions of 1 resulted in formation of 3 which contained less than 5% deuterium.

3-(β-Acetoxyethyl)-1-methyluracil (8b). Compound 3 (340 mg, 2.00 mmol) was added to 2 ml of pyridine containing 300 μl (3 mmol) of Ac_2O. The mixture was warmed briefly to achieve solution and then allowed to stand at room temperature overnight. TLC (AcOEt) indicated complete conversion to a new product. The reaction mixture was evaporated in vacuo, treated with water, and evaporated again. The residue, which resisted all attempts at crystallization, was chromatographed on 12 g of silica gel (AcOEt). The solvent was removed in vacuo from fractions (3 ml) 7–30, which contained the product: ir ($CHCl_3$) 3000 (m), 1740 (s), 1715 (s), 1655 (s), 1640 (sh), 1450 (m), 1435 (w), 1390 (m), 1375 (m), 1360 (w), 1350 (m), 1240 (s), 1140 (w), 1080 (w), 1065 (w), and 1025 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 212 (16), 169 (46), 153 (10), 152 (49), 151 (22), 140 (51), 139 (20), 128 (17), 127 (100), 84 (28), 83 (44), and 82 (49).

Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.81; H, 5.81; N, 13.31.

Reaction of 1 with $Na^{18}OH$. $H_2{}^{18}O$ (250 μl, 14% ^{18}O by mass spectrometry) was placed in a vial and weighed. The vial and contents were cooled in an ice bath and a small piece of sodium was added. After the vigorous hydrogen evolution ceased, the vial was weighed. The weight of sodium was ca. 13 mg (0.56 mmol). Compound 1 (36.4 mg, 0.15 mmol) was placed in a second vial and the $Na^{18}OH$ solution was injected into it. The vial was shaken vigorously for 5 min and then 30 μl (0.53 mmol) of glacial Ac**O**H was added. The solution was evaporated in vacuo and the residue was chromatographed on 8 g of silica with 1:1 AcOEt–EtOH. The product, 22 mg (93%) of 3, was dissolved in EtOH and this solution was divided into two equal parts. One part, after evaporation in vacuo, was treated with 200 μl (2.1 mmol) of Ac_2O in 1 ml of pyridine for 14 hr. TLC (AcOEt) indicated complete conversion to **8b.** The solvent and excess reagent were evaporated in vacuo and the residue was dissolved in 300 μl of $CHCl_3$. VPC of a 20-μl aliquot yielded a pure sample of **8b** which was used for mass spectrometric analysis. The isotopic composition was measured on the molecular ion and was found to contain 12% ^{18}O. The remaining portion of 3 was dissolved in 2 ml of 1,2-dichloroethane and treated with 50 μl (8.35 × 10^{-2} mmol) of thionyl chloride for 14 hr. TLC (AcOEt) indicated complete conversion to 4. The reaction mixture was evaporated in vacuo and the residue was dissolved in 300 μl of $CHCl_3$. VPC of a 20-μl aliquot yielded a pure sample which was used for mass spectrometric analysis. The isotopic composition was measured on the molecular ion and was found to be 12% ^{18}O.

Solvolysis of 1 with $H_2{}^{18}O$. Uracilium mesylate 1 (39.8 mg, 0.160 mmol) was placed in an airtight vial and 125 μl of $H_2{}^{18}O$ (14% ^{18}O) was injected. The solution was allowed to stand at room temperature for 8 days. An aliquot of the solution diluted with absolute EtOH had λ_{max} 267 nm and very little optical density at 290 nm. The remainder of the solution also was diluted with EtOH and then evaporated in vacuo. The residue was chromatographed on 8 g of silica gel with 1:1 AcOEt–EtOH. The product, 27 mg (100%) of 3, was dissolved in EtOH and divided into two equal parts. One portion was converted to **8b** and the other to 4, as described above. Samples for mass spectrometry were obtained by VPC. The acetate **8b** contained 12% ^{18}O and the chloride 4 contained 6% ^{18}O.

Reaction of 1 with Ethanolic Ethoxide. 4-Ethoxy-N^3,O^4-ethylene-1-methyl-3,4-dihydrouracil (7b). Compound 1 (460 mg, 1.86 mmol) was added to 250 ml of ice-cold absolute EtOH and 8 ml of freshly prepared 0.236 *N* EtONa in EtOH (1.89 mmol) was added. Within 75 min, a finely divided solid separated and the λ_{max} of the solution had shifted from 267 to 235 nm. When an aliquot of this solution was acidified with 1 *N* HCl, λ_{max} changed back to 290 nm, a value characteristic of 1. Filtration of the main portion of the solution and concentration of the filtrate in vacuo afforded a residue, **7b,** which could not be crystallized. Attempts to chromatograph the residue yielded 3. VPC of a portion of the residue led to isolation of **6b,** which was characterized by TLC (AcOEt) and mass spectroscopy.[2]

Reaction of 7b with Benzoic Acid. 3-(β-Benzoxyethyl)-1-methyluracil (8a). To 10 ml (0.171 mmol) of an ethanolic solution of **7b** was added benzoic acid (21 mg, 0.172 mmol). When a sample of the mixture was subjected to TLC (AcOEt) immediately after mixing, a new component was found. The residue obtained on evaporation of the reaction mixture in vacuo was dissolved in $CHCl_3$ and this solution was extracted with 1 *N* NaOH. It was dried ($MgSO_4$) and then evaporated in vacuo to give 37 mg (79%) of **8a.** An analytical sample was obtained from $CHCl_3$–petroleum ether: mp 142–144°; ir ($CHCl_3$) 1710 (s), 1665 (s), 1601 (w), 1450 (m), 1435 (w), 1385 (w), 1355 (w), 1350 (w), 1320 (w), 1280 (s), 1120 (m), and 1030 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 274 (8),

232 (10), 231 (78), 169 (21), 153 (18), 152 (64), 151 (20), 139 (7), 127 (8), 126 (8), 106 (23), 105 (100), 84 (16), 83 (15), 82 (36), and 77 (39).

Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.19; H, 5.09; N, 10.25. Found: C, 61.31; H, 5.14; N, 10.21.

Reaction of 1 with Sodium Benzoate. Compound 1 (24.2 mg, 9.77×10^{-2} mmol) and sodium benzoate (17.2 mg, 0.12 mmol) were dissolved in 1 ml of DMF. TLC (AcOEt) indicated complete conversion to **8a** within 0.5 hr. The reaction mixture, after evaporation to dryness, was dissolved in $CHCl_3$ and this solution was washed with water. The $CHCl_3$ layer was dried ($MgSO_4$) and after evaporation afforded 20 mg (75%) of **8a** identical with that obtained above.

Alcoholysis of 1. 3-(β-Methoxyethyl)-1-methyluracil (6a). A solution of the uracilium salt **1** (244 mg, 0.983 mmol) in 100 ml of dry MeOH was allowed to stand at room temperature. The λ_{max} shifted from 290 nm to a constant absorbance at 267 nm in 5 days. The solution was evaporated in vacuo and the residue was dissolved in 1,2-dichlorethane, washed (5% $NaHCO_3$), dried ($MgSO_4$), and concentrated in vacuo until crystallization began. The crude weight of product was 155 mg (86%). An analytical sample of **6a** was crystallized from AcOEt–petroleum ether: mp 97–98°; ir ($CHCl_3$) 1710 (s), 1665 (s), 1640 (sh), 1480 (m), 1450 (s), 1435 (m), 1390 (s), 1350 (m), 1320 (w), 1160 (w), 1140 (m), 1120 (m), 1020 (w), and 980 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 184 (12), 153 (6), 151 (20), 141 (6), 139 (14), 128 (9), 127 (100), 126 (25), 84 (19), 83 (13), and 82 (63).

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 51.99; H, 6.68; N, 15.10.

The uv spectrum of a solution of **1** (5.75 mg, 2.32×10^{-2} mmol) in 250 ml of absolute EtOH was measured within a few minutes of its preparation. The absorbance at 290 nm was found to be 20–25% lower than it would have been in MeCN or 0.1 *N* HCl and a shoulder was noted at *ca.* 235 nm. This absorption corresponds to that observed for **7b**. On acidification with 1 *N* HCl the absorbance increased at the λ_{max} for **1** and the shoulder disappeared.

Reaction of 1 with Ionic Chlorides. Stock solutions of **1** (7.35 mg, 2.96×10^{-2} mmol) and tetraethylammonium chloride (14.55 mg, 8.8×10^{-2} mmol), each in 10 ml of MeCN, were prepared. The solution of **1** (200 μl, 5.92×10^{-3} mmol) and 100 μl (8.8×10^{-3} mmol) of the chloride solution were added to a 10-ml volumetric flask containing MeCN and then diluted to the mark. The uv spectrum was recorded immediately; it showed a shoulder at 290 nm and a λ_{max} at 264 nm. The shoulder at 290 nm continued to decrease as the λ_{max} at 264 nm increased. After 20 min the reaction was complete.

A 200-μl aliquot (5.92×10^{-3} mmol) of the stock solution of **1** was diluted to 100 ml with 0.1 *N* HCl and the uv spectrum was obtained. The λ_{max} was at 288 nm (ε 9800) and after 3 hr it still had 97% of the original absorbance. After 48 hr the λ_{max} had shifted to 280 nm and after 5 days a shoulder was still present at 290 nm, but the λ_{max} was at 269 nm.[26]

A 200-μl aliquot (5.92×10^{-3} mmol) of the stock solution of **1** was added to 1 ml of 1 *N* HCl and MeCN was added to the mark. The uv spectrum was obtained immediately; it showed a shoulder at 290 nm and a λ_{max} at 270 nm.[26]

Lithium chloride (5.70 mg, 0.134 mmol) was added to the remainder of the stock solution of **1** (2.88×10^{-2} mmol). The solution became cloudy immediately and a new, finely divided solid separated. The lithium chloride did not dissolve completely. TLC (AcOEt) showed complete conversion of **1** to **4**.

Conversion of 2 to 1 in D_2O Solution. A 30-mg sample of **2** was dissolved in D_2O containing 1% DSS (w/w). The ^1H NMR spectrum obtained within 5 min showed ca. 55% of **2** and 45% of **1**. In 18 min the spectrum showed 100% conversion of **2** to **1**. At the end of 3 hr ca. 10% hydrolysis to **3** had occurred. Less than 5% exchange had taken place for H-5 or H-6 in **1** and **3**.

Reaction of 1 with NaOD in D_2O. To 30 mg (0.121 mmol) of **1** was added 200 μl (0.155 mmol) of 0.775 *N* NaOD and 100 μl of D_2O containing DSS. The ^1H NMR spectrum was that of **3** and showed less than 5% exchange for H-5 or H-6.

Reaction of 1 with MeONa–MeOD. Compound **1** (36.25 mg, 0.146 mmol) was added to 25 ml of MeOD. A 200-μl portion of 0.83 *N* MeONa in MeOD (0.166 mmol) was added. The λ_{max} of an aliquot was 237 nm. The MeOD was distilled off until ca. 5 ml remained. The residue was diluted with ether and filtered to remove sodium mesylate. TLC (AcOEt) indicated a single product with R_f equal to that of **3**.[43] Evaporation of the solution in vacuo left a white, crystalline solid. It was dissolved in absolute EtOH and the uv spectrum showed a λ_{max} at 267 nm corresponding to a 99% yield of **3**. The structure was confirmed by the ^1H NMR spectrum, which showed less than 5% deuterium incorporation at C-5 or C-6.

Reaction of 1 with Tetramethylammonium Hydroxide Pentahydrate in DMSO-d_6. Tetramethylammonium hydroxide pentahydrate (ca. 150 mg) was added to 6 ml of DMSO-d_6 and warmed on a steam bath. The solution was cooled to room temperature, filtered, and titrated with standard acid. The normality was ca. 0.144. Compound **1** (104 mg, 0.419 mmol) was placed in a 10-ml volumetric flask and 2.8 ml (0.403 mmol) of this solution was added. The reaction mixture was shaken vigorously for 4 min. The solid uracilium salt dissolved and a new solid separated. Water was added and the reaction mixture was diluted to 10 ml. The uv absorption spectrum had a λ_{max} at 267 nm corresponding to an 86% yield of **3**. The mixture was evaporated in vacuo and chromatographed on 8 g of silica gel with 1:1 AcOEt–EtOH. The ^1H NMR spectrum in D_2O confirmed that the compound was **3** with 15% deuterium at C-6 and less than 5% at C-5.

Reaction of 3 with Tetramethylammonium Hydroxide Pentahydrate in DMSO-d_6. Compound **3** (36.5 mg, 0.214 mmol) was placed in a 10-ml volumetric flask and 1.65 ml (0.237 mmol) of the above 0.144 *N* tetramethylammonium hydroxide solution were added. The mixture was shaken vigorously for 4 min and then 250 μl (0.25 mmol) of 1 *N* HCl was added. Next the flask was diluted to the mark with water. The uv spectrum indicated that 54% of the initial chromophore was present. The solution was evaporated in vacuo and the residue was chromatographed on 8 g of silica gel with 1:1 AcOEt–EtOH. Fractions 1–4 (3 ml) contained 46% (uv) of **3** (TLC, AcOEt). The ^1H NMR spectrum in D_2O showed that H-6 had exchanged completely and H-5 was 67% exchanged.

Reaction of 1 with Isopropylamine. 3-(β-Hydroxyethyl)-1-methyl-N^4-isopropylcytosine (9). Compound **1** (220 mg, 0.889 mmol) was added to 2 ml (23.3 mmol) of isopropylamine at room temperature. An exothermic reaction ensued and the solution boiled. The reaction mixture was evaporated in vacuo. The residue was dissolved in $CHCl_3$ and extracted with 10 ml of 0.1 *N* NaOH, dried ($MgSO_4$), and evaporated in vacuo. The residue, 184 mg (98%), was chromatographed on 7.5 g of silica gel with AcOEt to give 146 mg (78%) of material which resisted crystallization. A sample distilled in vacuo at 95–110° (5×10^{-2} mm) crystallized: mp 57–60°;[44] ir ($CHCl_3$) 2985 (w), 1690 (m), 1661 (s), 1601 (s), 1445 (m), 1431 (m), 1391 (m), 1381 (w), 1361 (m), 1340 (m), 1180 (m), 1040 (w), 980 (w), and 950 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 210 (7), 196 (46), 194 (9), 188 (7), 181 (12), 169 (32), 168 (100), 166 (22), 153 (28), 152 (60), 150 (15), 139 (10), 127 (11), 126 (53), 125 (29), 124 (16), 111 (25), 109 (17), 84 (12), 83 (14), 82 (25), and 81 (14).

Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.78; H, 8.05; N, 20.10.

Reaction of 1 with Diethylamine. *trans*-2-(β-Diethylaminoethenyl)-Δ²-oxazoline (10) and 3-(β-Diethylaminoethyl)-1-methyluracil (11). Uracilium salt **1** (238 mg, 0.96 mmol) was added to 2 ml (19.5 mmol) of diethylamine. An exothermic reaction ensued; the solution boiled and separated into two layers. After 2 hr the reaction mixture was evaporated in vacuo. The residue was dissolved in $CHCl_3$ and extracted with 3 × 10 ml of 1 *N* HCl. The $CHCl_3$ layer, after drying ($MgSO_4$) and evaporation, afforded 78 mg (62%) of an oil, *N,N*-diethyl-*N'*-methylurea:[45] ^1H NMR ($CDCl_3$) δ 3.92 (broad, 1, NH), 3.30 (q, 4, J_{Et} = 7 Hz, CH_3CH_2), 2.82 (s, 3, CH_3N–), and 1.15 (t, 6, J_{Et} = 7 Hz, CH_3CH_2). The acid extract was made alkaline with 1 *N* NaOH and extracted with 3 × 20 ml of $CHCl_3$. These extracts, after drying ($MgSO_4$) and evaporation, afforded 188 mg of an oil which contained three products (^1H NMR) in the ratio of 12, 27, and 61%. Chromatography on 30 g of silica gel (2.5% Et_3N in MeCN) separated two minor components (50 mg) from the major component (80 mg). An analytical sample of the major component, **10**, was purified by VPC: ir (film) 2980 (m), 2940 (m), 2900 (sh), 2880 (m), 1640 (s), 1470 (m), 1420 (s), 1370 (s), 1330 (w), 1265 (s), 1200 (m), 1125 (s), 1103 (sh), 1085 (w), 1040 (w), 1010 (s), 960 (s), 940 (w), 910 (w), 839 (m), and 785 cm^{-1} (m); mass spectrum *m/e* (rel intensity) 168 (100), 153 (8), 140 (11), 139 (99), 138 (16), 137 (12), 125 (13), 112 (11), 111 (11), 110 (9), 98 (17), 96 (21), and 95 (17).

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 63.91; H, 9.58; N, 16.81.

This compound was unstable in air and darkened quickly. Attempts to form a maleic anhydride adduct resulted in an exothermic reaction. The reaction mixture turned red, then brown, and finally to a black, carbon-like substance.[46]

The mixture of the two minor components obtained above was separated on analytical TLC plates (10% Et_3N–AcOEt). The slow-

er moving component was scraped from the plates and eluted from the silica gel with the same solvent. An analytical sample of **11** was obtained from the 35 mg (16%) of crude material by VPC: ir ($CHCl_3$) 2980 (m), 2940 (m), 2820 (m), 1712 (s), 1665 (s), 1635 (s), 1451 (s), 1440 (m), 1421 (w), 1390 (m), 1380 (m), 1355 (m), 1325 (w), 1181 (w), 1142 (m), and 1012 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 225 (7), 196 (4), 182 (4), 168 (13), 154 (27), 153 (24), 138 (6), 110 (28), 87 (21), 86 (100), 84 (15), and 82 (11).

Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.48; H, 8.49; N, 18.40.

For the third component: ^1H NMR ($CDCl_3$) δ 3.30 (s, 3, CH_3), ~3.84 and 4.30 (m, 4, CH_2CH_2), 5.76 (d, 1, $J_{5,6}$ = 8 Hz, H-5), and 6.81 (d, 1, $J_{5,6}$ = 8 Hz, H-6). After long standing on a TLC plate, the R_f of this component decreased to that of **3**.

Another sample of the two minor components (70 mg) was dissolved in 250 μl of Ac_2O. The solution was warmed briefly and then chromatographed on analytical TLC plates as described above. Compound **11** (52 mg) was unchanged. The ^1H NMR spectrum of the other component ($CDCl_3$) was δ 2.00 (s, 3, CH_3CO), 3.27 (s, 3, CH_3N), 4.34 (m, 4, CH_2CH_2), 5.69 (d, 1, $J_{5,6}$ = 8 Hz, H-5), and 6.67 (d, 1, $J_{5,6}$ = 8 Hz, H-6); uv max (95% EtOH) 280 nm (broad);[33] mass spectrum *m/e* (rel intensity) 212 (7), 196 (41), 180 (52), 169 (21), 155 (26), 154 (100), 153 (47), 152 (54), 140 (29), 139 (16), 138 (40), 127 (63), 125 (44), 123 (85), 111 (21), 87 (23), 83 (32), 82 (36), 81 (25), and 69 (21). A sample of acetylated material stored in a ^1H NMR tube for ca. 6 weeks, and from which the solvent had evaporated, was 50% transformed to **8b**.

Reaction of 1 with Pyridine. β-(1-Methyluracil-3)ethylpyridinium Mesylate (12). Compound **1** (30 mg, 0.121 mmol) was added to 300 μl of pyridine-d_5 and warmed briefly in an oil bath at 110°. The salt dissolved. The ^1H NMR spectrum was obtained and showed complete conversion to **12**, which had been fully characterized from a preparation starting with **2**.[2]

Registry No.—**1**, 54931-91-8; **1** BF_4, 54932-15-9; **2**, 54931-79-2; **3**, 1127-64-6; **4**, 54932-16-0; **5**, 54932-18-2; **6a**, 54931-87-2; **7b**, 54932-19-3; **8a**, 54932-20-6; **8b**, 54932-21-7; **9**, 54931-94-1; **10**, 54931-92-9; **11**, 54931-93-0; **12**, 54931-97-4; 1-methyluracil, 615-77-0; ethylene carbonate, 96-49-1; mesyl chloride, 124-63-0; silver tetrafluoroborate, 14104-20-2; ethanol, 64-17-5; benzoic acid, 65-85-0; isopropylamine, 75-31-0; diethylamine, 109-89-7.

References and Notes

(1) The authors are indebted to two anonymous donors for their generosity in providing partial support for this investigation. Additional support was provided by a Biomedical Sciences Support Grant from the General Research Support Branch, Division of Research Resources, Bureau of Health Professions Education and Manpower Training, National Institutes of Health.

(2) The synthesis of **2** was undertaken in connection with studies related to the role of Michael adducts in pyrimidine chemistry. See following paper in this issue: E. G. Lovett and D. Lipkin, *J. Org. Chem.*, **40**, 1722 (1975).

(3) See, for example, (a) S. Hünig, *Angew. Chem., Int. Ed. Engl.*, **3**, 548 (1964); (b) D. A. Tomalia and J. N. Paige, *J. Org. Chem.*, **38**, 422 (1973).

(4) Such compounds have been referred to also as ambident cations.[3a] This is a contradiction in terms if one takes into account the derivation of the word "ambident". It would be preferable to refer to such cations as dicoilate, tricoilate, etc., words which are derived from the Greek word "koilos" meaning "hollow".

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(8) Spectral data for all of the compounds are presented in Tables I and II.

(9) The values λ_{max} (pH 1–14) 266 nm (ϵ 8900) have been reported for this compound by D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).

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(11) Methyl methanesulfonate has two characteristic absorption bands at 1176 and 1355 cm^{-1}. See J. Pouchert, "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Milwaukee, Wis., 1970, Spectrum 403F.

(12) The ^1H NMR resonance of the CH_3SO_3 group of ethyl methanesulfonate in DMSO-d_6 is at δ 3.10 ppm.

(13) Electrophoreses could not be run at a higher pH because of the instability of the compound.

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(15) In sodium methanesulfonate the ^1H NMR absorption in DMSO-d_6 is at δ 2.38 ppm. In addition, as expected, there are two absorption bands in the infrared spectrum (1060 and 1200 cm^{-1}) characteristic of the sodium alkanesulfonates (~1064 and ~1198 cm^{-1}). See ref 11, Spectra *400C, D, and E*.

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(17) This may be an unstable intermediate in the formation of **1**, but this possibility is of no concern here. See J. L. Wong and D. O. Helton, *J. Chem. Soc., Chem. Commun.*, 352 (1973).

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(19) The CH_3S resonance in $(CH_3)_2S^+$–$OCH_3BF_4^-$ (DMSO-d_6), corresponding to six protons, is found at δ 3.28 ppm.

(20) The analysis could not be performed on **3** itself because in this compound the β oxygen could not be distinguished from O-4 by mass spectrometry. The analyses were performed on two derivatives, the β acetate (**8b**), which contains both oxygen atoms, and the β chloride (**4**), which contains only O-4.

(21) Note that the methoxyl derivative was unstable and was converted to **3** when an attempt was made to isolate it.

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(33) This assignment of structure is reasonable even though the uv spectrum of this compound disagrees with the uv spectral data reported for 2-imino-1,3-oxazines,[10a] which have ϵ ca. 2000. Our sample may have been contaminated with a small amount of **10**, which has ϵ 25,600. Lacey and Ward also state that the oxazines can be isomerized to the corresponding uracils. This is in agreement with our observations on this compound and its acetate.

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(41) Presumably this is the spectrum of the covalent mesyl ester **2**. It is unlikely that the ionic compound **1** would volatilize as such at the probe temperature which was used.

(42) This value has been corrected for the equilibrium amounts of **1** and **2** present.

(43) Compound **7a** either has the same R_f as **3** or is converted to it by the TLC plate. No solvent system succeeded in separating them.

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The Role of Michael Adducts in Pyrimidine Chemistry. Reactions of 3-(β-Methanesulfonyloxyethyl)-1-methyluracil with Bases[1,2]

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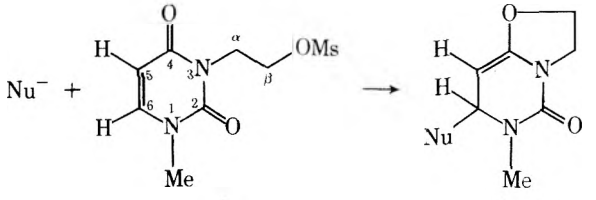
The reactions of 3-(β-methanesulfonyloxyethyl)-1-methyluracil with hydroxide in DMSO and DMSO-d_6 were investigated in an attempt to trap a Michael adduct. In spite of the demonstrated ease of formation, under a variety of conditions, of a product containing an oxazoline ring, the principal product was a malonsemialdehyde-substituted imidazolidone. This resulted from the addition of hydroxide at C-6 of the mesyl ester and subsequent cleavage between N-1 and C-6 of the pyrimidine ring. The course of the reaction was elucidated by the characterization of derivatives and then degradation of one of these. The results of the reactions between hydroxide and ester in deuterated media support the carbanion mechanism for exchange at C-6 of the mesylate and elucidate the nature of a competing pathway involving Michael addition. Finally, the reactions of 3-(β-methanesulfonyloxyethyl)-1-methyluracil with alcohols and amines were studied to complete the comparison with the behavior of the isomeric salt, N^3,O^4-ethylene-1-methyluracilium mesylate.

Michael additions have been suggested as intermediate steps in a variety of phenomena involving pyrimidines. These are the formation of O^6,5′-cyclonucleosides from 5-halopyrimidine nucleosides;[3] deuterium exchange at C-5 and C-6 in basic media;[4] the mode of action of thymidylate synthetase;[5] bisulfite addition;[6] nucleophilic addition to 5-nitropyrimidines;[7] alkaline degradation of methylated pyrimidine nucleosides;[8] and 5′-thiol additions.[9] To determine the role, if any, of Michael-type additions in these phenomena, the reactions of 3-(β-mesyloxyethyl)-1-methyluracil (**1**), other than those in which the initial step is conversion of **1** to N^3,O^4-ethylene-1-methyluracilium mesylate (**2**),[2] were explored. This ester, **1**, has the potential of forming an adduct which then is stabilized by intramolecular conversion to a 6-substituted N^3,O^4-ethylene-1-methyl-O^4,6-dihydrouracil (**3**), i.e. (Nu = nucleophile)



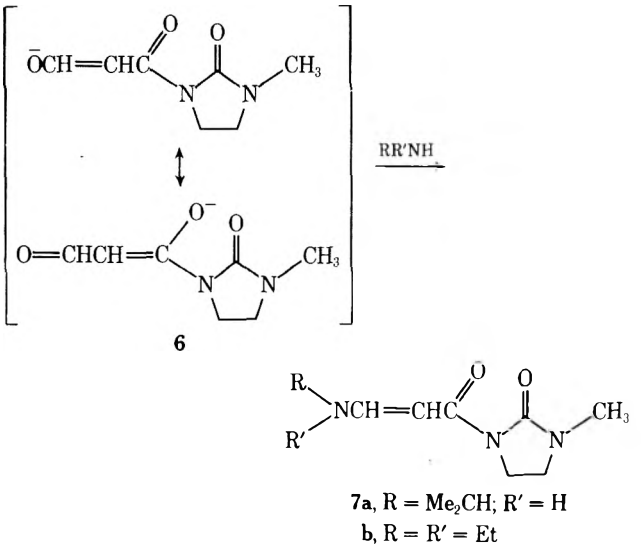
1 **3**

The emphasis in this paper is on reactions of **1** with hydroxide ion in DMSO. With this same base and solvent, 1,3-dimethyluracil has been reported to undergo rapid H-6 exchange,[4f] while 5-halopyrimidine nucleosides have been converted to O^6,5′-cyclonucleosides.[3] Alternative mechanisms, other than ones involving the formation of Michael adducts, have been suggested for these two latter reactions.[4e,f,8a]

Results and Discussion

A number of complexities were to be avoided in investigating the reactions of **1** with hydroxide in DMSO. This mesyl ester, as has been previously noted,[2] reacts slowly with DMSO to form *O*-[β-(1-methyluracil-3)ethyl]-*S*-dimethylsulfoxonium mesylate (**4**). This salt is converted rapidly by the addition of base to 3-(β-hydroxyethyl)-1-methyluracil (**5**), which would also be obtained by direct displacement of the mesyl group of **1** by hydroxide ion or via the cyclic salt **2** plus hydroxide. These reactions are irrelevant with respect to the reactions to be discussed here. Furthermore, the degradation of **5** in basic media also is in the same category.[2] In order to minimize the effect of these competing reactions, the solutions of base were usually added to the solid ester **1**. This makes reactions where the base is not intended to be in excess actually have an excess initially and introduces some problems with reproducibility. The results are least complicated with a large excess of base or a catalytic amount of base.

When a twofold excess of tetramethylammonium hydroxide pentahydrate (TMAH) in DMSO was added to a sample of the solid ester **1**, not **5**, but a new product (**6**),[10] was formed rapidly which could be fully characterized only as enamine derivatives (**7**). Support for the structure of **7** is

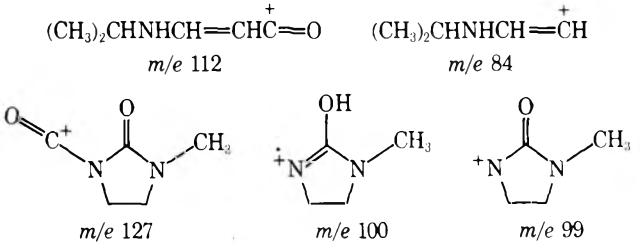


6

7a, R = Me_2CH; R′ = H
b, R = R′ = Et

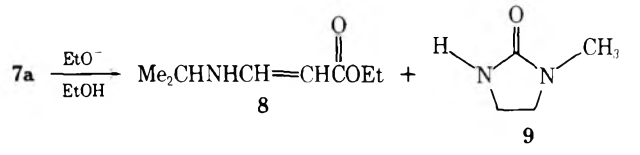
provided by the spectroscopic data. The relatively long wavelength uv absorption of **7** in neutral or alkaline solution is similar to that of enamine ketones. The shift of the maximum of **7** to a much shorter wavelength in acid solution must be due to N-, rather than O-, protonation.[11] The infrared spectra of **7** have two absorption bands (~1648 and ~1705 cm^{-1}) corresponding to those characteristic of 1-acetyl-3-methylimidazolidone (1670 and 1730 cm^{-1}).[12] In addition, however, the two compounds have another absorption (~1555 cm^{-1}) characteristic of enamino ketones (1535–1574 cm^{-1}).[13] The ^1H NMR spectrum provides further support for the assigned structure. In **7** the protons of the methylene group adjacent to the NMe group absorb at ca. δ 3.3 (DMSO-d_6) and those adjacent to the nitrogen atom flanked by two carbonyl groups absorb at ca. δ 3.7. These assignments are based on the fact that the methylene protons in 1-methylimidazolidone absorb at δ 3.45, while those in 1,3-diacetylimidazolidone are at δ 3.83.[12] The ^1H NMR data also demonstrate that in **7b** the trans isomer

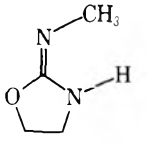
is the stable one in both chloroform and DMSO solutions. The compound **7a,** by contrast, is present as the trans isomer in DMSO, but in chloroform it exists mainly (>95%) as the cis isomer. This presumably is due to the formation of an intramolecular hydrogen bond between the NH group and the exocyclic carbonyl.[14] The mass spectra gave added confirmation to the structure written for **7.** Abundant ions corresponding to the following proposed structures are observed for **7a.** The diethylamino derivative, **7b,** gave an analogous series of abundant ions.



abundant ions.

Chemical evidence for the structures assigned to **7** includes a positive Ehrlich's test[15] (orange color) with **7a,** but not with **7b.** This is indicative of an active methylene group in the tautomer of **7a.** Degradation of **7a** with ethoxide in ethanol afforded an enamino ester (**8**) and 1-methylimidazolidone (**9**). The latter was identical with a sample prepared by an unequivocal route and ruled out the possibility that **9** is the isomeric 2-(methylamino)-2-oxazolidine.[16]

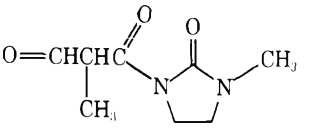




Compound **8** was isolated as a colorless oil which darkened on standing at room temperature for a few days.[17] It too gave a positive Ehrlich's test, as expected. Spectral data for **8** are in good agreement with those of Huisgen.[14]

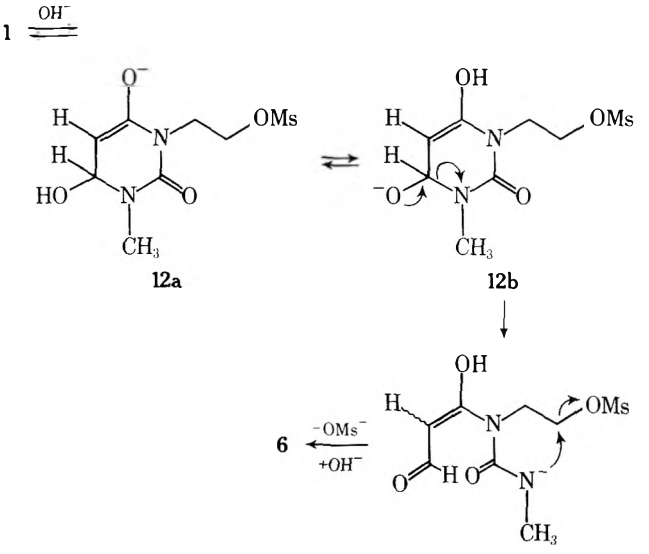
Enolate anion **6,** a malonsemialdehyde derivative, must be the precursor of enamines **7a** and **7b.** Both chemical and physical evidence support this assumption. On electrophoresis at pH 9.2 **6** migrated toward the anode, indicating a negatively charged species. The uv absorption of **6** in alkaline solution (λ_{max} 290 nm) and the fact that this absorption disappears on acidification, as well as a positive Ehrlich's test (orange), is indicative of an active methylene group.[15] By comparison, thio esters of malonsemialdehyde have λ_{max} ca. 299 nm.[18] The sulfur atom probably has a bathochromic effect on this absorption,[19] but then the substituted urea residue in **6** also may have a bathochromic effect.[20] The difference in λ_{max} for **7** and **8** also may be due, in part, to the same effect. The ^{1}H NMR data provide additional support for the structure of **6.** The marked downfield shift of the absorption of H-6 (the γ carbon atom of the malonsemialdehyde side chain[10]), relative to the corresponding proton in **7** or **8,** probably is due to the fact that **6** is to be represented by the two principal resonance structures depicted.

Extraction of an acidified solution of **6** yielded a compound (**10**) in which H-6 was even further downfield (in the typical aldehyde region). In addition, other changes in the ^{1}H NMR spectrum are consistent with the conversion of the enolate **6** to the corresponding aldehyde **10.** Furthermore, upon methylation of **6** with methyl iodide, presumably the homolog of **10** (**11**) was obtained. In **11** the H-5



resonance is a quartet (J_{5,CH_3} = 7.5 Hz), which is further split by coupling to H-6 ($J_{5,6}$ = 1 Hz). The H-6 resonance of **11,** which is at the same δ as in **10,** is now a doublet rather than a triplet with $J_{5,6}$ < 1 Hz. Except for the *C*-methyl group, the other absorptions are essentially the same as in **10.** The mass spectral fragmentation pattern of **11** is related to that of **7.** This lends further support to the structures proposed for **6** and **10.**

A reasonable course for the formation of **6** from **1** is as follows.



Two essential features of this scheme are that initial attack by hydroxide ion takes place at C-6 and that opening of the pyrimidine ring involves *the breaking of the bond between N-1 and C-6.* In contrast to expectations, the final product is a substituted imidazolidone, a cyclic urea derivative, rather than the anticipated compound, **3.** Furthermore, in light of the demonstrated ease of formation of an oxazoline from **1**,[2] the formation of a cyclic urea, **6,** also was surprising. A possible explanation for this observation is that ionization of the added hydroxyl in **12a,** accompanied by protonation of the C-4 oxygen to give **12b,** makes O-4 less nucleophilic.

Many examples are known of the degradation of substituted uracils by means of aqueous hydroxide[21] to acyclic ureas[4b,8,22] or substituted 2-oxo-4-imidazolines.[3b] By contrast with the reaction leading to the formation of **6,** these reactions take place by the Michael addition of water or an alcohol to the 5,6 double bond of the pyrimidine followed by cleavage of the bond *between N-3 and C-4* in the resulting 5,6-dihydrouracil derivative. This is a well-documented course for the alkaline degradation of substituted 5,6-dihydrouracils.[23]

As mentioned above, cleavage of the pyrimidine ring between N-1 and C-6 leads to the formation of an enolate. The formation of aldehyde intermediates in the alkaline degradation of pyrimidine derivatives has been suggested previously by two groups. Kondo et al. have found that N^3-methyl-2′,3′-*O*-isopropylideneuridine was converted by means of aqueous alkali to 3-methylurea riboside.[8] They have suggested that here too a 5,6-dihydrouracil was

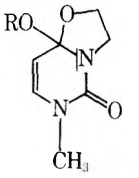
formed as an intermediate and that subsequently this was degraded to the final product through the breaking of the bond between N-1 and C-6 before the bond between N-3 and C-4 was broken. The data provided by these authors may not be in agreement with this suggestion. They observed a transient ^{1}H NMR absorption at 8.29 ppm which has been assigned to an aldehydic proton. This is in disagreement with the value given for the C-6 proton of **6** (δ 9.10), but in good agreement with the value (δ 8.44) suggested by Cushley et al.[4b] for the ^{1}H NMR signal due to the vinylic proton of an α,β-unsaturated 5-deuterated ureido acid, $D_2NC(O)N(R)CH{=}CDCO_2H$. Lozeron et al.[24] found that 5-fluoro-6-hydroxy-5,6-dihydrouracil was unstable in alkali and decomposed to form urea and, probably, α-fluoro-α-formylacetic acid. The data provided by both groups are insufficient to indicate which of the two bonds, that between N-1 and C-6 or between N-3 and C-4, was cleaved first.

In order to determine whether or not an intermediate such as **12** plays a role in C-6 exchange, three experiments were performed in which a solution of TMAH in DMSO-d_6 was added to mesyl ester **1**. The reaction mixtures were too dilute to permit direct observation by ^{1}H NMR. Analyses were performed on the end products and no rates were obtained. In one experiment the ratio of base to mesyl ester was 1:4. The mixture of **1**, **2**, **4**, and **5** which remained after the base was consumed was converted by a combination of hydrolysis and methanolysis to a mixture of **5** and 3-(β-methoxyethyl)-1-methyluracil.[2] Both of these products contained ca. 10–15% deuterium at C-6, but less than 5% at C-5. The fact that the methyl ether was deuterated confirms that exchange had occurred on the mesyl ester or on **4**, and not on **5** after its formation or on **2**.[2] A 1:1 ratio was used in the second experiment. The reaction mixture contained the enolate **6** in a yield of 40% based on the uv spectrum. It also contained **5** and possibly its acetate, 3-(β-acetoxyethyl)-1-methyluracil (**13**). Substitution of deuterium at both C-5 and C-6 of **5** and **13** was found to have taken place to the extent of ca. 10–15%.[25] The third experiment was one in which a 4.6:1 ratio of base to **1** was used. It was found that **6**, the principal identifiable product, this time contained 60% deuterium at C-6 and less than 5% at C-5. By contrast with the results of these experiments in DMSO, reaction of **1** with 0.4 *N* NaOD in D_2O resulted in unlabeled **5**.

These observations are consistent with the notion that there is competition between two primary reactions, i.e., carbanion formation at C-6 of the mesyl ester **1** and addition of hydroxide at this carbon atom to form **12**. At low base ratios the predominant reaction is carbanion formation leading to deuterium exchange. The equilibrium giving rise to the hydroxyl adduct **12** is unfavorable because the hydroxide ion concentration is low. This equilibrium is favored only when sufficient base is present to ionize the added hydroxyl. The reaction leading to the formation of **5** is not pertinent here. The second experiment with the higher base ratio indicates that the competition between carbanion formation and formation of **12** favors the latter. That adduct formation has become significant was substantiated by the fact that exchange at C-5, as well as C-6, is observed and that **6** is a reaction product. Exchange at C-5 takes place through the addition of hydroxide ion at C-6 and a proton at C-5.[4] Finally, in the third experiment with a large excess of base, the C-6 adduct **12** is stabilized by formation of the anion and it then can undergo further reaction to form **6**. There is also sufficient base to allow substantial carbanion formation at C-6. The latter reaction is obviously faster than the former. As a consequence, **6** is formed with a large amount of deuterium at C-6. Even though addition at C-6 has become an important reaction, there is no appreciable amount of substitution of deuterium at C-5 because the highly basic medium is deficient in available deuterium ions.

A more detailed examination of the products from the 1:1 experiment helped to identify the fate of **6** in the absence of excess base. After concentrating the reaction mixture, no absorptions due to the vinyl protons in **6** could be found in the complex ^{1}H NMR spectrum of the crude reaction mixture. This might have been due to the fact that little **6** was present at this point. Compound **6** decomposes quite rapidly except in very basic media. On the other hand, these protons may not have been detected because they already had been replaced by deuterium. The C-5 protons could have been exchanged for deuterium during the concentration of the reaction mixture, which was no longer strongly basic. Work-up of the residue afforded a 14% yield of **13**. The acetyl group of this compound contained 72% deuterium while C-5 and C-6 contained approximately equal amounts (ca. 15%). That the reagent for the acetylation of **5** present in the concentrate was not the acetic acid-h_4 used to neutralize the crude product was confirmed by isolating the same product, **13**, from a reaction mixture acidified with trifluoroacetic acid. The acetylating agent also could not have been 1-acetyl-3-methylimidazolidone. This was demonstrated by carrying out a reaction of **5** with this reagent under the same conditions which were used for the reaction of **1** with TMAH. The yield of **13** was negligible (1%). In all likelihood, **13** with the deuterated acetyl group was formed by reaction of **5** with **6**, or its keto tautomer, to give the formylacetate ester of **5**. This could then decompose in the deuterated medium to give **13** and formate.

Under neutral or basic conditions, addition of an alcohol at C-6 of **1** might be expected to lead to a stable adduct. However, alcohols solvolyzed **1** to a 3-(β-alkoxyethyl)-1-methyluracil.[2] The alcoholysis proceeded via **2** as an intermediate (uv), rather than by direct solvolysis of the ester. The mesyl ester **1** reacted slowly with alcoholic alkoxide solutions to form a compound (**14**) which resulted from addition at C-4 rather than C-6, probably again by way of **2**. A



14a, R = Et
b, R = Me

reasonable explanation for the formation of a C-4 adduct from alkoxide involves initial formation of the sought-for C-6 adduct, which then reacts at C-4 and expels the C-6 alkoxide. An analogous rationalization has been discussed previously.[2]

In a further experiment with alkoxides, the mesyl ester **1** was treated with sodium methoxide in methanol-*O*-*d*. Although an adduct, **14b**, was formed, there was no deuterium incorporation at C-5 or C-6. This demonstrates that addition of methoxide at C-4 of **1** is a more rapid reaction than exchange. On the other hand, as a basis of comparison, 1,3-dimethyluracil does undergo exchange with the same base and in the same solvent. It was found that there was incorporation of 73% deuterium at C-5 and 16% at C-6 in this uracil derivative.

In order to make more complete a comparison of the chemistry of the mesyl ester **1** and the uracilium cation **2**,

the reactions of **1** with amines were investigated. Isopropylamine reacted with **1** to give two products: 86% of 3-(β-hydroxyethyl)-1-methyl-N^4-isopropylcytosine and 14% of 3-(β-isopropylaminoethyl)-1-methyluracil. The latter probably arises by direct substitution of the mesyl group and the former via **2**. By contrast, **2** plus the amine yielded only the first of these products.[2] Pyridine slowly converted **1** to the quaternary salt, [β-(1-methyluracil-3)ethyl]pyridinium mesylate. The only example of the ability of **1** to form an adduct at C-6, other than its reaction with hydroxide to yield **6**, was the reaction with diethylamine. Two products were obtained: *trans*-2-(β-diethylaminoethenyl)-Δ^2-oxazoline (74%) and 3-(β-diethylaminoethyl)-1-methyluracil (26%). The latter probably arose by direct displacement of the mesyl group of **1** and the former via **2**. Again, by contrast, an additional product was obtained in the corresponding reaction of **2**.[2]

In conclusion, we have observed only two examples of products arising from Michael additions to **1**: the reactions of hydroxide and diethylamine. The former contrasts with the reaction of **2** with hydroxide to give **5**. In both examples, the products observed resulted from a cleavage of the bond between N-1 and C-6. While the diethylamine reaction gave rise to an oxazoline as the principal product, the reaction of **1** with hydroxide unexpectedly resulted in the formation of a cyclic urea derivative. Furthermore, our results confirm the carbanion mechanism for C-6 exchange in **1** and demonstrate a highly competitive pathway involving the formation of Michael adducts by the reaction of hydroxide ion with **1** at C-6. These latter intermediates are relevant to an addition–elimination mechanism for cyclonucleoside formation.[3a]

Further studies of the behavior of substituted pyrimidines in basic media are in progress in order to determine the generality of the type of reaction which was observed with **1**, i.e., a step in which the first bond-breaking reaction in the pyrimidine ring is cleavage of the bond between N-1 and C-6.

Experimental Section

^{1}H NMR spectra were obtained on a Varian A-60 spectrometer at room temperature using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standards. A Cary 14, a Beckman DU, and a Perkin-Elmer 457 grating infrared spectrophotometer were used to obtain uv and ir spectra. Mass spectra were obtained on a Varian M-66 mass spectrometer at an ionizing potential of 70 eV, an ionizing current of 30 μA, a resolution of ca. 2200, and with perfluorokerosene as a standard.

VPC was done on a 24 × 0.25 in. o.d. aluminum column packed with 1% SE-30 (Applied Science Laboratories, State College, Pa.) on ANAKROM AS, 40–50 mesh (Analabs, North Haven, Conn.). Column temperatures ranged from 110 to 155° with helium flow rates of 85–100 ml/min. Thin layer chromatography was performed on Analtech silica gel G thin layer plates containing fluorescent indicator (Analtech, Inc., Newark, Del.) and Chrom AR 500 sheets (Mallinckrodt, St. Louis, Mo.) Preparative chromatography (dry column) was performed on silica gel Woelm (Waters Associates, Inc., Framingham, Mass.).

Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reaction of 1 with Excess Tetramethylammonium Hydroxide in DMSO. Enolate Anion of N^1-(Formylacetyl)-N^3-methylimidazolidone (6). TMAH (2.0 g, 11 mmol) was added to 100 ml of DMSO, warmed to 80°, and filtered. This solution was approximately 0.1 *N*. Mesyl ester **1** (0.84 g, 3.39 mmol) was added to this solution at room temperature. The mixture turned bright red instantaneously. Paper electrophoresis of an aliquot in 0.05 *M* sodium borate (pH 9.2) demonstrated the presence of a uv-absorbing species (orange Ehrlich's test) which migrated 2.7 cm toward the anode. Barbituric acid migrated 3.5 cm while **5** did not migrate at all under the same conditions. Aliquots of the DMSO solution had λ_{max} 293 nm (ε ~19,000),[26] λ_{min} 246 nm (ε 3700) in 95% EtOH; λ_{max} 290 nm (ε ~20,000), λ_{min} 244 nm (ε 6300) in 0.1 *N* NaOH; no λ_{max} in 0.1 *N* HCl. The reaction mixture was concentrated in vacuo at 40° to a semisolid: ^{1}H NMR (DMSO-d_6) δ 9.10 (d, 1, J = 10 Hz, H-6), 5.50 (d, 1, J = 10 Hz, H-5), 4.00 and 3.43 (m, 4, CH_2CH_2), and 2.55 ppm (s, 3, NCH_3);[27] on acidification of this solution H-6 shifted to δ 9.67 (t, 1, J = 1 Hz) and H-5 to 3.96 ppm (d, 2, J = 1 Hz).

Attempts to isolate the enolate anion by crystallization, or charcoal or ion exchange chromatography, were unsuccessful. It was stable, however, in alkaline solution for days. It proved possible, however, to isolate N^1-(formylacetyl)-N^3-methylimidazolidone (**10**), the aldehyde corresponding to the enolate anion **6**. Compound **1** (220 mg, 0.89 mmol) was added to 25 ml of 0.1 *N* TMAH in DMSO (2.5 mmol). The λ_{max} of an aliquot of this solution was 290 nm in 0.1 *N* NaOH and the optical density (based on ε 20,000) corresponded to 61% conversion to enolate anion **6**. The solution was evaporated in vacuo and water was added to the residue. The mixture was neutralized with acetic acid and extracted with 1,2-dichloroethane. An assay of the organic extracts (uv) showed that 72% of the optical density was still present. A residue remained on evaporation of the solvent in vacuo: ^{1}H NMR ($CDCl_3$) δ 9.75 (t, 1, $J_{5,6}$ = 1 Hz, CH=O), 4.02 (d, 2, $J_{5,6}$ = 1 Hz, CH_2CH=O), 3.87 and 3.48 (m, 4, CH_2CH_2) and 2.87 ppm (s, 3, NCH_3).

Once again, **6** was prepared from **1** (220 mg, 0.89 mmol) and 25 ml of 0.1 *N* TMAH (2.5 mmol) in DMSO. The DMSO was removed in vacuo and 10 ml of MeOH was added to the residue. Methyl iodide (2 ml, 32 mmol) was added and the reaction mixture was allowed to stand at room temperature overnight. TLC (AcOEt) indicated four uv-absorbing components, two of which were major. The fastest moving component, which was obtained pure by VPC, is assigned structure **11**: mass spectrum *m/e* (rel intensity) 184 (7), 170 (7), 156 (100), 127 (23), 101 (26), 100 (79), 99 (100), and 84 (44). Column chromatography on silica gel (AcOEt) afforded 65 mg (40%) of **11**: ^{1}H NMR ($CDCl_3$) δ 9.72 (d, 1, $J_{5,6}$ = 1 Hz, CH=O), 4.71 (d of q, 1, $J_{5,6}$ = 1, $J_{CH_3,H}$ = 7.5 Hz, H-5), 3.90 and 3.41 (m, 4, CH_2CH_2), 2.88 (s, 3, NCH_3), and 1.35 ppm (d, 3, $J_{CH_3,H}$ = 7.5 Hz, CH_3CH).

Conversion of Enolate Anion 6 to N^1-(β-Isopropylaminoacrylyl)-N^3-methylimidazolidone (7a). The enolate anion **6**, prepared as above from 3.39 mmol of **1**, was dissolved in 10 ml of MeOH. Isopropylamine (1 ml, 11.7 mmol) and 0.8 ml of glacial AcOH (14.1 mmol) were added. The mixture, now neutral, was evaporated in vacuo and 20 ml of $CHCl_3$ was added to the residue. The solids were removed by filtration and washed with 2 × 10 ml of $CHCl_3$. The combined $CHCl_3$ washes were extracted with water, dried ($MgSO_4$), filtered, and evaporated in vacuo to give 0.47 g of crude product. TLC (AcOEt) of the aqueous extracts showed two uv-absorbing materials, the faster moving one of which gave a pink Ehrlich's test. The $CHCl_3$ layer gave a spot at the origin and halfway up the plate. The latter (**7a**) gave an orange Ehrlich's test. The $CHCl_3$-soluble material was chromatographed on 12 g of silica gel with $CHCl_3$ as the solvent. Fractions 5–23 (3 ml) afforded 355 mg (50%) of **7a**. An analytical sample was obtained from $CHCl_3$–Et_2O: mp 109.5–112.5°; ir (Nujol) 3220 (m), 1700 (s), 1655 (s), 1545 (s), 1332 (w), 1270 (s), 1230 (s), 1170 (w), 1040 (w), 1000 (w), 805 (w), 735 (w), and 705 cm^{-1} (m); uv (95% EtOH) λ_{max} 302 nm (ε 30,200) and 229 (7700), λ_{min} 255 nm (ε 1400); uv (0.1 *N* NaOH) λ_{max} 305 nm (ε 31,500), λ_{min} 258 nm (ε 2100); uv (0.1 *N* HCl) λ_{max} 222 nm (ε 12,800), λ_{min} 208 nm (ε 8500); ^{1}H NMR ($CDCl_3$) δ 7.00 (m, 1, $J_{NH,H-6}$ = 13 Hz, NH), 6.78 (d of d, 1, $J_{NH,H-6}$ = 13, $J_{5,6}$ = 8 Hz, H-6), 6.03 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 3.85 and 3.33 [m, 5, CH_2CH_2 and $(CH_3)_2CH$], 2.82 (s, 3, NCH_3), and 1.22 ppm [d, 6, $J_{i\text{-}Pr}$ = 6.5 Hz, $(CH_3)_2CH$]; ^{1}H NMR (DMSO-d_6) 7.46 (d of d, 1, $J_{NH,H-6}$ = 9 Hz, $J_{5,6}$ = 13 Hz, H-6), 7.02 (m, 1, $J_{NH,H-6}$ = 9 Hz, NH), 6.03 (d, 1, $J_{5,6}$ = 13 Hz, H-5), 3.68 and 3.30 [m, 5, CH_2CH_2 and $(CH_3)_2CH$], and 1.10 ppm [d, 6, $J_{i\text{-}Pr}$ = 6.5 Hz, $(CH_3)_2CH$]; mass spectrum *m/e* (rel intensity) 211 (100), 196 (8), 142 (7), 127 (19), 113 (23), 112 (96), 110 (13), 100 (29), 99 (21), 98 (21), 96 (68), 84 (54), and 70 (70).

Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.84; H, 8.15; N, 19.87.

Conversion of Enolate Anion 6 to N^1-(β-Diethylaminoacrylyl)-N^3-methylimidazolidone (7b). The enolate anion **6**, prepared as described above starting with 0.875 g of **1**, was dissolved in 13 ml of MeOH. To this solution was added 2.3 ml (22.4 mmol) of diethylamine and 1 ml (17.6 mmol) of glacial AcOH at 0°. It then was stored at 10° for 2 days. The residue obtained after evaporation was dissolved in $CHCl_3$ and washed with water. The $CHCl_3$ layer after drying ($MgSO_4$) and evaporation afforded 0.49 g of ma-

terial (62%) which crystallized, but by TLC (AcOEt) contained a fast-moving major component and two minor ones. Chromatography on silica gel G with $CHCl_3$ (fractions 5–24, 3 ml) afforded 380 mg (48%) of **7b**. An analytical sample was obtained from C_6H_6–petroleum ether: mp 134–135.5°; ir (Nujol) 1710 (s), 1640 (s), 1565 (s), 1380–1350 (s), 1320 (m), 1220 (s), 1180 (sh), 1135 (m), 1085 (m), 1047 (m), 1007 (w), 800 (s), 758 (w), and 730 cm^{-1} (w); uv (95% EtOH) λ_{max} 308 nm (ϵ 34,100) and 230 (8100), λ_{min} 260 nm (ϵ 800); uv (0.1 *N* NaOH) λ_{max} 315 nm (ϵ 37,000), λ_{min} 262 nm (ϵ 600); uv (0.1 *N* HCl) λ_{max} 222 nm (ϵ 12,800), λ_{min} 209 nm (ϵ 8000); ^1H NMR ($CDCl_3$) δ 7.67 (d, 1, $J_{5,6}$ = 13 Hz, H-6), 6.30 (d, 1, $J_{5,6}$ = 13 Hz, H-5), 3.88 and 3.33 (m, 4, CH_2CH_2), 3.27 (q, 4, J_{Et} = 7 Hz, CH_3CH_2), 2.85 (s, 3, NCH_3), and 1.17 ppm (t, 6, J_{Et} = 7 Hz, CH_3CH_2); ^1H NMR (DMSO-d_6) δ 7.49 (d, 1, $J_{5,6}$ = 13 Hz, H-6), 6.17 (d, 1, $J_{5,6}$ = 13 Hz, H-5), 3.70 and 3.32 (m, 4, CH_2CH_2), 3.23 (q, 4, J_{Et} = 7 Hz, CH_3CH_2), 2.73 (s, 3, NCH_3), and 1.11 ppm (t, 6, J_{Et} = 7 Hz, CH_3CH_2); mass spectrum *m/e* (rel intensity) 225 (84), 210 (5), 196 (7), 142 (5), 127 (41), 126 (100), 125 (21), 124 (8), 113 (12), 110 (11), 108 (10), 101 (13), 100 (19), 99 (22), 98 (60), 97 (8), 96 (26), 84 (10), and 82 (16).

Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.80; H, 8.53; N, 18.52.

Degradation of 7a with Ethoxide in Ethanol to Ethyl β-Isopropylaminoacrylate (8) and *N*-Methylimidazolidone (9). Compound **7a** (130 mg, 0.618 mmol) was dissolved in 10 ml of 0.275 *N* EtONa in EtOH (2.75 mmol) and refluxed for 2 hr. TLC (AcOEt) indicated complete conversion to two new products, one with uv absorption and giving a pink Ehrlich's test (faster moving), the other with no uv absorption and giving a yellow Ehrlich's test. The reaction mixture was evaporated to dryness and the residue, which was dissolved in Et_2O, was extracted with water. Only the uv-absorbing product remained in the Et_2O. Evaporation after drying ($MgSO_4$) afforded 55 mg of a sweet-smelling, colorless oil, **8**: ir ($CHCl_3$) 3560 (m), 2980 (s), 1660 (s), 1600 (s), 1390 (w), and 1050 cm^{-1} (m); for a sample purified by vpc, uv (100% EtOH λ_{max} 281 nm (ϵ 19,400); uv (0.1 *N* NaOH) λ_{max} 278 nm (ϵ 24,200), λ_{min} 238 nm (ϵ 2000); no λ_{max} in 0.1 *N* HCl; ^1H NMR ($CDCl_3$) of a 1:1 mixture of cis and trans isomers δ 7.65 (m, 1, NH), 7.33 (d of d, 0.5, $J_{5,6}$ = 13.5, $J_{NH,H\text{-}6}$ = 9 Hz, H-6, trans), 6.89 (d of d, 0.5, $J_{5,6}$ = 8, $J_{NH,H\text{-}6}$ = 13 Hz, H-6, cis), 4.52 (d, 0.5, $J_{5,6}$ = 13.5 Hz, H-5, trans), 4.33 (d, 0.5, $J_{5,6}$ = 8 Hz, H-5, cis), 4.12 (q, 2, J_{Et} = 7 Hz, CH_3CH_2), 3.55 [septet, 1, $J_{i\text{-}Pr}$ = 6.5 Hz, $CH(CH_3)_2$], 1.27 (t, 3, J_{Et} = 7 Hz, CH_3CH_2), and 1.22 ppm [d, 6, $J_{i\text{-}Pr}$ = 6.5 Hz, $(CH_3)_2CH$]; ^1H NMR (DMSO-d_6) of a 84% cis:16% trans mixture δ 7.65 (m, 1, NH), 6.67 (d of d, 1, $J_{5,6}$ = 8, $J_{NH,H\text{-}6}$ = 13 Hz, H-6, *cis*; $J_{5,6}$ = 13.5, $J_{NH,H\text{-}6}$ = 9 Hz, H-6, trans), 4.46 (d, 0.84, $J_{5,6}$ = 8 Hz, H-5, cis), 4.71 (d, 0.16, $J_{5,6}$ = 13.5 Hz, H-5, trans), 4.12 (q, 2, J_{Et} = 7 Hz, CH_3CH_2), 3.55 [septet, 1, $J_{i\text{-}Pr}$ = 6.5 Hz, $CH(CH_3)_2$], 1.25 (t, 3, J_{Et} = 7 Hz, CH_3CH_2), and 1.22 ppm [d, 6, $J_{i\text{-}Pr}$ = 6.5 Hz, $(CH_3)_2CH$]; mass spectrum *m/e* (rel intensity) 157 (41), 142 (31), 128 (31), 112 (34), 110 (16), 96 (100), and 70 (56). On standing in air at room temperature for several days, 8 darkened.[17]

The uv-transparent product, **9**, was obtained by evaporation of the aqueous extracts. Crystallization from toluene afforded a solid: mp 112–114°; mmp with an authentic sample of *N*-methylimidazolidone, 111.5–114°;[28] ir (Nujol) 3220 (s), 1660 (s), 1505 (m), 1410 (m), 1377 (s), 1285 (m), 1260 (m), 1090 cm^{-1} (m); ^1H NMR (DMSO-d_6) δ 6.20 (broad, 1, NH), 3.24 (m, 4, CH_2CH_2), and 2.60 ppm (s, 3, NCH_3).

Reaction of 1 with a Catalytic Amount of Tetramethylammonium Hydroxide in DMSO-d_6. A solution of 1.4 ml (0.16 mmol) of 0.11 *N* TMAH in DMSO-d_6 was added to 135 mg (0.542 mmol) of **1** dissolved in 600 μl of DMSO-d_6. After 2 hr, water was added to the reaction mixture, which was now neutral. The reaction mixture was evaporated to dryness in vacuo and then 10 ml of MeOH was added to the residue. After 3 days, this mixture was evaporated to dryness and the resulting residue was chromatographed on 8 g of silica gel (AcOEt). Two components were isolated: 20 mg (20%) of 3-(β-methoxyethyl)-1-methyluracil (fractions 7–38, 3 ml) and 67 mg (73%) of **5** (fractions 49–56, 3 ml). Both compounds contained approximately 10–15% deuterium at C-6 and less than 5% at C-5 (^1H NMR).

Reaction of 1 with 1 Equiv of TMAH in DMSO-d_6. A solution of TMAH (210 mg, 1.16 mmol) in 10 g of DMSO-d_6 was added to **1** (280 mg, 1.13 mmol) and the mixture was shaken vigorously for several minutes until all solids dissolved. The uv spectrum of an aliquot in 0.1 *N* NaOH had λ_{max} 280 nm. Based on the absorbance at 290 nm, the yield of enolate **6** was ca. 40%. The reaction mixture was concentrated in vacuo and the ^1H NMR spectrum of the residue showed only vinyl hydrogens like those of **5** and **13**, i.e., no enolate anion vinyl hydrogens. The H-5 and H-6 hydrogens had undergone ca. 10–15% exchange. The DMSO-d_6, which was used as the solvent in obtaining the ^1H NMR spectrum, was evaporated again and the residue was dissolved in 5 ml of MeOH. It was treated with 300 μl (2.91 mmol) of diethylamine and 100 μl (1.76 mmol) of glacial AcOH. TLC (AcOEt) showed a fast-moving component in addition to **5** and **7b**. The mixture was evaporated and the residue was taken up in $CHCl_3$ and extracted with water. The water layer contained most of the **5**, while the $CHCl_3$ contained the remaining two components. Chromatography on silica gel ($CHCl_3$ followed by AcOEt) afforded 15 mg of **13** (14%), which was identical by TLC with authentic material.[2] The ^1H NMR spectrum confirmed its identity. Added confirmation was obtained from a mass spectrum on a sample which was purified by VPC. Both sets of spectra showed that the acetyl group was 72% deuterated. The β-acetoxyethyl derivative **13** also was obtained in a similar reaction in nondeuterated solvent in which the reaction mixture was acidified with trifluoroacetic acid.

Reaction of 1 with Excess TMAH in DMSO-d_6. A 0.12 *N* solution of TMAH in DMSO-d_6 (8.9 ml, 1.06 mmol), prepared as described above, was added to **1** (57.6 mg, 0.23 mmol) dissolved in 0.6 ml of DMSO-d_6. The uv spectrum of an aliquot in 0.1 *N* NaOH had λ_{max} 290 nm and the absorbance corresponded to ca. 68% conversion to enolate anion **6**. The reaction mixture was evaporated in vacuo to dryness and the orange semisolid residue was redissolved in DMSO-d_6. The ^1H NMR spectrum showed 68% deuterium at C-6 and less than 5% at C-5.

Reaction of 1 with NaOD in D_2O. Compound **1** (87 mg, 0.35 mmol) was added to a solution of 200 μl of D_2O and 200 μl (0.155 mmol) of 0.775 *N* sodium deuteroxide in D_2O. The sample did not dissolve completely. A portion of the solution was transferred to a ^1H NMR tube. The spectrum obtained within 5 min was that of **5** only. No exchange of H-5 or H-6 was observed.

Attempted Preparation of 3-(β-Acetoxyethyl)-1-methyluracil (13) from 5 and 1-Acetyl-3-methylimidazolidone. 1-Acetyl-3-methylimidazolidone (70 mg, 0.5 mmol), prepared from methylimidazolidone according to Roberts,[12] and compound **5** (85 mg, 0.5 mmol) were dissolved in 1 ml of DMSO and 3 ml of 0.15 *N* TMAH solution (0.45 mmol) in DMSO was added. The solution turned yellow immediately. The reaction mixture was evaporated in vacuo and the residue was taken up in AcOEt. TLC (AcOEt) indicated a trace of **13** and a large amount of **5**. The AcOEt solution was extracted with water, dried ($MgSO_4$), and evaporated in vacuo. The residue, 12 mg, was chromatographed on Chrom AR 500 (AcOEt). The two uv-absorbing bands were cut out and eluted with methanol. One corresponded to 1% of **13** and the other to 10% of **5** (uv). The aqueous extracts contained an additional 70% of **5** (uv).

Methanolysis of 1. 3-(β-Methoxyethyl)-1-methyluracil. The mesyl ester **1** (68 mg, 0.27 mmol) was dissolved in 25 ml of dry MeOH. The uv spectrum was recorded periodically. The optical density at 267 nm decreased by 25% in 5.5 hr and a shoulder appeared at 290 nm. It reached a maximum value in 9 hr. The shoulder then steadily decreased and the optical density at 267 nm increased to a constant value. The reaction mixture was evaporated in vacuo after 8 days. $CHCl_3$ was added to the residue and the mixture was extracted with 10 ml of 1 *N* NaOH and then 10 ml of water. The $CHCl_3$ extract (dried with $MgSO_4$) afforded 48 mg (96%) of a crystalline solid on evaporation: mp 95.5–97°; mmp with 3-(β-methoxyethyl)-1-methyluracil, 96–97.5°.[2]

Ethanolysis of 1. 3-(β-Ethoxyethyl)-1-methyluracil. Compound **1** (318 mg, 1.24 mmol) was added to 10 ml of absolute EtOH. The solid dissolved as the reaction proceeded. After 6 days the solvent was evaporated in vacuo and the residue was dissolved in $CHCl_3$. TLC (AcOEt) indicated a fast-moving major new product, in addition to **5** and β-(1-methyluracil-3)ethyl ether[29] (slowest moving component). The $CHCl_3$ was washed with 2 × 10 ml of 1 *N* NaOH, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on 12 g of silica gel with AcOEt as eluent. Fractions 3–10 (3 ml) contained 174 mg (71%) of 3-(β-ethoxyethyl)-1-methyluracil. After evaporation of the AcOEt, the residue was sublimed at 60° ($2.5–5 \times 10^{-2}$ mm): mp 50–51.5°; ir ($CHCl_3$) 1711 (s), 1662 (s), 1630 (sh), 1485 (m), 1451 (s), 1438 (m), 1390 (s), 1380 (w), 1350 (s), 1325 (w), 1140 (s), 1120 (s), 1020 (w), and 955 cm^{-1} (w); uv (95% EtOH) λ_{max} 267 nm (ϵ 8200) and 207 (8200), λ_{min} 234 nm (ϵ 1800); uv (0.1 *N* NaOH) λ_{max} 267 nm (ϵ 8300), λ_{min} 236 nm (ϵ 1900); uv (0.1 *N* HCl) λ_{max} 267 nm (ϵ 8200), λ_{min} 235 nm (ϵ 1400); ^1H NMR ($CDCl_3$) δ 7.18 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 5.70 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 4.17 and 3.69 (m, 4, CH_2CH_2), 3.54 (q, 2, J_{Et} = 7 Hz, CH_3CH_2), 3.39 (s, 3, CH_3N), and 1.15 ppm (t, 3, J_{Et} = 7 Hz,

CH_2CH_3); mass spectrum *m/e* (rel intensity) 198 (6), 169 (8), 154 (30), 153 (23), 152 (28), 139 (16), 128 (17), 127 (100), 126 (42), 96 (7), 84 (35), 83 (28), 82 (49), 72 (44), and 70 (15).

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.70; H, 7.11; N, 13.94.

Preparation of β-(1-Methyluracil-3)ethyl Ether. N^3,O^4-Ethylene-1-methyluracilium mesylate[2] (190 mg, 0.775 mmol) and 130 mg (0.775 mmol) of **5** were dissolved in 2 ml of MeCN and allowed to stand at room temperature for 2 weeks. TLC (1:1 AcOEt–EtOH) indicated that some salt was still present. The reaction mixture was refluxed for 4 hr. It then was evaporated in vacuo and $CHCl_3$ was added to the residue. The $CHCl_3$ solution was extracted with 1 *N* NaOH, dried ($MgSO_4$), and evaporated in vacuo. Chromatography on 8 g of silica gel (AcOEt followed by AcOEt plus EtOH) afforded 62 mg (26%) of the product. An analytical sample was obtained from 1:1 $CHCl_3$–hexane: mp 154–156°; ir ($CHCl_3$) 1712 (s), 1665 (s), 1450 (m), 1387 (w), 1383 (w), 1190 (m), 1180 (w), 1140 (w), and 1078 cm^{-1} (m); uv (95% EtOH) λ_{max} 267 nm (ε 15,100) and 206 (14,400), λ_{min} 234 nm (ε 3200); uv (0.1 *N* NaOH) 267 nm (ε 15,500), λ_{min} 240 nm (ε 5400); uv (0.1 *N* HCl) λ_{max} 267 nm (ε 15,200), λ_{min} 235 nm (ε 3200); ^1H NMR ($CDCl_3$) 7.09 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 5.82 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 4.15 and 3.71 (m, 4, CH_2CH_2), and 3.37 ppm (s, 3, NCH_3); mass spectrum *m/e* (rel intensity) 322 (5), 169 (13), 154 (43), 153 (100), 152 (74), 151 (8), 140 (5), 127 (37), 126 (23), 96 (15), 84 (32), 82 (27), and 70 (35).

Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63; N, 17.38. Found: C, 52.20; H, 5.80; N, 17.45.

Reaction of 1 with Ethoxide–Ethanol. 4-Ethoxy-N^3,O^4-ethylene-1-methyl-3,4-dihydrouracil (14a). Mesyl ester **1** (245 mg, 0.99 mmol) was added to 25.8 ml of absolute EtOH containing 0.99 mmol of sodium ethoxide. After 24 hr a solid precipitate ($MeSO_3Na$) was present. Approximately 26% of the original uv chromophore remained and a new maximum was observed at 235 nm. When an aliquot of this solution was acidified with 1 *N* HCl, the λ_{max} shifted to 290 nm, that of the cyclic salt **2**. Filtration followed by evaporation of a portion of the solution afforded a residue which could not be crystallized. Attempts to chromatograph the material on silica gel afforded **5**. The ^1H NMR spectrum was identical with that of **14a** prepared from **2**.[2]

Reaction of 1 with Sodium Methoxide in Methanol-*O*-*d*. Compound **1** (250 mg, 1.0 mmol) was added to a solution of 20 ml of MeOD and 1.2 ml of 0.83 *N* sodium methoxide (1.0 mmol) in MeOD. The ester dissolved over a period of 30 min. The λ_{max} at 267 nm slowly decreased and the absorbance increased at 235 nm. After 22 hr, the solution was evaporated in vacuo and the residue was dissolved in absolute EtOH and filtered to remove sodium methanesulfonate. Evaporation in vacuo afforded 240 mg of material whose ^1H NMR spectrum in $CDCl_3$ indicated equal amounts of two kinds of products, **14**[30] and **5**,[31] both of which contained less than 5% deuterium at C-5 and C-6.

Reaction of 1,3-Dimethyluracil with Sodium Methoxide in Methanol-*O*-*d*. 1,3-Dimethyluracil (50 mg, 0.357 mmol) and 1 ml (0.83 mmol) of the above solution of sodium methoxide in MeOD were combined and allowed to stand at room temperature for 22 hr. Neutralization with glacial AcOH and evaporation in vacuo afforded a solid residue of 1,3-dimethyluracil. The ^1H NMR spectrum showed 73% deuterium at C-5 and 16% at C-6.

Reaction of 1 with Diethylamine. *trans*-2-(β-diethylaminoethenyl)-Δ²-oxazoline and 3-(β-Diethylaminoethyl)-1-methyluracil. Compound **1** (60 mg, 0.242 mmol) was dissolved in 300 μl of MeCN and 100 μl (0.97 mmol) of diethylamine. The solution turned yellow immediately. The reaction was complete after 5 days (TLC, 10% Et_3N in AcOEt) at room temperature. The reaction mixture was evaporated in vacuo. $CHCl_3$ was added to the residue and the solution was extracted with 2 × 5 ml of 1 *N* HCl. The $CHCl_3$ layer (dried with $MgSO_4$) on evaporation afforded 12 mg (38%) of *N,N*-diethyl-*N'*-methylurea. The acid extracts were made alkaline with 1 *N* NaOH and extracted with 3 × 15 ml of $CHCl_3$. The $CHCl_3$ layer (dried with $MgSO_4$) afforded 49 mg of oil which was 74% oxazoline[2] and 26% β-diethylamino derivative[2] (^1H NMR). Chromatography on Chrom AR 500 sheets with 2.5% Et_3N–MeCN was used to separate the components in order to obtain pure samples for uv spectra. These spectra confirmed the structure assignments.[2]

Reaction of 1 with Isopropylamine. 3-(β-Hydroxyethyl)-1-methyl-N^4-isopropylcytosine and 3-(β-Isopropylaminoethyl)-1-methyluracil. Ester **1** (66 mg, 0.27 mmol) was dissolved in 300 μl of MeCN and 100 μl (1.18 mmol) of isopropylamine. The reaction was complete after 5 days at room temperature (TLC, 10% Et_3N in AcOEt). $CHCl_3$ was added to the residue obtained after evaporation of the reaction mixture in vacuo. The resulting $CHCl_3$ solution was extracted with 3 × 15 ml of 1 *N* HCl. The organic layer contained less than 5 mg of **5** (TLC). The acidic extracts were made alkaline with 1 *N* NaOH and extracted with 3 × 15 ml of $CHCl_3$. After drying ($MgSO_4$), the $CHCl_3$ washings on evaporation afforded 42 mg (77%) of two components which were separated on Chrom AR 500 sheets (2.5% Et_3N in MeCN). The faster moving component (86%) was identical in all respects with 3-(β-hydroxyethyl)-1-methyl-N^4-isopropylcytosine prepared from **2**.[2] The slower moving component (14%) had uv max (95% EtOH, 0.1 *N* HCl, and 0.1 *N* NaOH) 268 nm; ^1H NMR ($CDCl_3$) δ 7.17 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 5.70 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 3.39 (s, 3, CH_3N), 2.86 [septet, 1, $J_{Me,H}$ = 6 Hz, $(CH_3)_2CH$], and 1.03 ppm [d, 6, $J_{Me,H}$ = 6 Hz, $(CH_3)_2CH$]; the remaining lines for the ethylene group and the NH were presumed to be under absorptions due to the other component.[32] These data are in agreement with the assigned structure, 3-(β-isopropylaminoethyl)-1-methyluracil, and with the data for the related compound, 3-(β-diethylaminoethyl)-1-methyluracil.

Reaction of 1 with Pyridine. [β-(1-Methyluracil-3)ethyl]pyridinium Mesylate. The mesyl ester **1** (360 mg, 1.45 mmol) was dissolved in 2 ml of pyridine and allowed to stand overnight. Electrophoresis (Millipore strip) in 0.05 *M* phosphate buffer (pH 7), with Methyl Green and **5** as markers, indicated almost total conversion to a positively charged species. The product and the dye moved 3.2 cm, while **5** did not migrate. Ether was added to the crystals which had appeared in the reaction flask. The product was collected by filtration (267 mg, 56%) and washed with ether. No attempt was made to recover the remainder from the filtrate. The product was hygroscopic. An analytical sample was obtained from absolute EtOH–Et_2O: mp 157–158°; ir (Nujol) 3020 (w), 3060 (w), 1710 (s), 1660 (s), 1495 (s), 1380 (m), 1360 (m), 1345 (m), 1320 (w), 1260 (w), 1200 (s), 1080 (m), 1065 (w), 1045 (m), 1015 (w), 990 (w), 845 (w), and 775 cm^{-1} (m); uv (95% EtOH) λ_{max} 261 nm (ε 11,400) and 207 (12,400), shoulder 265 (11,000), λ_{min} 237 nm (ε 3500); uv (0.1 *N* NaOH) λ_{max} 260 nm (ε 11,400), shoulder 266 (11,000), λ_{min} 237 nm (ε 3500); uv (0.1 *N* HCl) 261 nm (ε 11,000), shoulder 265 (10,700), λ_{min} 235 nm (ε 2500); ^1H NMR (D_2O) 8.88 and 8.58 (m, 5, aromatic protons) 7.60 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 5.77 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 4.88 and 4.62 (m, 4, CH_2CH_2), 3.35 (s, 3, NCH_3), and 2.80 ppm (s, 3, $CH_3SO_3^-$).

Anal. Calcd for $C_{13}H_{17}N_3O_5S$: C, 47.71; H, 5.24; N, 12.84; S, 9.77. Found: C, 47.53; H, 5.33; N, 12.74; S, 9.58.

Registry No.—**1**, 54931-79-2; **5**, 1127-64-6; **6** tautomer 1, 54931-80-5; **6** tautomer 2, 54931-81-6; **7a**, 54931-82-7; **7b**, 54931-83-8; *cis*-8, 54931-84-9; *trans*-8, 54931-85-0; **9**, 694-32-6; **11**, 54931-86-1; 3-(β-Methoxyethyl)-1-methyluracil, 54931-87-2; 3-(β-ethoxyethyl)-1-methyluracil, 54931-88-3; β-(1-methyluracil-3)ethyl ether, 54931-89-4; N^3,O^4-ethylene-1-methyluracilium mesylate, 54931-91-8; *trans*-2-(β-diethylaminoethenyl)-Δ²-oxazoline, 54931-92-9; 3-(β-diethylaminoethyl)-1-methyluracil, 54931-93-0; 3-(β-hydroxyethyl)-1-methyl-N^4-isopropylcytosine, 54931-94-1; 3-(β-isopropylaminoethyl)-1-methyluracil, 54931-95-2; [β-(1-methyluracil-3)ethyl]pyridinium mesylate, 54931-97-4.

References and Notes

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(10) The numbering system used for designating the atoms in **1** was retained for the purpose of simplification and ease of comparison.
(11) For example, 4-*N*-pyrrolidyl-3-penten-2-one, $CH_3COCH{=}C(CH_3)N\text{-}c\text{-}C_4H_8$, has uv max (EtOH) 312 nm (ϵ 32,000). β-Acetylvinyltrimethylammonium chloride, $CH_3COCH{=}CHN^+(CH_3)_3Cl^-$, has uv max (EtOH) 206.5 nm (ϵ 7300). On the other hand, ethyl(4-*N*-pyrrolidyl-3-penten-2-ylidene)oxonium iodide, $C_2H_5O^+{=}C(CH_3)CH{=}C(CH_3)N\text{-}c\text{-}C_4H_8\ I^-$, has uv max (EtOH) 302 nm (ϵ 24,600). See G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **30**, 1407 (1965).
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(20) For cinnamamide, the uv max (EtOH) is 269 nm (ϵ 26,300) [G. Tsatsas, *Bull. Soc. Chim. Fr.*, 1011 (1947)], while for cinnamylurea uv max (EtOH) is 288 nm (ϵ 28,200) [R. E. Stuckey, *J. Chem. Soc.*, 207 (1949)].
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(25) These measurements are subject to considerable error because of the complexity of the reaction mixture.
(26) The extinction coefficients were estimated by assuming 100% conversion to enolate anion.
(27) The sample also contains tetramethylammonium cations, mesylate anions, and DMSO-h_6. Although it integrates correctly, this resonance may not be due to the NCH_3 group. This resonance could be hidden under one of the others.
(28) *N*-Methylimidazolidone was prepared from imidazolidone by reaction with sodium hydride and methyl iodide in dimethylformamide. It was crystallized from toluene, mp 112–113.5°. A. N. Smirnov and I. F. Spasskaya found mp 114° from CCl_4 [*Zh. Obshch. Khim.*, **35**, 178 (1965)] and A. M. Fusco, G. J. Del Franco, and E. J. Aranaff report mp 116–116.5° for a vacuum-sublimed sample [*J. Org. Chem.*, **31**, 313 (1966)].
(29) These latter two were probably present in the starting material, which had been exposed to air several times prior to use.
(30) This product consists of both **14a** and **14b** (^{1}H NMR). Apparently **14a** was produced by a facile exchange which took place when absolute ethanol was added to the crude reaction mixture.
(31) In all likelihood **5** was formed by the action of adventitiotious moisture on the reaction mixture. An alternative, however, is that this came about by the action of methoxide on **14b**, a reaction reported by S. Hünig, *Angew. Chem., Int. Ed. Engl.*, **3**, 548 (1964).
(32) The ^{1}H NMR spectrum was obtained on a mixture of the two products.

Trapping of Thiaziridinimines with Heterocumulenes[1]

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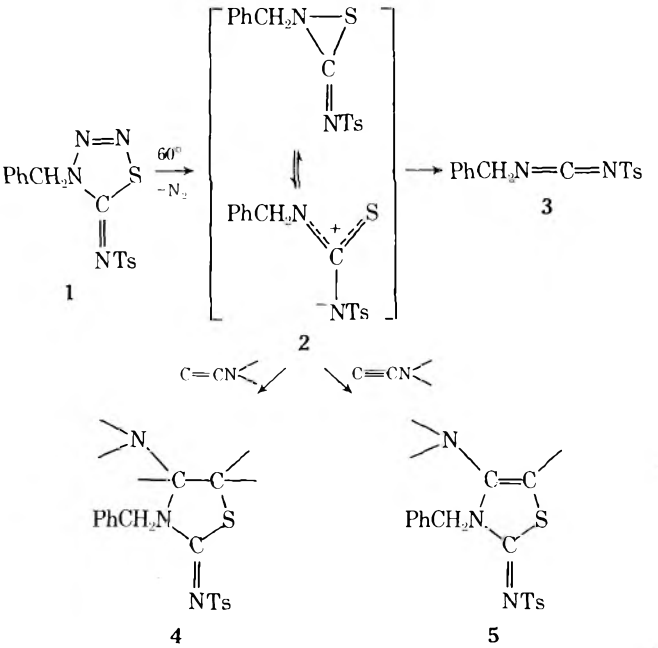
N-Sulfonyliminothiaziridines (e.g., 2), generated by thermolysis of 4-alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines (e.g., 1) react with ketenes, isocyanates, carbodiimides, and isothiocyanates to give five-membered heterocyclic compounds (**6**, **7**, **8**, and **9**) in good yields. Structure assignment was essentially based on independent synthesis and on comparison of the ^{13}C NMR data with those of pertinent model compounds from the chemical literature.

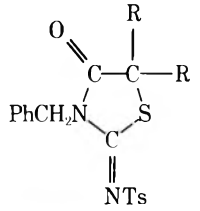
Recently, we reported that thiaziridinimines or their ring-opened dipolar species are formed as intermediates in the synthesis of sulfonylcarbodiimides by thermal decomposition of 4-alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines (e.g., 1 → 2 → 3).[2] Although **2** was too unstable to be isolated, it could be efficiently trapped with unsaturated systems. Thus, enamines and ynamines produced 4-aminothiazolidines (e.g., **4**) and 4-aminothiazolines (e.g., **5**), respectively. Keto-stabilized phosphorus ylides also trapped the thiaziridinimines to give thiazolines by loss of tertiary phosphine oxides.[2]

Since 4-alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines are readily obtained in good yields from the reaction of sulfonyl isothiocyanates with alkyl azides at room temperature,[2] their decomposition in the presence of unsaturated systems provides a new entry into synthetic heterocyclic chemistry. The present phase of our work involves the use of heterocumulenes as trapping reagents for **2**.

Reaction Products. When 1-benzyl-5-tosylimino-1,2,3,4-thiatriazoline (**1**) was decomposed at 60–80° in the presence of ketenes, isocyanates, carbodiimides, and isothiocyanates, compounds **6**, **7**, **8**, and **9** were obtained in reasonably good yields. The results are summarized in Table I.

The NMR spectra of the crude reaction mixtures indicated that single products were formed in all cases, except for the reaction of diphenylketene with **1**, which gave **10** (9%, mp 221–223°, C=N at 1525 cm^{-1}) and **11** (16%, mp 234–238°, C=N at 1535 cm^{-1}) in addition to **6a** (major product). Compound **10** results from cycloaddition of **2** with **3** (formed as side product) and compound **11** is formally the cycloaddition product of **2** with tosyl isothiocyanate. We assume that tosyl isothiocyanate is formed in this





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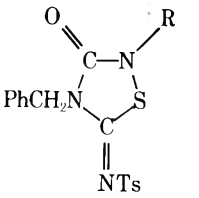

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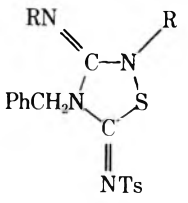

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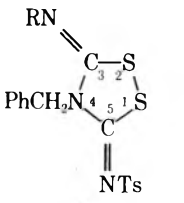

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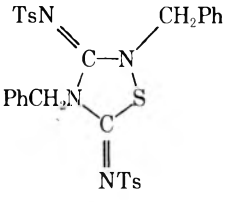

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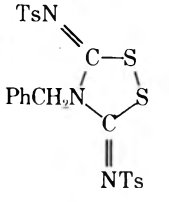

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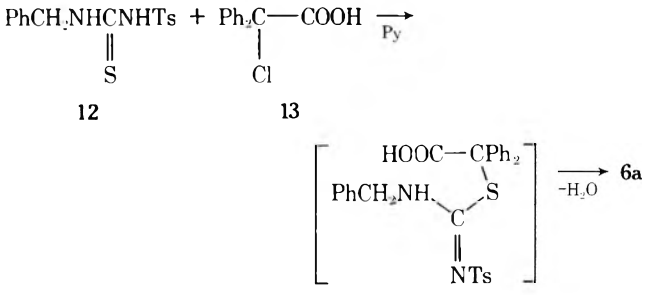
particular case by cycloreversion of **1** during the reaction conditions.

$$\mathbf{1} \xrightarrow[-PhCH_2N_3]{} TsN{=}C{=}S \xrightarrow{2} \mathbf{11}$$

The structures of the adducts were fully supported by elemental analyses, spectral data, and independent syntheses (see below). The presence of an exocyclic C=NTs bond in all the adducts is apparent from the broad and strong ir absorptions at ca. 1530 cm^{-1} (see Table I)[3] and also from the ^{13}C NMR spectra (see below).

Independent Syntheses. Since in principle the thiaziridinimine **2** can add to heterocumulenes in 12 different ways, we have focused on the regiochemistry of the addition products. An independent synthesis of **6a** was realized by treating *N*-benzyl-*N'*-tosylthiourea (**12**) with α-chlorodiphenylacetic acid (**13**) in the presence of pyridine as catalyst.[4]



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In the thiadiazolidinone series **7**, the three-step procedure of Ottmann and Hooks[5] was utilized to prepare **7b**

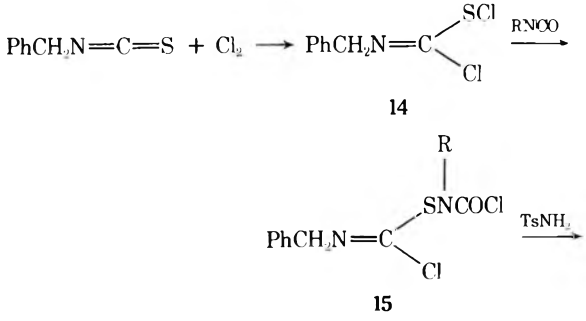

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Table I
Synthesis of Heterocycles from 1 and Heterocumulenes[d]

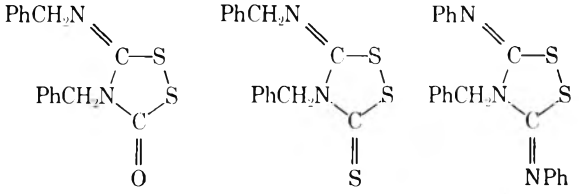
Compd	R	Yield, Method A[a]	Yield, Method B[b]	Mp, °C	Ir, C=N, cm^{-1}
6a	Ph		32–54	142–143	1540
6b	*t*-Bu and CN		40[c]	156–157	1565
7a	Et		66	112–115	1535
7b	*n*-Bu	77	50	117–119	1535
7c	Ph	63	25	160–161	1540
7d	*p*-$MeOC_6H_4$	81		141.5–142.5	1550
7e	*p*-ClC_6H_4	69	17	140–141.5	1540
8a	c-C_6H_{11}	90		103–105	1540, 1655
8b	$PhCH_2$	82		146–147	1525, 1675
8c	Ph	86		147.5–149	1528, 1649
9a	Me	72		168–170	1500, 1645
9b	*n*-Bu	93		101–102.5	1500, 1645
9c	$PhCH_2$	88	40	161–162	1510, 1642
9d	Ph	84		137–138.5	1503, 1627, 1640
9e	*p*-MeC_6H_4	92		144–146	1510, 1628
9f	*p*-ClC_6H_4	50		162–164	1510, 1638

[a] Reactions carried out with a tenfold excess of heterocumulene in the absence of solvent. [b] Reactions carried out with 1 equiv of heterocumulene (0.01 mol) in CCl_4 or benzene (50 ml) as solvent. [c] The yield of **6b** was 70% when 3 equiv of *tert*-butyl cyanoketene was used. [d] Satisfactory analytical values (±0.3% for C, H, N) were reported for all compounds tabulated except **8b,c** and **9a**, for which *m/e* values for the parent ion (±0.3 millimass units) were given. Ed.

and **7c**. Thus, the *S*-chloroisothiocarbamoyl chloride **14**, obtained by chlorination of benzyl isothiocyanate, was treated with *n*-butyl isocyanate or phenyl isocyanate to give the corresponding *S*-(chlorocarbonylamino)isothiocarbamoyl chloride **15**. Upon treatment with tosylamide, **15** was converted into **7b** and **7c**, respectively.

Finally, the structure of **8** was easily proven by acid hydrolysis of **8c**, giving **7c** in 94% yield.

^{13}C NMR Analysis. For convenience in discussing the ^{13}C NMR data, the atoms comprising the five-membered rings are all numbered in the same manner as shown in structure **9**. The absorption values are summarized in Table II. Since the chemical shift value of the C_3 atom of adduct **9** would provide diagnostic proof for the assigned structure, we have prepared three model compounds (**16**, **17**, and **18**) whose structures have been unambiguously set-



16 17 18

tled. 3-Benzylimino-4-benzyl-1,2,4-dithiazolidin-5-one (**16**, mp 93–94°) and 3-benzylimino-4-benzyl-1,2,4-dithiazolidine-5-thione (**17**, mp 68–69°) were prepared by the methods of Freund,[5,7] whereas 3,5-bis(phenylimino)-4-benzyl-1,2,4-dithiazolidine (**18**) was obtained during our research on the reaction of benzyl azide with phenyl isothiocyanate. Its symmetric structure is apparent from the ^{13}C NMR data and also from an X-ray analysis reported by Revitt.[9]

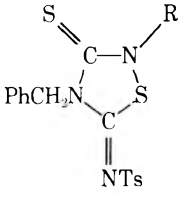
The C_3 atom absorptions of **9** at ca. δ 150 correspond with those of the model compounds **16**–**18** (see Table II). If addition of **2** would have occurred onto the C=N bond of the isothiocyanate to give **19**,[10] the C_3 atoms would reso-

Table II
^{13}C NMR Data of the New Heterocycles[a]

Compd	C_3	C_5	$PhCH_2N<$	Other shift values
6a	174.4	165.8	47.4	C_2 at 67.2
6b	167.2[b]	163.6[b]	48.2	C_2 at 59, C≡N at 114.5, $(CH_3)_3C$ at 25.2 and 41.3
7a	152.1	164.6	48.3[c]	CH_3CH_2 at 40.1
7b	152.4	164.5	48.4	$C_3H_7CH_2$ at 44.8
7c	150.5	163.8	48.5	
8a	144.5	167.3	48.5	
8b	147.9	167.2	48.8[c]	$PhCH_2N=$ at 51.8,[d] $PhCH_2$ in position 2 at 57.1[c]
8c	142.1	166	49.1	
9b	148.6	166.1	51.9	$C_3H_7CH_2$ at 53.6
9c	150.5	166.1	52.2[c]	$PhCH_2N=$ at 57.1[d]
9d	152.5	166.4	52.2[c]	
10	147.6	164.9	49.9[c]	$PhCH_2$ in position 2 at 55.1[c]
11	167.3	167.3	52.1	
16	148.5	169.2	50.15	$PhCH_2N=$ at 54.3[d]
17	154.6	193.9	53.1	$PhCH_2N=$ at 56.2[d]
18	153.5	153.5	51.1	

[a] All the spectra (δ values in parts per million from Me_4Si) were recorded in $CDCl_3$ except those of **6a** (C_6D_6) and **11** (DMSO-d_6). [b] The reversed assignment is possible. [c] $^1J_{C-H}$ = 142–144 Hz. [d] $^1J_{C-H}$ = 133–135 Hz.

nate at ca. δ 171–175 ppm. This is calculated from the C_3 absorption values of **7a–c** by use of the empirical relationship of Kalinowski and Kessler:[11] $\delta_{C=S} = 1.45\ \delta_{C=O} - 46.5$ ppm.



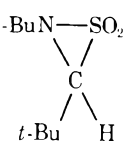
19

Measurement of the coupling constant $^1J_{C-H}$ for the benzyl methylene groups in **9c** further substantiates its structure. Indeed, the value of $^1J_{C-H}$ is known to be related to the extent of charge localization on the nitrogen atom.[12] In structure **9c**, the imine CH_2 group in position 3 (δ 57.1 ppm) exhibits a coupling constant of 133 Hz whereas the CH_2 group at the 4 position has $^1J_{C-H}$ = 143 Hz. This criterion was further used to assign structure **10** to one of the side-products from **1** and diphenylketene, $^1J_{C-H}$ being 143 Hz for both CH_2 groups.

From the viewpoint of ^{13}C NMR spectroscopy, it is interesting to compare the C=NTs, C=O, and C=S carbon absorptions at the 5 position of **9c, 16,** and **17.** Whereas the chemical shift value of C=NTs (δ 166 ppm) is comparable with that of C=O (δ 169 ppm) in this homologous series, the C=S absorption in **17** is found at lower field (δ 193.9 ppm). This value, however, is in good agreement with the estimated value (δ 198.5 ppm) obtained by applying the empirical equation of Kalinowski and Kessler.[11]

After our work had been completed, Neidlein and Salzmann[13] also reported on this topic, apparently without knowledge of our previous work.[2]

It is also interesting to note that the first thiaziridine derivative **20** has been isolated recently in 43% yield by Quast and Kees[14] from the reaction of *N*-sulfonyl-*tert*-butylamine and *tert*-butyldiazomethane.



20

Experimental Section

The ir spectra were taken on a Perkin-Elmer Model 157G spectrometer. Proton NMR spectra were recorded with a Jeol MH-100 or Varian XL-100 spectrometer using Me_4Si as an internal reference. For ^{13}C NMR spectra, the XL-100 apparatus was equipped with a device for pulsed Fourier transform operation.

1-Benzyl-5-tosylimino-1,2,3,4-thiatriazoline (**1**) was prepared as reported[2] by the reaction of benzyl azide with 1 equiv of tosyl isothiocyanate in CCl_4 at room temperature.

General Procedure for the Preparation of 6, 7, 8, and 9. Compound **1** (0.01 mol) was thermolyzed at 60° in the presence of a tenfold excess of heterocumulene for 2 hr and then heated at 80° for another 1 hr. The excess of heterocumulene was distilled off in vacuo and the residue was crystallized from ether (**7** and **8**) or from MeOH (**9**).

For the reaction of **1** with diphenylketene, the residue, after evaporation of the solvent, was fractionally crystallized from MeOH to give **6a, 10,** and **11.**

In the case of **6b**, *tert*-butyl cyanoketene was first generated in situ by thermolysis of 2,5-di-*tert*-butyl-3,6-diazidobenzoquinone (1 g) in dry benzene (30 ml) as reported by Moore and Weyler.[15] After cooling to room temperature, the thiaziridinimine precursor **1** (2.3 g) was added and the solution was heated at 70° for 2 hr. The solvent was removed in vacuo, and the residue was dissolved in ether or methanol (30–40 ml) and then cooled to give **6b.**

Independent Synthesis of 6a. Equimolar amounts (0.006 mol) of **12** and **13** were dissolved in CCl_4 (10 ml) containing 0.5 ml of pyridine. The solution was heated to reflux for 72 hr. After cooling to room temperature, 20 ml of CCl_4 was added to the heterogeneous mixture and the CCl_4 layer was separated and dried over $MgSO_4$. After removal of the solvent, the residue was crystallized from MeOH to give white crystals of **6a** in 72% yield.

Independent Synthesis of 7b and 7c. Nearly 1 equiv of chlorine was added to a solution of benzyl isothiocyanate (0.03 mol) in dry pentane (20 ml) at ca. −10°. After the excess of chlorine was removed in vacuo at 0°, the residue (**14**) was dissolved in dry pentane. To this solution phenyl isocyanate (0.03 mol) in pentane was added dropwise at ca. 10° during a period of 30 min. The mixture was allowed to react for another 1.5 hr and the slurry (containing **15**) was then dissolved in THF (100 ml). To this solution tosylamide (0.03 mol) in THF (25 ml) containing 6 g of NEt_3 was added with stirring at room temperature. After a reaction time of 2 hr, the precipitate (NEt_3·HCl) was removed by filtration and the mother liquor was evaporated in vacuo to give a yellow oil (**7b**) which was crystallized from MeOH (10 ml), overall yield 56%.

Compound **7b** (overall yield 35%) was obtained in a similar manner by using *n*-butyl isocyanate instead of phenyl isocyanate.

Acid Hydrolysis of 7c. A solution of **7c** in ethanol (0.5 g in 20 ml) containing 5 ml of H_2SO_4 was heated at reflux for 1 hr. The precipitate was filtered off, washed with water, dried, and crystallized from MeOH–$CHCl_3$, yield 94%.

Synthesis of 18. A mixture of phenyl isothiocyanate (0.1 mol)

and benzyl azide (0.2 mol) was heated at 100° until gas evolution ceased (72 hr). Addition of ether furnished **18** (55%) which was crystallized from ether–petroleum ether, mp 151–153°, ir (KBr) 1610 cm^{-1}.

Acknowledgment. We thank Dr. E. Van Loock for having carried out some preliminary experiments in this field. We are also indebted to the F. K. F. O. (Belgium) for financial support.

Registry No.—**1**, 42770-61-6; **6a**, 54999-84-7; **6b**, 54999-85-8; **7a**, 54999-86-9; **7b**, 54999-87-0; **7c**, 54999-88-1; **7d**, 54999-89-2; **7e**, 54999-90-5; **8a**, 54999-91-6; **8b**, 54999-92-7; **8c**, 54999-93-8; **9a**, 54999-94-9; **9b**, 54999-95-0; **9c**, 54999-96-1; **9d**, 54999-97-2; **9e**, 54999-98-3; **9f**, 54999-99-4; **10**, 55000-00-5; **11**, 55000-01-6; **12**, 53016-96-9; **13**, 7475-56-1; **14**, 55000-02-7; **15** (R = *n*-Bu), 55000-03-8; **15** (R = Ph), 55000-04-9; **16**, 55000-05-0; **17**, 21494-82-6; **18**, 55000-06-1; diphenylketene, 525-06-4; *tert*-butyl cyanoketene, 29342-22-1; ethyl isocyanate, 109-90-0; *n*-butyl isocyanate, 111-36-4; phenyl isocyanate, 103-71-9; *p*-methoxyphenyl isocyanate, 5416-93-3; *p*-chlorophenyl isocyanate, 104-12-1; dicyclohexylcarbodiimide, 538-75-0; dibenzylcarbodiimide, 6721-03-5; diphenylcarbodiimide, 622-16-2; methyl isothiocyanate, 556-61-6; *n*-butyl isothiocyanate, 592-82-5; benzyl isothiocyanate, 622-78-6; phenyl isothiocyanate, 103-72-0; *p*-tolyl isothiocyanate, 622-59-3; *p*-chlorophenyl isothiocyanate, 2131-55-7; benzyl azide, 622-79-7.

References and Notes

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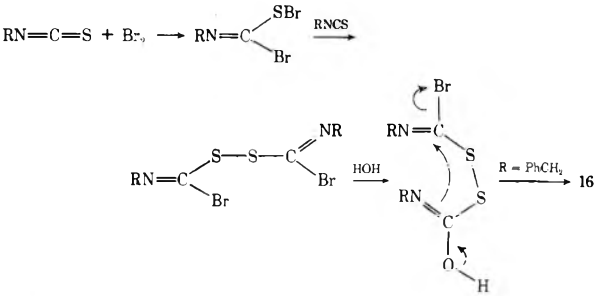
(7) Over 80 years ago, Freund[6] reported the reaction of isothiocyanates with bromine in the presence of some water to give a product of empirical formula $(RNCS)_2O$. Only very recently its correct structure (e.g., **16**) was elucidated,[8] but the mechanism of this unusual reaction remains to be resolved. Based on the work of Ottmann and Hooks,[5] we propose the following mechanism.



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(9) D. M. Revitt, *J. Chem. Soc., Chem. Commun*, 24 (1975).
(10) (a) Komatsu et al.[10b] assigned structure **19** (R = Ph, Ph instead of Ts) to the reaction product from *N*-benzyloxaziridine and phenyl isothiocyanate. In view of the ^{13}C NMR analysis discussed in this paper, this structure should now be revised in favor of **18**. (b) M. Komatsu, Y. Ohshiro, K. Yasuda, S. Ichijima, and T. Agawa, *J. Org. Chem.*, **39**, 957 (1974).
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2-Dialkylphosphonyl- and 2-Alkylidene-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazines

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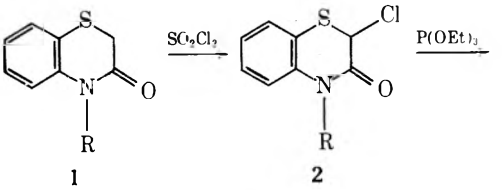
2-Chloro-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazines have been shown to react with triethyl phosphite in a Michaelis–Arbuzov manner to give the 2-phosphonates. These latter compounds react readily with aldehydes and ketones to give the 2-alkylidene derivatives. The olefins from aldehydes are assigned the *Z* stereochemistry on the basis of NMR data.

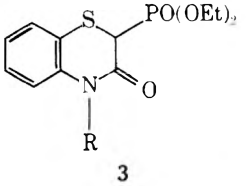
The reaction of various α-halocarbonyl systems with phosphorus nucleophiles has been well investigated. α-Haloamides normally react with trialkyl phosphites in a Michaelis–Arbuzov fashion to give phosphonates unless special structural requirements are met.[1-6] Although the possible influence of an α-thioether group in this reaction has not been reported previously, an α-thioether group generally is believed to enhance SN2 reactivity,[7] which is the usual mechanism of the Michaelis–Arbuzov reaction.

We now wish to report on the reaction of triethyl phosphite with 2-chloro-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazines (**2**), a cyclic α-haloamide system bearing an α-thioether linkage, and on the utility of the products of this reaction in a new general route to alkylidene benzothiazines.



1 **2**

a, R = H
b, R = Me
c, R = CH_2CO_2Et



3

Results and Discussion

Reaction of 2 with Triethyl Phosphite. The three chlorobenzothiazinones **2a–c** were obtained from treatment of the corresponding **1** with 1 equiv of sulfuryl chloride. Reaction of **2** with neat, excess, refluxing triethyl phosphite gave the analogous phosphonate (Michaelis–Arbuzov product) in good yield. The structure of **3** is confirmed in each case by the observation of an infrared band for the amide carbonyl group at 1660–1675 cm^{-1} and a ^1H NMR signal for the 2-H as a doublet at δ 4.57–4.35 with J_{H-P} = 21.2–22.6 Hz.

Thus, in this case the presence of an α-thioether group

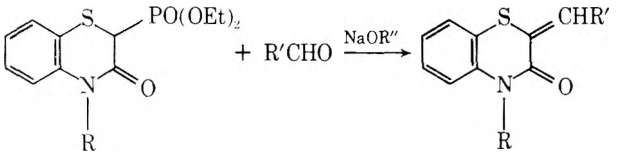
Table I
2-Alkylidene-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazines (4)[a,b]

Compd	R	R′	Yield, %	Mp, °C	NMR ($CDCl_3$), δ =CHR′	NCH_3	Other
4a	H	C_6H_5	90	202–204[c]	7.90		
4b	Me	C_6H_5	68	86–87.5[d]	7.93	3.54	
4c	Me	p-MeC_6H_4	72	139–140	7.85	3.50	2.35 (p-CH_3)
4d	Me	3,4-$(OCH_2O)C_6H_3$	85	151–152	7.79	3.52	6.00 (OCH_2O)
4e	Me	2-Thienyl[e]	64	90–91	8.02	3.48	
4f	H	3,4-$(OCH_2O)C_6H_3$	86	216–218[f]	7.82		6.03 (OCH_2O)
4g	H	p-$MeOC_6H_4$	94	208–210[g]	7.76		3.84 (p-OCH_3)
4h	CH_2CO_2Et	m-$F_3CC_6H_4$	76	131–131.5	7.90		4.80 (NCH_2)
4i	Me	o-FC_6H_4	50	94–95	7.99	3.53	
4j	Me	o-$O_2NC_6H_4$	82	107–108	8.18	3.58	
4k	Me	9-Anthryl	87	173–174	8.65[h]	3.60	
4l	Me	PhCH=CH	55	110–111	*i*	3.47	
4m[j]	H	H	85	>260 dec	6.47 5.69		

[a] Satisfactory analytical data (±0.30% for C, H, and S) were obtained for all new compounds and have been made available to the editors. [b] New *N*-methyl compounds exhibited an infrared band in $CHCl_3$ at ca. 1645 cm^{-1}. [c] Lit.[13i] mp 202–204°. [d] Lit. mp 85–86°: H. Kugita, H. Inoue, M. Ikezaki, M. Konda, and S. Takeo, *Chem. Pharm. Bull.*, **18**, 2284 (1970). [e] Crude product was an oil which crystallized after 1 day. [f] Lit.[13d] mp 212–214°. [g] Lit.[13d] mp 207–208°. [h] This assignment is not unambiguous. An additional singlet at δ 8.44 is assigned to the 10-H of the anthracene ring, since this signal is broader than the one at δ 8.65. The broadening is assumed to be due to long-range coupling with the other aromatic protons. [i] Vinyl proton absorption obscured in aromatic region (δ 7.68–6.65). The predicted values, based on the values observed for **4m** (see text), would be δ 7.71 for the *Z* isomer and δ 6.93 for the *E* isomer. [j] Product obtained using 37% aqueous formaldehyde; crude product analytically pure. This compound is white; **4a–l** are yellow to orange.

does not alter the usual mode of reaction of monohaloamides with trialkyl phosphites.[8] It does allow the preparation of some novel heterocyclic phosphonates which are useful synthetic intermediates, however.

Reaction of 3 with Aldehydes. The phosphonates **3** should undergo Wadsworth–Emmons reaction[9] readily, since the intermediate carbanion can be stabilized by both α-thioether and α-carbamoyl groups. In fact, addition of sodium alkoxide to an alcohol solution of equivalent amounts of **3** and an aromatic aldehyde, cinnamaldehyde, or formaldehyde results in the almost immediate separation of the olefins **4**. Crude products are obtained in fair to

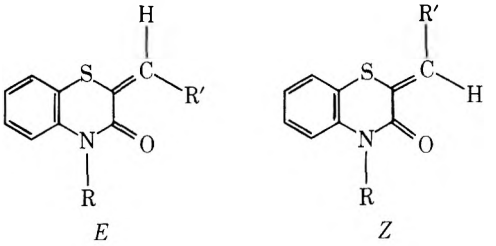


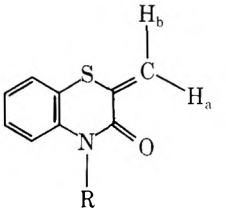
3 **4**

good yields (50–94%), regardless of the steric or electronic nature of the aldehyde, and they are of quite good chemical and geometrical purity as judged by their NMR spectra and melting points.

The scope of the reaction and the physical properties of the products are summarized in Table I.

The products from reaction with aromatic aldehydes are assigned the *Z* stereochemistry on the basis of the chemical shift of the vinyl proton. Application of substituent shielding constants for vinyl proton absorption[10] to compound **4m** gives predicted δ values in $CDCl_3$ for H_a and H_b of 6.15 and 5.47, respectively. The observed values are 6.47 and 5.69, respectively. The differences between the calculated and observed values are somewhat greater than the standard deviation of 0.17 ppm associated with the additivity calculations.[10b] The differences can be attributed to the fact that the RS group here is an arylthio group rather than an alkylthio group[11] and/or the fact that the fixed geometry of the amide carbonyl group in relation to the vinyl protons in **4m** probably causes these protons to be abnormally deshielded.[10a]





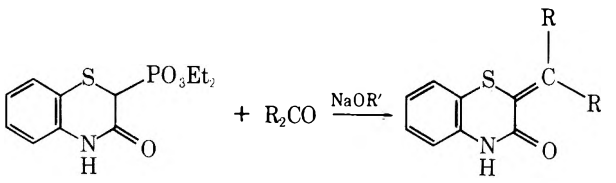
4m

Whatever the source of the deviation, the observed chemical shifts of H_a and H_b in **4m** serve as models for predicting chemical shifts in **4a–l** and therefore for establishing the stereochemistry of these compounds. The substituent shielding constant[10b] for replacing a geminal proton in an olefin with an aromatic group is 1.38 ppm. For an ortho-substituted aromatic group the value of 1.65 ppm is used. The predicted δ values for **4a–h** then are 7.07 for the *E* isomer and 7.85 for the *Z* isomer, and the predicted values for **4i–k** are 7.34 for the *E* isomer and 8.12 for the *Z* isomer. The data in Table I show that the observed δ value for each of these compounds except **4k** (R′ = 9-anthryl) falls within ±0.17 ppm of the predicted value for the *Z* isomer. In **4k**, the anthryl group is probably of great enough steric bulk that it is significantly distorted from coplanarity with the rest of the olefinic system, and therefore the *gem*-vinyl proton would be expected to be abnormally deshielded.[10d]

The reaction of phosphonates **3** with aldehydes thus shows the normal high stereoselectivity associated with the Wadsworth–Emmons reaction but does not appear to exhibit complete stereospecificity. Both TLC on silica gel–20% silver nitrate and NMR spectroscopy of reaction

mixtures in some cases indicate the presence of small amounts of *E* isomers.

Reaction of 3 with Ketones. The reaction of phosphonates **3** with ketones has not been as thoroughly investigated, but **3a** does react readily with diethyl ketomalonate and more slowly with the enolizable ketone, acetone. No reaction was observed with acetophenone.



3a **5a**, R = CO_2Et; **b**, R = Me

At least seven previous methods[13] have been reported for the preparation of various 2-alkylidene-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazines, including one[13i] of scope generally comparable to that of the present method, but geometrical isomerism in this system has been considered only briefly in one example.[13h] Where comparison is possible, the melting points reported for previous examples agree with those now assigned to the *Z* isomers.

Experimental Section

General. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian T-60 or EM-360 spectrometer. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc.

3,4-Dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazine (1b). This compound was obtained in 73% yield from 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine[14] (**1a**) and methyl iodide by the general procedure of Pachter and Kloetzel[15] for the alkylation of amides with potassium hydroxide in acetone: mp 50–53° (lit.[16] mp 55°); NMR ($CDCl_3$) δ 7.17 (m, 4), 3.37 (s, 3), and 3.43 (s, 2).

3,4-Dihydro-3-oxo-2*H*-1,4-benzothiazine-4-acetic Acid Ethyl Ester (1c). This compound was obtained similarly from **1a** and ethyl bromoacetate in 88% yield: mp 54–55° [recrystallized from ethanol, mp 57–58° (lit.[17] mp 48.5–50.5°)]; NMR ($CDCl_3$) δ 7.50–6.72 (m, 4), 4.63 (s, 2), 4.22 (q, 2, *J* = 7 Hz), 3.43 (s, 2), and 1.27 (t, 3, *J* = 7 Hz).

Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.37; H, 5.17; N, 5.30.

Chlorination of 1 with Sulfuryl Chloride. General Procedure. A stirred mixture of **1** in methylene chloride (ca. 0.1 mol/100 ml) was treated dropwise in 0.5 hr with 1 equiv of sulfuryl chloride. The mixture was stirred for 2–5 hr more and then was concentrated to a solid or viscous liquid residue. The residue was stirred for a few minutes with petroleum ether, and the resulting mixture was filtered to give solid product.

2-Chloro-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (2a). Crude product (mp 202–207°) obtained in 86% yield from **1a** by the above procedure was suitable for subsequent reaction with triethyl phosphite but could be recrystallized twice from acetone to give purified material: mp 221–223° (lit.[18] mp 215°); NMR (DMSO-d_6) δ 11.17 (broad s, 1), 7.60–6.90 (m, 4), and 6.23 (s, 1).

Anal. Calcd for C_8H_6ClNOS: C, 48.12; H, 3.03; Cl, 17.76. Found: C, 48.20; H, 3.05; Cl, 17.93.

2-Chloro-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazine (2b). Crude product from **1b** was obtained in 91% yield and was used without further purification: mp 95–97°; NMR ($CDCl_3$) δ 7.55–6.95 (m, 4), 5.68 (s, 1), and 3.51 (s, 3).

Anal. Calcd for C_9H_8ClNOS: Cl, 16.59. Found: Cl, 16.26.

2-Chloro-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-4-acetic Acid Ethyl Ester (2c). This material was obtained from **1c** in 84% yield and also was used without additional purification: mp 76–78°; NMR ($CDCl_3$) δ 7.45–6.81 (m, 4), 5.60 (s, 1), 5.03 (asymmetrical d, 1, *J* = 17 Hz), 4.38 (asymmetrical d, 1, *J* = 17 Hz), 4.18 (q, 2, *J* = 7 Hz), and 1.27 (t, 3, *J* = 7 Hz).

Anal. Calcd for $C_{12}H_{12}ClNO_3S$: Cl, 12.41; S, 11.22. Found: Cl, 12.45; S, 11.22.

2-Diethylphosphonyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (3a). A stirred mixture of **2a** (26.5 g, 0.13 mol) and triethyl phosphite (101 ml, 0.58 mol) was heated to ca. 100°. A vigorous exothermic reaction began, and soon a clear orange solution was obtained. The solution was stirred under reflux for 1.5 hr more and then was cooled to ca. 60° and diluted with 100 ml of petroleum ether (bp 30–75°). Cooling of the mixture to room temperature and filtration gave 31.2 g (78%) of pale yellow solid, mp 131–133.5°. Recrystallization from 250 ml of benzene–petroleum ether (2:3) gave 29.8 g of product: mp 134–136°; NMR (DMSO-d_6) δ 10.80 (broad s, 1), 7.44–6.90 (m, 4), 4.35 (d, 1, J_{H-P} = 21.2 Hz), 4.27–3.54 (m, 4), 1.17 (t, 3, *J* = 7.2 Hz), and 1.00 (t, 3, *J* = 7.2 Hz); ir ($CHCl_3$) 3400, 3000, 1675, 1590, 1480, 1370, 1250, 1160, 1050, 1020, and 975 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}NO_4PS$: C, 47.84; H, 5.35; S, 10.64. Found: C, 47.94; H, 5.38; S, 10.77

2-Diethylphosphonyl-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazine (3b). A mixture of **2b** (64.0 g, 0.30 mol) and triethyl phosphite (112 ml, 0.64 mol) was refluxed for 19 hr. After standing for 1.5 hr, the resulting mixture was filtered to give a pale yellow solid. Recrystallization from 175 ml of benzene–petroleum ether (4:3) gave 61.2 g (65%) of white product: mp 127–129°; NMR (DMSO-d_6) δ 7.50–6.89 (m, 4), 4.50 (d, 1, J_{H-P} = 22.2 Hz), 4.20–3.45 (complex, 4), 3.35 (d, 3, *J* = 1.1 Hz), 1.13 (t, 3, *J* = 7.2 Hz), and 0.98 (t, 3, *J* = 7.2 Hz); ir ($CHCl_3$) 3000, 1660, 1590, 1480, 1445, 1360, 1250, 1050, 1020, and 975 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}NO_4PS$: C, 49.52; H, 5.75; S, 10.17. Found: C, 49.73; H, 5.88; S, 10.31.

2-Diethylphosphonyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-4-acetic Acid Ethyl Ester (3c). A mixture of **2c** (40.0 g, 0.14 mol) and triethyl phosphite (51.0 g, 0.31 mol) was refluxed for 28 hr. Volatile materials were removed from the resultant solution by heating it on a rotary evaporator at 100° for 0.5 hr at 0.1 Torr. The residue was treated with 20 ml of warm ethanol and then 200 ml of petroleum ether. Cooling (Dry Ice) of the solution gave separation of an oil which crystallized upon trituration to give 32.0 g of tan solid, mp 65–68°. Evaporation of the filtrate gave an additional 18.0 g of brown solid, mp 60–65°, combined crude yield 50.0 g (92%). Chromatography of 43.0 g of this material on alumina (20% chloroform–carbon tetrachloride to 100% chloroform) gave 24.0 g of solid. Recrystallization from benzene–petroleum ether gave 18.5 g white product: mp 73–75°; NMR (DMSO-d_6) δ 7.58–6.95 (m, 4), 4.92 (asymmetrical d, 1, *J* = 18.0 Hz), 4.59 (asymmetrical d, 1, *J* = 18.0 Hz), 4.57 (d, 1, J_{H-P} = 22.6 Hz), 4.34–3.60 (complex, 6), and 1.32–0.88 (complex, 9); ir ($CHCl_3$) 1750, 1665, 1390, 1255, 1190, 1050, and 1025 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}NO_6PS$: C, 49.61; H, 5.72; N, 3.62; S, 8.28. Found: C, 49.78; H, 5.83; N, 3.63; S, 8.41.

2-Alkylidene-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazines. General Procedure. To a stirred solution of the aldehyde (0.010 mol) and **3** (0.010 mol) in alcohol (50 ml of 80% aqueous ethanol for **3a**, 30 ml of methanol for **3b**, and 30 ml of ethanol for **3c**) was added 5.0 ml of a 2.0 *N* solution of base (sodium ethoxide in ethanol for **3a** and **3c**, sodium methoxide in methanol for **3b**). If a solid product did not separate immediately, the reaction flask was cooled in an ice bath after 5 min and the inside wall of the flask was scratched with a glass rod. Product then crystallized readily. In all cases, after the appearance of solid material, the mixture was stirred for 10 min more and then filtered to obtain product, which was judged by its melting point and NMR spectrum to be of good chemical and geometrical purity. The melting point of the product normally increased less than 3° upon purification. Analytical samples were obtained in the following manner. The crude product was dissolved in 20 ml of chloroform, and this solution was washed with two 10-ml portions of water, dried ($MgSO_4$), and concentrated to a residue. The residue was recrystallized one or two times from 30 ml of 2:1 or 1:1 carbon tetrachloride–petroleum ether. The properties of the products are summarized in Table I.

3,4-Dihydro-3-oxo-$\Delta^{2\alpha}$-2*H*-1,4-benzothiazine-2-malonic Acid Diethyl Ester (5a). To a stirred mixture of 3a (6.02 g, 0.020 mol) and diethyl ketomalonate (3.5 g, 0.020 mol) in 50 ml of ethanol was added 20 ml of a 1.0 *N* solution of sodium ethoxide. A clear solution was obtained, and after approximately 1 min a yellow precipitate occurred. An additional 100 ml of ethanol was added to the mixture, and stirring was continued for 0.5 hr. Filtration then gave 6.3 g (98%) of bright yellow solid, mp 162–163°. Recrystallization from ethanol gave the analytical sample: mp 163–163.5°; NMR (DMSO-d_6) δ 7.50–6.90 (complex, 4), 4.24 (q, 4, *J* = 7 Hz), 1.23 and 1.20 (two triplets, 6, *J* = 7 Hz).

Anal. Calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.71; S, 9.98. Found: C, 56.11; H, 4.77; S, 10.05.

3,4-Dihydro-2-isopropylidene-3-oxo-2*H*-1,4-benzothiazine (5b). To a stirred solution of **3a** (4.5 g, 0.015 mol) and 10 ml of acetone in 20 ml of methanol was added 7.5 ml of a 2.0 *N* sodium methoxide solution. The solution was stirred for 48 hr. The mixture was then diluted with 5 ml of water and subsequently filtered to obtain 2.0 g (65%) of white product: mp 217–219° (lit.[13c] mp 213–215°); NMR (DMSO-d_6) δ 7.42–6.84 (complex, 4), 2.22 (s, 3), and 2.05 (s, 3).

Registry No.—**1a,** 5325-20-2; **1b,** 37142-87-3; **1c,** 6376-75-6; **2a,** 55043-49-7; **2b,** 55043-50-0; **2c,** 55043-32-8; **3a,** 55043-33-9; **3b,** 55043-34-0; **3c,** 55043-35-1; **4a,** 55043-20-4; **4b,** 55043-21-5; **4c,** 55043-22-6; **4d,** 55043-23-7; **4e,** 55043-24-8; **4f,** 55043-25-9; **4g,** 55043-26-0; **4h,** 55043-27-1; **4i,** 55043-28-2; **4j,** 55043-29-3; **4k,** 55043-30-6; **4l,** 55043-31-7; **4m,** 55043-51-1; **5a,** 55043-52-2; **5b,** 55043-53-3; SO_2Cl_2, 7791-25-5; $P(OEt)_3$, 122-52-1; methyl iodide, 74-88-4; ethyl bromoacetate, 105-36-2; benzaldehyde, 100-52-7; *p*-methylbenzaldehyde, 104-87-0; 3,4-methylenedioxybenzaldehyde, 120-57-0; 2-thiophenecarboxaldehyde, 98-03-3; formaldehyde, 50-00-0; *p*-methoxybenzaldehyde, 123-11-5; *m*-trifluoromethylbenzaldehyde, 454-89-7; *o*-fluorobenzaldehyde, 446-52-6; *o*-nitrobenzaldehyde, 552-89-6; 9-anthracenecarboxaldehyde, 642-31-9; cinnamaldehyde, 104-55-2; acetone, 67-64-1; diethyl ketomalonate, 609-09-6.

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$$\mathrm{PhSCHClCONEt_2} + \mathrm{P(OEt)_3} \longrightarrow \underset{\text{i}}{\mathrm{PhSCH(PO_3Et_2)CONEt_2}} + \underset{\text{ii}}{\mathrm{PhSPO_3Et_2}} + \underset{\text{iii}}{\mathrm{Et_2O_3PCH_2CONEt_2}}$$

are secondary products derived from attack of triethyl phosphite on thioether sulfur of the primary product i. Such a process would be less favored in the benzothiazinone system since there it would require opening of the ring.
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Benzopyranopyridine Derivatives. 2. Reaction of Azaxanthones with Hydroxylamine[1]

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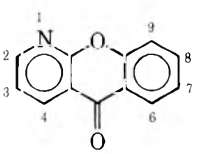
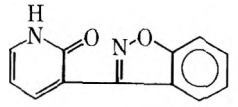
5*H*-[1]Benzopyrano[2,3-*b*]pyridin-5-one, referred to throughout this series as 1-azaxanthone (**1**), reacted in an anomalous manner with an alcoholic KOH solution of $HONH_2$·HCl to give a mixture of 3-(2-1*H*-pyridinon-3-yl)-1,2-benzisoxazole (**2**) and 3-*o*-hydroxyphenyl(2-1*H*-pyridinon-3-yl) ketoxime (**3**). The structure of **2** was established by the usual spectral analyses as well as total synthesis from 3-*o*-chlorobenzoylpyridine. It was shown that **3** is not the intermediate necessary for the formation of **2** and that **2** is formed by a direct attack of the $HONH_2$ anion on 1-azaxanthone.

5*H*-[1]Benzopyrano[2,3-*b*]pyridin-5-one, **1**, referred to throughout this series as 1-azaxanthone,[2] failed to form an oxime under the usual conditions, i.e., $HONH_2$·HCl in pyridine and EtOH. In contrast, the 2- and 4-azaxanthones were readily converted into oximes.

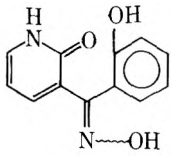


1

Under forcing conditions,[3] excess KOH in EtOH, ketone-**1** reacted with $HONH_2$·HCl to give a mixture of two products, 3-(2-1*H*-pyridinon-3-yl)-1,2-benzisoxazole (**2**) and 3-*o*-hydroxyphenyl-(2-1*H*-pyridinon-3-yl) ketoxime (**3**). These compounds were separated by column chromatography on silica gel.



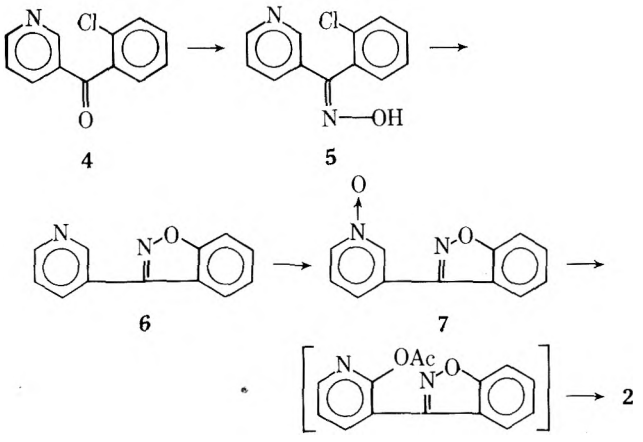
2



3

The benzisoxazole **2** shows a strong carbonyl frequency in the ir (6.0 μ), a C=N band at 6.2 μ, and a pair of bands at 11.1 and 11.5 μ which was subsequently found in the ir spectrum of representative 1,2-benzisoxazoles prepared in this work. The NMR spectrum of **2** showed a triplet (J = 6.7 Hz) at δ 6.40 characteristic of 3-substituted 2-pyridones.[4] Confirmation of structure **2** was established by total synthesis (Scheme I).

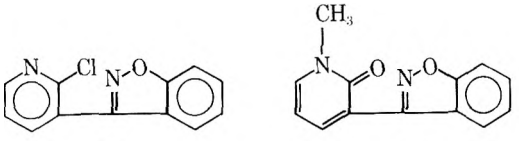
Scheme I



4 5 6 7

3-*o*-Chlorobenzoylpyridine (**4**) was converted into the oxime **5**. The higher melting isomer of **5**, on heating with KOH in ethylene glycol monomethyl ether by standard procedures,[5] gave the pyridylbenzisoxazole **6** in excellent yield. Rearrangement of the 1-oxide **7** with acetic anhydride and subsequent hydrolysis gave **2** identical in all respects with the original sample.

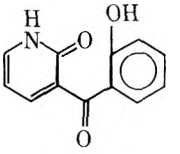
Compound **2** on reaction with phosphorus oxychloride or with phenylphosphonic dichloride was converted into the 2-chlorpyridyl analog **8**, the NMR spectrum of which did



8 9

not show the typical pyridone resonance structure referred to above. Methylation of **2** (dimethyl sulfate in aqueous NaOH) resulted in the isolation of **9**, the NMR spectrum of which showed, in addition to the triplet at δ 6.25, a singlet at δ 3.68 (three protons), due to the *N*-methyl group. Evidence for the intact benzisoxazole ring in **8** and **9** was established by the pair of absorptions at 11.0 and 11.5 μ in the ir spectrum of both compounds.

To study the possible mechanism of this reaction 1-azaxanthone was treated with KOH in EtOH, whereby the pyridone ketone **10** was isolated as the sole product. This

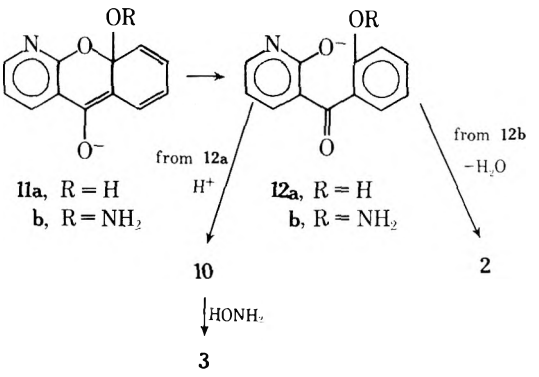


10

compound readily formed oxime **3** on reaction with $HONH_2$·HCl either in the presence of KOH in EtOH or in pyridine–EtOH. Attempts to effect closure of **3** to the benzisoxazole **2** under the original reaction conditions or under more strenuous basic conditions (KOH in ethylene glycol or fusion with KOH) were futile and compound **3** was recovered unchanged. Even under the sequential addition after 1 hr of $HONH_2$·HCl to a refluxing solution of the 1-azaxanthone in KOH and EtOH, only oxime **3** was obtained. These experiments indicate that **2** is not formed through the intermediate oxime **3**.

As reaction path we propose, therefore, a competitive direct attack of the hydroxide ion and the hydroxylamine anion on the 1-azaxanthone (Scheme II) to give a mixture

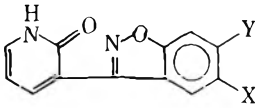
Scheme II



of intermediates of the type **11a** and **11b**, respectively, opening the oxygen bridge as in **12a** and **12b**, resulting in formation of **10**, which reacts with the excess $HONH_2$ to give **3**. The intramolecular loss of water from **12b** results in the formation of **2**.

Additional support for the proposed intermediate **11b** was obtained when the preformed anion of hydroxylamine prepared by reaction of $HONH_2$·HCl with NaH in anhydrous DMF was allowed to react with the ketone **1**. Under these conditions only the pyridone benzisoxazole **2** was ob-

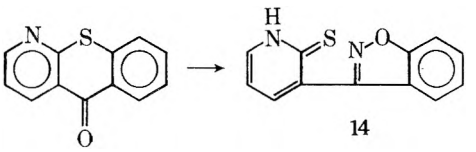
Table I
Compounds of Formula[a]



X	Y	Registry no.	Mp, °C	Yield, %	Formula[b]	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
H	Cl	54999-81-4	238–230	65	$C_{12}H_6ClN_2O_2$	58.43	2.85	11.35	58.61	3.10	11.48
Cl	H	54999-82-5	291–292	67	$C_{12}H_7ClN_2O_2$	58.43	2.85	11.35	58.33	3.04	11.53
OCH_3	H	54999-83-6	253–255	69	$C_{13}H_{10}N_2O_3$	64.46	4.16	11.57	64.21	4.25	11.46

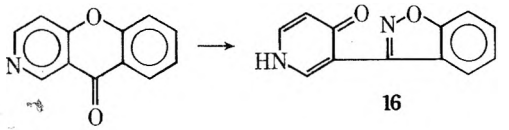
[a] From the ketones reported in ref 1, using method 1. [b] All products recrystallized from EtOH.

tained in a yield of 74%. Under similar reaction conditions 1-azathioxanthone (13) was converted into the thiopyridone benzisoxazole 14 in excellent yield. The structure 14



13 14

was assigned on the basis of spectral data and analogy with the oxygen isostere. Similarly, the benzisoxazole derived from 3-azaxanthone (15), is assigned the structure 16. The



15 16

β proton in the NMR spectrum of 16 resonates as a doublet at δ 6.38 (J = 7.2 Hz), characteristic of the structure indicated.[4]

Table I lists some substituted 2-pyridone benzisoxazoles prepared in this work.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Unless otherwise indicated all products showed one spot on TLC [silica gel plates using $CHCl_3$ (90%)–MeOH (9%)–NH_4OH (1%) as solvent]. Ir spectra were recorded on a Perkin-Elmer Model 137 spectrometer in Nujol mulls. NMR spectra were obtained in DMSO-d_6 on a Varian A-60A spectrometer using tetramethylsilane as internal reference.

3-(2-1*H*-Pyridinon-3-yl)1,2-benzisoxazole (2) and 3-*o*-Hydroxyphenyl(2-1*H*-pyridinon-3-yl) Ketoxime (3). Method 1. In a typical experiment, a mixture of 9.9 g (0.05 mol) of 1-azaxanthone and 4.2 g (0.06 mol) of $HONH_2$·HCl was added in one portion to a solution of 38 g (0.2 mol) of KOH in 250 ml of EtOH. The mixture was heated on the steam bath for 2 hr and approximately 50% of the solvent was removed in vacuo. The residue was poured into water and the precipitated unreacted starting ketone was filtered. The filtrate was acidified with HOAc and the products were allowed to crystallize. The product was recrystallized from 600–700 ml of EtOH, yield of crude product 9.3 g, mp 220–227°.

Nine grams of this mixture was placed on a column of silica gel (450 g) and eluted with a mixture of $CHCl_3$ (90%), MeOH (9%), and NH_4OH (1%). Fractions of 200–250 ml were collected and monitored by TLC. Similar one-spot fractions were combined. Compound 2, being less polar, was eluted first and the major portion was obtained in the first five fractions. The pure oxime 3 was collected in fractions 9–15. The combined fractions were concentrated to a residue and recrystallized from EtOH.

Compound 2 was obtained in a yield of 2.8 g (31% recovery) and 3 (2.6 g, 29% recovery).

Compound 2 had mp 230–231°. Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.97; H, 3.89; N, 13.37.

Compound 3 had mp 257–258°. Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.49; H, 4.40; N, 12.42.

3-(2-1*H*-Pyridinon-3-yl)-1,2-benzisoxazole (2). NaH Method, Method 2. To a suspension of 8.5 g (0.2 mol) of 57% NaH in mineral oil in 100 ml of anhydrous DMF was added to several small portions 6.9 g (0.1 mol) of $HONH_2$·HCl and the mixture was stirred for 0.5 hr in an ice bath. A suspension of 9.9 g (0.05 mol) of 1-azaxanthone in 200 ml of DMF was added all at once and the mixture was warmed on the steam bath for 2 hr. The mixture was poured into ice water (200 ml) and extracted with $CHCl_3$. The aqueous solution was acidified with HOAc, and the product was filtered and recrystallized from EtOH, mp 230–231°. The ir was superimposable and behavior on TLC was identical with that of the sample prepared in total synthesis, yield 7.9 g (74%).

3-(2-1*H*-Thiopyridinon-3-yl)-1,2-benzisoxazole (14). Using method 2, compound 14 was obtained from 10.7 g (0.05 mol) of 1-azathiaxanthone in a yield of 8.8 g (77%), mp 235–236° (EtOH).

Anal. Calcd for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.28. Found: C, 63.32; H, 3.59; N, 12.54.

This compound was also obtained in 53% yield using the KOH method.

3-(4-1*H*-Pyridinon-3-yl)-1,2-benzisoxazole (16) was obtained from 3-azaxanthone (15) and $HONH_2$·HCl and KOH in EtOH by method 1, mp 294–296° (EtOH). Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.55; H, 3.88; N, 12.95.

3-*o*-Chlorobenzoylpyridine (4). Our preparation of this ketone differs from that previously reported.[6]

Step 1. A solution of 76.4 g (0.4 mol) of 2-bromochlorobenzene was converted into the Grignard reagent in Et_2O using 9.6 g (0.4 g-atom) of magnesium. 3-Pyridinealdehyde (32.1 g, 0.3 mol) was added and stirring was continued for 0.5 hr. The product was isolated in the usual manner to give 53.9 g (81%) of a white solid, mp 115–116°.

Step 2. The carbinol from step 1 was oxidized with aqueous $KMnO_4$ at 70–80° for 2 hr to give the title compound in 72% crude yield as a brown oil used directly for compound 5. The HCl salt melted at 182–185° (reported[6] mp 185–187°).

***o*-Chlorophenyl-3-pyridyl Ketoxime (5).** The crude ketone, 4 (72g), 75 g of $HONH_2$·HCl, 150 ml of pyridine, and 400 ml of EtOH was heated under reflux for 6 hr and the solvent was removed in vacuo. The residue was poured into water and allowed to crystallize. The product was filtered and recrystallized from EtOH to give 33 g of a solid, mp 204–207°.

Anal. Calcd for $C_{12}H_9ClN_2O$: C, 61.94; H, 3.90; N, 12.04. Found: C, 61.77; H, 3.93; N, 12.05.

A second crop (34 g) of oxime, mp 197–200°, was obtained by dilution with water.

3-(3-Pyridyl)-1,2-benzisoxazole (6). A mixture of 36 g of oxime 5, 390 ml of 50% aqueous KOH, and 90 ml of ethylene glycol monomethyl ether was heated under reflux with stirring for 3 hr.[5] After cooling the product was filtered and recrystallized from i-Pr_2O to give 17.2 g (84%) of 6, mp 89–90°.

Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.10; H, 4.25; N, 14.17.

3-(3-Pyridyl 1-oxide)-1,2-benzisoxazole (7). To a solution of 17.0 g (0.087 mol) of 6 in 60 ml of acetic acid was added dropwise 30 ml of 30% H_2O_2 and the mixture was heated for 20 hr at 60°. The mixture was poured into ice water and the precipitated product was recrystallized from benzene–hexane, yield 11.6 g (63%), mp 149–151°.

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.61; H, 3.86; N, 13.21.

Rearrangement of 7 to 2. The 1-oxide 7 (4.2 g, 0.02 mol) was added portionwise to 25 ml of Ac_2O and the mixture was heated under reflux for 3 hr. At the end of 2.5 hr an aliquot was removed, poured into water, made alkaline ($NaHCO_3$), and extracted with $CHCl_3$. The $CHCl_3$ was removed and the residue was examined in the ir, showing carbonyl bands at 5.75 and 6.0 μ. Heating of the main batch was discontinued after 3 hr and the excess Ac_2O was removed in vacuo. To the residue 25 ml of concentrated HCl was added and the mixture was allowed to reflux overnight. A white precipitate formed on pouring the mixture into ice water, which was filtered and recrystallized from EtOH, yield 3.3 g (78%), mp 228–230°. An additional crystallization from EtOH brought the melting point to 230–231°. This product was identical (TLC, mixture melting point, ir, NMR) with the material previously isolated.

3-(2-Chloro-3-pyridyl)-1,2-benzisoxazole (8). A mixture of 8.4 g (0.043 mol) of 2 and 12 g of phenylphosphoric dichloride was heated at 180° for 2.5 hr, poured into water, and warmed on the steam bath to dissolve the tar-like material. After cooling, the solution was basified (NH_4OH) and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with water and concentrated to a residue which was recrystallized from hexane, yield 6 g (66%), mp 92–93°.

Anal. Calcd for $C_{12}H_7ClN_2O$: C, 62.48; H, 3.06; N, 12.15. Found: C, 62.60; H, 3.14; N, 12.31.

This same product was obtained in comparable yield from 2 by refluxing with a large excess of phosphorus oxychloride for 3 hr.

3-(1-Methyl-2-1*H*-pyridinon-3-yl)-1,2-benzisoxazole (9). To a solution of 2.5 g of 2 dissolved in 200 ml of 2 N NaOH was added 5 ml of dimethyl sulfate and the mixture was stirred for 3 hr at room temperature. A heavy white precipitate formed which was filtered and recrystallized from EtOAc–hexane to give 2.0 g of product, mp 146–147°.

Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01: H, 4.46; N, 12.38. Found: C, 69.22; H, 4.37; N, 12.52.

3-(*o*-Hydroxybenzoyl)-2-pyridone (10). 1-Azaxanthone (19.7,

0.1 mol), 50 g of KOH, and 300 ml of EtOH was heated under reflux for 2 hr and poured into water. The clear solution was acidified (HOAc), cooled, and filtered, and the precipitate was washed with water and recrystallized from EtOH, mp 236–238°, yield 16.3 g (76%).

Anal. Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found:, 67.27; H, 4.26; N, 6.72.

3-*o*-Hydroxyphenyl(2-1*H*-pyridinon-3-yl) Ketoxime (3). A solution of 21.5 g (0.1 mol) of ketone **10**, 10.4 g (0.15 mol) of $HONH_2$·HCl, and 36 g of KOH in 200 ml of EtOH was refluxed for 2 hr, poured into 250 ml of H_2O, and acidified (HOAc). The precipitated product was recrystallized from EtOH, mp 257–258°.

This same product was obtained from **10** (0.1 mol) by refluxing with 0.15 mol of $HONH_2$·HCl in 200 ml of pyridine and 100 ml of EtOH.

4-Azaxanthone 5-Oxime. One gram of 4-azaxanthone, 0.5 g of $HONH_2$·HCl, 20 ml of pyridine, and 40 ml of EtOH were refluxed on the steam bath for 6 hr. The excess solvents were removed in vacuo and ice water was added. The product was filtered, washed with H_2O, and recrystallized from dilute EtOH, yield 0.8 g, mp 152–154°.

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.30; H, 3.78; N, 13.47.

2-Azaxanthone 5-Oxime. This compound was prepared by same method as above, yield 0.6 g, mp 259–260°.

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: 67.88; H, 3.66; N, 13.21.

Acknowledgment. The authors are grateful to Professor Sir Derek Barton, Imperial College, London, and to Professor Leon Mandell, Emory University, Atlanta, Ga., for their helpful discussions and suggestions during the course of this work.

Registry No.—**1**, 6537-46-8; **2**, 54999-68-7; **3**, 54999-69-8; **4**, 42374-49-2; **5**, 54999-70-1; **6**, 54999-71-2; **7**, 54999-72-3; **8**, 54999-73-4; **9**, 54999-74-5; **10**, 54999-75-6; **13**, 5698-68-0; **14**, 54999-76-7; **15**, 54629-30-0; **16**, 54999-77-8; 2-bromochlorobenzene, 694-80-4; 3-pyridinealdehyde, 500-22-1; α-(3-pyridyl)-2-chlorobenzyl alcohol, 54999-78-9; 4-azaxanthone 5-oxime, 54999-79-0; 4-azaxanthone, 54629-31-1; 2-azaxanthone 5-oxime, 54999-80-3; 2-azaxanthone, 54629-29-7.

References and Notes

(1) For part 1 in this series see F. J. Villani et al., *J. Med. Chem.*, **18**, 1 (1975).
(2) For convenience and consistent with the numbering system adopted in this and related series of compounds (see ref 1 and references cited therein), we prefer to use the numbering system shown in **1**.
(3) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 4th ed, Wiley, New York, N.Y., 1956, p 255.
(4) P. W. von Ostwalden and J. D. Roberts, *J. Org. Chem.*, **36**, 3792 (1971).
(5) J. F. King and T. Durst, *Can. J. Chem.*, **40**, 882 (1962).
(6) G. A. Archer, A. Stempel, S. S. Ho, and L. H. Sternbach, *J. Chem. Soc. C*, 1031 (1966).

The Behavior of Thioxanthenol Sulfoxides and Related Compounds in 96% Sulfuric Acid[1]

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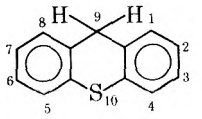
Thioxanthen-9-ol 10-oxides react with 96% sulfuric acid to produce, after quenching, thioxanthone (85%) as the major product. The mechanism, studied by NMR, absorption, and fluorescence spectroscopy, involves the loss of H_3O^+ from sulfinyl-O-protonated thioxanthen-9-ol 10-oxide. Minor components arise via a hydride transfer from starting material to O-protonated thioxanthone. Based upon isotope exchange studies, a thiaanthracene analog of thioxanthenol sulfoxide is considered an unlikely intermediate in this dehydration.

The course of the reaction of derivatives of thioxanthene (**1**) with acids depends upon the nature of both the derivative and the acid. For example, **1** and its 9-alkyl and 9,9-dialkyl derivatives react with "magic acid" to produce the corresponding S-protonated thioxanthene derivatives (and *not* thiaanthracenes).[2] Sulfuric acid converts 9,9-dialkylthioxanthenes into the corresponding *radical cations*.[3] On the other hand, **1**, thioxanthenol (**2**), and thioxanthene sulfoxide (**3**) react with concentrated sulfuric acid to produce the thioxanthylium cation (**4**).[4] In contradistinction, trifluoroacetic acid converts **2**, but not **3**, into **4**.[5]

As part of our continuing study of the chemistry of the thioxanthene ring system and of the reactions of organosulfur compounds in acidic media,[6] we now present an account of the behavior of the isomeric thioxanthenol sulfoxides (**5**)[7] and related compounds in concentrated (96%) sulfuric acid.[8]



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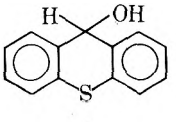

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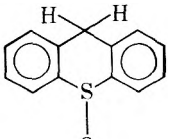
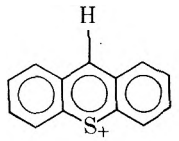


3

Results

cis- or *trans*-thioxanthenol sulfoxide (**5**) reacts with concentrated sulfuric acid (or its deuterated analog) to produce, after 1 hr, a solution whose NMR spectrum is similar to, but not identical with, that of thioxanthone (**6**) in the same medium.[9] A salient difference is the presence, in solutions of **5**, of a highly structured group of absorptions in the aryl region and a sharp singlet at δ 9.98. Both of these features are characteristic of solutions of the thioxanthylium



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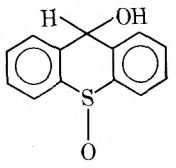
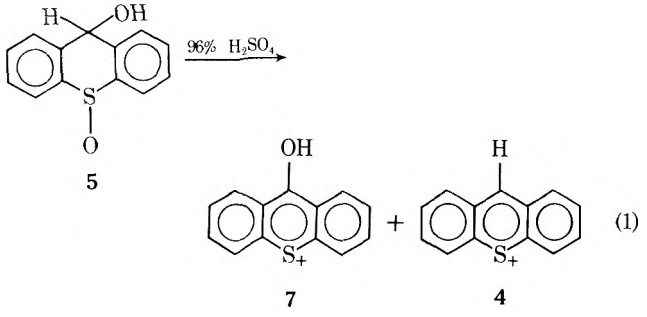


5

cation, 4, in concentrated sulfuric acid.[10] These NMR results suggest, therefore, that the major species present in a solution of *cis*- or *trans*-**5** in 96% sulfuric acid are **4** and O-protonated thioxanthone, **7** (eq 1). The relative integrated



(1)

5 **7** **4**

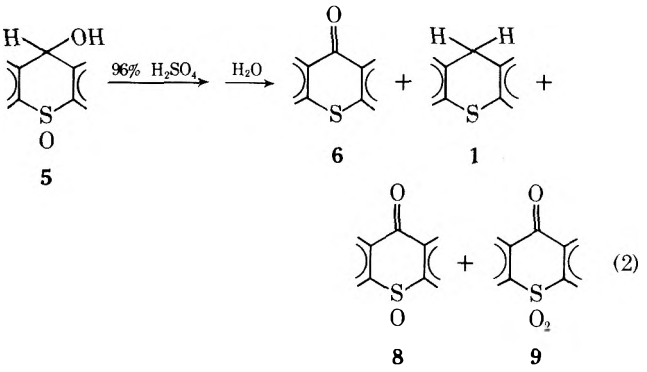
intensity of the singlet at δ 9.98 compared to the integrated intensity of the aryl protons (1:18) implies that the concentration of **4** is slightly less than the concentration of **7** in these solutions.

To test this view, a solution of a mixture of **1** and **6** in 96% sulfuric acid also was examined. (Such a solution is expected to produce a mixture of **4** and **7**.) The NMR spectrum of an approximately equimolar mixture of **1** and **6** in 96% sulfuric acid is different from that of either pure **1** or pure **6** in 96% sulfuric acid but is very similar to that of *cis*- or *trans*-**5** in this medium. This, therefore, supports our contention.

The presence of **4** and **7** in solutions of **5** in 96% sulfuric acid is further supported by ultraviolet spectral data. A solution of both **1** and **6** in 96% sulfuric acid (0.25×10^{-5} and 0.5×10^{-5} *M*, respectively) exhibits an ultraviolet spectrum which, after 24 hr, is almost indistinguishable from that of a solution of **6** in 96% sulfuric acid and also is very similar to a 24 hr old solution of **5** in sulfuric acid. At concentrations of 0.75×10^{-5} *M*, *cis*- and *trans*-**5** react with 96% sulfuric acid to produce solutions with a weak, broad absorption band (219–223 nm) which disappears with time.[11] In addition to this change, weak bands at 242 and 349 nm, and a strong band at 275 nm, appear with time. (The electronic absorption spectrum appears to be nearly constant after 3 hr.) Using a 5×10^{-5} *M* solution, three bands appear in the visible region with time (381, 448, and 469 nm). All of these are ascribable to either **4** or **7**. The changes in the ultraviolet spectrum of **5** pass through an isosbestic point at 236 nm.

The fluorescence excitation spectrum of either *cis*- or *trans*-**5** (0.75×10^{-5} *M*) in 96% sulfuric acid initially has peaks corresponding to the absorption spectrum (275, 350, 380, 450, and 470 nm). The peaks grow with time but eventually reach maximum intensities. The fluorescence emission spectrum also changed with time and appeared eventually to correspond closely to that of **7** obtained from solutions of **6** in 96% sulfuric acid.

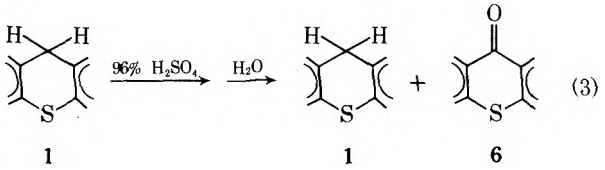
Quenching a solution of either *cis*- or *trans*-**5** in 96% sulfuric acid with water produces about 85% **6** and lesser amounts of **1** and thioxanthone sulfoxide (**8**) (eq 2). In addition, *trace* amounts of what appeared to be thioxanthone sulfone (**9**) also were detected (TLC).



(2)

5 **6** **1** **8** **9**

Dilution, with water, of a 10% solution of **1** in 96% sulfuric acid, which was 24 hr old, produces a mixture of **1**, **6**, and three *trace* components (eq 3). One of these was iden-



(3)

1 **1** **6**

tified (TLC) as **8**. As already noted,[9] **6** is recovered quantitatively from solutions of **6** in 96% sulfuric acid.

Because they were detected as minor products of the reaction of water with solutions of **5** in 96% sulfuric acid, the behavior of **8** and **9** in 96% sulfuric acid also was examined. Dilution, with water, of a 10% (w/v) solution of **8** in 96% sulfuric acid which had been stored for 15 min at 25° produces a very large quantity of starting material along with a small amount of **6**. A third, trace component was identified (TLC) as **9**. The NMR spectrum of **8** in 96% sulfuric acid, taken immediately after preparation of the solution, is not unlike that of **8** in deuteriochloroform or in deuteriochloroform containing 10% of 96% sulfuric acid. Thus, a 10% (w/v) solution of **8** in 96% sulfuric acid exhibits two structured multiplets at δ 7.9–8.4 and 8.4–8.8 (external Me_4Si). In deuteriochloroform **8** exhibits the corresponding multiplets at δ 7.6–8.1 and 8.1–8.5 (internal Me_4Si).

A solution of **8** (2.5×10^{-5} *M*) in 96% sulfuric acid exhibits an initially strong absorption at 246 nm, a weak absorption at 274 nm, and a very broad band at 320 nm. The spectrum changes slowly with time—the peak at 246 nm diminishes slightly, the absorption at 320 nm increases slightly, and the maximum at 274 nm increases greatly. Absorptions at 445 and 469 nm appear in the visible region with the passage of time, using solutions of 5×10^{-5} *M*.

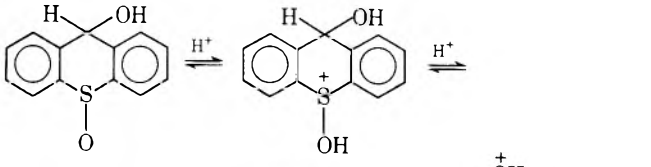
Dilution, with water, of a 5% (w/v) solution of **9** in 96% sulfuric acid which was 24 hr old produces essentially pure (TLC) starting material. A solution of **9** (0.5×10^{-5} *M*) in 96% sulfuric acid possesses an absorption spectrum with broad bands at 268 and 305 nm. Electronic absorption spectra of such solutions are time-invariant.

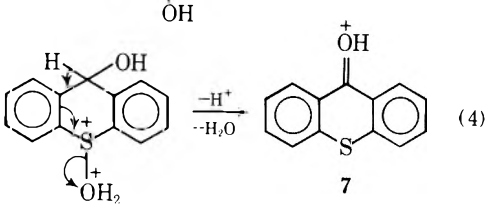
Discussion

The data presented above indicate that either *cis*- or *trans*-thioxanthenol sulfoxide (**5**) is dehydrated by 96% sulfuric acid to produce, after dilution with water, thioxanthone (**6**) along with lesser amount of thioxanthene (**1**), thioxanthone sulfoxide (**8**), and *traces* of thioxanthone sulfone (**9**).[12] Both absorption and fluorescence spectra and the NMR data indicate that the major species present in solutions of **5** in 96% sulfuric acid are O-protonated thioxanthone (**7**) and the thioxanthylium ion (**4**). The isomers of **5** may be viewed as hydrates of **6** and their dehydration in sulfuric acid is not, therefore, unexpected.[13] However, the

formation of **1** and **8** is somewhat surprising and suggests a process which has a competing redox component.

The sequence presented below (eq 4–6) accounts for the





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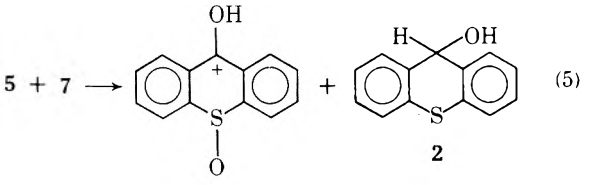
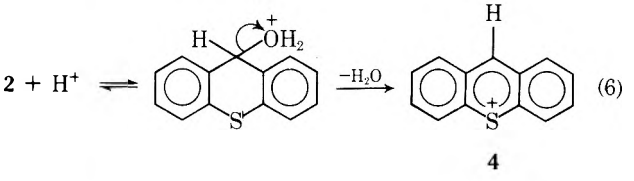


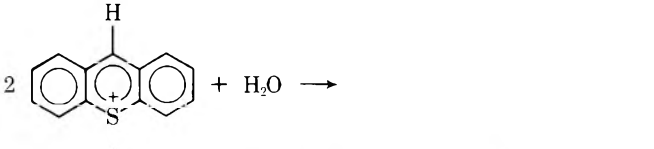
(5)



(6)

formation of the major species (i.e., **4** and **7**) observed in solutions of **5** in sulfuric acid and, when considered in light of eq 7, accounts for the major product isolated when these solutions are quenched with water. While this scheme requires the presence of O-protonated thioxanthone sulfoxide (**10**) in solutions of **5** in 96% sulfuric acid, the spectral properties of **4** and **7**, when coupled with the large quantity of these present, make it difficult to establish unequivocally that a small quantity of **10** is present in these solutions.

The **6** which is formed upon addition of water to these solutions has at least two origins. First, there is the deprotonation of **7** (eq 4) with water. Second, **4** reacts with water to produce **2**, which is known to disproportionate under a variety of conditions,[14] including the presence of acid,[4] to yield **1** and **6**. The disproportionation of **4** (eq 7) also ac-

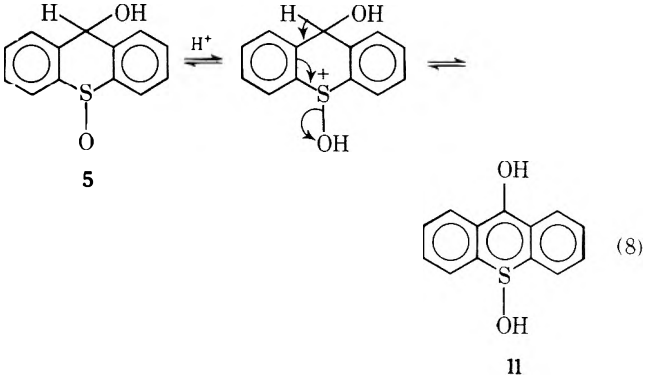


(7)

counts for the formation of **1** upon addition of water to solutions of **5** in sulfuric acid.

A hydride transfer between **5** and **7**, similar to that between **4** and **2**,[4] leads to **10** (eq 5) and deprotonation of **10** by water affords **8**. The production of traces (<1%) of **9** is more difficult to explain and we are not yet able to set out reliably the way in which it was formed in these systems.

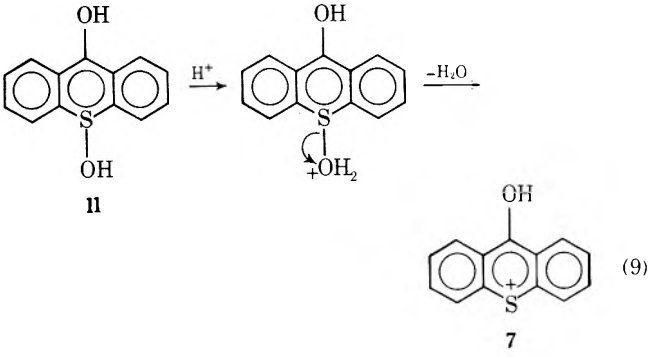
One may view thioxanthone sulfoxide as a thiaquinone, i.e., as a sulfur analog of anthraquinone.[15] This idea is supported by the formation[16] of the radical anion of **8**. This same species also is presumed to be formed during the base-catalyzed dehydration of **5**.[13] One might, as an extension of this idea, suggest that thioxanthenol sulfoxides are isomeric tautomers of the corresponding hydroquinone, **11**. Thus far we have not been able to detect **11** in solutions of either isomer of **5** in a variety of organic solvents or in the solid state.[5,7] The NMR spectra of solutions of **5** in solvents such as CCl_4, CS_2, $CDCl_3$, and C_6D_6 display characteristics of a secondary diarylcarbinol (a methine proton and, where detectable, an O–H resonance). One might, however, suggest that in a strongly acidic medium **5** could be protonated at the sulfinyl oxygen[6] and, by deprotonation at C-9, convert to **11** (eq 8).



(8)

Our observation that the NMR spectrum of **5** in D_2SO_4 exhibits the C-9 H resonance characteristic of the thioxanthylium ion (**4**) suggests that **11** is *not* in rapid equilibrium with **5** in this medium. Had the equilibrium depicted in eq 8 been established rapidly, the **4** produced in the reaction of **5** with deuterated sulfuric acid should have lacked a proton at C-9.

To the extent that **11** can be precluded in this equilibrium, it seems reasonable that **11** does not serve as a significant precursor to **7** in sulfuric acid even though one can construct a pathway for converting **11** to **7** (eq 9). This is



(9)

consistent with the view that compounds such as **11** should not be viewed as aromatic (i.e., highly stabilized) sulfur analogs of anthracene.[17]

Experimental Section

Syntheses. All of the compounds employed in this study have already been described.[4,5,7]

Electronic Spectra.[19] The various compounds were dissolved in 95% ethanol and diluted to an appropriate concentration. An aliquot was pipetted into a volumetric flask and evaporated to dryness to leave a film of substance on the surface of the flask. Sulfuric acid was added to the mark and the solutions were transferred to 1-cm, ground-glass stoppered cells. Absorption spectra were recorded on a Beckman Model DK-2A or a Cary Model 15; fluorescence spectra were recorded on an Aminco-Bowman spectrofluorometer.

Nuclear Magnetic Resonance Spectra. Solutions were prepared by dissolving the sample directly in the solvent in the NMR

tube. Spectra were recorded (Varian Models A-60, T-60, and Ha-100) within 5 min of the preparation of the solution unless otherwise indicated.

Thin Layer Chromatography. Thin layer chromatographies were performed employing glass plates coated with 0.25 mm of Kieselgel (A. H. Thomas Co.). Elution was accomplished with benzene, chloroform, ethyl acetate, and chloroform–ethyl acetate (5:1) mixtures. Substances were identified by comparing their R_f values with those of authentic compounds on the same chromatogram. Visualization was achieved using both ultraviolet light and iodine vapor.

In a typical experiment, 80–100 mg of a substance was dissolved in 0.3 ml of sulfuric acid and, after 5 min, the resulting solution was diluted with water. The resultant solid was removed by filtration and dissolved in chloroform, and the solution was analyzed by TLC as described above. An alternate work-up procedure, involving extraction of the aqueous phase with methylene chloride, produced identical results.

Reaction of Thioxanthenol Sulfoxide (5) with 96% Sulfuric Acid. Product Study. A 10% solution of **5** in 96% sulfuric acid was maintained at 26° for 7 days. The solution was diluted with water and the resulting solid was removed by filtration. A solution of this solid in methylene chloride was analyzed by TLC as described above, using several eluents including ethyl acetate. The major component was found to be thioxanthone (**6**), with other spots being ascribed to **1**, **5**, and **8**. A *very* weak spot had an R_f value similar to that of **9** and is assigned to **9**. Several different reactions afforded 80–85% **6** after recrystallization from ethanol.

Reaction of *cis*-5 with 96% Sulfuric Acid. NMR Analysis. A small amount of *cis*-**5** was added to frozen sulfuric acid in an NMR tube. The sample was placed in the probe and spectra were obtained periodically. Initially, the solution contained an aryl multiplet extending from δ 7.66 to 8.49 and a singlet at δ 6.88. After 1 hr, the structure of the multiplet had altered and its position "shifted" to δ 7.84–9.02. This was accompanied by the disappearance of the singlet at δ 6.88 and the appearance of a singlet at δ 9.98. The singlet at δ 6.88 is ascribed to C-9 H of the starting material while the singlet at δ 9.98 is ascribed to C-9 H of **4**.

Acknowledgments. The research at the University of Texas at Arlington was supported by Grant Y-484 from the Robert A. Welch Foundation; the NMR spectrometer was purchased by an award from the Research Corporation. This support is gratefully acknowledged. Support at Texas Tech University by the Robert A. Welch Foundation (Grant D-028) is gratefully acknowledged. We thank Dr. W. Kurtin (now at Trinity University, San Antonio, Texas) for the fluorescence spectra.

Registry No.—*cis*-**5**, 13096-56-5; *trans*-**5**, 13096-57-6.

Supplementary Material Available. Full electronic spectral data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1737.

References and Notes

(1) A portion of this work was presented at the VI Symposium on Organic Sulphur Chemistry, Bangor, Wales, July 1974.
(2) D. Deavenport, S. A. Evans, and A. L. Ternay, Jr., manuscript in preparation.
(3) D. Deavenport, J. T. Edwards, A. L. Ternay, Jr., E. T. Strom, and S. A. Evans, *J. Org. Chem.*, **40**, 103 (1975).
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(5) A. L. Ternay, Jr., and D. W. Chasar, *J. Org. Chem.*, **33**, 3641 (1968).
(6) For reviews of this area see, for example, (a) H. J. Shine, *Organosulfur Chem.*, 93 (1967); (b) G. Modena, *Int. J. Sulfur Chem., Part C*, **7**, 95 (1972).
(7) A. L. Ternay, Jr., D. W. Chasar, and M. Sax, *J. Org. Chem.*, **32**, 2465 (1967).
(8) In an earlier report[5] we noted that *cis*- and *trans*-**5** are converted to a mixture (1:4) of the corresponding *cis*- and *trans*-**9**-trifluoroacetoxythioxanthene sulfoxides in trifluoroacetic acid.
(9) Solutions of **6** in sulfuric acid are known[4] to produce only O-protonated thioxanthone (the 9-hydroxythioxanthylium ion, **7**). These solutions, which have absorption maxima at 218, 243, 274, 348, 448, and 469 nm, do not change their absorption spectra with time. Dilution with water of a 5% (w/v) solution of **6** in 96% sulfuric acid which was 24 hr old produces essentially pure (TLC) **6**.
(10) Solutions of **4** in 96% sulfuric acid may be produced by dissolving **1** in the acid.[4] These solutions exhibit a characteristic C-9 H methine resonance near δ 10. A solution of **1** in 96% sulfuric acid (0.75×10^{-5} *M*) has a fluorescence excitation spectrum with maxima at 260 and 380 nm and a broad band with maxima at 475 and 525 nm. The fluorescence emission spectrum of this solution exhibits a slender peak with a maximum at 545 nm.
(11) This corresponds to unreacted starting material.
(12) *cis*- and *trans*-**9**-trimethylsiloxythioxanthene sulfoxides react with sulfuric acid to produce, after dilution with water, **6**, **1**, and **8**. Another component, identified as **9** by TLC, was produced in *trace* quantities: A. L. Ternay, Jr., and D. W. Chasar, unpublished results.
(13) Thioxanthenol sulfoxide dehydrates in alkaline solution: A. L. Ternay, Jr., and D. W. Chasar, *J. Org. Chem.*, **32**, 3814 (1967).
(14) Thioxanthenol is converted to **1** and **6** during gas chromatography: A. L. Ternay, Jr., unpublished results.
(15) A. L. Ternay, Jr., and D. W. Chasar, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, No. 0-105.
(16) A. Trifunac and E. T. Kaiser, *J. Phys. Chem.*, **74**, 2236 (1970).
(17) A 1,4-sigmatropic shift of a hydroxy group from sulfur to C-9 could, in principle, convert **11** to **7** via the *gem*-diol of **6**. This would parallel the mechanism of the isomerization of *S*-alkyl "thiaanthracenes" to 9-alkylthioxanthenes.[18] However, our inability to detect **4** containing a deuteron at C-9 where dehydration is carried out in 96% D_2SO_4 (this manuscript) *and* our inability to detect even the transient formation of "thiaanthracene" from 9,9-dideuterothioxanthene and HSO_3F–SbF_5–SO_2 (−50°) suggest that this is unlikely.[2] We are grateful to Professor Mislow for discussions of his results with us.
(18) G. H. Senkler, Jr., J. Stackhouse, B. E. Maryanoff, and K. Mislow, *J. Am. Chem. Soc.*, **96**, 5650 (1974), and subsequent papers in this series.
(19) See paragraph at end of paper regarding supplementary material.

Synthesis and Rearrangement of Glycidic Thiol Esters. Migratory Aptitudes[1]

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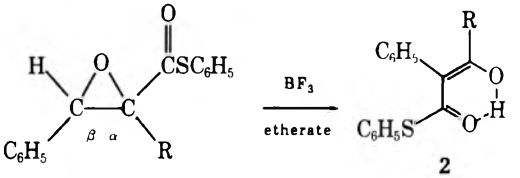
The boron trifluoride etherate induced rearrangement of glycidic thiol esters has been studied. Migration of an α substituent occurs in those cases where at least one phenyl or two methyl groups are attached to the β position of the thiolglycidate allowing for stabilization of positive charge at the β position when the epoxide ring is opened by the Lewis acid. 3-Phenylthiolglycidates (**4a** and **4c**) undergo rearrangement with thiol ester group migration in preference to migration of the α-hydrogen atom to give the corresponding β-oxo thiol esters (**5a** and **5c**), respectively. However, the α-phenyl group migrates in preference to the thiol ester function in the rearrangement of *S*-phenyl 3,3-dimethyl-2-phenylthiolglycidate (**4d**) to give thiolpyruvate (**14**) as the major product. In one example involving the rearrangement of *S*-phenyl 2-phenylthiolglycidate (**4e**) to form β-oxo thiol ester (**2a**), a β hydrogen serves as the migrating group. The rearrangement of **4e** also gives a smaller amount of β-lactone **16**, formed in a novel ring expansion reaction involving the shift of the phenylthio group to the α position.

Intramolecular Wagner–Meerwein rearrangement processes involving a 1,2 migration to an electron-deficient center have been studied extensively. It is well known that aryl groups, alkyl groups, and hydrogen atoms may serve as migrating groups in this reaction. More recently a large variety of electron-withdrawing substituents have been observed to function as migrating groups, including ketone,[2] ester,[3] amide,[4] amidate,[5] nitrile,[6] phosphonate ester,[7] phosphinyl,[8] sulfoxide,[9] sulfone,[9] nitro,[10] and halogen groups.[11] In this connection the rearrangement of epoxides substituted with electron-withdrawing groups has received the greatest attention. We have been interested in the synthesis and chemistry of glycidic thiol esters (**1**). These compounds undergo boron trifluoride induced rearrangement with thiol ester group migration to give the enol tautomer (**2**) of the corresponding β-oxo thiol ester.[12] This is the first reported example of migration of the thiol ester function during a nonenzymatic rearrangement process.[13]



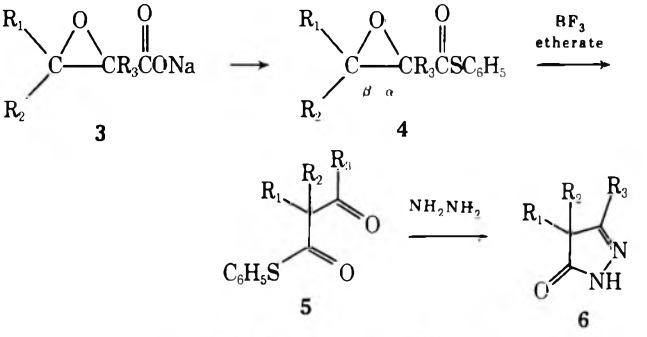
1a, R = H
b, R = CH_3

2

We wish to report here on the migratory aptitude of the thiol ester group relative to other groups such as methyl, phenyl, hydrogen, and carbethoxy. Similar studies on the migratory aptitude of ketone[2b] and carbethoxy groups[3a] in related epoxide rearrangement processes have been reported. Also with the recent development of a high-yield procedure for the preparation of thiolglycidates,[14] the BF_3-induced rearrangement of glycidic thiol esters provides a convenient synthetic route to β-oxo thiol esters and also certain α-keto thiol esters. Despite the importance of these functional groups in biological systems, relatively few methods have been found for their preparation.[15,16]

Results and Discussion

Initially we synthesized glycidic thiol esters from the corresponding salts using thionyl chloride or oxalyl chloride Schotten–Baumann procedures. The oxalyl chloride method that we used is similar to that developed by Speziale and Frazier[17] for the synthesis of glycidamides. Thus, for example, glycidic thiol esters **4a** and **4b** were prepared by allowing glycidate salts **3a** and **3b** to react with oxalyl chloride in benzene followed by treatment with benzenethiol and pyridine in ether solvent. Glycidic thiol ester **4c** was prepared by treatment of **3c** with *S*-phenyl thiolchlorocarbonate in tetrahydrofuran at 0°.



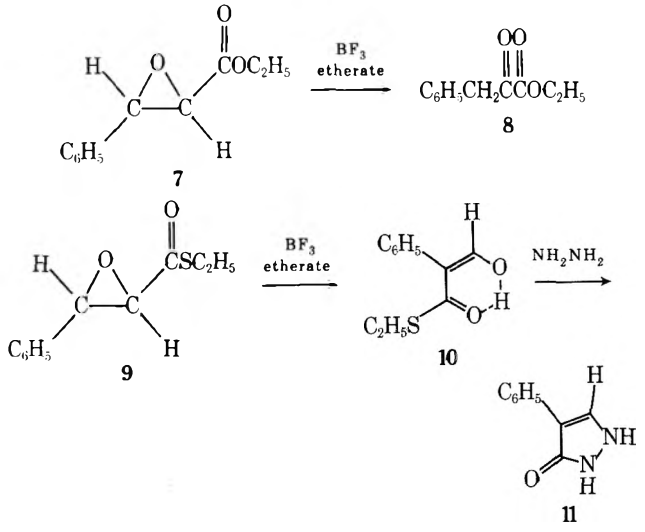
a, $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = H$
b, $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = CH_3$
c, $R_1 = C_6H_5$; $R_2 = C_6H_5$; $R_3 = H$

All of the BF_3-induced rearrangements of glycidic thiol esters that we have studied were found to proceed rapidly (within 30 min or less) when the glycidic thiol esters (**4**) were treated with excess boron trifluoride etherate (4 equiv) in ether solvent at room temperature. These conditions were used by House[2] in the rearrangement of α,β-epoxy ketones, although stronger conditions were needed in some cases. Somewhat more severe conditions involving BF_3 gas in benzene solvent were used by Kagan and Singh[3a] in the rearrangement of glycidic (oxygen) esters. The rearrangement products obtained in our study were isolated in high yield by evaporation of the ether solvent followed by direct column chromatography on silica gel.

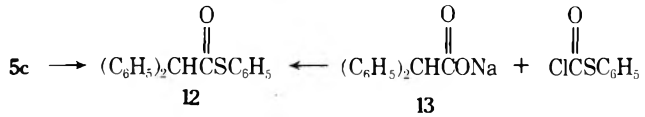
The BF_3-induced rearrangement of *S*-phenyl 3-methyl-3-phenylthiolglycidate (**4a**) gave *S*-phenyl 2-methyl-2-phenyl-3-oxopropanethioate (**5a**) as the major product (87%). In a similar way thiolglycidate **4b** gave β-keto thiol ester **5b** in 91% yield. The structure of the rearrangement products, **5a** and **5b**, were established on the basis of spectral data and by conversion to the corresponding 2-pyrazoline-5-ones, **6a** and **6b**, by treatment with hydrazine hydrate in ethanol. The formation of **5a** from **4a** may be explained by assuming initial opening of the epoxide ring by the Lewis acid followed by 1,2 migration of the thiol ester function from the α to the electron-deficient β carbon atom.[18] We have reported earlier that **1a** and **1b** undergo rearrangement to give **2a** and **2b** involving migration of the thiol ester function.[12] These results together with the results presented here suggest that the *S*-phenyl thiol ester function has higher migratory aptitude than methyl or hydro-

gen in the BF_3-induced rearrangement of glycidic thiol esters. A similar preference for carbonyl group migration has been observed in the rearrangement of chalcone epoxides.[2b] In the case of glycidic esters the carbethoxy group migrates in preference to methyl in the BF_3-induced rearrangement of ethyl 2-methyl-3-phenylglycidate.[3a,19]

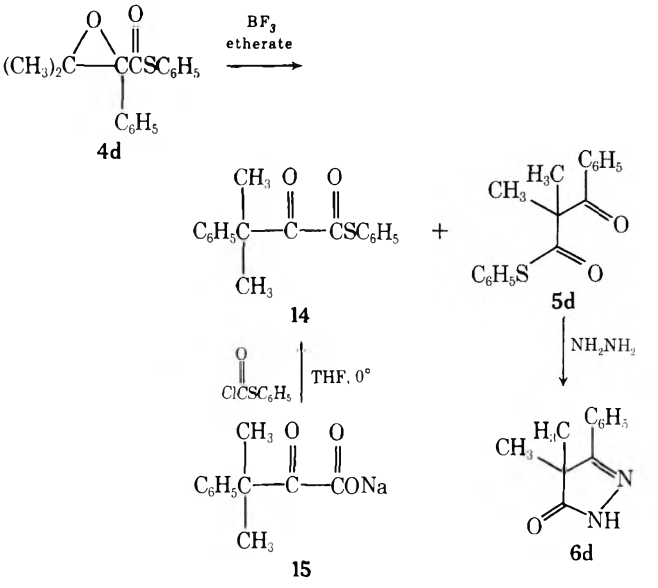
Interestingly the rearrangement of ethyl 3-phenylglycidate (**7**) has been reported to give ethyl 3-phenylpyruvate (**8**) involving apparent migration of the α hydrogen.[3a] In this connection we have examined the rearrangement of *S*-ethyl 3-phenylthiolglycidate (**9**). Rearrangement of **9** gave primarily the enol tautomer of *S*-ethyl 2-phenyl-3-oxopropanethioate (**10**). It is probable that the thiol ester group migrates in the conversion of **9** to **10** in view of the fact that we have already shown with a ^{14}C labeling study[12b] that the thiol ester group and not the β-phenyl group migrates in the corresponding conversion of *S*-phenyl ester **1a** to **2a**. In any case, when these results are compared to those obtained by Kagan and Singh[3a] they suggest that the presence of the sulfur atom has a major influence on the migratory aptitude of the thiol ester function in this system.



Furthermore, these results support the conclusion that the thiol ester group has higher migratory aptitude than the normal (oxygen) ester in these rearrangement reactions. In agreement with this interpretation we find that *S*-phenyl 3,3-diphenylthiolglycidate (**4c**) underwent BF_3-induced rearrangement with thiol ester group migration to give *S*-phenyl 2,2-diphenyl-3-oxopropanethioate (**5c**) in 85% yield. In contrast, ethyl 3,3-diphenylglycidate rearranges in the presence of HCl at 200° to give ethyl diphenylpyruvate involving migration of a hydrogen atom.[20] The structure of **5c** was established by deformylation using the method of House[2a] to give *S*-phenyl diphenylethanethioate (**12**). **12** was synthesized independently from sodium diphenylacetate (**13**) and *S*-phenyl thiolchlorocarbonate.

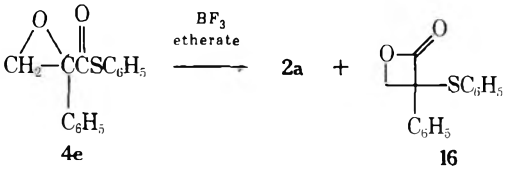


Also in this connection we have examined the rearrangement of *S*-phenyl 3,3-dimethyl-2-phenylthioglycidate (**4d**). Two products, thiolpyruvate **14** (80% yield) and β-keto thiol ester **5d** (10% yield), were obtained. The structure of **14** was established by independent synthesis involving treatment of sodium 3,3-dimethyl-3-phenylpyruvate (**15**) with *S*-phenyl thiolchlorocarbonate in THF at 0°. The BF_3-induced rearrangement of **4d** to **5d** would appear to involve migration of the thiol ester function. This is noteworthy[3d] in view of the fact that it is the first reported case where a carbonyl group has been found to compete with phenyl as the migrating group in the rearrangement of α,β-epoxy carbonyl systems. In contrast only the phenyl group has been observed to migrate in the BF_3-induced rearrangement of ethyl 2-phenyl-3,3-dimethylglycidate.[3a] The major product obtained from the rearrangement of **4d** is thiolpyruvate **14**, which would result from migration of the α-phenyl. This suggests that the α-phenyl group has higher migratory aptitude than the thiol ester function in the rearrangement of α-phenyl glycidic thiol esters.



In summary, in the BF_3-induced rearrangement of *S*-phenyl glycidic thiol esters involving shifts from the α position to the electron-deficient β carbon atom, the relative migratory aptitudes would be as follows: phenyl > *S*-phenyl thiol ester > methyl or hydrogen. A similar order has been found for the benzoyl group in the rearrangement of chalcone epoxides[2b] and for the carbethoxy group in the rearrangement of glycidic esters.[3a] We have also obtained results that suggest that the thiol ester group has higher migratory aptitude than the carbethoxy group in these rearrangement reactions.

House[2c] has shown that the BF_3-induced rearrangement of 2,3-epoxy-2-phenylpropiophenone leads to initial generation of positive charge at the α position owing to resonance stabilization by the α-phenyl substituent. One of the β hydrogen atoms then migrates to the α position (or alternatively the hydrogen is lost as a proton) to give after work-up with phenylhydrazine the corresponding pyrazole derivative of α-formyldeoxybenzoin. In a similar manner ethyl 2-phenylglycidate is converted into ethyl 2-phenyl-3-oxopropanoate, although in low yield.[3a] We have found that the rearrangement of *S*-phenyl 2-phenylthiolglycidate (**4e**) provides a similar rearrangement product, **2a**, in 55% yield. We also isolated from this rearrangement reaction β-lactone **16** in about 20% yield. The structure assignment



for **16** is based on elemental analysis and spectral data. The ir spectrum shows a β-lactone carbonyl at 1815 cm^{-1} while the NMR spectrum shows an AB quartet at δ 4.47 and 4.61 (J_{AB} = 5.5 Hz). In the mass spectrum the molecular ion oc-

curs at *m/e* 256 while the base peak is at *m/e* 212 ($M^{\cdot+} - CO_2$). We would rationalize the formation of **16** by initial attachment of the BF_3 catalyst to the thiol ester carbonyl oxygen atom followed by intramolecular coordination of the electrophilic carbonyl carbon with the epoxide oxygen atom resulting in opening of the epoxide ring and formation of the four-membered ring. A 1,2 shift of the phenylthio group to the α-carbon position would generate β-lactone **16**. Migration of the phenylthio group and formation of the four-membered ring may occur simultaneously. The conversion of **4e** to **16** represents a novel ring expansion reaction not previously observed in the Lewis acid induced rearrangement of other α,β-epoxy carbonyl systems.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60A spectrometer using tetramethylsilane (Me_4Si) as an internal standard except where otherwise noted. Mass spectral analysis was performed on a Varian MAT CH-5 instrument. THF was dried over sodium metal–anthracene complex and distilled prior to use. Benzene was dried over sodium metal while ether was dried over $LiAlH_4$. Both were distilled prior to use. The petroleum ether had a boiling point range of 60–110°. The silica gel used for column chromatography was Baker reagent grade (60–200 mesh). Merck silica gel GF-254 was used for preparative thin layer chromatography. Melting points and boiling points are uncorrected. The elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. *S*-Phenyl thiolchlorocarbonate was purchased from Columbia Organic Chemicals Co.

Sodium 2,3-dimethyl-3-phenylglycidate (3b), believed to be the trans (*E*) isomer, was obtained from a mixture of sodium (*E*)- and (*Z*)-2,3-dimethyl-3-phenylglycidate[21] by fractional crystallization from ethanol and water as colorless plates: mp 314–316° dec; NMR (D_2O, Me_4Si external standard) δ 7.30 (s, 5 H), 1.53 (s, 3 H), 1.10 (s, 3 H).

***S*-Phenyl 3-Methyl-3-phenylthiolglycidate (4a).** Sodium 3-methyl-3-phenylglycidate (**3a**,[22] 2.25 g, 0.011 mol) was suspended in anhydrous benzene (25 ml) under nitrogen at 0°. This was treated with pyridine (3–5 drops) followed by the dropwise addition over a period of 1 hr of freshly distilled oxalyl chloride (2.22 g, 0.0175 mol) in benzene (5 ml). The reaction mixture was stirred at 0° for 30 min and the benzene was removed by evaporation under reduced pressure maintaining the temperature below 15°. Fresh benzene (20 ml) and pyridine (3–5 drops) were added and then evaporated under reduced pressure. Anhydrous ether was added to the residue and the temperature was lowered to −40 to −50°. Benzenethiol (1.00 g, 0.0091 mol) in ether (5 ml) and pyridine (0.92 g, 0.012 mol) in ether (5 ml) were added dropwise separately and simultaneously over a period of 20 min. The reaction mixture was stirred at −40 to −50° for an additional 2 hr and then warmed to room temperature before water (25 ml) was added. The ether layer was separated and the water was reextracted with ether (25 ml). The combined ether extracts were dried (Na_2SO_4) and concentrated and the crude product was subjected to column chromatography on silica gel eluting with petroleum ether followed by benzene–petroleum ether, which upon evaporation gave what is believed to be the trans (*E*) isomer of **4a** (1.16 g, 4.3 mmol, 38%). Recrystallization (*n*-hexane and benzene) gave colorless needles: mp 68–69°; NMR (CCl_4) δ 7.33 (s) and 7.27 (s) (10 H), 3.48 (s, 1 H), 1.83 (s, 3 H); ir (KBr) 1690 cm^{-1} (broad).

Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86. Found: C, 71.33; H, 5.14; S, 11.69.

***S*-Phenyl 2,3-dimethyl-3-phenylthiolglycidate (4b),** believed to be the trans (*E*) isomer, was obtained using a similar procedure from sodium 2,3-dimethyl-3-phenylglycidate (**3b**), oxalyl chloride, benzenethiol, and pyridine in 17% yield. Recrystallization (*n*-hexane and benzene) gave colorless needles: mp 61–62°; NMR (CCl_4) δ 7.33 (s) and 7.26 (s) (10 H), 1.78 (s, 3 H), 1.18 (s, 3 H); ir (KBr) 1690 cm^{-1} (broad).

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28. Found: C, 71.66; H, 5.40; S, 11.13.

***S*-Phenyl 2-phenylthiolglycidate (4e)** was obtained using a similar procedure from sodium 2-phenylglycidate,[23] oxalyl chloride, benzenethiol, and pyridine in 35% yield. Recrystallization (*n*-hexane and benzene) gave colorless plates: mp 55.5–57°; NMR (CCl_4) δ 7.42 (s) superimposed on a multiplet 7.80–7.20 (10 H), 3.35 (d, 1 H, J = 6.5 Hz), 2.97 (d, 1 H, J = 6.5 Hz); ir (KBr) 1690 cm^{-1} (broad).

Anal. Calcd for $C_{15}H_{12}O_2S$: 70.29; H, 4.72; S, 12.51. Found: C, 70.11; H, 4.84; S, 12.32.

***S*-Phenyl 3,3-Diphenylthiolglycidate (4c).** Sodium 3,3-diphenylglycidate (**3c**,[20] 2.62 g, 0.010 mol) was suspended in dry THF (30 ml) under nitrogen atmosphere at 0°. It was treated with pyridine (3–5 drops) followed by the dropwise addition over a period of 30 min of *S*-phenyl thiolchlorocarbonate (1.72 g, 0.010 mol) in dry THF (5–10 ml). The reaction mixture was stirred for 30 min at 0° and then at room temperature for an additional 60 min before it was poured into cold water (200 ml) and ether (200 ml). The ether layer was separated and the water layer was extracted again with ether (100 ml). The combined ether extracts were dried (Na_2SO_4) and concentrated to give an oil which was subjected to column chromatography on silica gel eluting with petroleum ether followed by benzene–petroleum ether (1:1) to collect the product (2.4 g, 0.0072 mol, 72%). Recrystallization (*n*-hexane and benzene) gave pure **4c** as colorless plates: mp 93–95°; NMR (CCl_4) δ 7.22 (s) superimposed on multiplet 7.60–6.70 (15 H), 3.90 (s, 1 H); ir (KBr) 1675 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}O_2S$: C, 75.87; H, 4.85; S, 9.65. Found: C, 75.67; H, 4.58; S, 9.51.

***S*-Phenyl 2-phenyl-3,3-dimethylthiolglycidate (4d)** was obtained in a similar manner from sodium 2-phenyl-3,3-dimethylglycidate[21] and *S*-phenyl thiolchlorocarbonate in 72% yield. Recrystallization (*n*-hexane and benzene) gave colorless needles: mp 66–67°; NMR ($CDCl_3$) δ 7.28 (s) superimposed on multiplet at 7.65–7.10 (10 H), 1.62 (s, 3 H), 1.07 (s, 3 H); ir (KBr) 1700 cm^{-1} (broad).

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; H, 11.28. Found: C, 72.01; H, 5.65; S, 11.11.

Rearrangement of 4a. Boron trifluoride etherate (0.55 ml, 4.4 mmol) was added to **4a** (0.298 g, 1.1 mmol) in dry ether (15 ml) under nitrogen atmosphere and the reaction was stirred at room temperature for 30 min before concentrating under reduced pressure. The residual oil was subjected to column chromatography on silica gel eluting with benzene. Concentration of the benzene eluent containing the product gave *S*-phenyl 2-methyl-2-phenyl-3-oxopropanethioate (**5a**) as a faint yellow oil (0.260 g, 0.96 mmol, 87%): NMR (CCl_4) δ 10.00 (s, 1 H), 7.42 (s) and 7.25 (s) (10 H), 1.83 (s, 3 H); ir (thin film) 1725, 1685 cm^{-1}.

The product (0.260 g, 0.96 mmol) in ethanol (3 ml) was treated with hydrazine hydrate (0.20 g, 4.0 mmol) and the solution was refluxed for 20 min and then allowed to stand at room temperature. Crystals began to form after approximately 1 day. After 3 days the crystalline derivative was washed with warm hexane (to remove diphenyl disulfide) and recrystallized from ethanol and water to give 4-methyl-4-phenyl-2-pyrazolin-5-one (**6a**), mp 101–102° (lit. mp 99–101°,[24] 107–110°[25]).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.20; H, 5.61; N, 15.89.

Rearrangement of 4b. Using the same general procedure **4b** was converted to *S*-phenyl 2-methyl-2-phenyl-3-oxobutanethioate (**5b**), which was obtained as a faint yellow oil in 91% yield. **5b** crystallized after trituration with ether. Recrystallization from *n*-hexane gave pure **5b**: mp 65–66°; NMR (CCl_4) δ 7.32 (s) and 7.28 (s) (10 H), 2.07 (s, 3 H), and 1.85 (s, 3 H); ir (thin film) 1715, 1685 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28. Found: C, 71.73; H, 5.78; S, 11.22.

5b was converted to 3,4-dimethyl-4-phenyl-2-pyrazolin-5-one (**6b**) on treatment with hydrazine hydrate in ethanol. Recrystallization from ethanol and water gave colorless plates, mp 156–158° (reported[26] mp 158–159°). The mixture melting point with an authentic sample (mp 156–158°) prepared from hydrazine hydrate and ethyl 2-methyl-2-phenyl-3-oxobutanoate[3a] in ethanol was not depressed.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.99; H, 6.66; N, 14.80.

Rearrangement of 9. Using the same general procedure 9[14] was converted to the *Z* enol tautomer of *S*-ethyl 2-phenyl-3-oxopropanethioate (**10**). It was necessary to purify this product further by a second column chromatography on silica gel eluting with benzene–petroleum ether (1:1) followed by short-path distillation (bath temperature 115–120°, 0.4 mm) to give the product as a faint yellow oil in 53% yield: NMR (CCl_4) δ 12.30 (d, 1 H, J = 12.0 Hz), 7.22 (s, 5 H), 6.90 (d, 1 H, J = 12.0 Hz), 2.88 (q, 2 H, J = 7.0 Hz), 1.24 (t, 3 H, J = 7.0 Hz); ir (thin film) 1725 (m), 1670 (shoulder), 1625 cm^{-1} (s). The structure of the rearrangement product was

confirmed by conversion of the chromatographed material to 4-phenylpyrazolone (11) (mp 221–223°) using hydrazine hydrate in ethanol. The mixture melting point of this pyrazolone with an authentic sample was not depressed.[27]

Rearrangement of 4c. In a similar way **4c** was converted to *S*-phenyl 2,2-diphenyl-3-oxopropanethioate (**5c**) which was obtained as a light yellow oil in 85% yield: NMR ($CDCl_3$) δ 10.02 (s, 1 H), 7.28 (s, 15 H); ir (thin film) 1730, 1685 cm^{-1}.

The rearrangement product was deformylated using the procedure of House.[2a] A solution of the rearrangement product (1.0 g) and sodium acetate (1.2 g) in ethanol (150 ml) was allowed to reflux for 3 hr. The reaction mixture was cooled to room temperature before adding ether (150 ml). The ether was extracted with 20% sodium chloride solution (3 × 150 ml), dried (Na_2SO_4), and concentrated to give an oil which solidified on standing. The NMR of this product suggested that it was a mixture of ethyl diphenylacetate and *S*-phenyl diphenylethanethioate (**12**). Recrystallization from hexane and benzene gave pure **12** as colorless needles: mp 81–83°; NMR (CCl_4) δ 7.28 (s) and 7.23 (s) (15 H), 5.13 (s, 1 H); ir (KBr) 1690 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.91; H, 5.30; S, 10.53. Found: C, 78.54; H, 5.11; S, 10.31.

The mixture melting point of this compound with an authentic sample (prepared as described below) was not depressed. In a later attempt to purify **5c** by preparative thin layer chromatography on silica gel **12** was obtained instead, mp 80–82°. The mixture melting point of this material with authentic **12** (described below) was also not depressed.

***S*-Phenyl Diphenylethanethioate (12).** Using the same *S*-phenyl thiolchlorocarbonate procedure described for the synthesis of *S*-phenyl 3,3-diphenylthiolglycidate (**4c**), sodium diphenylacetate was converted to **12** in 64% yield after column chromatography. Recrystallization (*n*-hexane and benzene) gave colorless needles, mp 81–83°.

In a separate experiment the rearrangement product **5c** was converted to 4,4-diphenyl-2-pyrazolin-5-one (**6c**) on treatment with hydrazine hydrate in ethanol. The crystals were washed with *n*-hexane followed by recrystallization from ethanol and water to give colorless plates: mp 204–206°; ir (KBr) 3320 (sharp), 1705, 1725 cm^{-1} (shoulder).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.03; H, 5.12; N, 11.84.

Rearrangement of 4d. Using the same procedure **4d** was converted to *S*-phenyl 3,3-dimethyl-3-phenylthiolpyruvate (**14**), which was obtained as a thick yellow oil that crystallized on standing. Recrystallization (*n*-hexane and benzene) gave the pure thiolpyruvate **14** as yellow plates in 70% yield: mp 47–48°; NMR (CCl_4) δ 7.18 (s, 10 H), 1.58 (s, 6 H); ir (KBr) 1715, 1695 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28. Found: C, 71.67; H, 5.54; S, 11.31.

The mother liquors obtained from the recrystallization of **14** on concentration gave a mixture of **14** (10%) along with *S*-phenyl 2,2-dimethyl-3-phenyl-3-oxopropanethioate (**5d**, 10%) which were separated by careful column chromatography on silica gel eluting with benzene–petroleum ether (1:9). **5d** was obtained as a colorless oil: NMR (CCl_4) δ 8.1–7.8 (m, 2 H), 7.35 (s) superimposed on a multiplet at 7.6–7.2 (8 H), 1.62 (s, 6 H); ir (thin film) 1695, 1675 cm^{-1}. This was converted to 4,4-dimethyl-3-phenyl-2-pyrazolin-5-one (**6d**) on treatment with hydrazine hydrate in ethanol. The product was purified by chromatography on a silica gel column eluting with 2% ethanol in benzene. Recrystallization from benzene–*n*-hexane followed by a second recrystallization from ethanol and water gave the pure pyrazolone **6d**, mp 117–118° (lit.[28] mp 118°). The mixture melting point with an authentic sample (mp 117–118°) prepared from ethyl 2,2-dimethyl-3-phenyl-3-oxopropionate[29] and hydrazine hydrate in ethanol was not depressed. An analytical sample was obtained after two recrystallizations from ethanol and water.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.08; H, 6.61; N, 15.16.

Sodium Phenyldimethylpyruvate (15). Ethyl phenyldimethylpyruvate[3a] was converted to **15** in 56% yield using Claisen's method.[30] The salt was obtained as an amorphous, faint yellow powder: NMR (D_2O, Me_4Si external standard) δ 7.38 (s, 5 H), 1.55 (s, 6 H).

***S*-Phenyl 3,3-Dimethyl-3-phenylthiolpyruvate (14).** Using the *S*-phenyl thiolchlorocarbonate procedure described for the synthesis of *S*-phenyl 3,3-diphenylthiolglycidate (**4c**), pyruvate salt **15** was converted to thiolpyruvate **14** in 59% yield after column chromatography. Recrystallization (*n*-hexane and benzene) gave **14** as yellow plates, mp 47–48°. The NMR and ir spectra of this compound were identical with the NMR and ir spectra of **14** obtained from the rearrangement of **4d**. The mixture melting point was not depressed.

Rearrangement of 4e. Using the same general rearrangement procedure, **4e** was converted to a mixture of products containing the *Z* enol tautomer of *S*-phenyl 2-phenyl-3-oxopropanethioate (**2a**) and a second compound, β-lactone **16**. The mixture was separated by a second column chromatography on silica gel eluting with benzene–petroleum ether (1:4). The β-lactone **16** was eluted first (20% yield). Recrystallization (*n*-hexane and benzene) gave colorless plates: mp 99–100°; NMR ($CDCl_3$) δ 7.32 (s) superimposed on a multiplet at 7.60–7.15 (10 H), 4.47 and 4.61 (AB quartet, 2 H, J = 5.5 Hz); ir (KBr) 1815 cm^{-1} (strong); mass spectrum (92°, 70 eV) *m/e* (rel intensity) 256 ($M^{\cdot+}$, 15), 212 ($M^{\cdot+} - CO_2$, 100), 211 (31), 165 (10), 147 ($M^{\cdot+} - C_6H_5S$, 17), 110 (57).

Anal. Calcd for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72; S, 12.51. Found: C, 70.21; H, 4.78; S, 12.70.

Further elution of the silica gel column with benzene–petroleum ether (1:4) gave the *Z* enol tautomer of *S*-phenyl 2-phenyl-3-oxopropanethioate (**2a**) (55% yield): NMR (CCl_4) δ 12.35 (d, 1 H, J = 12.5 Hz), 7.23 (s, 10 H), 6.85 (d, 1 H, J = 12.5 Hz); ir (neat) 1700, 1625 cm^{-1}. The structure of this rearrangement product was established by conversion to 4-phenylpyrazolone (**11**) (mp 223–224°) using hydrazine hydrate in ethanol. The mixture melting point with an authentic sample[12a,27] was not depressed.

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Registry No.—**2a**, 30031-66-4; **3a**, 54984-42-8; *trans*-**3b**, 54934-18-8; *cis*-**3b**, 54934-35-9; **3c**, 54934-19-9; **4a**, 54934-20-2; **4b**, 54934-21-3; **4c**, 54934-22-4; **4d**, 54934-23-5; **4e**, 54934-24-6; **5a**, 54934-25-7; **5b**, 54934-26-8; **5c**, 54934-27-9; **5d**, 54934-28-0; **6a**, 941-18-4; **6b**, 18182-57-5; **6c**, 40110-22-3; **6d**, 24979-47-3; **9**, 54885-09-5; **10**, 54934-29-1; **11**, 54934-30-4; **12**, 54934-31-5; **14**, 54934-32-6; **15**, 54934-33-7; **16**, 54934-34-8; benzenethiol, 108-98-5; sodium 2-phenylglycidate, 24568-17-0; *S*-phenyl thiolchlorocarbonate, 13464-19-2; sodium 2-phenyl-3,3-dimethylglycidate, 24568-18-1; sodium diphenylacetate, 1716-11-6; ethyl phenyldimethylpyruvate, 54934-36-0.

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Synthesis of 10-Thiofolic Acid. A Potential Antibacterial and Antitumor Agent[1a]

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An unambiguous synthesis of 10-thiofolic acid has been carried out in good yield starting from *p*-carbomethoxy thiophenol. Methods have been developed for the quantitative conversion of **6** to the bromo ketone **8**. *p*-Carbomethoxy thiophenol (**3**) and the acid (**2**) were found to be unstable in organic solvents in the presence of oxygen and were converted to the corresponding disulfides (**4** and **5**). A reduction procedure has been developed for the rapid and clean conversion of **14** to **15**, and a procedure for the simultaneous cyclization–oxidation of **15** to **16**. 10-Thiofolic acid (**1**) has been tested for its ability to inhibit the growth of two folate-requiring organisms and showed good antifolate activity. It has also shown moderate activity in preliminary screening against L-1210 leukemia in mice.[23]

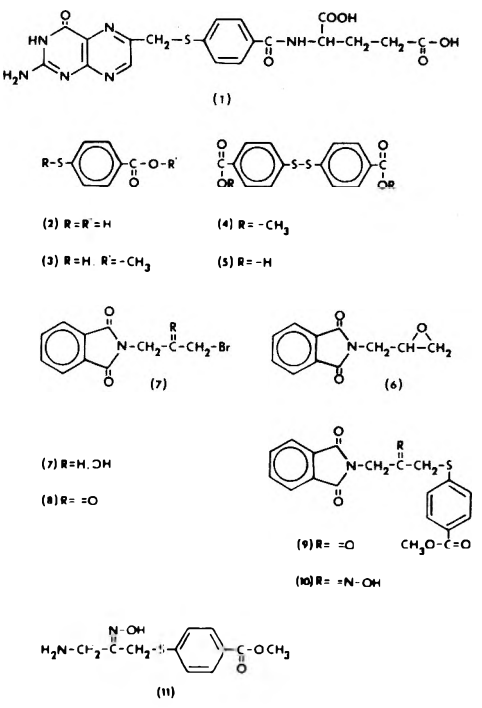
The synthesis and biological evaluation of homofolic acid[1b] and its reduced derivatives (**20**)[2,3] have given impetus to the search for folic acid analogs which are altered in the region corresponding to the C^9–N^{10} bridge in folic acid. A number of analogs in this class have been reported recently.[4–10] It appeared to us that the replacement of the 10-amino group of folic acid by a heteroatom would result in folate analogs whose tetrahydro forms[2,3] could contribute interference to the thymidylate synthesis reaction owing to their inability to form cyclic one-carbon intermediates through positions 5 and 10. This paper details the synthesis and preliminary antifolate activity of such a compound, 10-thiofolic acid (**1**).

At the outset, a convenient procedure for the preparation of *p*-carbomethoxythiophenol (**3**) was required. This was accomplished by a route previously described by Wiley,[11] and the disulfide **4** was also isolated from the reaction mixture. Hydrolysis of **3** gave *p*-carboxythiophenol (**2**), which was converted to the disulfide **5** during crystallization. The quantitative conversion of *N*-(2,3-epoxypropyl)phthalimide to the bromo ketone **8** was carried out by modifications of the original literature procedures.[12–14] Reaction of **3** with **8** in pyridine produced **9** in 75% yield, which was subsequently converted to the oxime **10**. This compound was isolated as a 1:1 mixture of the syn and anti isomers as evidenced by NMR spectroscopy and thin layer chromatography. Since the eventual removal of this carbonyl protective group was required at a later step, no attempt was made to separate and identify the individual isomers.

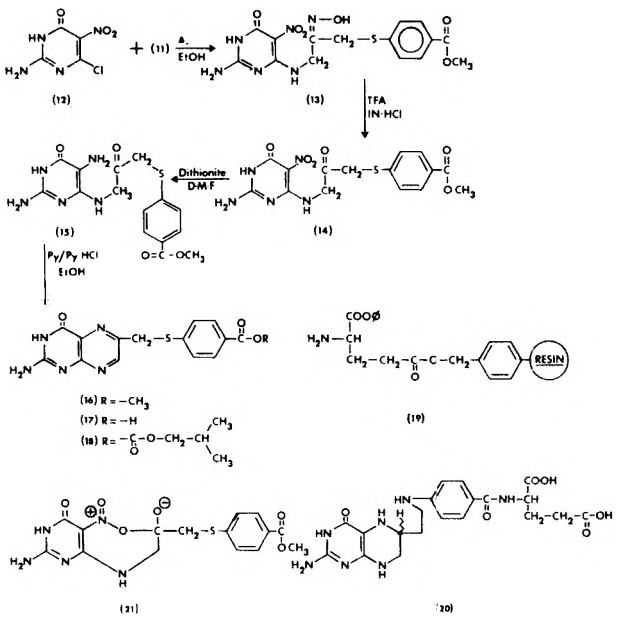
The NMR spectral observations also excluded a possibility that the product might be a thioketal formed by the reaction of 2 mol of thio ester with the carbonyl moiety of **8** in preference to the nucleophilic displacement of the bromide by **3**.

Although several methods are described in the literature for the cleavage of the phthalimide function for compounds similar to **10**, including treatment with strong acids and bases, the use of hydrazine[15] was preferred because of its ability to cleave such systems under mild conditions. This was accomplished smoothly and in high yield. These reactions are summarized in Scheme I. Several attempts were

Scheme I



Scheme II



made at this stage to cleave the oxime back to the ketone, but always resulted in the recovery of the starting material or tarred products unsuitable for further investigations. An attempt was made, however, to hydrolyze the ester function of **11** to the carboxylic acid by standard procedures. None of these experiments gave the desired products, and consequently compound **11** was condensed directly with 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine (**12**) in ethanol to compound **13** in excellent yield (Scheme II). Reductive cyclization of **13** by Raney nickel[16-19] catalysts was ruled out by the presence of sulfur and the compound's insolubility in solvents commonly used for hydrogenations.

The carbonyl function in **13** was deprotected easily by the use of a 1:1 mixture of trifluoroacetic acid and 1 *N* HCl at 60° for 20 min to the corresponding ketone (**14**). Treatment of ketone **14** with several reducing agents, including stannous chloride, and catalytic hydrogenation in DMF with Pt and Pd did not accomplish the desired reduction of the nitro group as evidenced by the persistence of the absorption due to the 5-nitro group of **14**. The resistance of **14** toward reducing agents is not immediately apparent, but a neighboring group participation by the nitro group and the carbonyl group could presumably result in an ionic species (**21**). Therefore, the use of reagents such as sodium dithionite in highly polar solvents like DMF was considered for this reaction. In fact, an excellent reduction procedure was worked out which reduces compound **14** to **15** at 50° in 15 min. This behavior appears to be general to such systems, and we are presently investigating this phenomenon in detail. The reduction product was subsequently cyclized by the use of a pyridine–pyridine hydrochloride buffer in ethanol for several hours, which also resulted in the spontaneous oxidation of the cyclization product to **16** in 90% yield. Hydrolysis of **16** in the usual manner and subsequent workup gave compound **17** in ~50% yield after purification by ion exchange chromatography. The material showed a uv spectrum similar to that of pteroic acid, and the structure was confirmed by examination of the NMR spectrum of **17** in TFA.

The problem of attaching the glutamate moiety to 10-thiopteroic acid remained. This was accomplished in the following way. Briefly, 10-thiopteroic acid was converted to the mixed anhydride **18** by dissolving the compound in 50:50 DMSO–dioxane and treating with 1 molar equiv of isobutyl chloroformate at 0° in the presence of *N*-methylmorpholine as a proton acceptor. *t*-Boc-L-glutamic acid α-benzyl ester was attached to the Merrifield chloromethyl resin by standard procedure[19] and the amino group was deprotected as described earlier[20] to **19**. The coupling of the active anhydride **18** to **19** was done overnight at room temperature. Cleavage from the resin and final purification was accomplished as described previously by this laboratory[5,20] for similar compounds.[21]

10-Thiofolic acid showed all the spectral characteristics expected of this compound and the structure was conclusively established by ultraviolet and NMR spectroscopy. Relevant among the spectral data are the NMR signals in D_2O due to the C_7 proton of the pteridine moiety, which appeared as a singlet at 8.54 ppm, and the characteristic AB pattern of the resonances due to the aromatic protons as two clean doublets at 7.8 and 7.4 ppm. The rest of the anticipated signals due to the C_9 methylene protons and the glutamate protons appeared in the usual pattern. The uv spectrum of 10-thiofolic acid was as expected and was very similar to that of folic acid, showing λ_{max} at 369, 285, and 261 nm when run in 0.1 *N* NaOH. These spectral observations are in perfect agreement with the required structure (**1**).

Both 10-thiofolic acid and 10-thiopteroic acid were tested for their ability to inhibit the growth of two standard folic acid requiring bacteria, *Streptococcus faecium* (ATCC 8043) and *Lactobacillus casei* (ATCC 7469). These studies employed Difco folic acid assay media for the specific organism and were carried out in duplicate. For *S. faecium*, 9×10^{-10} g/ml of 10-thiofolic acid and 1.5×10^{-9} g/ml of 10-thiopteroic acid were required for 50% inhibition of growth as monitored turbidimetrically at 650 nm. For *L. casei*, 8×10^{-9} g/ml of 10-thiofolic acid gave 50% inhibition. No inhibition of *L. casei* was seen with 10-thiopteroic acid at 10^{-5} g/ml. In the *L. casei* inhibition studies, the folic acid concentration was 5×10^{-11} g/ml and in the *S. faecium* it was 2.5×10^{-10} g/ml.

Experimental Section

Melting points are uncorrected and were determined on a Fisher-Johns apparatus. NMR spectra were run in $CDCl_3$ on a 90-MHz Perkin-Elmer R-32 spectrometer with Me_4Si or TSP as internal lock signal. Field strengths of the various proton resonances are expressed in parts per million and coupling constants as hertz. Peak multiplicity is depicted as usual: s, singlet; d, doublet; t, triplet; q, quartet; br, broadened singlet or unresolved multiplet; and c, complex signal whose center is given. Uv spectra were determined in a Beckman Model 25 spectrophotometer. Chromatography was carried out on DEAE cellulose in the chloride form with 1.2 × 22 cm packing unless otherwise specified. A linear NaCl gradient in 0.005 *M* phosphate buffer pH 7, 1 l. each from zero to 0.5 *M* NaCl, was used to elute the column. Mass spectra were run at Research Triangle Institute in North Carolina. Elemental analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn.[22] Yields represent the actual amount of pure compound isolated, assuming 100% reaction.

Preparation of *p*-Carbomethoxythiophenol (3) and Disulfide 4. The synthetic sequence starting with 17.1 g of *p*-aminobenzoic acid to the esterification step (as described by Wiley[11]) was repeated. Crystals were formed while cooling this reaction mixture containing **3**. These were removed by filtration. This compound was identified as disulfide **4** by observing the molecular ion in the high-resolution mass spectrum at 334.0336 (calcd, 334.0333): yield 2.0 g; mp 124°; NMR 8.3 d, 7.84 d (J = 9 Hz, aromatic), and 4.2 ppm (methoxyl). Anal. Calcd for $C_{16}H_{14}O_4S_2$: C, 57.48; H, 4.19; S, 19.16. Found: C, 57.34; H, 4.12; S, 19.36.

Vacuum distillation of the filtrate at 11 mm gave **3** boiling at 134–140°: yield 9.0 g; NMR 7.85 d, 7.35 d (J = 9 Hz, aromatic), 3.85 (methoxyl), and 3.75 ppm (thiol). Anal. Calcd for $C_8H_8O_2S$: C, 57.4; H, 4.76; O, 19.04. Found: C, 57.28; H, 4.59; O, 19.21.

Preparation of *N*-(3-Bromo-2-hydroxypropyl)phthalimide (7). In a typical experiment, 10 g of *N*-(2,3-epoxypropyl)phthalimide was dissolved in 75 ml of dry dichloromethane and gaseous hy-

drogen bromide was bubbled through until saturated, requiring approximately 20 min. The reaction mixture was evaporated to dryness under vacuum, and the crude product melted at 110–112°: NMR 7.82, c (aromatic protons), 4.2, c (C_2H), 3.95 and 3.55, dd (J = 8 Hz, C_3 and C_1 methylene protons), and 3.02 ppm s (hydroxyl, completely exchangeable with D_2O).

Preparation of *N*-(3-Bromo-2-oxopropyl)phthalimide (8). In an erlenmeyer flask, 10 g of the hydroxy bromide 7 was stirred with 400 ml of acetone at room temperature. When all of the material was in solution, the solution was cooled to 15° and 100 ml of Jones reagent was added portionwise with stirring in such a manner that the temperature did not rise above 30°. After the addition, which took 10 min, the mixture was stirred at room temperature for 15 min, transferred to a round-bottomed flask, and evaporated to ~150 ml under vacuum. The outside bath temperature was kept at 35°. Treatment of this reaction mixture with 1 l. of ice-cold water gave crystals which were removed by filtration and washed several times with distilled water until the filtrate was colorless: yield 9.5 g; mp 151–152°; NMR 7.85, c (aromatic protons), 4.80, s and 4.06 ppm s (C_3 and C_1 methylene protons). Anal. Calcd for $C_{11}H_8BrNO_3$: C, 46.81; H, 2.84; Br, 28.37; O, 17.02. Found: C, 46.92; H, 2.97; Br, 28.21; O, 16.92.

Displacement of Bromine in 8 by *p*-Carbomethoxythiophenol. Preparation of 9. In an oven-dried three-necked flask, fitted with a reflux condenser and nitrogen inlet, were placed 2 mmol each of bromo ketone 8 and thio ester 3. The reactants were slowly heated in a stream of nitrogen to 90° with the aid of an oil bath, and pyridine was added slowly from a dropping funnel until the mixture went into solution (~3 ml). The reaction mixture was then heated to reflux in nitrogen for 45 min, when crystals began to appear. The reaction product was cooled and poured over 100 g of crushed ice, then stirred. The cream-colored solid thus obtained was collected by filtration and recrystallized from methanol: yield 75%; mp 153–154°; NMR 8.05, d (J = 8 Hz, two aromatic protons adjacent to carbomethoxy), 7.38, d (J = 8 Hz, two aromatic protons adjacent to sulfur), 7.85, c (four aromatic protons of the phthalimide moiety), 4.78, s and 3.92, s (methylene protons), and 3.95 ppm (carbomethoxy). Anal. Calcd for $C_{19}H_{15}NO_5S$: C, 61.79; H, 4.07; O, 21.68; S, 8.67. Found: C, 61.76; H, 4.13; O, 21.54; S, 8.50.

Preparation of the Oxime 10. Compound 9 (4.3 g) and 1.21 g of hydroxylamine hydrochloride were suspended in a three-necked, round-bottom flask and the flask was swept with a slow stream of nitrogen. To this was added 48 ml of 1:1 pyridine–ethanol mixture and the mixture was refluxed for 2 hr. The reaction product was evaporated to dryness under vacuum and the resulting pale yellow, gummy material was treated with 25 ml of ethyl acetate and 24 ml of distilled water. After shaking vigorously, the contents were poured into a separatory funnel and the aqueous layer was discarded. The ethyl acetate layer was washed twice with 100 ml of distilled water. The ethyl acetate layer was then dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated to dryness. The viscous gum thus obtained was recrystallized from methanol, yield 4.0 g, mp 135–136°. Anal. Calcd for $C_{19}H_{16}N_2O_5S$: C, 59.38; H, 4.17; N, 7.29; S, 8.33. Found: C, 59.71; H, 4.27; N, 7.35; S, 8.32.

Cleavage of 10 by Hydrazine to the Amino Ester 11. The oxime (3.8 g, 9.9 mmol) was suspended in a three-necked round-bottom flask with 100 ml of absolute alcohol and stirred under reflux in a slow stream of nitrogen with repeated addition of four 100-ml portions of alcohol when all the material went into solution. The solution was cooled to room temperature and 9.9 mmol of 95% hydrazine in 10 ml of absolute alcohol was added. This mixture was stirred for 72 hr in nitrogen at room temperature, then refluxed for 30 min. After the reaction mixture was cooled to 0°, it was filtered. The filtrate was evaporated to dryness and the residue was treated with 9.9 ml of 1 N HCl in 20 ml of water and stirred vigorously for 1 hr. The pH was adjusted to 3 by the addition of more HCl and the mixture was filtered. The clear filtrate thus obtained was treated with 10% ammonium hydroxide so that the pH became 10. A white precipitate was formed in the solution. After cooling to 0°, the precipitate was separated by filtration, washed with water, and recrystallized from methanol: yield 1.6 g; mp 154–156°; relevant NMR signals in polysol-D at 7.86, d (J = 9 Hz, aromatic), 7.45, dd (J = 9 Hz, aromatic), 4.0, s and 3.92, s (methylene protons attached to sulfur), 3.85, s (carbomethoxy), 3.51, s and 3.39 ppm, s (methylene protons attached to amino group). Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.97; H, 5.51; N, 11.02; S, 12.60. Found: C, 51.93; H, 5.39; N, 10.95; S, 12.51.

Reaction of 2-Amino-6-chloro-4-hydroxy-5-nitropyrimidine with Amino Ester 11. Preparation of Intermediate 13. In an atmosphere of nitrogen, 560 mg of 12 was dissolved in 140 ml of absolute alcohol and refluxed with 700 mg of 11 for 30 min. After this period, 0.7 ml of N-methylmorpholine was added and the mixture was again refluxed for 30 min. The crystals which appeared at this point were collected by filtration, washed with water and a small amount of alcohol, and recrystallized from absolute alcohol: mp 185°; yield 1.05 g; $\lambda_{292}/\lambda_{347}$ 1.08. Anal. Calcd for $C_{15}H_{16}N_6O_6S$: C, 44.12; H, 3.92; N, 20.59; S, 7.84. Found: C, 43.9; H, 3.86; N, 20.46; S, 7.74.

Deprotection of the Carbonyl Group of 13. Preparation of 14. In an erlenmeyer flask, 1 g of oxime 13 was treated with 50 ml of trifluoroacetic acid with stirring and slowly heated to 50° until all the material was dissolved. An equal volume of 1 N HCl was added and the flask was kept in a water bath at 60°. Crystals began to appear slowly. After 20 min, the reaction mixture was cooled to 0°, filtered, and washed several times with water and finally with absolute alcohol: mp 247–250°; yield 900 mg; λ_{max} (0.1 N NaOH) 294 nm (ϵ 16,011) and 332 (14,673). Anal. Calcd for $C_{15}H_{15}N_5O_6S$: C, 45.80; H, 3.92; N, 17.81; O, 24.43. Found: C, 45.71; H, 3.77; N, 17.91; O, 24.37.

Dithionite Reduction of 14. The deprotected nitro compound 14 was suspended in an erlenmeyer flask (350 mg) and dissolved in 100 ml of purified DMF. The solution was heated to 50° and 5 g of solid purified sodium dithionite was added. Water was added to this stirring suspension, portionwise, while maintaining the temperature until all the dithionite went into solution. The mixture was allowed to stir for an additional 15 min, then diluted to 700 ml with ice-cold water. A white, fluffy precipitate was formed, which was collected by filtration, washed several times with water and finally with absolute alcohol, and then dried under vacuum. The compound is unstable on exposure to air and rapidly degraded to products unsuitable for further work: yield 300 mg; mp >300°; λ_{max} (0.1 N NaOH) 335 and 280 nm; $\lambda_{280}/\lambda_{335}$ 1.65.

Simultaneous Cyclization–Oxidation of 15 to 16 and Hydrolysis to 10-Thiopteroic Acid (17). The dithionite reduction product (15, 300 mg) was added to a deaerated mixture of 25 ml of pyridine, 25 ml of absolute alcohol, and 5 drops of concentrated HCl and refluxed in a nitrogen atmosphere for 2.5 hr. The solution was cooled to room temperature and allowed to stir in the presence of air for 48 hr. The contents in the flask were evaporated under vacuum to dryness. Distilled water (25 ml) was added, and the contents were evaporated again. Ice (50 g) was then added and the mixture was triturated with a spatula followed by filtration and several water washes. The uv spectrum of this compound in 0.1 N NaOH showed λ_{max} at 365, 280, and 260 nm, which is typical of a 6-substituted, fully oxidized form of 2-amino-4-hydroxypteridine.

The product thus obtained was transferred to a three-necked flask fitted with a nitrogen inlet and reflux condenser and 25 ml of 0.75 N NaOH was added. It was refluxed in nitrogen for 2 hr. The solution was cooled to room temperature and adjusted to pH 7.2 with 1 N HCl. The solution was then diluted to 1 l. with distilled water and applied to a 27 × 2.5 cm DEAE Cl^- column. The column was washed with distilled water and eluted with a linear NaCl gradient from zero to 0.5 M, in 0.005 M phosphate buffer, pH 7.0. 10-Thiopteroic acid eluted at 0.375 M NaCl concentration. All the tubes corresponding to this peak were pooled and concentrated to 100 ml, cooled to 0°, and acidified to pH 3.5 with 1 N HCl. The precipitate thus obtained was washed several times with water and dried under vacuum over P_2O_5 for 48 hr: yield 140 mg; λ_{max} (0.1 N NaOH) 369 nm (ϵ 9638), 285 (21,068), and 261 (32,850); NMR (TFA with Me_4Si as internal standard) 9.05, s (C_7), 8.1, d (J = 9 Hz, $H_{2'6'}$); 7.55, d (J = 9 Hz, $H_{3'5'}$), and 4.62 ppm, s (C_9 methylene protons). Anal. Calcd for $C_{14}H_{11}N_5O_3S$: C, 51.06; H, 3.34; N, 21.28; O, 14.59; S, 9.73. Found: C, 50.97; H, 3.40; N, 21.27; O, 14.63; S, 9.58.

Solid-Phase Coupling of 10-Thiopteroic Acid with L-Glutamic Acid. Preparation of 10-Thiofolic Acid (1). t-Boc-L-glutamic acid α-benzyl ester was esterified to the chloromethylated Merrifield resin as usual. The resin ester, corresponding to 2 mmol of glutamic acid, was deprotected by the use of 20% trifluoroacetic acid in methylene chloride for 20 min at room temperature, washed, neutralized, and kept ready for coupling (19).

10-Thiopteroic acid (1 mmol) was dissolved in 20 ml of dry DMSO by heating. The solution was cooled to room temperature, an equal volume of dry THF was added, and the solution was chilled to 0°. Then 1.25 mmol of N-methylmorpholine was added, allowed to mix well by shaking, and kept at 0° for an additional 15 min. To this solution was added exactly 1 equiv (1 mmol) of freshly distilled isobutyl chloroformate and the reaction was allowed to proceed for 15 min at 0° to form the mixed anhydride (18). This

mixed anhydride (18) was then poured into the reaction vessel containing 19, and the coupling reaction was carried out by rocking the reaction vessel at room temperature for 18 hr. After this period, the reaction mixture was filtered and the resin-bound product was washed successively with DMSO, DMSO–THF mixture, and p-dioxane.

The resin was then suspended in 20 ml of 1:1 dioxane–2 N NaOH mixture, which was deaerated previously, and mixed well in a closed vessel for 1 hr at room temperature and for 20 min at 50°. The filtered solution was diluted to 100 ml and slowly acidified with 1 N HCl at 0° to pH 3.5. The yellow precipitate of 1 thus formed was collected by filtration, washed several times with distilled water, and dried under vacuum over P_2O_5: yield 80%; mp >300°; λ_{max} (0.1 N NaOH) 369 mm (ε 9638), 285 s (21,068), and 261 (32,850); NMR (D_2O–NaOD with SDSS as internal standard) 8.54, s (C_7 H), 7.8, d (J = 9 Hz, $H_{2'6'}$), 7.40, d (J = 9 Hz, $H_{3'5'}$), 4.42, t (α proton of glutamate moiety), and 1.0–2.5 ppm, c (four protons of glutamic acid). Anal. Calcd for $C_{19}H_{18}N_6O_6S$: C, 49.78; H, 3.93; N, 18.34; O, 20.96; S, 6.99. Found: C, 49.69; H, 3.96; N, 18.46; O, 21.08; S, 6.99.

10-Thioaminopterin, the 4-amino-4-deoxy analog of 1, has also been synthesized in this laboratory by a similar procedure and will be discussed in a later communication in this series.

Acknowledgments. This work was supported by Grant CI-86N of the American Cancer Society and by NIH Grant 1-R01-CA-16048. We are grateful to Miss Eleanor Braverman for her interest and assistance in this work and to Mr. D. J. Underwood for his technical assistance.

Registry No.—1, 54931-98-5; 3, 6302-65-4; 4, 35190-68-2; 6, 5455-98-1; 7, 6284-27-1; 8, 6284-26-0; 9, 54931-99-6; 10, 54932-00-2; 11, 54932-01-3; 12, 1007-99-4; 13, 54932-02-4; 14, 54932-03-5; 15, 54932-04-6; 16, 54932-05-7; 17, 54932-06-8; L-glutamic acid, 56-86-0.

References and Notes

(1) (a) Trivial names in general usage will be used for these compounds: 10-thiofolic acid = N-[p-[[(2-amino-4-hydroxy-6-pteridinyl)methyl]-thio]benzoyl]glutamic acid; 10-thiopteroic acid = 2-amino-4-hydroxy-6-(p-carboxythiophenoxymethyl)pteridine; homofolic acid = N-[p-[[(2-amino-4-hydroxy-6-pteridinyl)ethyl]amino]benzoyl]glutamic acid. Other abbreviations include: DHFR, dihydrofolate reductase; DEAE, diethylaminoethyl; t-Boc, tert-butyloxycarbonyl; SDSS, sodium 2,2-dimethyl-2-silapentane-5-sulfonate. (b) L. Goodman, J. DeGraw, R. L. Kisliuk, M. Friedkin, E. J. Pastore, E. J. Crawford, L. T. Plante, A. A. Nahas, J. F. Morningstar, G. Kwok, L. Wilson, E. F. Donovan, and J. Ratzan, J. Am. Chem. Soc., 86, 308 (1964).
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(22) Where analyses are indicated only by symbols of elements, analytical results obtained for these elements or functions were within ±0.4% of the theoretical values.
(23) Increase in mean survival time of 27% at 8 mg/kg. We are thankful to Dr. H. B. Wood of NCI for the antitumor screening data.

Prostaglandins. VII. A Stereoselective Total Synthesis of Prostaglandin E_1[1]

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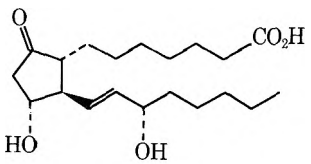
The stereoselective total synthesis of (±)- and (−)-prostaglandin E_1 (1) is described. Chromous sulfate reduction of 7-(2-formyl-3-tetrahydropyranyloxy-5-oxocyclopent-1-enyl)heptanoic acid (3b) afforded the saturated aldehyde 10b, which was condensed with n-hexanoylmethylenetriphenylphosphorane (7) to form 11-O-tetrahydropyranyl-15-dehydroprostaglandin E_1 (11). Reduction of 11 with thexyl tetrahydrolimonyllithium borohydride followed by hydrolysis gave 1. The mechanism of stereochemical control is discussed in detail. The total synthesis was extended to the preparation of (±)-ω-homoprostaglandin E_1 (32c) and (±)-15-methyl-ω-homoprostaglandin E_1 (32d).

The prostaglandins,[2a,b] a family of oxygenated C_{20} fatty acids of widespread occurrence in animal tissues, exhibit a broad range of biological activities[2c] and presumably play an important role in several physiological processes. Prostaglandin E_1 (PGE_1, 1), one of the most active and ubiquitous hormones of this species, has been synthesized[3-10] chemically by several different groups. Some[4,7,8b,9b] of these total syntheses of PGE_1 were stereochemically controlled.



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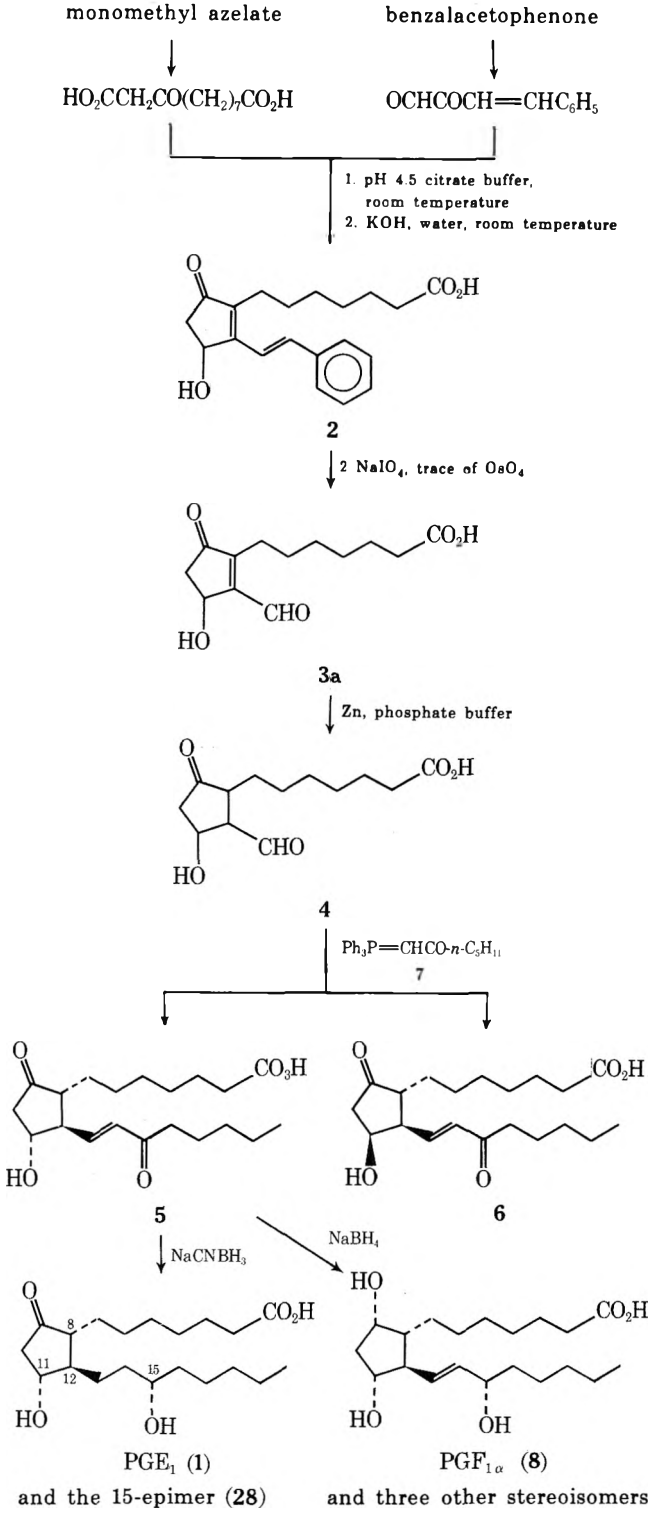
The primary objective of our study was to develop an efficient general route to new prostaglandin analogs which might possess more selective biological activities. This target was partly achieved with a facile seven-step total synthesis[8a,11] of racemic PGE_1 (1) and $PGF_{1\alpha}$ (8) along with their stereoisomers as outlined in Scheme I. This scheme was not stereoselective in some steps. Thus, almost equal amounts of 5 and 6 were obtained after the Wittig condensation. Also, comparable amounts of (±)-PGE_1 (1) and its 15 epimer (28) were formed in the reduction step. Some of the stereoisomers[11] exhibited interesting biological activities.[12]

Later, large quantities of PGE_1 were required for biological study. Owing to the inevitable formation of the stereo-

Scheme I
Nonstereoselective Total Synthesis of PGE_1 (1) and $PGF_{1\alpha}$ (8)

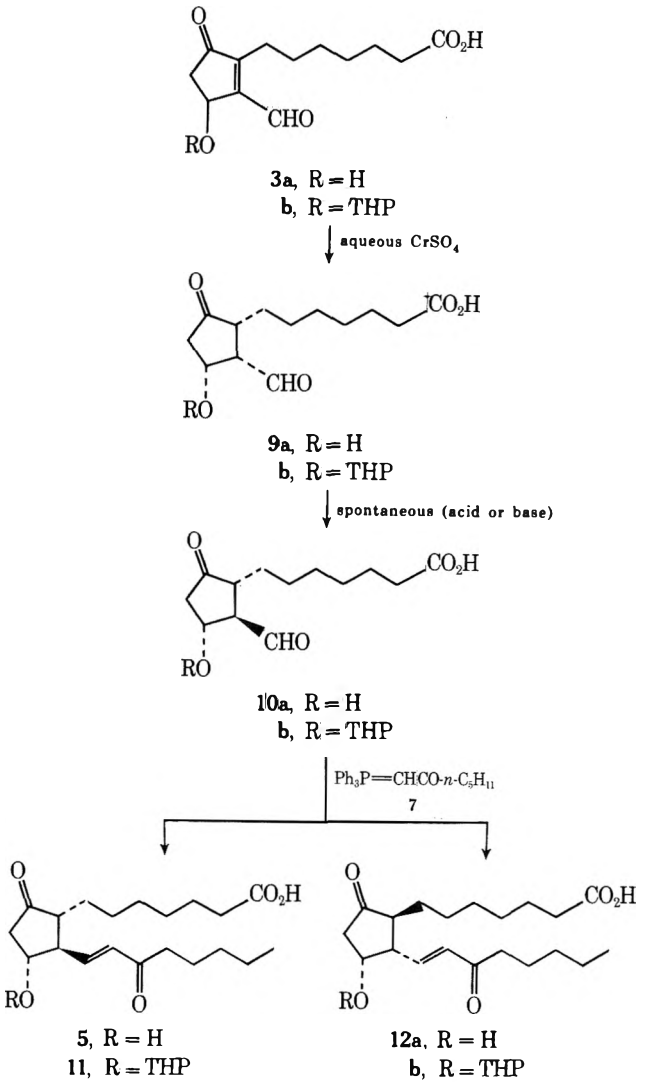


isomers, Scheme I was not practical for a large-scale production of PGE_1, and therefore we attempted to modify this synthetic route by incorporating more stereochemical control. A successful approach toward this goal is the subject of the present communication. For racemic compounds, only one enantiomer is depicted for convenience.

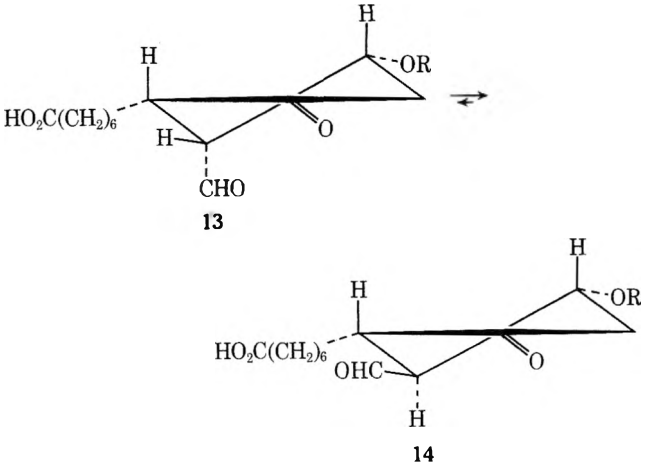
Results and Discussion

A unique feature of Scheme I is that the relative stereochemistry of C-8, C-11, and C-12 in the final product (1) is determined by a single step, that is, the reduction of **3a** to

Scheme II
Stereoselective Route to 15-Dehydro-PGE_1



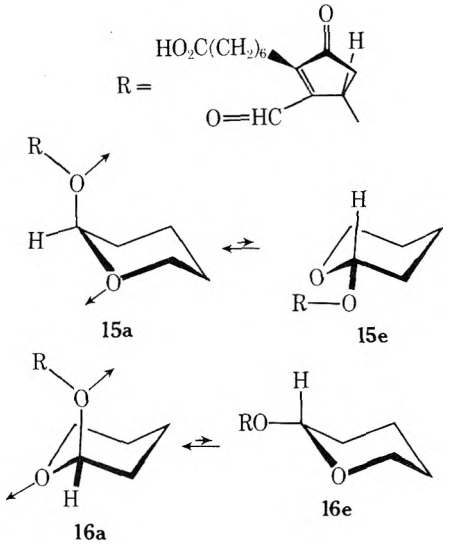
4. In all likelihood, the reduction of **3a** occurs from the less hindered side[13] to afford the all-cis isomer **9a**, which is thermodynamically less stable than the trans isomer, and therefore is isomerized to the more stable "natural" configuration (**10a**) as depicted in **13** → **14**. To put this seemingly



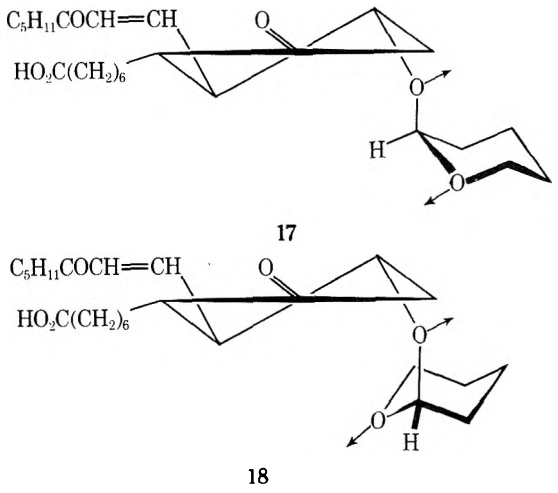
prosaic idea into practice, some pertinent problems were considered carefully. First, the hydroxyl group in **3a** may not be bulky enough to dictate satisfactory stereoselectivity.[14] Second, the reduced aldehyde (**9a, 10a**) may not be stable enough to survive the acid- or base-catalyzed equili-

bration (**9a** → **10a**). Finally, as reported earlier,[11] the aldehyde (**10a**) does not exist as such, but in fact as a mixture of intra- and intermolecular acetal ketals in which isomer **10a** may not necessarily be more stable than **9a**. A logical solution to these problems was to use the tetrahydropyranyl (THP) derivatives (**3b, 9b, 10b**). The THP-oxy group is bulkier; hence it would dictate better stereoselectivity than the hydroxy group. It may be a less effective leaving group than hydroxy; thus **9b** and **10b** might be less susceptible to acid or base elimination. Also, **9b** and **10b** cannot participate in acetal formation owing to the absence of the hydroxy group.

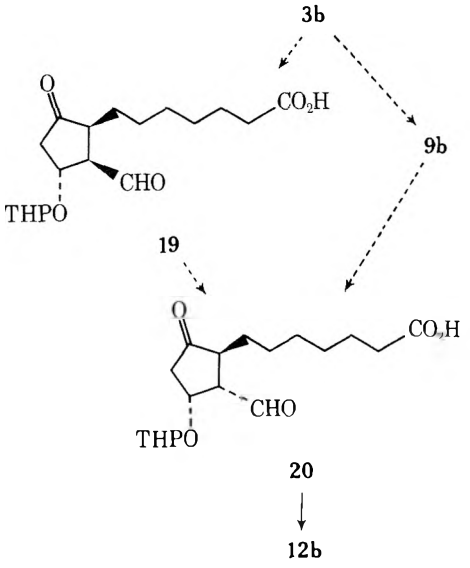
The readily available **3a**[11] was converted into the THP ether **3b**. To our surprise, however, **3b** was not reduced with zinc in aqueous acid under conditions used in the reduction[11] of **3a** to **4**. It was discovered that the calculated amount of aqueous chromous sulfate solution[15] effected reduction of the double bond of **3b** in a few minutes at room temperature. No purification of the reduction product was attempted. It was instead promptly treated with *n*-hexanoylmethylenetriphenylphosphorane in benzene to afford **11** as the major product accompanied by a small amount of 8,12-bisepi isomer[16] (**12b**). The ratio of **11** to **12b** was usually 80:20 or better. Isomerization of **9b** to **10b** must have taken place prior to the Wittig condensation, possibly during the work-up of the chromium reduction. Presumably, the more stable conformation of **3b** contains an axial THP-oxy group such as **15a** or **16a**, rather than the equatorial counterparts **15e** or **16e**. Only in the axial conformations can two ether linkages be stabilized by two ethereal dipoles taking an antiparallel relationship. A similar situation is encountered in the configuration of pyranoside sugars[17a,b] with regard to the "anomeric effect". The energy difference of an axial (α-glycoside) and equatorial (β-glycoside) isomer was estimated to be 0.9 (in polar solvent) to 1.3 kcal (in nonpolar solvents)/mol.[17a] The THP-oxy group in **15a** or **16a** would shield the α side of the molecule much more effectively than the equatorial counterparts (**15e** and **16e**). Hence, after electron transfer from Cr^{II}, a water molecule (proton donor) would approach from the β side to afford all-cis **9b**.



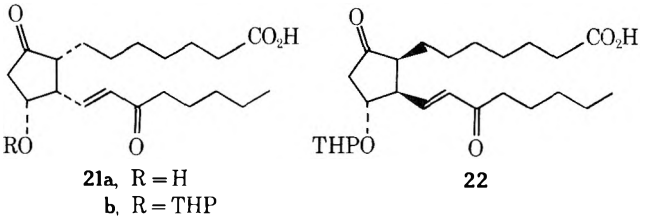
The NMR spectrum of **11** showed that this substance is approximately a 1:1 mixture of two diastereoisomers (**17, 18**) both of which exist in the axial conformations in deuteriochloroform. The NMR signal of the acetal protons of both isomers appeared as a narrow multiplet ($W_{1/2}$ <6.5 Hz) at δ 4.65 ppm which is compatible only with an equatorial acetal proton, that is, the axial THP-oxy structure.



Formation of a small amount of **12b** might be rationalized by either formation of **19** followed by the isomerization to **20** or isomerization of **9b** to **20**. The Wittig condensation



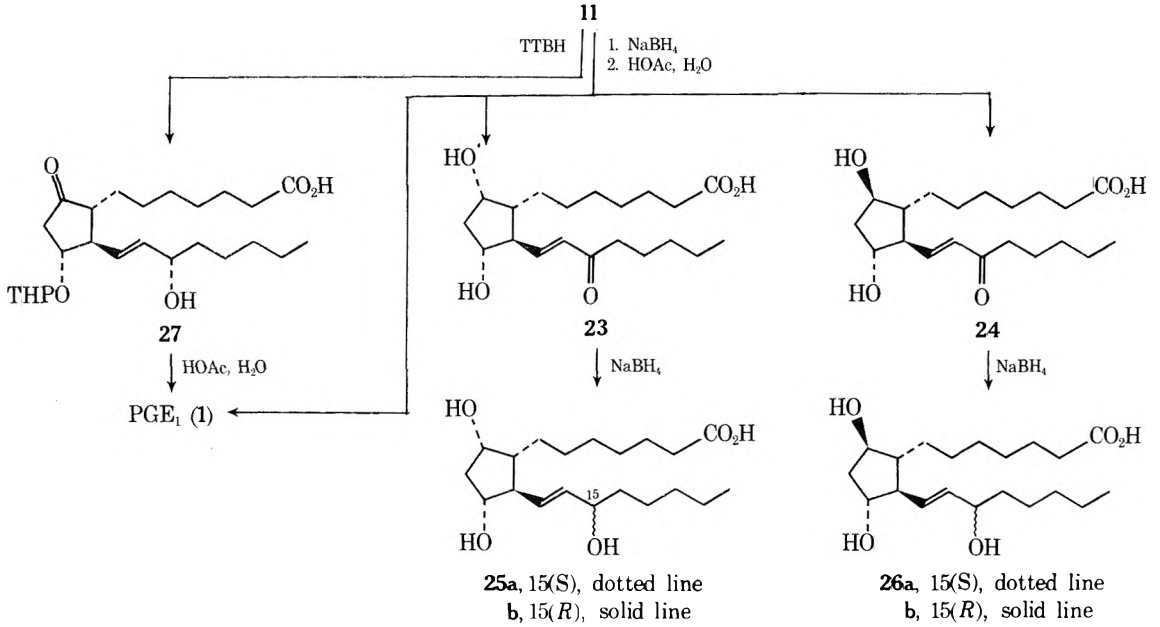
(**10b** → **11**) is slightly inhibited by a weak base (pyridine), strongly inhibited by a strong base (imidazole), and accelerated by a weak acid (isobutyric acid). Since **10b** is a weak acid, the self-catalyzed condensation takes place at 25° in benzene. Contrary to the nonstereoselective scheme,[11] very little 12 epimer (**21b**) was formed in the present scheme, but a small amount of 8 epimer (**22**) was found. The 15-



dehydro-PGE_1 THP ether (**11**) thus obtained (25–30% from **3a**) was sufficiently pure to be used for the next step. The analytical sample of **11** was prepared by hydrolysis of the THP group, chromatography, and retetrahydropyranylation.

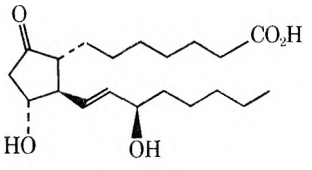
Reduction of **11** with sodium borohydride in cold methanol followed by hydrolysis gave rise to three products in comparable amounts. The least polar substance of mp 81–82° exhibited a uv (methanol) absorption at 233 nm (ϵ 13,500). The NMR (100 MHz, CD_3OD) spectrum suggested that the C-9 carbinol proton (δ 3.64, m, $W_{1/2}$ = 13 Hz) was equatorial; that is, the 9-OH was axial. The structure (**23**)

Scheme III
Reduction of 15-Dehydro-PGE$_1$ Tetrahydropyranyl Ether



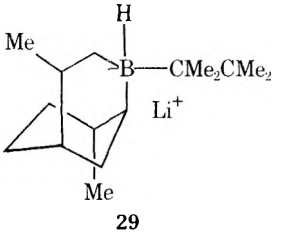
was unequivocally proven by formation of $PGF_{1\alpha}$ (**25a**) and 15-epi-$PFG_{1\alpha}$ (**25b**)[11] upon reduction with borohydride. The polar fraction was readily separated by partition chromatography[11] into two pure compounds. The less polar substance of mp 112–113° was indistinguishable from (±)-PGE_1 in its melting point, 100-MHz NMR in deuteriomethanol, its TLC, and its biological activities. The more polar substance showed the uv (methanol) absorption at 232 nm (ϵ 13,100). The NMR (100 MHz, CD_3OD) spectrum suggested that the C-9 carbinol proton (δ 3.58, q, J = 7.5 Hz) was axial; that is, 9-OH was equatorial. Structure **24** was unambiguously confirmed by formation of $PGF_{1\beta}$ (**26a**) and 15-epi-$PGF_{1\beta}$ (**26b**)[11] upon reduction with borohydride. The optically active form of **23** and its borohydride reduction has been recorded.[18]

Although 15-epi-PGE_1 (**28**) was not isolated, its presence



28

in a minute amount cannot be precluded. Although **11** was not reduced regioselectively, there was little doubt that the 15-keto group was reduced stereoselectively. Corey and his coworkers demonstrated[19] that the reduction of the 15-keto group of one of the prostaglandin derivatives with thexyl tetrahydrolimonyllithium borohydride (**29**, TTBH) took



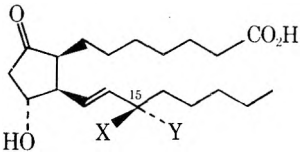
29

place to afford preferentially the 15(S) carbinol (natural) in a ratio of 9:2. This reagent[19,4e] was successfully applied to the regio- and stereoselective reduction of **11**. In our hands treatment of **11** with 1.5 equiv of TTBH in THF at −78° gave rise to **27** as the only major reduction product. A small amount of 15-epi compound was formed. The extent of conjugate reduction (reduction of the 13,14 double bond) appeared to be negligible, though it was not investigated quantitatively.

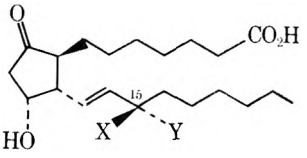
The THP group of crude **27** was hydrolyzed with aqueous acetic acid at room temperature to afford (±)-PGE_1 (**1**) in 27% yield from **11**.

The total synthesis of PGE_1 outlined in Schemes II and III possessed, in addition to enhanced stereoselectivity, several advantages. First, the THP derivatives (**11, 12b, 22**) were found to be reasonably stable substances which could be set aside at room temperature for a couple of weeks without any recognizable decomposition. The corresponding hydroxy compounds, especially **5** and **6**, were very unstable and underwent a series of complicated irreversible reactions even in a freezer. Second, the THP group modified solubility; thus, **10b** (or **9b**) was substantially less soluble in water compared with its hydroxy counterpart, hence easier to handle. Finally, the THP group modified the elution pattern from the column. More specifically, chromatography of the Wittig condensation product afforded **11** (desired and major product, equatorial[20] THP-oxy group), **12b** (a minor product, axial[20] THP-oxy), and triphenylphosphine oxide in this sequence. In the hydroxyl series, triphenylphosphine oxide, **6** (axial hydroxy), and **5** (desired product, equatorial hydroxy) were eluted in this sequence, which was inconvenient as the desired material came off last.

Pure 8 epimer **22** could not be obtained. TTBH reduction of a mixture containing (±)-**22** afforded (±)-8,15-bisepi-PGE_1 (**30a**) after hydrolysis of the THP group. Al-



30a, X = OH; Y = H
b, X = H; Y = OH



31a, X = OH; Y = H
b, X = H; Y = OH

though it could not rigorously be determined, much more **30a** (15R) than **30b** (15S) appeared to be formed; that is, the stereoselectivity of TTBH reduction is reversed in the

8-epi series. The configuration of **30a** was readily confirmed by the isomerization to 15-epi-PGE_1 (**28**) upon mild base treatment.[18] The TTBH reduction of (±)-8,12-bis epimer (**12b**)[16] afforded comparable amounts of (±)-11-epi-PGE_1 (**31a**) and (±)-11,15-bisepi-PGE_1 (**31b**). Here the stereoselectivity of the reduction appeared to be lost.

The natural PGE_1, (−)-11α,15(*S*)-dihydroxy-9-oxo-13-*trans*-prostenoic acid, was prepared from (−)-7-[2-*trans*-styryl-3(*R*)-hydroxy-5-oxocyclopentenyl]heptanoic acid[1] in the same manner. The synthetic PGE_1 was indistinguishable from natural PGE_1 in melting point, NMR in deuteriomethanol or deuterioacetone, optical rotation in tetrahydrofuran, and in a variety of TLC systems. The synthetic PGE_1 exhibited equal (within experimental error) biological activities to the authentic natural PGE_1 prepared from bishomo-γ-linolenic acid by sheep seminal tissue.

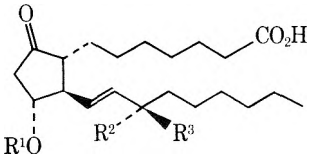
Optically active **5** and **12a** were obtained by hydrolysis of the corresponding THP derivatives (**11** and **12b**). The CD data of **5** and **12a** (Table I) demonstrates that **5** takes the same conformation as natural PGE_1 whereas **12a** takes the enantiomeric conformation rendering additional evidence for the configurations previously proposed[11] for the racemic compounds.

Table I
ORD[a] and CD[b] of PGE_1 (1), 5, and 12a

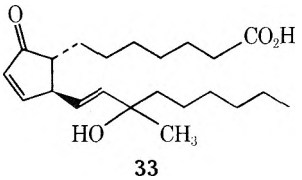
	(−)-PGE_1 (1)	5	12a
ORD n→π*			
peak	272 nm	~260 nm	315 nm
	+7161	+6000	+3870
trough	314 nm	315 nm	254 nm
	−6168	−4400	−14,100
CD n→π*			
	296 nm	297 nm	296 nm
	−11,100	−12,000	+10,200

[a] Molecular rotation. [b] Molecular ellipticity.

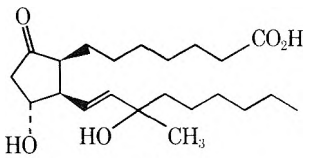
The total synthesis (Schemes II and III) was readily applied to the preparation of (±)-ω-homo-PGE_1 (**32c**) by replacing the Wittig reagent with *n*-heptanoyl triphenylphosphorane (**10b** → **32a** → **32b** → **32c**). The total synthesis could be modified for the preparation of 15-alkyl prostaglandins. Thus, the 15-keto intermediate (**32a**) in this sequence was treated with methylmagnesium bromide in tetrahydrofuran at −78° to give, after mild hydrolysis, an approximately 55:45 mixture of (±)-15(*S*)-15-methyl-ω-homo-PGE_1 (**32d**) and (±)-15(*R*)-15-methyl-ω-homo-PGE_1 (**32e**). It is noteworthy that the unsaturated ketone **32a** reacted preferentially in the presence of the saturated ketone. The latter did not undergo Grignard reaction at all under these conditions. The configuration at C-15 was determined by comparison with the biological activities of 15(*S*)- and 15(*R*)-15-methyl-PGE_1.[21] The major by-product in the Grignard reaction was the elimination product (**33**).[22] A small amount of (±)-8-epi-15(*R*,*S*)-15-methyl-PGE_1 (**34**) was also obtained as a minor by-product which could be isomerized to **32d** and **32e** with potassium acetate in ethanol.[18]



32a, R^1 = tetrahydropyranyl; R^2 and R^3 = O
b, R^1 = tetrahydropyranyl; R^2 = OH; R^3 = H
c, R^1 = H; R^2 = OH; R^3 = H
d, R^1 = H; R^2 = OH; R^3 = CH_3
e, R^1 = H; R^2 = CH_3; R^3 = OH



33



34

Experimental Section[23-26]

(+)-9,15-Dioxo-11α-tetrahydropyranyl-13-*trans*-prostenoic Acid (11) and Its (±)-8(*S*),12(*S*) Isomer (12b). A. (+)-11 from 5. To a solution of 1.014 g of **5**[11] and 0.42 ml of dihydropyran in 2.5 ml of methylene chloride was added 0.10 ml of 10% *p*-toluenesulfonic acid in THF. The reaction mixture was set aside for 2 hr, then diluted with methylene chloride and washed with aqueous sodium sulfate. The organic layer was dried over sodium sulfate and concentrated. The residue was chromatographed[25] on 75 g of CC-4. The desired material **11** (982 mg) was found in the 15% ethyl acetate eluate: uv (MeOH) 228.5 nm (ε 12,400); ir ($CHCl_3$) 1746, 1713, 1632, 1039, 979, 913 cm^{-1}; NMR (100 MHz, $CDCl_3$) for one diastereomer (**17** or **18**) δ 4.10 (q, *J* = 8.5 Hz, H-11), 4.65 (m, $W_{1/2}$ < 6.5 Hz, acetal H), 6.27 (d, *J* = 16 Hz, H-14), 6.81 (q, *J* = 16 and 8.5 Hz, H-13); NMR for the other diastereomer (**18** or **17**) δ 4.26 (q, *J* = 8.5 Hz, H-11), 4.65 (m, $W_{1/2}$ < 6.5 Hz), 6.31 (d, *J* = 16 Hz, H-14), 6.86 (q, *J* = 16 and 8.5 Hz, H-13); R_f on TLC[24] 0.623 (a single dark-brown spot).

Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.55; H, 9.55.

B. (±)-12b from 12a. Pure **12b** (330 mg, inseparable mixture of two diastereomers similar to **17**, **18**) was prepared from 420 mg of **(±)-12a** in the same manner as in A: uv (MeOH) 228.5 nm (ε 12,900); ir ($CHCl_3$) 1746, 1714, 1632, 1121, 1029, 989 cm^{-1}; NMR (100 MHz, $CDCl_3$) for one diastereomer δ 4.47 (t, *J* = 4 Hz, H-11), 4.65 (m, acetal H), 6.22 (d, *J* = 16 Hz, H-14), 7.11 (q, *J* = 16 and 8.5 Hz, H-13); NMR for the other diastereomer δ 4.35 (t, *J* = 4.5 Hz, H-11), 4.60 (m, acetal H), 6.22 (d, *J* = 16 Hz, H-14), 6.92 (q, *J* = 16 and 8 Hz, H-13); R_f on TLC[24] 0.57 (a single dark-brown spot).

Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.55; H, 9.24.

C. (±)-11 and (±)-12b from 3a. To a solution of 40 g of crude **3a**[11] (prepared from 50 g of **2**) and 22 ml of dihydropyran in 120 ml of methylene chloride was added 2 ml of 10% *p*-toluenesulfonic acid in THF. After the exothermic reaction subsided, 700 ml of freshly prepared cold (10°) aqueous chromous sulfate solution[15b] was added under a nitrogen stream. The mixture was vigorously stirred under nitrogen at room temperature for 30 min. To this mixture was added in sequence with vigorous stirring 60 g of ammonium sulfate, 500 g of sucrose, 300 ml of 1 *M* citric acid, and 1 l. of ether. The ethereal extract (total 4 l.) was washed with 200 ml of saturated ammonium chloride solution, then with a saturated sodium chloride solution, and dried over sodium sulfate. Upon evaporation of the solvent, 44 g of crude **10b** was obtained, which was treated immediately with 100 g of triphenyl-*n*-hexanoylmethylenephosphorane[28] in 500 ml of benzene for 6 days at 25°. The reaction mixture was washed with cold 2% citric acid, then with 1% salt solution, and dried over sodium sulfate. Concentration gave 77 g of product. This was chromatographed on 1.4 kg of CC-4. The desired material was found in the 15% ethyl acetate eluates, which were pooled in three fractions: I (4.12 g, **11b** containing the 8 epimer **22**, the latter R_f on TLC[24] 0.685); II (13.7 g, **11** identified by NMR with pure **11b** prepared in A); and III (11.5 g, **11** containing **12b**). I, II, and III were reduced with TTBH separately to produce **27**.

D. Determination of Ratio of 11 and 12b. Crude **3a** (2.0 g, 8 mmol) was converted into a mixture containing **11** and **12b** by the

procedure described in C. The THP group was removed by treatment with 150 ml of HOAc–water–THF (20:10:3)[4d] at 38–40° for 4 hr. The hydrolysis mixture was diluted with water and extracted with benzene. The benzene extract was washed with 1% sodium chloride solution, dried over sodium sulfate, and concentrated to give 3.2 g of residue. Separation[26] on a partition column made from 75 g of CC-4 afforded 670 mg of **5**,[11] 44 mg of **12a**,[11] and 57 mg of $\Delta^{8(12)}$ derivative.[28]

(±)-9,15-Dioxo-11α-tetrahydropyranyloxy-13-*trans*-12(*S*)-prostenoic Acid (21b) from 21a. **21b** was prepared in the usual manner (see A for preparation of **11**) from 207 mg of crystalline **21a**.[11] R_f on TLC[24] (0.554) was almost identical with that of **12b** but the NMR spectrum was evidently different, demonstrating that no isomerization[11] (**21** → **12**) took place during the reaction: NMR (100 MHz, $CDCl_3$) of one diastereoisomer δ 6.20 (d, J = 16 Hz, H-14), 6.64 (q, J = 6.76 (q, J = 16 and 10.5 Hz, H-13).

Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.21; H, 8.90.

(±)-15-Dehydro-PGF$_{1\alpha}$ (23), (±)-15-Dehydro-PGF$_{1\beta}$ (24), and (±)-PGE$_1$ (1) by Reduction of 11. A solution of 208 mg of crude **11** (fraction II, procedure C, vide supra) in 20 ml of methanol was chilled to −78° to which 1.5 ml of 3.2% methanolic triethylamine was added followed by 18.2 mg of sodium borohydride in 1 ml of water. The mixture was warmed to 0°. After 2 hr, the reaction mixture was treated with acetone to destroy excess borohydride, diluted with ether, washed with cold 2% citric acid and with 1% sodium chloride, dried over sodium sulfate, and concentrated. The product was chromatographed on 5 g of CC-4 and eluted with 20% ethyl acetate–benzene. The first 40 ml gave 52 mg (R_f on TLC[24] 0.62) of the starting material which was recycled, the next 36 ml gave 40 mg of a reduction product (I, R_f on TLC[24] 0.48), and the last 132 ml gave 63 mg of a reduction product (II, R_f on TLC[24] 0.47). Fraction I was dissolved in 10 ml of HOAc–water–THF (20:10:3),[4d] left at 25° for 20 hr, stripped of the solvent, and chromatographed on a partition column.[26] The half-crystalline product was recrystallized from ethyl acetate–cyclohexane to give pure **23**: mp 81–82°; uv (MeOH) 233 nm (ε 13,500); NMR (100 MHz, $CDCl_3$) δ 2.27 (t, 2, J = 7 Hz, H-2), 2.60 (t, 2, J = 7 Hz, H-16), 3.96 (complicated q, J = 7 Hz, H-11), 4.14 (m, $W_{1/2}$ = 13 Hz, H-9), 6.19 (d, J = 16 Hz, H-14), 6.80 (q, J = 16 and 9 Hz, H-13).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.61; H, 10.00.

Fraction II was hydrolyzed in the same manner and chromatographed on a partition column[26] made from 10 g of CC-4, and fractions of 13 ml were collected. Fractions 14–16 (R_f on TLC[24] 0.138, dark brown spot) gave crystalline (±)-PGE$_1$ melting at at 112–113° (lit.[7a] mp 112–113°, lit.[4a] mp 112.8–113.1°) after recrystallization from ethyl acetate–cyclohexane. Its NMR (100 MHz, CD_3OD) was indistinguishable from that of natural PGE$_1$ in every detail: δ 4.05 (m, 2, H-11 and H-15), 6.58 (complicated q, 2, $J \cong$ 2.5 Hz, H-13 and H-14).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.61; H, 9.96.

Fractions 17–19 (R_f on TLC[24] 0.185, blue spot) of the partition column gave **24** as a colorless gum: uv (MeOH) 232 nm (ε 13,100); NMR (100 MHz, CD_3OD) δ 2.25 (t, 2, J = 7 Hz, H-2), 2.59 (t, 2, J = 7 Hz, H-16), 3.91 (complicated q, $J \cong$ 5 Hz, H-11), 4.08 (q, J = 5.5 Hz, H-9), 6.14 (d, J = 16 Hz, H-14), 6.84 (q, J = 16 and 9 Hz, H-13).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.24; H, 9.54.

Sodium Borohydride Reduction of 23. The procedure followed was that described by Pike.[18] The reduction product was found to be a mixture of PGF$_{1\alpha}$ (**25a**) and 15-epi-PGF$_{1\alpha}$ (**25b**) by careful examination of TLC [silica gel plate and uppler layer of EtOAc–HOAc–2,2,4-trimethylpentane–water (22:4:3:20)] against authentic PGF$_{1\alpha}$[11] and 15-epi-PGF$_{1\alpha}$.[11]

Sodium Borohydride Reduction of 24. The reduction product was identified as a mixture of PGF$_{1\beta}$ (**26a**) and 15-epi-PGF$_{1\beta}$ (**26b**). For the procedure employed, see the preceding paragraph.

(±)-PGE$_1$ (1) by Thexyl Tetrahydrolimonyl Borohydride Reduction of 11. A. From Crude 11. Over a period of 1 hr, a solution of 26.8 mmol of TTBH (**29**)[19] in 88 ml of THF–*n*-pentane was added to a solution of 7.258 g of **11** (fractions I and II of procedure C, vide supra) in 50 ml of THF at −78° under a nitrogen stream. The reaction mixture was immediately diluted with 100 ml of ether and treated with 10% citric acid while it was still cold. The ethereal extract was washed with 1% sodium chloride solution, dried over sodium sulfate, concentrated, and chromatographed[25] on 500 g of CC-4. Results were as follows: recovered starting material (15% ethyl acetate–benzene, 3.048 g); a mixture (I, 1.396 g, 25% ethyl acetate) containing impure **27**; pure **27** (II, 1.798 g, 25–35% ethyl acetate); a mixture (III, 0.767 g, 50% ethyl acetate) containing impure **27**; and finally free PGE$_1$ (IV, 0.158 g, crystalline, 75–100% ethyl acetate). Fraction II was hydrolyzed with 200 ml of HOAc–water–THF (20:10:3)[4d] for 20 hr at 25°. The solvent was removed and the residue was recrystallized from ethyl acetate to give 588 mg of (±)-PGE$_1$. The mother liquor gave a second crop (200 mg) after chromatography on CC-4. Fraction III, upon hydrolysis, gave (±)-PGE$_1$ containing PGF$_{1\alpha}$. Fraction I, upon hydrolysis followed by chromatography[25] on CC-4, gave 75 mg of 8,15-bisepi-PGE$_1$ (**30a**), less than 255 mg of crude 15-epi-PGE$_1$ (**28**), and 52 mg of crystalline (±)-PGE$_1$.

(±)-PGE$_1$ obtained in this experiment (946 mg, 27% based on consumed **11**) melted at 112–113° and was identical with the specimen obtained by sodium borohydride reduction. Thus the stereospecificity of the reduction (ratio of PGE$_1$ to **28**) was better than 4:1.

(±)-15-epi-PGE$_1$ was oily: NMR (60 MHz, CD_3OD) δ 4.10 (m, 2, H-11 and H-15), 5.69 (m, 2, H-13 and H-14).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.95; H, 10.05.

B. From Pure 11. Pure **11** (3.834 g, prepared from **5** as in procedure A) in 150 ml of THF was reduced with 15 mmol of TTBH (**29**)[19] in 40 ml of THF–*n*-pentane at −78° under nitrogen. After the addition of the reagent was completed the reaction mixture was stirred at −78° for 20 min and worked up as in A. Chromatographic separation[25] gave 1.95 g of recovered starting material, 1.5 g of **27**, 1.0 g of crude **27**, 0.185 g of 15-epi-PGE$_1$ (**28**), and 740 mg of crystalline PGE$_1$.

(−)-PGE$_1$. Cleavage[11] of 21.6 g of the 3(*R*)-(−) enantiomer[1] of **2** afforded 15 g of 3(*R*)-**3a** which was then converted into the THP derivative **3b**, reduced to **9b**, and finally treated with the Wittig reagent in the same manner as described for the racemic series. Chromatographic separation on 500 g of CC-4 using 15% ethyl acetate gave fraction A [0.948 g, a mixture containing 11(*R*)-**11** and 11(*R*)-**22**], fraction B [2.980 g, 11(*R*)-**11**], fraction C [5.378 g, 11(*R*)-**11** containing a small amount of 11(*R*)-**12b**], and fraction D [0.401 g, ca. 1:1 mixture of 11(*R*)-**11** and 11(*R*)-**12b**] in order of increasing polarity. Fraction B exhibited an identical NMR spectrum (100 MHz, $CDCl_3$) with that of the corresponding racemic **11**.

Fraction C, which was mostly **11** as demonstrated by the NMR, was dissolved in 50 ml of THF and treated with 12.2 mmol of TTBH (**29**)[19] in 40 ml of THF–*n*-pentane for 1.5 hr at −78° under nitrogen. An additional 12.2 mmol of TTBH was added and the solution was stirred for an additional 30 min at −78°. The reaction mixture was worked up as in the racemic series and chromatographed[25] on 220 g of CC-4. The 35% ethyl acetate fraction gave 138 mg of crude 11(*R*)-**27** (fraction I), 970 mg of pure 11(*R*)-**27** (fraction II), and 307 mg of crude 11(*R*)-**27** (fraction III). Fraction II was analyzed: NMR δ 4.73 (m, acetal H), 5.67 (m, H-13 and H-14); [α] −5.0 (c 0.993, MeOH).

Anal. Calcd for $C_{25}H_{42}O_6$: C, 68.46; H, 9.65. Found: C, 69.21; H, 10.10.

A portion (875 mg) of fraction II (**27**) was hydrolyzed with 70 ml of HOAc–water–THF[4d] and chromatographed[25] as in the racemic series. The crystalline (−)-PGE$_1$ (255 mg) was recrystallized from ethyl acetate: mp 114–114.5° (lit.[4e] mp 113.5–114°, lit.[9] mp 115–116°); $[\alpha]^{24}D$ −53.2 (c 0.977, THF) (lit.[9] −54.3, natural PGE$_1$ purchased from Unilever −55.8); NMR (100 MHz, CD_3OD) identical with that of the natural product.

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.60; H, 9.46.

Fraction B (pure **11**, 2.980 g) was reduced with 11.7 mmol of TTBH (**29**) and worked up in the same manner to give 355 mg of the starting material, 1.4 g of **27**, 270 mg of crystalline PGE$_1$, and 210 mg of a mixture of PGE$_1$ and PGF$_{1\alpha}$.

(−)-9,15-Dioxo-11α-hydroxy-13-*trans*-prostenoic Acid (5) and (−)-9,15-Dioxo-11α-hydroxy-13-*trans*-8(*S*),12(*S*)-prostenoic Acid (12a). Approximately a 1:1 mixture of optically active **11** and **12b** (401 mg, fraction D of the preceding preparation) was hydrolyzed with HOAc–water–THF (20:10:3)[4d] for 20 hr at 25° and worked up as in the racemic series. Chromatographic separation[25] on 50 g of CC-4 afforded 30 mg of crystalline **12a** (R_f on TLC[24] 0.323, 30% ethyl acetate fraction) followed by a mixture of **5** and **12a**, and then 47 mg of pure **5** (R_f on TLC[24] 0.300).

Recrystallization from ether–*n*-pentane gave **12a**: mp 67°; $[\alpha]^{25}D$ −10.12 (c 1.038, MeOH). This specimen was spectroscopically indistinguishable from the racemic compound used (**6**)[11] and was for the ORD–CD study (see Table I). Oily **5** was used for the

optical study: $[\alpha]^{25}D$ −41.6 (c 1.009, MeOH); see Table I for ORD and CD.

(±)-11-epi-PGE_1[16] and (±)-11,15-bisepi-PGE_1.[16] Pure (±)-**12b** (2.495 g) prepared from **12a** was reduced with 12.7 mmol of TTBH (**29**)[19] in the usual manner (vide supra) and chromatographed[25] on 700 g of CC-4. The 30% ethyl acetate fractions gave rise to 851 mg of 11,15-bisepi compound (R_f on TLC[24] 0.50, fraction I) followed by 888 mg of crude 11-epi compound (R_f on TLC[24] 0.49, fraction II). Fraction I, upon hydrolysis with HOAc–water–THF (20:10:3)[4d] for 20 hr at 25°, afforded 199 mg of crystalline (±)-11,15-bisepi-PGE_1 (recrystallized from ethyl acetate), mp 91–92° (lit.[4b] mp 88.6–89.3°), R_f[24] on TLC 0.228, identical with a specimen obtained by sodium cyanoborohydride reduction[8a] of **12a**.

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.70; H, 9.80.

Fraction II was also hydrolyzed with HOAc–water–THF and recrystallized from ethyl acetate to give 193 mg of 11-epi-PGE_1, mp 92.5° (lit.[4b] mp 92.5–93°), R_f on TLC[24] 0.160, identical with the specimen obtained from **12a** by sodium cyanoborohydride reduction.[8a]

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.64; H, 9.79.

(±)-9-Oxo-11α,15(*S*)-dihydroxy-8(*S*)-13-*trans*-prostanoic Acid (8-epi-PGE_1, 30b)[18] and (±)-9-Oxo-11α,15(*R*)-dihydroxy-8(*S*)-13-*trans*-prostenoic Acid (8,15-Bisepi-PGE_1, 30a). The pure starting material (**22**) could not be prepared. Crude **11** (chromatographic fraction I in procedure C was rechromatographed[25] to produce **22** which still contained a small amount of **11**. This substance (584 mg) was reduced with 9 ml of 0.3 *M* **29** in 40 ml of THF (−78°, 1.5 hr). The reaction mixture was worked up in the usual manner and chromatographed on 200 g of SilicAR CC-4; 129 mg of the THP ether of **30a** (30% ethyl acetate–benzene), 97 mg of the THP ether of **30b** (30–50% ethyl acetate–benzene), 106 mg of **30a** (50% ethyl acetate–benzene), 41 mg of **30b** (ethyl acetate), and 19 mg of **1** (ethyl acetate) were obtained. The partial hydrolysis had apparently taken place on the CC-4 column. The THP ethers were hydrolyzed in HOAc–water–THF (20:10:3) (25°, 24 hr)[4d] to **30a** and **30b**, respectively. In a similar experiment, 4.5 g of crude **22** afforded 939 mg of the THP ether of **30a**, 554 mg of the THP ether of **30b**, 1.204 g of **30a**, and 282 mg of **30b**. **30a** was oily: R_f[24] on TLC 0.262; NMR (60 MHz, CD_3OD) δ 5.73 (q, *J* = 15.5 and 5 Hz, H-14), 5.30 (q, *J* = 15.5 and 8.5, H-13), 4.25 (m, H-11), 4.05 (m, H-15).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 68.08; H, 9.52.

Isomerization of 30a and 30b to 28 and 1. The structure of **30b**[18] was confirmed by potassium acetate induced isomerization[18] to **1**. Under the same conditions, **30a** was isomerized to **28** (R_f on TLC[24] 0.200) confirming the structure of **30a**.

(±)-9,15-Dioxo-11α-tetrahydropyranyloxy-20-methyl-13-*trans*-prostenoic Acid (32a). This was prepared in the same manner as in procedure C for **11** starting from **10b** and *n*-heptanoylmethylenetriphenylphosphorane.[28] The desired material was eluted[25] with 15% ethyl acetate–benzene and used for the next step without further purification.

(±)-ω-Homo-PGE_1 (32c). Reduction of 5.511 g of **32a** with **29**[19] was similar to the reduction of **11**. The THP ether (**32b**, 1.928 g) was eluted[25] with 35% ethyl acetate–benzene: NMR (60 MHz, $CDCl_3$) δ 5.65 (m, 2, H-13 and H-14), 4.77 (m, acetal H), 4.07 (m, 2, H-11 and H-15), 3.67 (m, 2, OCH_2– in THP).

Anal. Calcd for $C_{26}H_{44}O_6$: C, 67.57; H, 9.93. Found: C, 67.67; H, 9.98.

The THP group was removed by treatment of 1.707 g of **32b** with 100 ml of HOAc–water–THF (20:10:3)[4d] for 20 hr at 25°. The hydrolysis solution was concentrated in vacuo and the residue was chromatographed.[25] Crystalline (±)-ω-homo-PGE_1 (**32c**, 752 mg) was found in the 75% ethyl acetate–benzene fractions. It was recrystallized from ethyl acetate (mp 100.5–101°).[29] The NMR (60 MHz, CD_3OD) was identical with that of authentic (−)-ω-homo-PGE_1 kindly provided by the Unilever Co.: δ 5.64 (m, 2, H-13 and H-14), 4.08 (m, 2, H-11 and H-15).

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.80; H, 10.07.

(±)-9-Oxo-11α,15-dihydroxy-15,20-dimethyl-15(*S*)-13-*trans*-prostenoic Acid (32d) and (±)-9-Oxo-11α,15-dihydroxy-15,20-dimethyl-15(*R*)-13-*trans*-prostenoic Acid (32e). A solution of 3.20 g of crude **32a** in 50 ml of THF was added to a stirred solution of 20 ml of 3 *M* ethereal methylmagnesium bromide in 150 ml of THF at −70°. After 20 min, the reaction mixture (−78°) was poured into aqueous citric acid and extracted with ether. The ethereal extract was washed with 5% ammonium chloride and water, dried over sodium sulfate, and concentrated. The residue was treated with 100 ml of HOAc–water–THF (20:10:3)[4d] for 24 hr at 25°. The aqueous acetic acid solution was concentrated in vacuo and chromatographed.[25] A mixture of **32d** and **32e** was eluted with 50–60% ethyl acetate–benzene and was recrystallized from ethyl acetate–Skelly B to give approximately a 1:1 mixed crystal of **32d** and **32e**, mp 73–76°. **32d** and **32e** form a mixed crystal at any ratio. The separation of **32d** and **32e** was carried out by Misses Linda Petrosky and Janet Mueller of the Chromatography Department using 4% deactivated Woelm silica as the adsorbent and ethyl acetate–acetic acid–cyclohexane (100:1:99) as the solvent. The "unnatural" **32e** was eluted first closely followed by the "natural" isomer (**32d**). (±)-15(*S*) isomer (**32d**) was recrystallized from ether–Skelly B (mp 88–89°): NMR (100 MHz, CD_3OD) δ 5.64 (m, 2, H-13 and H-14), 4.07 (q, *J* = 8 Hz, H-11), 2.70 (q, *J* = 18 and 7.5, H-10β), 2.12 (q, *J* = 18 and 9.5 Hz, H-10α), 1.285 (s, 15-CH_3).

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 68.80; H, 9.91.

(±)-15(*R*) isomer (**32e**) was recrystallized from ethyl acetate–Skelly B (mp 83–84°): NMR (100 MHz, CD_3OD) δ 5.64 (m, 2, H-13 and H-14), 4.07 (q, *J* = 8 Hz, H-11), 2.70 (q, *J* = 18 and 7.5 Hz, H-10β), 2.12 (q, *J* = 18.5, 9 Hz, H-10α), 1.280 (s, 15-CH_3(/

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 68.80; H, 9.88.

The ratio of **32d** and **32e** obtained was approximately 55:45. R_f on TLC (Woelm silica gel F on an 8-in. plate, 2% acetic acid in ethyl acetate) for **32d** and **32e** was 0.214 and 0.243, respectively.

(±)-9-Oxo-11α,15-dihydroxy-15,20-dimethyl-8(*S*),15(*R,S*)-13-*trans*-prostenoic Acid (34). This compound was obtained as a minor product in the preparation of **32d** and **32e**. It was not clear whether the epimerization at C-8 took place during the Grignard reaction, or whether the starting **32a** contained a small amount of 8 epimer. The earlier chromatographic fractions[25] (50% ethyl acetate–benzene) in preparation of **32d,e** were purified by the partition column[11] to afford oily **34** which was a mixture of 15(*R*) and 15(*S*) isomers: NMR (100 MHz, CD_3OD) δ 5.73 (d, *J* = 16 Hz, H-14), 5.24 (q, *J* = 16 and 10 Hz, H-13), 3.03 (broad t, *J* = 8 Hz, H-12), 1.22 (s, 15-CH_3).

Isomerization of 34 to 32d and 32e. A solution of 21 mg of **34** in 10 ml of 4.2% ethanolic potassium acetate was allowed to stand at 25° for 70 hr. Approximately one-half of **34** had been isomerized to a mixture of **32d** and **32e** as demonstrated by TLC.[24] The R_f values[24] of **32d**, **32e**, and **34** were 0.19, 0.19, and 0.28, respectively.

Acknowledgment. Large-scale preparations of **2** were performed by Drs. T. Harrow and P. Chatfield, G. D. Searle & Co., High Wycombe, England. The Wittig reagents were prepared by Mr. J. Schulz. The spectral and optical data presented here were taken by Mr. A. J. Damascus. The elementary analyses were carried out by Mr. E. J. Zielinski. Some of the chromatographic separations were carried out by Mr. R. T. Nicholson and staff. The optically active **2** was prepared by Dr. W. Marsheck, Department of Microbiology. We express our sincere thanks to those who are mentioned above. The authors are indebted to Dr. F. Colton, Dr. R. A. Mueller, and Mr. C. R. Dorn for several very helpful discussions during the course of this work and also to Dr. R. Bible and Mrs. L. Swenton for assistance in interpretation of the NMR spectra.

Registry No.—(±)-**1**, 20348-58-7; (−)-**1**, 745-65-3; (±)-**3a**, 34388-79-9; 3(*R*)-**3a**, 41693-78-1; (±)-**5**, 34402-60-3; (−)-**5**, 22973-19-9; (±)-**11**, 52163-83-4; 11(*R*)-**11**, 41638-40-8; (±)-**12a**, 34388-82-4; (−)-**12a**, 54984-02-0; (±)-**12b**, 41638-39-5; 11(*R*)-**12b**, 55028-41-6; (±)-**21a**, 34388-90-4; (±)-**21b**, 54984-03-1; (±)-**22**, 54984-04-02; (±)-**23**, 52087-42-0; (±)-**24**, 52087-41-9; 11(*R*)-**27**, 54889-37-1; (±)-**28**, 20897-96-5; (±)-**30a**, 23203-65-8; (±)-**32a**, 54984-05-3; (±)-**32b**, 54984-06-4; (±)-**32c**, 55028-42-7; (±)-**32d**, 54889-38-2; (±)-**32e**, 54931-78-1; (±)-15(*R*)-**34**, 55028-43-8; (±)-15(*S*)-**34**, 55028-51-8; (±)-11,15-bisepi-PGE_1, 20348-69-0; (±)-11-epi-PGE_1, 20348-68-9.

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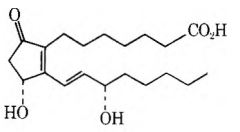

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(20) With respect to the five-membered ring. It is always axial with respect to the THP ring.
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(22) Mr. C. R. Dorn of these laboratories found that the trimethylsilyl group is a better protecting group than THP for the Grignard reaction, reducing the elimination product to a negligible amount.
(23) Melting points were taken on a Thomas-Hoover Unimelt in open capillaries and were not corrected. The NMR spectra were recorded at 60 MHz on Varian A-60 or at 100 MHz on Varlan XL-100 NMR spectrometers in either deuteriochloroform or deuteriomethanol, using Me_4Si as an internal reference. $W_{1/2}$ denotes peak width at half-height of the multiplets. All uv spectra were determined in a 1 mg % methanol solution.
(24) R_f values for thin layer chromatography were determined on a 1 × 3 in. silica gel plate using benzene–ethyl acetate–acetic acid (25:25:1) sprayed with ethanolic phosphomolybdic acid.
(25) Unless otherwise mentioned adsorption column chromatography was carried out on Mailinckrodt SilicAR CC-4 (100–200 mesh) using benzene containing increasing percentages of ethyl acetate.
(26) Partition column chromatography was carried out by the procedure described in ref 11.
(27) Two diastereoisomers, **17** and **18**, were inseparable.
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(29) The melting point of (±)-ω-homo-PGE_1 could not be found in the literature.

Total Synthesis of (±)-β-Gorgonene

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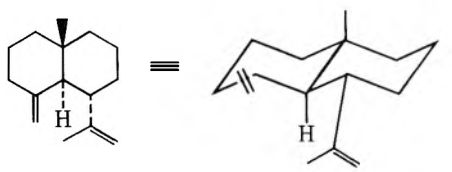
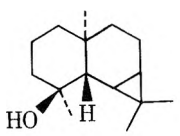
A synthetic approach to a novel nonisoprenoid sesquiterpene skeleton is described. The skeleton is derived from a rearrangement of the cationic intermediate leading to the germacrane skeleton resulting in a misplaced isopropenyl group. The key construction sequence involves the stereoselective introduction of the isopropenyl to 10-methyl-8(9)-octal-1-one. This intermediate was synthesized by two routes, both proceding through *cis*- and *trans*-10-methyl-1-decalone.

A considerable amount of synthetic chemistry has been directed toward the preparation of various members of the decalin-derived bicyclic sesquiterpenes.[1] One particular member of this general class, (+)-β-gorgonene (1), isolated



1

by Weinheimer and coworkers,[2] was of particular interest to us since it apparently represented an example of the violation of the usually observed biogenetic substitution pattern. Since the initial report of our synthesis,[4] a biogenetic-like conversion of maaliol (2) to (−)-β-gorgonene by dry HCl presumably through cation 3 has been reported which



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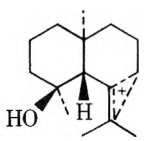

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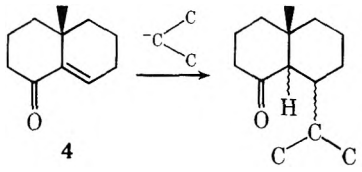
confirms the absolute stereochemistry of (+)-β-gorgonene (1) and supports the rearrangement hypothesis for its biosynthesis.[5]

A synthetic approach to this class of molecules requires that one deal with the problem of stereoselective introduction of the required equatorial isopropenyl group. This problem is compounded by the presence of the angular methyl group and the fact that the point of attachment is a peri-like position in the decalin ring system in a 1,3 relation to the angular group.

We felt that octalone (4) represented one plausible pre-

cursor. The required three-carbon segment might then be introduced via a Michael-type process utilizing an appropriate three-carbon carbanion (eq 1). The stereochemical

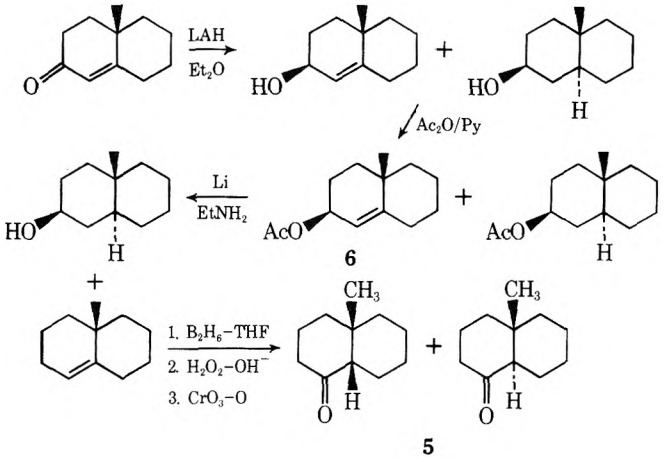


(1)

4

problems associated with this process provide a particularly good system in which to test the effects of steric interactions in the transition state upon the stereochemical outcome of conjugate addition of organometallic and other carbanionic reagents.

Octalone (4) had been prepared previously by Djerassi and Marshall[6] by a synthesis not well suited to preparation of sizable quantities, as it involved a low-yield rearrangement of a 2-bromo-3-decalone precursor. We prepared octalone (4) via two routes both passing through a mixture of *cis*- and *trans*-10-methyl-1-decalone (5) as shown below.



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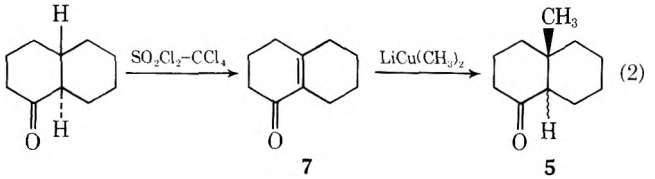
The first preparation of 10-methyl-1-decalone by ketone transposition is that of Marshall and Hochstetler.[7] We encountered some difficulties in loss of material after reductive elimination of the allylic acetate 6. The nature of the problem was finally recognized by isolation of *trans*-10-methyl-2β-decalol[8] from the reaction mixture. This byproduct presumably results from a nontrivial amount of overreduction during treatment with lithium aluminum hydride.

Since the foregoing sequence was multistep and suffered from relatively poor overall yields, the shorter sequence below was also utilized. Commercial α-decalone was treated

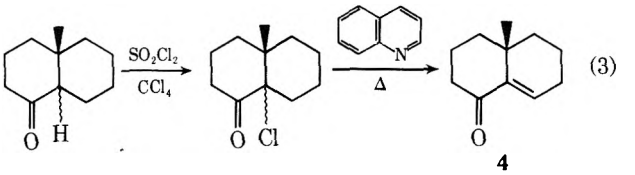


(2)

7 5

with SO_2Cl_2 in carbon tetrachloride and the crude mixture of chlorides was dehydrohalogenated in hot collidine[9] to 9,10-decal-1-one (7, 49%). Treatment of 7 with excess (2.5 equiv) lithium dimethylcuprate in ether at −20° for 23 hr gave a mixture of *cis*- and *trans*-10-methyl-1-decalone (5) in 91% yield (eq 2).

Ketones 5 prepared by either method were chlorinated with sulfuryl chloride in carbon tetrachloride to a mixture of tertiary chlorides and dehydrochlorinated by refluxing quinoline (84%) (eq 3).



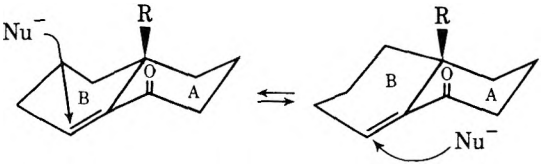
(3)

4

Studies of Conjugate Addition. Our initial attempts to introduce the three-carbon segment were based upon the assumption that the carbanionic species must undergo reversible addition to 4. The stereoelectronic factors controlling the Michael addition reaction favor kinetic antiparallel addition of the carbanion. In most cases this coincides with introduction of an axial group. Weakly nucleophilic carbanions appear to add reversibly and therefore under thermodynamic control. This is evidenced by the addition of malonate reported by Abe and coworkers[10] which resulted in an equatorial disposition of the side chain.

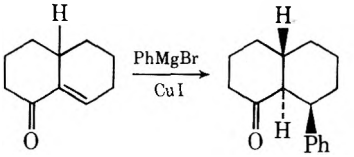
Despite numerous attempts under a variety of conditions, we were unable to effect the desired Michael addition either with sodiodimethyl malonate or sodiomethyl acetoacetate. Only starting material was recovered. Upon utilizing a prolonged reaction period or vigorous reaction conditions, polymerization of 4 was observed. Djerassi previously pointed out the susceptibility of this particular unsaturated ketone to polymerization.[6] Peri interactions in the product and/or interactions with the angular group apparently result in an unfavorable equilibrium constant for the addition.

We next considered the direct addition of organometallic reagents catalyzed by copper or of the stoichiometric organocuprate reagent. This presumably would allow the introduction of the intact isopropenyl group. The stereochemical result was expected to be the desired equatorial introduction of the isopropenyl group. Work of Allinger[11] and Marshall[12] suggested that an antiparallel approach[13] of the reagent is a primary pathway. This pathway leads to a half-chair enolate intermediate which is presumably more favorable. However, attack on conformer 8 would lead to a severe 1,3-nonbonded interaction of the incoming reagent with the angular methyl group in the transition state. This



8a, R = CH_3 9a, R = CH_3
b, R = H b, R = H

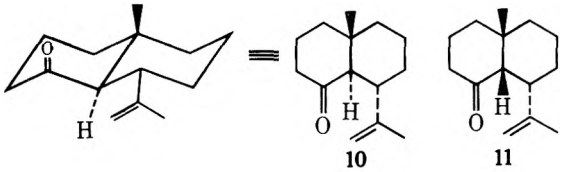
particular unsaturated ketone has an alternative pathway available which satisfies the antiparallel stereoelectronic requirement and yet circumvents the severe 1,3 interaction in the transition state. Attack of the reagent can occur upon the alternative half-chair conformation 9 of ring B from the α direction resulting in eventual equatorial disposition of the added group. Only one case of a study of a related enone was available which indicated that, in the absence of an angular group, antiparallel addition to the conformer analogous to 8 was apparently favored[14] (eq 4).



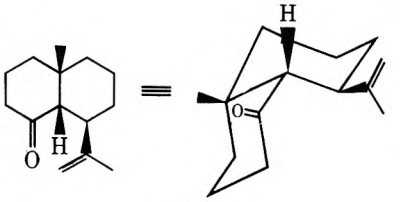
(4)

Addition of enone 4 in tetrahydrofuran (THF) to a solution of 2 equiv of the Grignard reagent prepared from 2-

bromopropene in THF containing 10 mol % CuI gave upon work-up a mixture of three saturated ketones in the approximate ratio of 7:2:1 (45%). The ketones were separated by preparative VPC. The structures of the ketones were tentatively assigned as **10**, **11**, and **12**, respectively, on the

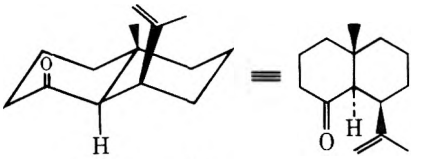


10 **11**



12

basis of the following data. The major product (**10**) had an angular methyl resonance at δ 0.81 which suggested a trans ring junction. Examination of spectral data for a large number of compounds in the literature indicated that *trans*-10-methyl-1-decalones characteristically had C-10 chemical shifts in the range δ 0.75–0.9, whereas the corresponding cis isomers had C-10 methyl chemical shifts in the range δ 1.05–1.20.[15] Treatment of pure **10** with dilute $NaOCH_3$ in CH_3OH at room temperature afforded an equilibrium mixture of **10** and **11** (~70:30), establishing the epimeric relationship of **10** and **11**. Chemical equilibration to a mixture of **10** and **11** (~66:34) and the chemical shift of the C-10 methyl of **11** (δ 1.20) further confirmed the assignment of **11** as a cis ring junction isomer. Tentative assignment of the stereochemistry of the isopropenyl group rested upon examination of the spectral and chemical characteristics of the minor product (**12**). Attempted equilibration of **12** ($NaOCH_3$–CH_3OH) resulted in the recovery of this material unchanged. The presence of a high-field methyl resonance (δ 0.79) in **12** implied a stereochemical relationship of the carbonyl and angular group of the type found in **10**. This could only occur if **12** were epimeric with **10** and **11** at the point of attachment of the isopropenyl group (assuming only all-chair conformations). If one considers conformations of the two possible epimeric ketones **12** and **13**, it is possible to assign the stereochemistry of the



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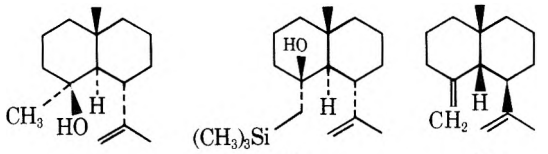
isopropenyl and ring junction in **12** as β. Only the conformation shown for the cis ring junction leads to equatorial disposition of the isopropenyl and angular methyl groups relieving steric interactions. Note also that the other possible cis conformation does not possess the proper spatial relationship of angular group and carbonyl leading to a high-field methyl signal (cf. **10**). The trans ring junction isomer possesses such a relationship; however, it allows no relief of the large 1,3 interaction. The only stable epimer is **12**, which is confirmed by the equilibration experiment. Therefore, **10** and **11** must have the isopropenyl group equatorially disposed.

Attempts to improve the steroselectivity of the conjugate addition by altering the temperature, the amount of cuprous salt added, and the nature of the salt were unsuccessful. Decreasing the temperature led to lower yields with some recovery of starting material. Increasing the ratio of cuprous salt from 10 mol % to 50 and 100 mol % resulted in larger amounts of coupling products but no substantial changes in stereoselectivity. Substitution of CuBr or $Cu(OAc)_2$ for CuI had also no effect.

Attempts to utilize the stoichiometric lithium cuprates prepared from isopropenyllithium in ether (2 equiv) and CuI (1 equiv) at −50 to −30° led to inferior yields of the conjugate addition products. In general, this has not been found to be the case,[16] although Ireland and coworkers have observed another instance of this behavior.[17] Upon isolation of the mixture of saturated ketones, no increase in stereoselectivity was observed.

Conversion to (±)-β-Gorgonene. Final confirmation of the foregoing structural assignments clearly lay in the conversion of **10** to (±)-β-gorgonene. Marshall and coworkers had observed a peculiar characteristic of 10-methyl-1-decalones which we attempted to exploit.[9] Wittig reactions in a number of cases performed upon an equilibrium mixture of cis and trans isomers resulted in olefin products enriched in the desired trans ring junction. This implies a reversible enolization and more rapid decomposition of the betaine derived from the trans ring junction isomer. Unfortunately, attempts to effect the methylenation of **10** or a mixture of **10** and **11** by treatment with methylenetriphenylphosphorane in DMSO[18] or THF resulted in no characterizable products but rather eventual destruction of the starting ketone. Apparently the addition process is markedly retarded by the equatorial isopropenyl group. Eventually base-catalyzed destruction of **10** occurred by some unknown mechanism. In choosing an alternative method for introduction of the exocyclic methylene, we reasoned that a reagent which would irreversibly add to the hindered carbonyl would be required. We established that organometallic reagents could successfully add to the carbonyl of **10** by reaction of **10** with methyllithium and methylmagnesium bromide in ether, which both produced a single tertiary carbinol (**14**); the stereochemistry was assigned by analogy



14 **15** **16**

to other cases in the literature. As expected, upon dehydration of **14** with $POCl_3$ or $SOCl_2$, complex mixtures of olefinic products were produced containing only minor amounts of (±)-β-gorgonene by VPC. To allow the use of an organometallic reagent and to direct the subsequent dehydration, we employed the olefination reagent described by Peterson[19] and Chan.[20] Trimethylsilylmethylmagnesium chloride in THF reacted with **10** (reflux 18 hr) to afford a tertiary carbinol assigned structure **15**. Decomposition of **15** (crude) by stirring in 3:1 acetic acid–water at room temperature for 3 hr gave a crude olefin product which was purified by chromatography (25% $AgNO_3$–SiO_2) and identified as (±)-β-gorgonene (**1**, 15%) by comparison of spectral characteristics and VPC retention time with an authentic sample of (±)-β-gorgonene.[21] Isomeric ketone **12** was also carried through the methylenation sequence in the same manner to afford an isomeric olefin with different spectral characteristics and VPC behavior than (±)-β-gorgonene (**1**), which was assigned structure **16** by the foregoing arguments.

Conjugate Addition Stereochemistry. It is clear from

the foregoing result that in this case the conjugate addition reaction is controlled by secondary steric interactions with the angular methyl group. This result will be generally true only in the event that the primary stereoelectronic requirement of antiparallel addition is satisfied as it was in this system. One must consider that the system may undergo a relatively facile conformational interconversion in order to satisfy this primary requirement.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on Varian A-60A and T-60 spectrometers and are reported in δ downfield from Me_4Si. Infrared (ir) spectra were obtained on a Perkin-Elmer 138 infrared spectrophotometer. Mass spectra were determined on an AEI-MS-9 spectrometer. VPC analyses were carried out on the Hewlett-Packard 5750 chromatograph utilizing flame ionization detection and nitrogen as carrier gas. Preparative VPC separations were performed on an F & M Model 776 prepmaster with a flame detector and nitrogen as the carrier gas.

10-Methyl-1(9)-octal-2-ol Acetate (6). 10-Methyl-1(9)-octal-2-one[24] (48.0 g, 0.292 mol) was dissolved in 125 ml of ether and added dropwise at 0° under nitrogen to a suspension of lithium aluminum hydride (10.0 g, 0.264 mol) in 300 ml of ether over 3 hr. The mixture was allowed to warm to room temperature and stir for 12 hr. The excess lithium aluminum hydride was decomposed by successive addition of water (10 ml), 15% sodium hydroxide (10 ml), and water (30 ml). The granular salts were filtered and washed well with ether (3 × 100 ml). The filtrate was dried over anhydrous magnesium sulfate and evaporated in vacuo to afford 51 g of oily octalol.

The crude octalol was dissolved in 200 ml of anhydrous pyridine and acetic anhydride (68.4 ml, 0.724 mol) was added. The mixture was stirred at room temperature under nitrogen for 24 hr. The crude mixture was poured into saturated sodium chloride and the layers were separated. The aqueous layer was extracted with ether (100 ml) three times. The combined organic layers were washed with water (100 ml) three times, 3.5% hydrochloric acid (100 ml) three times or until pH of the wash was ~2, 5% sodium bicarbonate (100 ml), and saturated sodium chloride and dried over anhydrous magnesium sulfate. The ether was evaporated and the residue was distilled under reduced pressure to afford 10-methyl-1(9)-octal-2-ol acetate (58 g, 95%): bp 92–95° (0.75 mm) [lit.[7] bp 62–63° (0.08 mm)]; ir (film) 1735, 1665, 1240, 1020 cm^{-1}; NMR (CCl_4) δ 5.2 (m, 3), 1.93 (s, 3), 1.11 (5, 3). This material is apparently contaminated with some *trans*-10-methyl-2-decalol acetate.

10-Methyl-1(9)-octalin. A 13.72-g sample of 10-methyl-1(9)-octal-2-ol acetate (0.066 mol) was dissolved in 200 g of anhydrous ethylamine and the solution was treated with 4.8 g (0.686 mol) of lithium metal in small pieces with vigorous stirring over about 40 min. The solution remained deep blue after the final addition. Excess lithium was destroyed by cautious addition of solid ammonium chloride until the solution was colorless. After evaporation of the ethylamine, saturated sodium chloride was added and the reaction mixture was extracted with ether (75 ml) seven times. The combined extracts were washed with water (100 ml), 2% sulfuric acid (50 ml), and saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of the ether and distillation afforded 5.5 g (55%) of 10-methyl-1(9)-octalin: bp 73–76° (10 mm) [lit.[7] bp 86–88° (26 mm)]; ir (film) 1665, 1380, 1360, 1010, 988 cm^{-1}; NMR (CCl_4) δ 5.24 (m, 1), 1.04 (s, 3).

A substantial amount of pot residue remained which possessed a strong OH absorption in the infrared. Crystallization of the pot residue from petroleum ether (bp 20–40°) at −70° after decolorization by Norit afforded 2.5 g (22%) of *trans*-10-methyl-2β-decalol, mp 65.5–67° (lit.[8] mp 64–68°), which was identified by comparison with an authentic sample.

***cis*- and *trans*-10-Methyl-1-decalone (5)** 10-Methyl-1(9)-octalin (19.6 g, 0.131 mol) was dissolved in 100 ml of dry (sodium) dimethoxyethane and cooled to 0° and sodium borohydride (6.16 g, 0.162 mol) was introduced. Freshly distilled boron trifluoride etherate (23 g, 0.162 mol) was added dropwise over 2 hr. The mixture was allowed to warm to room temperature and stir for 19 hr. Water (10 ml) was added slowly, followed by sufficient aqueous 15% sodium hydroxide to bring the pH to 9. Hydrogen peroxide (30%, 20 ml) was then introduced slowly over 1 hr with stirring. If all the peroxide had been consumed then additional peroxide was added until a starch–iodide test was positive for 1 hr after the addition was completed. Aqueous 10% sodium sulfite was utilized to destroy excess peroxide and the mixture was poured into water and extracted with chloroform (100 ml) seven times. The combined extracts were washed with water (100 ml), dried, and evaporated to afford crude oily alcohols.

The crude alcohol mixture was taken up in 150 ml of dry acetone and cooled to 0°. Jones reagent[25] was introduced dropwise until excess oxidant was present for 30 min after the last addition. Isopropyl alcohol was utilized to destroy excess oxidant and the mixture was poured into ether–saturated sodium chloride. The aqueous layer was extracted with ether twice (100 ml) and the combined organic solutions were washed with water (50 ml) twice and saturated sodium chloride. Evaporation of the solvent after drying over anhydrous magnesium sulfate and fractionation under vacuum afforded a mixture of *cis*- and *trans*-10-methyl-1-decalone (12.95 g, 60%): bp 70° (0.35 mm) [lit.[7] bp 72–73° (0.7 mm)]; ir 1710 cm^{-1}; NMR (CCl_4) δ 1.05 (s, 3) cis, 0.80 (s, 3) trans.

10-Methyl-8(9)-octal-1-one (4). *cis*- and *trans*-10-methyl-1-decalone (9.95 g, 0.060 mol) was dissolved in 100 ml of carbon tetrachloride and the mixture was cooled to 0°. Freshly distilled sulfuryl chloride (8.91 g, 0.066 mol) was dissolved in 50 ml of carbon tetrachloride and the solution was added dropwise to the ketone solution over 1 hr. The mixture was stirred for 24 hr and completion was monitored by TLC. The solution was washed with water and cautiously with 5% aqueous sodium bicarbonate (until gas evolution ceased), dried, and evaporated to a crude mixture of oily chlorides. The NMR spectrum of the crude chlorides precluded chlorination at the secondary site.

The crude chlorides were taken up in 40 ml of freshly distilled quinoline and the mixture was heated at 150° for ~1 hr (monitored by TLC), at which time no starting chloride was observed. Ether and water were added to the cooled reaction mixture and the aqueous layer, after separation, was extracted with ether (50 ml) five times. Combined extracts were washed twice with 10% hydrochloric acid and once with 5% sodium bicarbonate and dried over anhydrous sodium sulfate and the solvent was evaporated. Short-path vacuum distillation afforded 10-methyl-8(9)-octal-1-one (4, 8.25 g, 84%), bp 72° (0.3 mm), which was about 90% pure (3% SE-30 at 135°): ir (film) 1680, 1630, 1260, 1225, 870, 840, 805 cm^{-1}; NMR (CCl_4) δ 6.50 (t, J = 3.5 Hz), 1.08 (s, 3); uv (EtOH) 243 nm. The analytical sample was prepared by preparative VPC. Anal. Calcd for $C_{11}H_{16}O$: C, 80.49; H, 9.76; Found: C, 80.58; H, 9.62.

9(10)-Octal-1-one[9] (7). *trans*-1-Decalone (30.4 g, 0.2 mol) was dissolved in 125 ml of carbon tetrachloride and maintained at 20° during the addition of a solution of 32.4 g (0.24 mol) of freshly distilled sulfuryl chloride in 75 ml of carbon tetrachloride dropwise (1 hr). Evolution of SO_2 was noted after a short induction. The mixture was stirred at room temperature for ~4 hr, by which time TLC showed essentially no starting material. The mixture was washed with water and cautiously with 5% sodium bicarbonate and saturated sodium chloride. The dried solution was evaporated to afford the crude chloro ketone (34.0 g).

The crude ketone with no further purification was dissolved in collidine (practical, 75 ml) and heated to reflux under nitrogen for approximately 1 hr. The reaction monitored by TLC appeared to proceed rapidly at first, then very slowly. Further heating did not seem to diminish the starting material markedly; however, the yield was lowered. The mixture was cooled and diluted with ether (400 ml) and water (200 ml). The organic layer was washed with 3.5% hydrochloric acid until the pH of the wash was ~2 and then 5% sodium bicarbonate. The solution was dried over magnesium sulfate and evaporated. The crude unsaturated ketone (21 g) was chromatographed on silica gel (400 g) in hexane. Elution with mixtures of hexane and benzene afforded pure unsaturated ketone (14.6 g, 49%): ir (film) 1665, 1632, 1389, 1285, 1194 cm^{-1}; NMR, no absorption δ <7.

***cis*- and *trans*-10-Methyl-1-decalone (5) from 9(10)-Octal-1-one.** A solution of lithium dimethylcuprate was prepared by dropwise addition of ethereal methyllithium (0.4 mol) to a stirred suspension of purified cuprous iodide (38.0 g, 0.2 mol) in 700 ml of anhydrous ether at 0° under nitrogen. To this solution was added dropwise 9(10)-octal-1-one (12.0 g, 0.08 mol) in 100 ml of anhydrous ether. The mixture was stored at −20 to 0° for 23 hr, then poured into 1000 ml of 10% ammonium hydroxide solution. After the salt dissolved, the ether layer was separated and washed with 10% ammonium hydroxide (100 ml), water (100 ml), and saturated sodium chloride, dried over magnesium sulfate, and evaporated to 13.6 g of crude ketone. NMR analysis showed that approximately 10% starting enone remained. The mixture was chromatographed

on silica gel (120 g) in hexane; elution with 25% benzene–hexane afforded a mixture of the 10-methyl-1-decalones (**5**, 12.2 g, 91%). The cis and trans isomers showed identical retention times with those derived from 10-methyl-1-(9)-octalin (5% Carbowax, 180°).

Conjugate Addition of Isopropenyl Grignard to 10-Methyl-8(9)-octal-1-one (4). A solution of isopropenylmagnesium bromide was prepared in anhydrous tetrahydrofuran (75 ml) from 960 mg (0.04 mol) of magnesium turnings and 5.32 g (0.044 mol) of 2-bromopropene. The mixture was cooled to −30° and 760 mg (0.004 mol) of cuprous iodide was added. After this mixture was stirred for 1 hr at −30°, a solution of 10-methyl-8(9)-octal-1-one (3.28 g, 0.02 mol) in 20 ml of anhydrous tetrahydrofuran was added dropwise over 1 hr. After warming slowly to 10° for 2 hr, the mixture was quenched with 10% ammonium chloride (pH 8) and the ether layer was separated. The ether layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated to a yellow oily crude ketone mixture. This material was crudely fractionated by chromatography on silica gel (100 g) in hexane to afford on elution with hexane–benzene (1:1) 2.0 g of ketones (45%). The purified ketone mixture was separated into three isomeric ketones by preparative VPC (0.375 in. 20% Carbowax 20M at 170°). Analytical VPC (20% Carbowax 20M) indicated the ratio of isomers to be 7:2:1.

The major fraction (**10**) had ir (film) 1705, 1650, 890 cm^{-1}; NMR (CCl_4) δ 4.55 (m, 1), 4.43 (br s, 1), 0.81 (s, 3); MS p^+ 206. The second fraction (**11**) had ir (film) 1705, 1650, 890 cm^{-1}; NMR (CCl_4) δ 4.71 (br s, 2), 1.20 (s, 3); MS P^+ 206. The minor component (**12**) had ir (film) 1705, 1650, 890 cm^{-1}; NMR (CCl_4) δ 4.71 (br s, 2), 0.79 (s, 3); MS P^+ 206.

Equilibration of Decalones 10 and 11. A solution of sodium methoxide in methanol was prepared by dissolving 23 mg (1.0 mmol) of sodium metal in 10 ml absolute methanol. To 1 ml of this solution was added a sample of pure ketone **10** (25 mg). After 12 hr at room temperature, the ketone was recovered by ether extraction (16 mg). VPC analysis (10 ft 5% Carbowax 20M, 150°) showed that equilibration had occurred to a mixture of **10** and **11** (~70:30). Similarly a pure sample of **11** (10 mg) was equilibrated to a mixture of **10** and **11** (~66:34).

Attempted Equilibration of Decalone 12. A pure sample of ketone **12** was treated in the manner described above for ketones **10** and **11**. Analysis of the recovered ketone indicated that no detectable equilibration had taken place. Allowing the ketone to be in contact with the base for 24 hr lowered the recovery but did not show any evidence of equilibration. The recovered samples were examined by NMR and showed no new angular methyl absorptions.

(±)-β-Gorgonene. A solution of trimethylsilymethylmagnesium chloride in 10 ml of dry tetrahydrofuran was prepared from chloromethyltrimethylsilane (140 mg, 1.14 mmol) and magnesium metal (30 mg, 1.25 mmol) under nitrogen in the usual fashion. A solution of ketone **10** (206 mg, 1.0 mmol) in 2 ml of dry tetrahydrofuran was added dropwise at room temperature. The mixture was heated to reflux for 18 hr and then cooled and quenched with 10% ammonium chloride. The mixture was extracted with ether (25 ml) four times. Combined organic extracts were washed with water and saturated sodium chloride, dried over anhydrous magnesium sulfate, and evaporated to a colorless oily carbinol (240 mg).

This material was dissolved in aqueous acetic acid (3:1) and stirred at room temperature for 3 hr. The reaction mixture was diluted with water and extracted with hexane (20 ml) three times. The combined extracts were washed with water, dried over magnesium sulfate, and evaporated to a crude mixture of olefinic materials (86 mg). Purification by chromatography on 25% silver nitrate impregnated silica gel in pentane afforded on elution with pentane (±)-β-gorgonene (31 mg, 15%) identical in every respect with an authentic sample of (+)-β-gorgonene: ir (film) 3070, 1645, 1380, 885 cm^{-1}; NMR (CCl_4) δ 4.60 (m, 3), 4.46 (t, J = 2 Hz, 1), 1.57 (t, J = 1 Hz, 3), 0.80 (s, 3).

8,9-Epi-β-gorgonene (16). A solution of trimethylsilylmethylmagnesium chloride (1.14 mmol) was prepared as above in 10 ml of dry tetrahydrofuran. A solution of ketone **12** (206 mg, 1.0 mmol) in 1 ml of dry tetrahydrofuran was added dropwise at room temperature, and the solution was heated at reflux under nitrogen for 5 hr. The cooled reaction mixture was quenched with 10% ammonium chloride and the products were isolated by extraction with ether (50 ml) three times. The combined extracts were washed with water, dried over magnesium sulfate, and evaporated to the oily carbinol.

The crude material was dissolved in 3:1 acetic acid–water (10 ml) and stirred for 3 hr at room temperature under nitrogen. The mixture was diluted with water and extracted with hexane (30 ml) four times. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated to the crude oily olefin. Filtration through a short column of silica gel in pentane afforded 130 mg of colorless olefin **16**: ir (film) 3080, 1645, 990 cm^{-1}; NMR (CCl_4) δ 4.63 (br s, 4), 0.78 (s, 3); MS P^+ 204. Comparison by VPC on 10 ft 20% SE-30 (135°) of **16** and authentic (+)-β-gorgonene showed them to be nonidentical.

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Registry No.—**1**, 51260-29-8; **4**, 51174-52-8; *cis*-**5**, 54869-91-9; *trans*-**5**, 54869-92-0; **6**, 54910-87-1; **7**, 18631-96-4; **10**, 51174-54-0; **11**, 51174-55-1; **12**, 51174-56-2; 10-methyl-1(9)-octal-2-one, 40573-28-2; 10-methyl-1(9)-octalin, 51260-28-7; *trans*-10-methyl-2β-decalol, 54869-93-1; *trans*-1-decalone, 5784-57-6.

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Preparation and Fluorescence of Substituted 2-Methyl-1-isoquinolones

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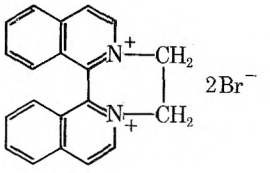
Various derivatives of 2-methyl-1-isoquinolone have been synthesized and their fluorescence examined to determine how the nature and position of the substituent affect the fluorescence maximum and quantum efficiency. An amino or dimethylamino group in the 4 position red-shifts the fluorescence maxima from 383 nm (methanol) to 530 or 505 nm, respectively, with some decrease in the quantum efficiency (5.4, 2.6, and 4.7%, respectively). An amino group in the 5 position improves the quantum efficiency (15%) but only red-shifts the fluorescence maximum about 23 nm. 2-Methyl-1-isoquinolone and the 4-amino compound undergo oxidation and/or oxidation–condensation reactions, some of which have been investigated.

The chemiluminescence, which results from the air oxidation of certain 1,1′-biisoquinolinium salts such as **1** in basic alcoholic or aqueous alcoholic systems, has been investigated recently.[1-3] The luminescing species are excited, fluorescent oxidation products, **2**, where X = H, OH, or



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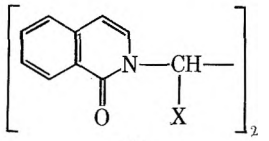
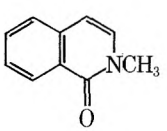


2

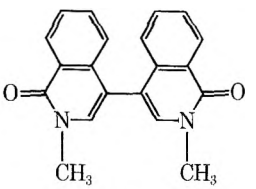
OR. These compounds fluoresce in the region 385–390 nm with fluorescent quantum efficiencies in the range 4–7%. Both of these factors are undesirable, however, if one wants to develop a practical chemiluminescent system. From the photopic standpoint, the fluorescence maximum should be in the region around 555 nm. Furthermore, since the overall chemiluminescence efficiency is a product of the chemical excitation efficiency and the fluorescence efficiency, the higher the latter, the easier it is to get bright systems with high light output. Finally, the chemical excitation efficiency should be larger for products with lower excitation energies if the Eyring–Rauhut effect holds in this case.[4] A study was undertaken, therefore, to determine whether and how the fluorescence maximum and quantum efficiency were affected by kind and position of substituents on either the hetero or benzo rings of the isoquinolone. The synthesis aspects were greatly simplified by making this study with derivatives of 2-methyl-1-isoquinolone (**3**). The fluorescence of the latter is essentially the same as that noted for the oxidation products from the 1,1′-biisoquinolinium salts, which are not easily accessible.

Synthesis and Chemistry. Most of the compounds were made by conventional procedures which are outlined in the Experimental Section. Several observations, however, are worthy of note and discussion.

(a) The preparation of **3** by the classical method of Decker,[5] namely, oxidation of 2-methylisoquinolinium iodide with potassium ferricyanide in basic medium, consistently gave a by-product (**4**) in low yield. Coupling at the 4,4′ positions is assigned on the basis of ^{1}H NMR evidence.

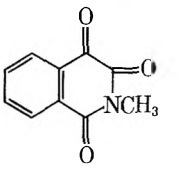


3



4

(b) Solid **3** is air oxidized at room temperature to the triketo compound **5**. The same compound has been previously reported as being formed by air oxidation of 2-methyl-3-isoquinolone[6] as well as by dichromate–sulfuric acid oxidation of 1,2,3,4-tetrahydro-2-methyl-4-isoquinolone.[7]



5

(c) 2-Methyl-1-isoquinolone undergoes electrophilic attack in the 4 position with great ease, as previously observed by Horning, Lacasse, and Muchowski.[8] For example, it has been found that nitration can be effected rapidly and exothermically at 25° with 8 *N* nitric acid to yield 4-nitro-2-methyl-1-isoquinolone (**6**). On the other hand, nitration in 96% sulfuric acid at 5° with potassium nitrate yields approximately equal amounts of 5- and 7-nitro-2-methyl-1-isoquinolone (**7** and **8**) together with some of the 4 isomer (**6**) and a minor amount of 4,7-dinitro-2-methyl-1-isoquinolone (**9**). The species being nitrated in this case is probably the protonated amide rather than the neutral species as in the aqueous nitric acid systems. These results are consistent with those reported by Kawazoe and Yoshioka[9] for the nitration of isocarbostyril in sulfuric acid with potassium nitrate. Nitration at the 4 position is also rapid with 5-nitro-2-methyl-1-isoquinolone (**7**) in 16 *N* nitric acid at 30–35°.

(d) 2-Methyl-1-isoquinolone shows enamine character in that it can be alkylated in the 4 position (heating with benzyl bromide).

(e) Like other 1,2-dihydroisoquinoline derivatives,[10] 2-methyl-1-isoquinolone and benzaldehyde condense in the presence of concentrated hydrochloric acid; attack is again in the 4 position.

(f) Although both 5- and 7-nitro-2-methyl-1-isoquinolone (**7** and **8**) are catalytically hydrogenated (Adams' catalyst) in alcoholic hydrochloric acid to the corresponding amines without difficulty, the reduction of the 4 isomer (**6**) under similar conditions is more complicated, because of the reactivity of 4-amino-2-methyl-1-isoquinolone (**10**). The triketo compound (**5**) was consistently formed in 15–20% yield. Other evidence of the instability is the observation that 4-amino-2-methyl-1-isoquinolone hydrochloride (**11**) is no longer completely water soluble after being stored for a month in a desiccator. Samples in tightly stoppered bottles slowly lose their water solubility. The triketo compound (**5**) precipitates from aqueous solutions of the amine hydrochloride after several days at 25°.

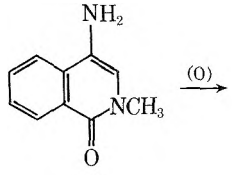
In addition to **5**, which is an oxidation–hydrolysis product, intermolecular condensation products such as the poorly soluble, high-melting pyridazine derivative (**12**) are

Table I
Substituted 2-Methyl-1-isoquinolones

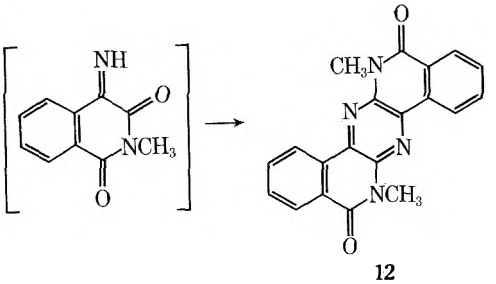
Compd	Position and substituent(s)	Empirical formula	Mp, °C	Recrystn solvent
3	Unsubstituted	$C_{10}H_9NO^g$	56.5–57.5[a]	3:1 cyclohexane–benzene
18	4-Cl	$C_{10}H_8ClNO^h$	132–134	Cyclohexane
17	4-Br	$C_{10}H_8BrNO^i$	129–130[b]	Cyclohexane
19	4-I	$C_{10}H_8INO^i$	126.5–127.5	Ethanol
20	4-CN	$C_{11}H_8N_2O^h$	197.5–198.5[c]	Ethanol
21	4-CO_2H	$C_{11}H_9NO_3^h$	270.5–271.5 dec	Ethanol
6	4-NO_2	$C_{10}H_8N_2O_3^h$	161.5–162.5[d]	7:3 cyclohexane–benzene
7	5-NO_2	$C_{10}H_8N_2O_3^h$	116–117	Water
8	7-NO_2	$C_{10}H_8N_2O_3^h$	214–216	Ethanol
25	4,5-Di-NO_2 · H_2O	$C_{10}H_9N_3O_6^h$	220.5–221.5	Ethanol
9	4,7-Di-NO_2	$C_{10}H_7N_3O_5^h$	294–296	DMF–ethanol
15	4-Br-7-NO_2	$C_{10}H_7BrN_2O_3^i$	254–256 dec	Ethanol
10	4-NH_2	$C_{10}H_{10}N_2O^g$	117–119	Benzene
11	4-NH_2 · HCl	$C_{10}H_{11}ClN_2O^i$	235–237[e]	Ethanol–ether
	4-Salicylamino	$C_{17}H_{16}N_2O_2^h$	155–156	Cyclohexane
23	5-NH_2	$C_{10}H_{10}N_2O^g$	138–140	3:2 benzene–cyclohexane
22	5-NH_2 · HCl	$C_{10}H_{11}ClN_2O^i$	261–263	2-Propanol–H_2O Ether
	5-$C_6H_5NHCSNH$	$C_{17}H_{15}N_3OS^g$	208–209	Ethanol
16	7-NH_2 · HCl · H_2O	$C_{10}H_{13}ClN_2O_2^g$	265–270 dec	Absolute Ethanol
	7-NH_2 · picrate	$C_{16}H_{13}N_5O_8^g$	254–255 dec	Ethanol
26	4,5-Di-NH_2 · 2HCl · $2H_2O$	$C_{10}H_{17}Cl_2N_3O_3^i$	260–270	Ethanol–Ether
27	4-$(CH_3)_2N$ · HI	$C_{12}H_{15}IN_2O^h$	208–211 dec	Absolute Ethanol
28	3-CH_3-4-NO_2	$C_{11}H_{10}N_2O_3^g$	151	Ethanol
29	3-CH_3-4-NH_2-HCl · $0.5H_2O$	$(C_{11}H_{14}ClN_2O)_2O^i$	250–260 dec	Ethanol
30	4-$C_6H_5CH_2$	$C_{17}H_{15}NO^h$	99.5–100.5	Cyclohexane
31	4-$C_6H_5C{\equiv}C^f$	$C_{18}H_{13}NO^h$	129.5–130.5	Cyclohexane

[a] Reported mp 57°: A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956). [b] E. Bamberger and W. Frew, *Ber.*, 27, 198 (1894), reported mp 132° for the product obtained when 2-methyl-1-isoquinolone was brominated in chloroform; the position of substitution was not established. Also see ref 8. [c] Reported mp 198°: G. Thuillier, B. Marcot, J. Cruanes, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 4770 (1967); also reported in ref 8, 197–199°. [d] Reported (ref 8) 163–165°. [e] Resolidifies, then decomposes at 270–290°. [f] Both parent and base peak in the mass spectra were at *m/e* 259; calcd mol wt, 259. [g] Satisfactory analytical data (±0.4%) were reported for N. [h] Satisfactory analytical data (±0.4%) were reported for C, H, N, and Hal (if present). [i] Satisfactory analytical data (±0.4%) were reported for N and Hal.

recovered from reactions involving the free 4-amino-2-methyl-1-isoquinolone. One possible route to **12** involves an *intermediate oxidation stage, analogous to* **5**, *which then* condenses with another molecule of **10**, followed by oxidation to yield **12**.

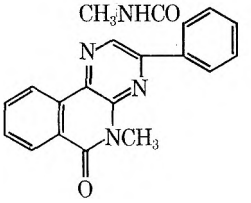


10

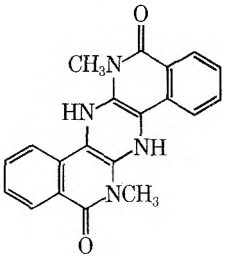


12

The structure of **12** is based on the elemental analysis, molecular weight determination, and ^1H NMR data. Another closely related product, **13**, which appears to have the following structure, was also isolated from reactions involving the free base. This structural assignment is made rather than the isomeric **14** (which is dihydro-**12**) largely because



13



14

the ^1H NMR spectrum (two more protons than in **12**) shows (1) two kinds of methyl groups, one of which is a doublet that coalesces to a singlet when D_2O is added, rather than one type of methyl group as should be expected in **14**; (2) one exchangeable NH group rather than two; and (3) a singlet (one proton) at δ 8.77 which is similar to the chemical shift seen for the protons in the hetero ring of quinoxaline (δ 8.86). The infrared spectrum of **13** also shows two types of carbonyl absorption (**12** has only a single carbonyl stretch and one would expect **14** to behave similarly). In addition, the mass spectral fragmentation pattern for **13** is very complex when compared with that for

Table II
^{1}H NMR Spectral Data for Substituted 2-Methyl-1-isoquinolones

Compd	Solvent	Frequency, MHz	δ, ppm NCH$_3$	H$_3$	H$_4$	H$_5$	H$_6$	H$_7$	H$_8$	Other data
3	$CDCl_3$	100	3.62 (s)	6.40 (d)	6.95 (d)		7.2–7.6 (m)		8.34 (m)	J_{34} = 7.0 Hz
17	$CDCl_3$	60	3.58 (s)	7.37 (s)			7.5–7.9 (m)		8.58 (m)	
20	$CDCl_3$	60	3.67 (s)	7.78 (s)			7.4–7.9 (m)		8.49 (m)	
6	$CDCl_3$	60	3.62 (s)	8.77 (s)		8.40 (m)	7.54 (dd)	7.80 (dd)	8.77 (m)	$J_{56} = J_{67} = J_{78} = 7.0$, $J_{57} = J_{68} = 2.0$ Hz
7	$CDCl_3$	60	3.64 (s)	7.25 (s)			8.70 (dd)	7.52 (t)	8.47 (dd)	$J_{67} = J_{78} = 8.0$, $J_{68} = 1.6$ Hz
8	Polysol ($CDCl_3$ + DMSO-d_6	60	3.57 (s)	6.62 (d)	7.55 (d)	7.75 (d)	8.33 (dd)		8.98 (d)	$J_{34} = 7.5$, $J_{56} = 8.5$, $J_{68} = 2.3$ Hz
25	DMSO-d_6	100	3.64 (s)	9.10 (s)			8.61 (dd)	7.85 (t)	8.47 (dd)	$J_{78} = J_{76} = 7.9$, $J_{68} = 1.4$ Hz
9	$CF_3COCF_3 \cdot 1.6D_2O$	60	3.89 (s)	9.08 (s)		9.15 (d)	8.87 (m)		9.53 (dd)	$J_{56} = 9$, $J_{68} = 2.3$ Hz
15	$CDCl_3$	100	3.65 (s)	7.57 (s)		7.97 (d)	8.50 (dd)		9.28 (dd)	$J_{56} = 8.7$, $J_{68} = 2.5$ Hz
a	$CDCl_3$	100	3.53 (s)	7.30 (s)		7.60 (d)	7.76 (dd)		8.51 (d)	$J_{56} = 8.7$, $J_{68} = 2.2$ Hz
23	$CDCl_3$	60	3.65 (s)	6.42 (d)	7.07 (d)		6.7–7.5 (m)		7.93 (d)	δ 5.2 (NH)
16	CD_3COCD_3	100	3.56 (s)	6.40 (d)	7.02 (d)	7.34 (d)	7.08 (dd)		7.55 (d)	$J_{34} = 7.3$, $J_{56} = 8.5$, $J_{68} = 2$ Hz
27	D_2O	100	3.67 (s)	7.98 (s)			7.6–8.0 (m)		8.38 (dd)	δ 3.42 [$N(CH_3)_2$]
28	$CDCl_3$	60	3.68 (s)				7.3–7.9 (m)		8.45 (dd)	δ 2.52 (CCH_3)
30	$CDCl_3$	60	3.55 (s)	6.77 (s)			7.4–7.6 (m)		8.44 (m)	δ 4.01 (CH_2), 7.2 (C_6H_5)
31	$CDCl_3$	60	3.60 (s)				7.3–8.2 (m)		8.45 (dd)	

[a] Unpurified 4,7-dibromo-2-methyl-1-isoquinolone.

12. It is not readily evident how one of the isoquinoline rings is reductively cleaved to furnish 13 unless a ring in an intermediate product is opened by a sequence analogous to that postulated by Gensler[11] to explain the products formed in the oxidation of substituted tetrahydroisoquinolines.

(g) Debromination occurs when 4-bromo-7-nitro-2-methyl-1-isoquinolone (15) is catalytically hydrogenated, the product being 7-amino-2-methyl-1-isoquinolone (as its hydrochloride), 16.

Experimental Section

Properties and analytical data for many of the compounds are summarized in Table I; ^{1}H NMR spectral data are given in Table II. Electronic spectral data are given in Table III.

1

2,2'-Dimethyl-1,1'-diketo-1,1',2,2'-tetrahydro-4,4'-biisoquinoline (4): This compound was always formed in low yield as a by-product in the preparation of 2-methyl-1-isoquinolone (3) by the oxidation of 2-methylisoquinolinium iodide with basic potassium ferricyanide.[5] It was recovered as follows: The crude (3) was dissolved in diethyl ether (3.6 g per 25 ml) and chilled at −68° until no more gummy material separated. The supernatant was decanted and the gum triturated with a small volume of ethanol. The white crystalline solid was filtered, washed with more solvent, and recrystallized from a large volume of ethanol. The compound did not melt up to 350° although sublimation occurred about 330–340°. ^{1}H nmr ($CF_3COCF_3 \cdot 1.6\ D_2O$, 100 MHz) δ 3.75 (s, 3H, NCH_3), 7.25 (m, 1H, H_3), 7.29 (s, 1H, H_3), 7.60 (m, 2H, H_6, H_7) 8.25 (m, 1H, H_8).

Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86; mol wt, 316.3. Found: C, 75.70; H, 5.05; N, 8.95; mol wt (mass spectrum) 316 (both parent and base peak).

Trace amounts of this compound were found when equal weights of isoquinoline methiodide and sodium peroxide were allowed to stand for several months.

The same compound (identical ir spectrum) was made as follows: 0.77 g of 4-bromo-2-methyl-1-isoquinolone, 5 ml of ethanol, 6.5 ml of 5% ethanolic potassium hydroxide, 0.2 g of 5% Pd/$CaCO_3$, and 0.06 g of 95% hydrazine were stirred at 25° for 5 hrs. An additional 0.1 g of hydrazine was added and the stirring continued for 19 hrs. The solid mass was filtered and washed once with cold ethanol (nothing precipitated from the mother liquors and washings upon dilution with water).

2

The cake was extracted with three 15-ml portions of boiling ethanol. Cooling the extracts at 5° furnished a white crystalline solid which was removed and washed with water. The compound melted above 320°.

1,2,3,4-Tetrahydro-2-methyl-1,3,4-trioxoisoquinoline (5): When (3) was allowed to stand at 50° exposed to air for several months, it gradually changed to an orange-red semi-solid mass. Recrystallization from absolute ethanol furnished orange needles, mp 186.5–188°. The infrared and ^{1}H nmr spectra are the same as those reported.[6]

Anal. Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.71; H, 3.72; N, 7.46.

The mono-tosylhydrazone was made by stirring 0.32 g of the above triketo compound, 0.7 g of tosylhydrazine, 11 ml of acetic acid and 18 ml of water for 66 hrs at room temperature. The product was filtered, washed well with water, dried, and recrystallized from absolute ethanol; 0.36 g. The orange-yellow, felted needles decomposed at 171.5–172.5°; reported,[12] 167.5–168°; ^{1}H nmr (DMSO-d_6, 100 MHz) δ 2.36 (s, NCH_3), 3.28 (s, CH_3 of tolyl), 7.74 (m, H_7), 8.11 (dd, H_8).

Anal. Calcd for $C_{17}H_{15}N_3O_5S \cdot H_2O$: N, 11.18; S, 8.54. Found: N, 11.15; S, 8.52.

This tosylhydrazone was converted to 1,2,3,4-tetrahydro-4-diazo-1,3-dioxo-2-methylisoquinoline when a solution in DMSO was allowed to stand at 25° in the dark for 5 days. The product recovered by pouring into water, melted at 142–143°; reported,[12] 147–148°; ir (mull) 2120 cm^{-1} ($=N_2$), 1690, 1645 cm^{-1} (CO); ^{1}H nmr (DMSO-d_6, 100 MHz) 3.30 (s, 3H, NCH_3), 7.37 (m, 1H, H_6), 7.48 (m, 1H, H_5), 6.75 (m, 1H, H_7), 8.13 (dd, 1H, H_8).

3

4-Bromo-2-methyl-1-isoquinolone (17) was obtained in 80% yield by reacting equivalent amounts of N-bromosuccinimide and (3) in acetic acid at room temperature. The initial reaction was mildly exothermic. An identical material was prepared in 70% yield by oxidizing a basic aqueous solution of 4-bromo-2-methylisoquinolinium iodide with potassium ferricyanide at 35–40°.

The 4-chloro analog (18) was similarly made using N-chlorosuccinimide.

4-Iodo-2-methyl-1-isoquinolone (19). Iodine (2.5 g, 0.01 mole) was added portionwise to a stirred, cooled slurry of 1.6 g (0.01 mole) of (4) and 2.2 g (0.01 mole) of silver trifluoroacetate in 50 ml of ether. The iodine color was rapidly discharged after each addition. After removing the silver iodide, the ether solution was washed once with a small volume of 3% aqueous sodium bisulfite and once with water. Evaporation of the ether left 1.9 g (65%) of crude product. This procedure is an adaptation of one by Henne and Zimmer.[13]

4-Cyano-2-methyl-1-isoquinolone (20) was made in 87% yield from the (17) and cuprous cyanide in DMF by the procedure of Friedman and Schecter.[14] Hydrolysis in 10% ethanolic potassium hydroxide followed by neutralization gave the 4-carboxy compound (21).

4-Nitro-2-methyl-1-isoquinolone (6): 2-Methyl-1-isoquinolone (1.4 g) was added to 15 ml of 8N nitric acid at room temperature. The isoquinolone dissolved completely; the temperature rose slowly to 37° (some oxides of nitrogen were evolved) and soon the solution became turbid. After about 20 minutes the reaction mixture was filled with pale yellow, felted needles, which were filtered and washed well with cold water. The yield of crude product was 1.1 g (61%); mp 157–159°. An additional amount of less pure material separated from the diluted, cooled nitric acid solution.

4

Catalytic hydrogenation in ethanol plus hydrochloric acid over platinum furnished the 4-amino derivative as its salt (*11*). The product was recovered just as soon as the hydrogenation was completed by removing the catalyst and precipitating the amine salt with excess diethyl ether. *Evaporating the ether-alcohol mother liquors and adding water to* the residue precipitated (*5*) (15-20% yield).

5-Nitro-, 7-Nitro-, and 4,7-Dinitro-2-methyl-1-isoquinolone (*7*, *8* and *9*): 2-Methyl-1-isoquinolone (1.59 g, 0.01 mole) was added portionwise during 5 min to 15 ml of 96% sulfuric acid, stirred and cooled to 5°. Then 1.01 g of powdered potassium nitrate was added over 20 min, keeping the temperature 5-10°. After 30 min more, the dark red-brown solution was quenched on 50 g of ice. The orange-red product which crystallized after 16 hr at 5° was broken up, filtered, and washed well with cold water; 1.4 g, mp 90-150°. Extracting this mixture with 70 ml of boiling 95% ethanol left 0.08 g (3.2%) of insoluble, mp 280-285°, which was recrystallized by dissolving in a small volume of DMF and adding an equal volume of ethanol. The small plates melted at 294-296° after drying at 66°, 25 mm. The elemental analysis agrees with those required for a dinitro derivative; the ^{1}H nmr data are consistent with the 4,7-dinitro-2-methyl-1-isoquinolone (*9*) assignment.

Cooling the ethanolic solution to 5° gave orange needles (0.3 g, 14.7%), mp 214-216°. The nmr evidence supports 7-nitro-2-methyl-1-isoquinolone (*8*).

The ethanolic mother liquors were cooled to -15°, decanted from some amorphous material, and evaporated. By extracting the residue with boiling cyclohexane, filtering off insoluble (0.2 g, 9.8% more of *8*),

5

concentrating the extract and cooling, there was recovered 0.5 g (24.4%) of bright yellow felted needles, mp 102-105°. A tlc on Eastman silica gel chromatogram sheet using 95:5 benzene:ethanol to develop indicated three compounds: R_f = 0.63 (4-nitro), 0.51 (5-nitro) and 0.37 (7-nitro). The first and last were present in small amounts (< 15%). The mixture was then chromatographed on 2:1 silicic acid-celite with benzene-ethanol (95:5) to elute, and the main fraction recrystallized from water as bright yellow felted needles, mp 116-117°; reported[5] for 5-nitro-2-methyl-1-isoquinolone (*7*) about 120°.

The ^{1}H nmr also agrees with that required by (*7*). Catalytic reduction of the latter in ethanolic hydrochloric acid gave the 5-amino-2-methyl-1-isoquinolone as its salt (*22*). The free base (*23*) and derivatives were prepared by conventional methods.

4-Bromo-7-nitro-2-methyl-1-isoquinolone (*24*): Powdered potassium nitrate (0.9 g) was dissolved in 6 cc of 96% sulfuric acid with stirring and cooling in ice bath. Then 1.18 g of *17* was added portionwise over 5 min. The solution was stirred for 24 hr at ambient temperature before quenching over 20 g of ice. This acid solution was neutralized with cold conc. ammonium hydroxide, the solid product filtered and washed well with cold water. The still wet cake was recrystallized from 75 ml of 95% ethanol; 0.1 g (7%). Trace amounts more of the title compound were recovered by prolonged cooling of the recrystallization mother liquors at -15°. These mother liquors were heated to boiling and treated with an equal volume of water; the first material to separate upon cooling was amorphous. After removing the latter, a material melting 180-185° slowly crystallized (low yield). The infrared spectrum was significantly different than that of the above nitro compound.

6

Elemental analysis (Found: Br, 42.88; Calcd: Br, 50.42), ^{1}H and ^{13}C nmr spectra suggested that this material was impure 4,7-dibromo-2-methyl-1-isoquinolone. It was not further purified.

4,5-Dinitro-2-methyl-1-isoquinolone (*25*): 5-Nitro-2-methyl-1-isoquinolone, *7*, (0.6 g) was added all at once to 10 ml of 70% nitric acid. Complete solution was quickly attained. The temperature rose slowly from ambient to 35° and was then held at 30-35° by cooling in water bath. After standing for 45 min, the solution was poured over ice, the yellow solid filtered and washed with cold water. The yield of dried product was 0.32 g (44%), mp 210-215°. Recrystallization from 50 ml of ethanol raised the mp to 220.5-221.5°; small red-orange plates; ir (mull) 1680,1630 cm^{-1}. The same yield was obtained when the nitration was done in 12N nitric at ambient temperature (2 hr).

Reduction of *25* in ethanolic HCl was done catalytically over platinum. The solution of diamino dihydrochloride (*26*) so obtained was initially colorless but soon turned yellow, orange and finally red; addition of ether to turbidity and cooling gave the salt as a pale tan, crystalline powder; ir (mull) 3320 (NH), 1645 cm^{-1} (C=O).

From the reddish mother liquors there was recovered another salt, dec. 215-220 as a brown powder; ir (mull) 3360 (NH), 1670, 1650, 1635, 1610 cm^{-1} (C=O). This multiplicity of carbonyl absorptions suggests an amino triketone derivative, resulting from oxidation of the diamino compound.

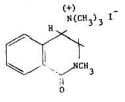
4-Dimethylamino-2-methyl-1-isoquinolone Hydroiodide (*27*): 4-Amino-2-methyl-1-isoquinolone hydrochloride (*11*) (0.7 g) was dissolved in 8 ml of 60% ethanol, made basic with 20% aq. sodium hydroxide solution, diluted with 20 ml of 95% ethanol and 50 ml of ether. Excess methyl

7

iodide was added to the solution, which had a strong green fluorescence and the flask tightly stoppered; after 6 days at ambient temperature, the solution was evaporated. The gummy residue was extracted with 20 ml of boiling absolute ethanol; cooling the extracts deposited a pale pink crystalline solid, decomposing 201-207°. One recrystallization from abs. ethanol raised the decomposition temperature to 209-211°. This salt was water soluble. The elemental analysis and ^{1}H nmr spectrum are in agreement with those required for the dimethylamino derivative, rather than the monomethylamino compound; ir (mull), 1650, 1670 cm^{-1} (C=O).

By evaporating the ethanolic mother liquors used for the extraction step and triturating the residue with water there was obtained about 40 mg of a yellow solid, melting above 300°. It could be recrystallized from DMF; a solution in conc. sulfuric acid had a pale green fluorescence; ir (mull), 3260 (NH or OH), 1650 (sh), 1615 cm^{-1} (C=O). It was not further investigated.

In another experiment the free-base, *10*, in absolute ethanol plus sodium hydroxide (1.5 molar equivalent) was treated with excess methyl iodide and allowed to stand several days at ambient temperature. Addition of ether to turbidity gave a tan solid which melted 193-194° after recrystallization from 1:1 abs. ethanol-2-propanol. This compound showed only a sharp, single carbonyl absorption at 1660 cm^{-1} and no OH or NH. The ^{1}H nmr spectrum and the analyses suggest that this material is trimethyl(3,4-dihydro-2-methyl-1-isoquinolonyl-4)ammonium iodide:



8

^{1}H nmr (100 MHz, DMSO-d_6) δ3.18 (s, 12H, NCH_3), 4.26 (m, 2H, CH_2), 5.16 (m, 1H, CH), 7.81 (m, 3H, H_5, H_6, H_7), 8.07 (m, 1H, H_8).

Anal. Calcd for $C_{13}H_{19}IN_2O$: C, 45.10; H, 5.53; I, 36.66; N, 8.09. *Found:* C, 44.97; H, 5.99; I, 36.61; N, 8.06. The picrate of the lacter compound melted 206.5-207.5° after recrystallization from ethanol; yellow plates.

Anal. Calcd for $C_{19}H_{21}N_5O_8$: C, 51.00; H, 4.73; N, 15.65. Found: C, 50.94; H, 4.80; N, 15.58

The condensation products *12* and *13* were also recovered in another attempt to methylate *10*. The free base from 1.4 g of *11* in 100 ml of benzene, 50 ml of ether and 10 ml of abs. ethanol was treated with 2 ml of methyl iodide and stored in a tightly stoppered flask in the dark for several days. The initial green fluorescence gradually changed to a blue-purple fluorescence and an orange solid slowly crystallized. After cooling to 5°, the solid was filtered. The solid was first extracted several times with warm water to remove the hydroiodide salts (extracts contained iodide), then with three 15 ml portions of hot ethanol (these extracts were saved - see below). There was left 0.24 g of yellow-orange solid; recrystallization from DMF yielded orange, felted needles, mp 394° (dta, 5°/min). (This compound can also be recrystallized from ethanol, in which it is only sparingly soluble; the solution has a bright blue fluorescence.) Solutions in conc. sulfuric acid have an intense blue-green fluorescence. The spectral and analytical evidence agree with those required for *12*: ^{1}H nmr (100 MHz, 96% H_2SO_4) δ4.19 (s, 3H, NCH_3), 7.6-8.1 (m, 2H, H_6, H_7), 8.25 (d, *J* = 7 Hz, 1H, H_5), 8.92 (d, *J* = 7 Hz, 1H, H_8); ir (mull), 1665 cm^{-1} (C=O).

9

Anal. Calcd for $C_{20}H_{14}N_4O_2$: C, 70.15; H, 4.12; N, 16.37; mol wt 342.3. Found: C, 69.88, 69.65, 69.34; H, 4.53, 4.47, 3.98; N, 16.25, 16.08; mol wt (mass spec. parent) 342.

The 45 ml of ethanolic extracts were cooled to 5°, filtered from a trace of *12* and evap. to about 10 ml; cooling gave very pale yellow to white, felted needles of *13*, mp 263-264°: ^{1}H nmr (100 MHz, $CDCl_3$) δ2.93 (d, 3H, $NHCH_3$, *J* = 5 Hz, doublet collapses to a singlet in presence of D_2O), 3.90 (s, 3H, NCH_3), 5.84 (broad singlet, 1H, NH, exchanges in D_2O), 7.5-7.9 (m, 6H, $H_{aromatic}$), 8.52 (m, 1H, H_8), 8.77 (s, 1H, pyrazine ring), 8.80 (m, 1H, $H_{8'}$); ir (mull), 3230 (sharp, narrow absorption NH); 1665, 1645 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.75; H, 4.68; N, 16.27; mol wt 344.4. *Found:* C, 69.26; H, 4.71; N, 16.34; mol wt (mass spec. parent), 344.

Additional amounts of both *12* and *13* could be recovered by reworking the original reaction mother liquors.

2,3-Dimethyl-4-nitro-1-isoquinolone (*28*): 2,3-Dimethylisoquinolinium iodide was oxidized in basic solution with potassium ferricyanide using the usual procedure; much ether-insoluble tar was formed. The ether-soluble 2,3-dimethyl-1-isoquinolone was obtained in 30% yield; the mp of the off-white crude product was 95-98°. Attempts to recrystallize were unsuccessful, the compound always becoming dark and tarry. Nitration at 25° with 6N nitric acid proceeded rapidly to furnish the more stable 4-nitro derivative which was readily recrystallized from 95% ethanol as orange crusts.

Reduction to the corresponding amino compound (*29*) was done catalytically.

10

4-Benzyl-2-methyl-1-isoquinolone: 2-Methyl-1-isoquinolone (0.8 g) and benzyl bromide[15] (0.9 g) was heated at 160-180° for 3 hr. The dark viscous product was cooled, slurried with 15 ml of ethanol, and chilled to -15°. The yellow solid was removed, washed with cold ethanol and dried; 23 mg; mp above 320°. It was recrystallized by dissolving in warm DMF adding water to incipient turbidity and cooling. The bright yellow powder was filtered, washed well with water, and dried at 100°, 25 mm, for 1 day. Solutions in DMF or chloroform had an intense blue fluorescence. The analyses correspond to those required for tris-(2-methyl-1-isoquinolonyl-4)-phenylmethane.

Anal. Calcd for $C_{37}H_{29}N_3O_3$: C, 78.84; H, 5.19; N, 7.46; mol wt, 563.6. Found: C, 78.87; H, 4.93; N, 7.40; mol wt, 564.

The original ethanolic mother liquors were evaporated to dryness and the gummy residue extracted with two 20 ml portions of boiling cyclohexane. Evaporation of the latter furnished the crude 4-benzyl-2-methyl-1-isoquinolone (*30*), as an oil that crystallized. Two wasteful recrystallizations from cyclohexane finally gave sparkling, colorless prisms. The yield was not determined.

Bis-(2-methyl-1-isoquinolonyl-4)phenylmethane: 2-Methyl-1-isoquinolone (0.8 g, 0.005 mole), 1.1 g of benzaldehyde, 12.5 ml of 95% ethanol and 12.5 ml of conc. hydrochloric acid were refluxed for 2 hr. The cooled solution was diluted with 50 ml of water and chilled at 5° for several days. When the oil which separated had crystallized, the supernatant phase was decanted and the crystals washed with a small volume of alcohol; 0.7 g, mp 280-282°. The compound can be recrystallized from either benzene or ethanol; mp 281-282.5°. Two strong carbonyl absorptions are present at 1630 and 1655 cm^{-1}.

11

Anal. Calcd for $C_{27}H_{22}N_2O_2$: C, 79.78; H, 5.46; N, 6.89; mol wt, 406.5. Found: C, 80.01; H, 5.62; N, 6.89; mol wt (mass spectrum), 406.

Bis-(2-Methyl-1-isoquinolonyl-4) methane: This compound was obtained in 5% yield during an attempted Mannich reaction on 2-methyl-1-isoquinolone with piperidinium chloride and paraformaldehyde. After recrystallization from 98% ethanol the mp was 299-301° (dec); reported,[8] 302-305°; ^{1}H nmr (60 MHz, $CDCl_3$), δ3.50 (s, 3H, NCH_3), 4.06 (s, 2H, CH_2), 6.73 (s, 1H, H_3), 7.63 (m, 3H, H_5,H_6,H_7), 8.53 (m, 1H, H_8).

Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.35; H, 5.49; N, 8.48; mol wt, 330. Found: C, 76.51; H, 5.73; N, 8.16; mol wt, 330 (mass spectrum).

4-Phenylethynyl-2-methyl-1-isoquinolone (*31*). Equivalent amounts of *13* and cuprous phenylacetylide in dry pyridine were refluxed and stirred for 16 hrs under nitrogen. The product was separated from the cuprous iodide by evaporating the pyridine under reduced pressure, extracting the residue several times with boiling cyclohexane and evaporating the latter; the yield was quantitative.

Use of the *17* was much less satisfactory; even after 52 hr refluxing unreacted cuprous phenylacetylide was present. Isolation and purification of the phenylethynyl compound were also more difficult.

N-Methylnaphthostyril (*32*) was prepared from naphthostyril by the procedure of Roshinskii and Mostovalavskii;[16] recrystallization per their instructions gave the reported melting point (~ 80°). However, it was immediately evident when the fluorescence was examined that this material was a mixture of two compounds (emission$_{max}$ 395 and 525 nm). This result was confirmed by ^{1}H nmr ($CDCl_3$) which revealed both N-methyl (δ3.45) and O-methyl (δ3.71). The latter was present to the extent of 20-25%. Chromatographic separation on 2:1 silicic acid-Celite, using

12

ethylene dichloride as the eluent (the O-methyl isomer moved slightly faster), gave a fraction which melted 86-87° after recrystallization from n-hexane. The ^{1}H nmr now showed essentially no O-methyl peak; the fluorescence peak at 395 nm was absent. The O-methyl isomer was not obtained in pure form.

N-Methylphenanthridone (*33*) melted at 107° after recrystallization from 50% ethanol; reported,[17] 108°.

Photoluminescence Measurements. All measurements were made with a Turner Model 210 Spectrofluorometer; this instrument automatically corrects the emission spectra and the excitation energy.[18] Spectra from this instrument appear to agree well with those from other corrected spectrum instruments.[19]

The absorbances were typically measured in solutions of about 10^{-3} *M*, the emission and excitation from solutions of about 10^{-5} *M*.

Quantum yields were made using the comparison technique versus quinine sulfate as q = 0.55. The details have been discussed elsewhere.[19] The results, summarized in Table 3, were obtained on solutions under 700 torr of air. Stern-Volmer quenching constants for O_2 are given for three compounds as K in units of torr^{-1}.

Phosphorescence was examined by cooling solutions to -196° in test tubes and irradiating with a filtered ultraviolet lamp. All the isoquinolones examined phosphoresced yellow with lifetimes, by eye, of a few to several tenths of seconds. The reported colors of fluorescence and phosphorescence were observed, respectively, during and immediately after irradiation by a near uv lamp.

Table III
Electronic Spectra of Compounds

Compd	Substituent	Solvent	Absorption[a] peaks λ, nm	ε × 10⁻³	λ, nm	ε × 10⁻³	Excitation peaks, nm 1st	2nd	Emission peaks, nm 1st	2nd	Quantum yield[b]	K 10⁻³/Torr
			A. 2-Methyl-1-isoquinolones									
3		CH_3OH	325	3.2	288	6.2	325	288	368	383	0.054	0.07
17	4-Br	CH_3OH	326	5.4	294	9.8	322	291	395			
	4-HO	CH_3OH	313	2.1	254	9.2			(355)[c]	415		
	4-C_6H_5CO	CH_3OH							359	403	Low	
11	4-NH_2 · HCl	CH_3OH	318	6.3	290.5	8.1	310		513	530	0.027	0.26
11	4-NH_2 · HCl	H_2O	305	3.9			310		530		0.026	
11	4-NH_2 · HCl	H_2O + NaOH	305		295		310		529			
11	4-NH_2 · HCl	CH_3CN	322		295				410	428		
11	4-NH_2 · HCl	C_6H_6					317		500			
22	5-NH_2 · HCl	CH_3OH	346	8.7	300	12.2	345	304	406		0.15	0.27
16	7-NH_2 · HCl	CH_3OH	332	2.5	292	8.0	344	298	456		0.076	
26	4,5-DiNH_2 · HCl	CH_3OH	326	4.0	255		325	255	427		0.068	
27	4-$(CH_3)_2N$ · HI	CH_3OH	305	11.8	265	5.5	310		505			
27	4-$(CH_3)_2N$ · HI	CH_3OH + NaOH							502		0.047	
27	4-$(CH_3)_2N$ · HI	CH_3CN					314		525			
27	4-$(CH_3)_2N$ · HI	CH_3CN + 2%CH_3OH					314		525			
27	4-$(CH_3)_2N$ · HI	C_6H_6					316		490			
31	$C_6H_5C{\equiv}C$	CH_3OH	309	18.2	257	16.2	310	257	420			
			B. Related Compounds									
Isocarbostyril		CH_3OH					318		367[d]	382		
Isocarbostyril		0.01 *M* $NaOCH_3$ in CH_3OH	318		268		320	281				
5		CH_3OH		1.3					417			
32	*N*-Methylnaphthostyril	CH_3OH	367		337	1.7	340		506	525	0.086	
32	*N*-Methylnaphthostyril	H_2O	367						506	525		
33	*N*-Methylphenanthridone	CH_3OH					325		362	378		

[a] Molar absorbance, ε, in l. mol^{-1} cm^{-1}. [b] Under air (700 Torr) vs. quinine as 0.55. [c] It seems likely that this emission is due to an impurity. [d] Reported[21] 369 mm (95% ethanol).

Table IV
Phosphorescence Relative to Fluorescence of Certain Isoquinolones

Compd	In benzene 25° Fluor	−196° Fluor	−196° Phos	In methanol 25° Fluor	−196° Fluor	−196° Phos
3	Violet	Violet	Yellow-green	Violet		Blue-green
11	Blue-violet	Blue	Yellow-green	Yellow		Yellow-green
22	Blue-violet	Blue-violet	Yellow-green			
27				Yellow-green	Yellow-green	Yellow-green

Discussion

Fluorescence Theories. The enhancement of molecular fluorescence has mainly been a pragmatic procedure. A few general ideas have been developed and are presented in a recent book on laser dyes.[20] Certainly the amino group is the major substituent for enhancing fluorescence. Schäfer[20] discusses molecular fluorescence in terms of the length L of a π electron cloud associated with a chain of conjugated double bonds. The absorption maximum wavelength is given by

$$\lambda = \frac{8mc_0}{h}\frac{L^2}{N+1} \quad (1)$$

where N is the number of π electrons. Adding amino groups at the ends of the chain increases L without increasing N, thus increasing λ substantially.

The molar absorbance is generally increased by the addition of amino group auxochromes. This is often paralleled by an increase in the fluorescence quantum yield. In long-chain compounds the direction of L is simple to determine. In polycyclics, there seem to be more than one axis, each with its own L and λ. Furthermore, linear polycyclics like anthracene act longer than phenanthrene where the rings are angular.

In heterocyclics and compounds with carbonyl groups the π electron clouds are skewed in relation to the geometric axes. One way to find the ends of the axes might be to place amino groups in various positions and note the effect.

However, with heterocyclic compounds there is another effect having to do with n,π^* and π,π^* transitions in the singlet manifold. The former is much more likely to give intersystem crossing to the triplet. Any molecular change which lowers the relative energy of the (π,π^*) S_1^* state will

therefore enhance the fluorescence while decreasing the phosphorescence.

Although our results can be explained by the "theories" stated, there is really not enough data and too much leeway in the theories to make a real test. The pertinent possibilities will be pointed out below.

Phosphorescence and Fluorescence. Visual examination of the phosphorescence in a few of the isoquinolones was made by freezing methanolic solutions in liquid nitrogen. Table IV shows the results. The phosphorescence was quite long lived and could generally be distinguished from fluorescence by moving a solution away from the exciting uv lamp.

Compound **3** shows the expected red shift of phosphorescence from fluorescence. The shift was larger in benzene than in methanol.

Compound **11** acts much like **3** in benzene, showing a red shift of phosphorescence. However, in methanol it fluoresces in the yellow. The phosphorescence is then to the blue side of the fluorescence. This surely means that the excited singlet either forms some sort of exciplex or is protonated before emitting. The triplet in solid methanol presumably cannot form a similar exciplex. The fluorescence from the solid could not be seen since the phosphorescence competed with it in brightness.

Compound **22** was much like **3**, while **27** was much like **11**. Both **22** and **27** decomposed before the measurements were completed.

The large phosphorescence of all these compounds indicated that the fluorescence quantum efficiency was not very high.

Impurities and Decomposition. The fluorescence studies showed the presence of fluorescent impurities in some of the isoquinolones and of instability (oxidation or decomposition) in their solutions. For the important compounds it was necessary to repurify and to resynthesize samples just prior to use in order to repeat results. Impurities which show up in fluorescence spectra can be maximized or minimized by shifting the excitation wavelength. The size of an impurity peak depends not only upon its concentration, but upon its quantum yield and absorbance relative to the major compound.

Compound **3** was pure and relatively stable as a solid and in alcohols or water for weeks. Eventually it air oxidizes to give **5**.

Compound **11** showed a small extraneous fluorescence at 315 nm when excited at 290 nm. It decomposed as a solid within a few months and in alcoholic solution within several days. In acetonitrile (AN) it seemed to react very rapidly. Upon dissolution in O_2-free AN there were two fluorescent bands around 420 and 490 nm. These bands then disappeared within hours. Oxygenated AN caused a different pattern which was not further examined.

Compound **22** showed a fluorescent impurity at 493 nm when excited at 300 nm. This impurity peak did not show during excitation at 347 nm. Solutions were stable for a few days and the solid decomposed slowly.

The 7-amino isomer, **16**, was pure and stable in solution for short periods. The excitation peaks are inaccurate since they were measured in a concentrated solution.

The 4,5-diamino compound, **26**, had a very small fluorescent impurity peak at 350 nm. The 4-dimethylamino derivative, **27**, was initially pure, but it decomposed before measurements were completed.

Like the amino compound, 4-hydroxy-2-methyl-1-isoquinolone was unstable (and hence impure). The 4-benzoyl derivative also appeared to contain small amounts of fluorescent impurities. Hence the results for these are uncertain.

By way of contrast, derivatives such as the 4-bromo (**17**) or 4-phenylethynyl (**31**) were both pure and stable from a fluorescence standpoint.

Fluorescence Results. Table III shows the data gathered on fluorescence. A spectrum of the parent compound **3** has been published earlier.[2] Here only the peaks of absorption and emission are given. The molar absorbance, ϵ, is given at the peaks where

$$A = \epsilon c \approx \log I_0/I$$

and A is the optical density read on the Turner used as a double beam spectrometer.[18]

The quantum yields were calculated using the formula

$$q = q_{std}\frac{A_{std}\theta n^2\lambda_{std}}{A\theta_{std}n_{std}^2\lambda}$$

The general procedure has been described before.[19] With the unstable compounds all the measurements were made within a few hours of preparing the solutions.

Quenching studies with O_2 were done by deaerating the solutions in a N_2 box and running a spectrum in cuvettes sealed with Teflon caps. Then spectra were run with the caps removed from the cuvettes and finally with oxygenated solutions. This gave us points at 0, 147, and 700 Torr of O_2. The Stern–Volmer equation

$$F = \frac{F_0}{1 + KP_{O_2}}$$

was used to calculate the quenching constant K from the emission peak heights without oxygen, F_0, and with oxygen, F.

Examination of the fluorescence results in Table III shows that every substitution on the parent, **3**, caused some red shift of the emission with the possible exception of benzoyl. However, the effect was relatively small with the groups 4-bromo, 5-amino, 4-benzoyl, and 4-hydroxy. Other amino groups had a much more pronounced effect. For example, the 4-amino compound **11** had a Stokes shift of 203 nm in methanol. Part of this may be due to a different mechanism in the excited state. That is, excited **11** probably forms an exciplex, which may also account for the lower quantum yield. A similar Stokes shift is observed with the 4-dimethylamino group in compound **27** but the quantum yields are not lowered as much with this methylated amine.

Amino groups on the 5 or 7 position show much less effect on the Stokes shift, but do increase the quantum yield of fluorescence. 3-Amino-2-methyl-1-isoquinolone was previously reported[21] to fluoresce at 456.5 nm in 95% ethanol.

Compound **26**, 4,5-diamino-2-methyl-1-isoquinolone, was prepared to see whether it would show both a large Stokes shift *and* a large quantum yield increase. The result was a moderate shift and a moderate increase. Clearly the groups on the 4 and 5 position interact and as a consequence the effects are not additive.

Several compounds related to **3** were also examined. Isocarbostyril or isoquinolone has the same emission peaks as **3**, showing that the *N*-methyl group has little effect. The main air oxidation product of **3**, namely 1,2,3,4-tetrahydro-2-methyl-1,3,4-trioxoisoquinoline (**5**), fluoresces at 417 nm; **5** does not appear to be an impurity in the sample of **3** while fluorescence was measured. *N*-Methylphenanthridone (**33**) can be viewed as **3** with a longer group fused onto the 3,4 position. As such it is the only substituted isoquinolone examined which showed a blue shift of the emission peaks. On the other hand, *N*-methylnaphthostyril (**32**) fluoresced in about the same region as the 4-amino-2-methyl-1-isoquinolone.

One hope for increasing the fluorescence quantum yield

is to lower the energy of the π,π^* transition below that of the n,π^* transition. This would decrease singlet–triplet crossover and decrease phosphorescence. Since strong phosphorescence was always observed, none of the substitutions examined accomplished this energy inversion.

Compounds **11** and **27** in particular show large red shifts, which suggest that the axis of L in eq 1 goes near the 4 position. This axis must be for an n,π^* transition based on the argument in the foregoing paragraph. There should be another axis for the π,π^* transition which presumably goes near the 6 position. It is unfortunate that a 6-amino compound was not available for testing this idea.

These two amino compounds, **11** and **27**, are much more strongly quenched by oxygen than is **3**. The Stern–Volmer constant $K = k_q\tau$, where k_q is the quenching rate constant and τ the excited-state lifetime. It is possible that the amino compounds have a longer lifetime, τ, than **3**. However, it would be expected that they would form stronger charge transfer complexes with O_2 and thus have a larger k_q and no change of τ.

There are some differences between **11** and **27**. For example, the dimethylamino group in **27** effects a smaller red shift in fluorescence than does the amino group in **11** (both compared with **3**) but at the same time causes less of a decrease in quantum yield.

Acknowledgment. We wish to thank Dr. J. G. Lombardino for a sample of 4-hydroxy-2-methyl-1-isoquinolone and Mr. D. E. Horning for the one of 4-benzoyl-2-methyl-1-isoquinolone. Dr. T. Pavlopoulos and Professor M. El-Sayed discussed the effects of substituents on fluorescence and phosphorescence with us.

Registry No.—**3**, 4594-71-2; **4**, 54931-49-6; **5**, 21640-33-5; **5** monotosylhydrozone, 54931-50-9; **6**, 33930-79-9; **7**, 42792-96-1; **8**, 54931-51-0; **9**, 54931-52-1; **10**, 54931-53-2; **11**, 54931-54-3; **11** salicyl derivative, 54931-55-4; **12**, 54931-56-5; **13**, 54931-57-6; **16** HCl, 54931-58-7; **16** picrate, 54931-60-1; **17**, 33930-63-1; **18**, 27187-01-5; **19**, 54931-61-2; **20**, 20334-97-8; **21**, 54931-62-3; **22**, 54931-63-4; **22** phenylthiourea derivative, 54931-64-5; **23**, 42792-97-2; **24**, 54931-65-6; **25**, 54931-66-7; **26**, 54931-67-8; **27**, 54931-68-9; **28**, 54931-69-0; **29**, 54931-70-3; **30**, 54931-71-4; **31**, 54931-72-5; **32**, 1710-20-9; **33**, 4594-73-4; 2-methylisoquinolinium iodide, 3947-77-1; 1,2,3,4-tetrahydro-4-diazo-1,3-dioxo-2-methylisoquinoline, 6075-60-1; *N*-bromosuccinimide, 128-08-5; 4-bromo-2-methylisoquinolinium iodide, 54931-73-6; *N*-chlorosuccinimide, 128-09-6; trimethyl(3,4-dihydro-2-methyl-1-isoquinolonyl-4)ammonium iodide, 54931-74-7; trimethyl(3,4-dihydro-2-methyl-1-isoquinolonyl-4)ammonium picrate, 54931-76-9; 2,3-dimethylisoquinolinium iodide, 32431-36-0; 2,3-dimethyl-1-isoquinolone, 7114-78-5; tris(2-methyl-1-isoquinolonyl-4)phenylmethane, 54931-77-0; bis(2-methyl-1-isoquinolonyl-4)phenylmethane, 17054-56-7; bis(2-methyl-1-isoquinolonyl-4)methane, 27330-16-1

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Lithium Aluminum Hydride Reduction of Terpene Sultones

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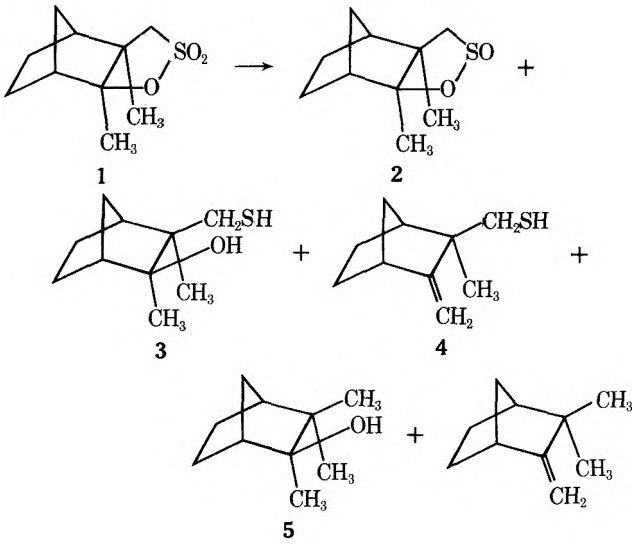
Lithium aluminum hydride reduction of camphene sultone, 10-isobornyl sultone, and 6-bornyl sultone yield, depending on exact conditions, sulfinate esters, mercapto alcohols, or sulfur-free alcohols. Mercaptans are slowly, and sulfides even more slowly, converted to hydrocarbons by lithium aluminum hydride at 100°.

During an investigation of the chemistry of camphene sultone (**1**)[2] it was discovered that desulfurization to camphene hydrate (**5**) took place on reduction with lithium aluminum hydride. The desulfurization reaction not only provided a powerful method for structural and stereochemical elucidation,[2] but also permitted the facile synthesis of bornane derivatives[3] and the selective introduction of a deuterium atom into the bornane and camphane ring systems.[2] We have now examined the lithium aluminum hydride reduction of terpene sultones in greater detail and wish to report that in addition to the sulfur-free alcohol, cyclic sulfinate esters and mercapto alcohols are also produced.

Camphene Sultone. Treatment of camphene sultone (**1**) with an excess of lithium aluminum hydride in THF at reflux for 6 hr, followed by work-up with aqueous hydrochloric acid, gave 33% of camphene sulfinate ester (**2**), 18% 9-mercaptocamphene hydrate (**3**), 45% of 9-mercaptocamphene (**4**), 1% of camphene hydrate (**5**), and 3% of camphene. Camphene and 9-mercaptocamphene (**4**) were not present to any appreciable extent in the crude product, but were formed in varying amounts by dehydration of **3** and **5** during GLC isolation.

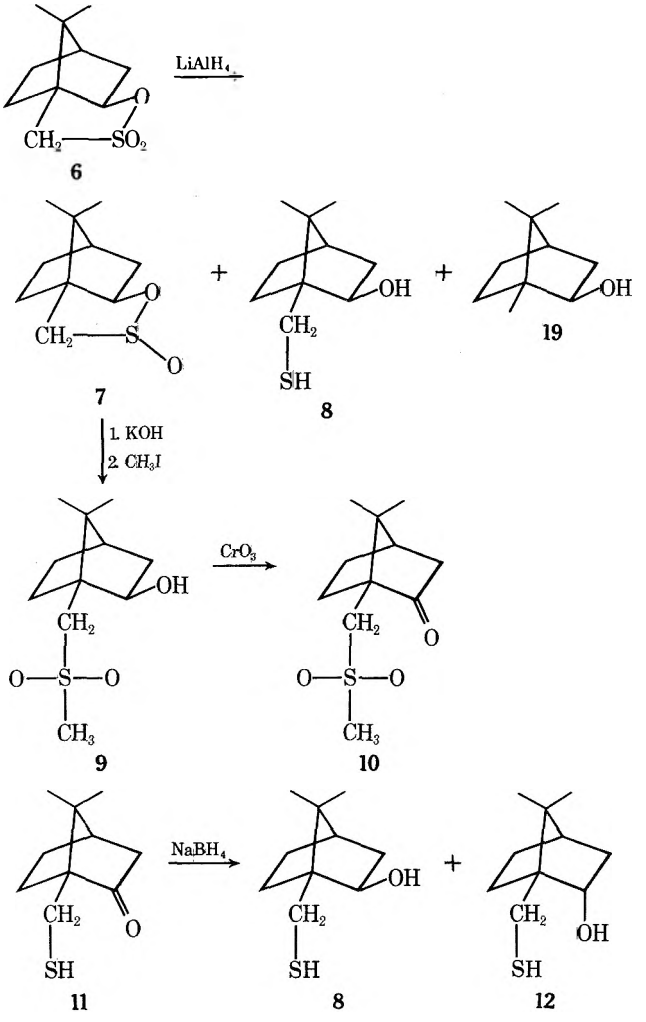
The structure assigned camphene sulfinate **2** was based on elemental and mass spectral analysis, which confirmed a



molecular formula of $C_{10}H_{16}O_2S$. Characteristic sulfinate ester[4] absorption was shown at 8.80 μ,[5] while the NMR spectrum was similar to that of camphene sultone (1). Chromic acid oxidation of 2 using the Jones procedure[7] gave camphene sultone (1).

10-Isobornyl Sultone. Reduction of 10-isobornyl sultone (6) with 1.1–2.0 equiv of lithium aluminum hydride in ether, followed by an acidic work-up, gave 10-isobornyl sulfinate (7) in good to excellent yield. When the reduction was carried out for 44 hr in THF at reflux, 10-mercaptoisoborneol (8) became the major product.

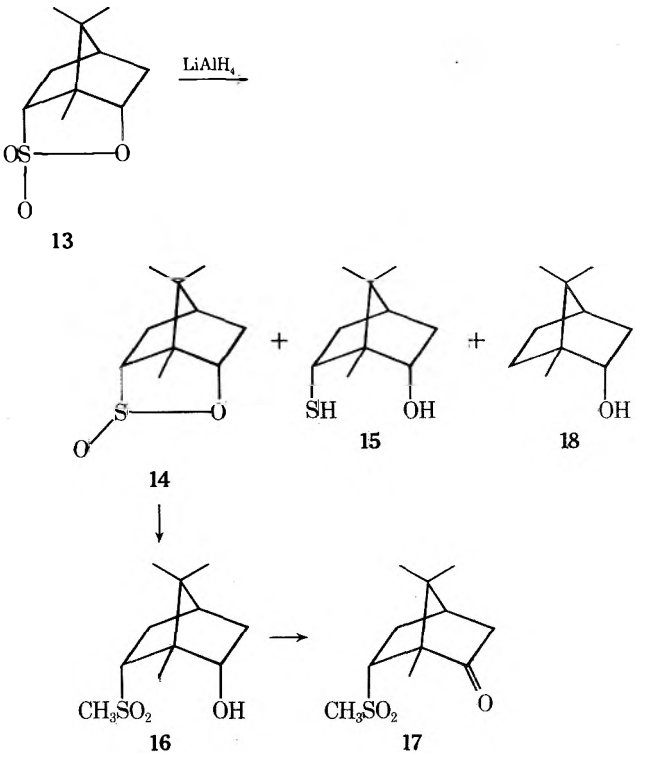
10-Isobornyl sulfinate (7) displayed sulfinate ester absorption at 8.80 μ and an NMR spectrum similar to that of



sultone 6. Treatment of 7 with potassium hydroxide and then methyl iodide afforded 10-methylsulfonylisoborneol (9) which was converted by Jones oxidation[7] to 10-methylsulfonylcamphor (10).

10-Mercaptoisoborneol (8) proved to be identical with one of the alcohols obtained by sodium borohydride reduction of 10-mercaptocamphor (11). The NMR spectrum of 10-mercaptoisoborneol (8) showed an apparent triplet at 3.88 ppm for the 2-endo hydrogen and singlet methyl signals at 0.83 and 1.03 ppm. 10-Mercaptoborneol (12) displayed a characteristic eight-line pattern for the 2-exo proton at 4.25 ppm and a singlet at 0.90 ppm for the *gem*-dimethyl group.

6-Bornyl Sultone. Lithium aluminum hydride reduction of 6-bornyl sultone (13)[3] gave, depending on the exact conditions, 6-bornyl sulfinate (14), 6-*endo*-mercaptoborneol (15),[3] and borneol (18). Oxidation of sulfinate 14 afforded sultone 13, while treatment with base and methyl iodide gave 6-*endo*-methylsulfonylborneol (16), which was oxidized to 6-*endo*-methylsulfonylcamphor (17).

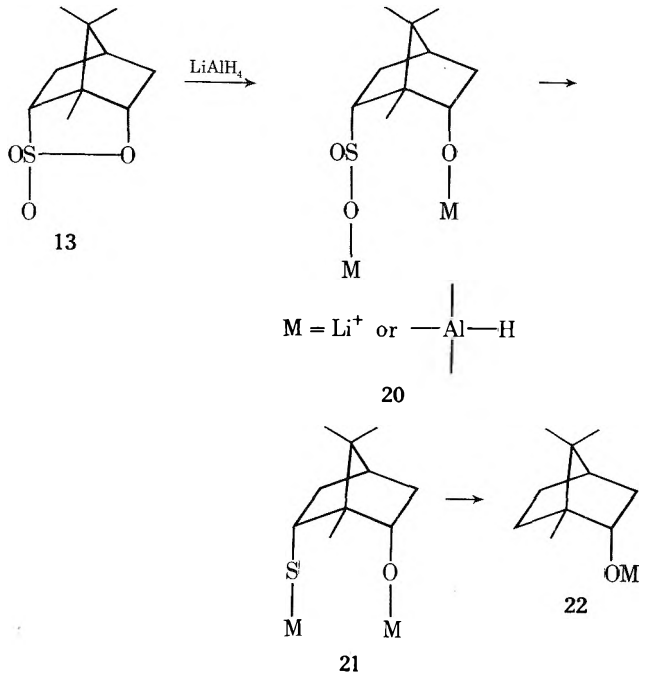


Discussion

Lithium aluminum hydride reduction of terpene sultones, followed by an acid work-up, affords a mixture of sulfinate ester, mercapto alcohol, and sulfur-free alcohol. Reduction of 6-bornyl sultone (13) with an excess of hydride was followed by removing, hydrolyzing, and analyzing aliquots at different time intervals. Sulfinate ester 14 forms initially, but is then consumed as the proportion of mercapto alcohol 15 rises to a maximum and then diminishes as the amount of borneol (18) increases. By controlling the concentration of hydride, temperature, and reaction time, any one of the three products can be made to predominate.

These observations suggest that hydride initially attacks at the sulfur atom of the sultone to produce an alkoxy sulfinate 20, which is slowly reduced to an alkoxy mercaptide 21. The mercaptide 21 is reduced even more slowly to 22.

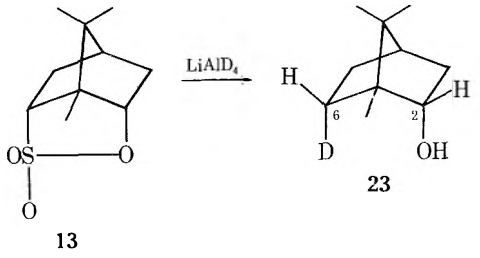
The neighboring alkoxide appears to play a role in facilitating the desulfurization step,[8] since under comparable conditions the desulfurization of mercaptans is extremely slow. For example, the conversion of dodecylmercaptan to



dodecane using lithium aluminum hydride in THF at 65° has a half-time of approximately 115 hr. In dioxane at 100° complete desulfurization requires 96 hr.

Sulfides are also desulfurized by lithium aluminum hydride at 100° using dioxane as a solvent, albeit the rate is extremely slow (70% conversion to hydrocarbons after 19 days).

The participation of the neighboring alkoxide is also inferred by the production of 6-*endo*-deuterioborneol (**23**) in low yield on reduction with lithium aluminum deuteride.



The endo configuration of the deuterium was indicated by the presence of an eight-line NMR signal for the exo C-2 proton. This observation requires the presence of an exo C-6 proton which has the proper "W" relationship for long-range spin coupling.

Experimental Section[9]

Lithium Aluminum Hydride Reduction of Camphene Sultone (1). A solution of 2.88 g (13.4 mmol) of camphene sultone (1)[10] in 20 ml of dioxane was added to a slurry of 2.0 g (51 mmol) of lithium aluminum hydride in 20 ml of dioxane. The mixture was heated at reflux for 6 hr and cooled, and water was added carefully. The precipitated salts were dissolved by adding 10% hydrochloric acid and the mixture was extracted with ether. The ether was removed and the products were separated by GLC. Camphene (3%) and camphene hydrate (1%)[11] were not isolated, but their presence was indicated by coincidence of GLC retention times with those of authentic samples. 9-Mercaptocamphene (**4**, 45%) was a liquid: ir 3.9, 6.05, and 11.35 μ; NMR (CCl_4) 1.10 (s, 3, CH_3), 4.52, and 4.75 ppm (s, C=CH_2); mass spectrum *m/e* (rel intensity) 168 (37), 153 (9), 140 (12), 135 (14), 121 (100), 93 (89), 79 (55).

Anal. Calcd for $C_{10}H_{16}S$: C, 71.36; H, 9.58; S, 19.05. Found: C, 71.48; H, 9.78; S, 19.11.

3-Mercaptocamphene hydrate (**3**, 18%) was a liquid: ir 2.85, 3.9, and 9.05 μ; NMR (CCl_4) 0.99 (s, 3, CH_3), 1.21 (s, 3, CH_3), 1.40 (X of ABX, 1, $-CH_2SH$), 1.72 (d, 1, OH), 2.36 and 2.92 ppm (A and B portions of ABX, 2, J_{AX} = 8, J_{BX} = 7, J_{AB} = 13 Hz, $-CH_2SH$); mass spectrum *m/e* (rel intensity) 168 (12), 153 (27), 152 (56), 135 (20), 121 (14), 109 (73), 93 (24), 43 (100).

Anal. Calcd for $C_{10}H_{18}OS$: C, 64.46; H, 9.74. Found: C, 64.69; H, 9.56.

Camphene sulfinate (**2**, 33%) was further purified by sublimation in vacuo and showed mp 145°; ir 8.8 μ ($-SO_2-$); NMR (CCl_4) 1.33 (s, 3, CH_3), 1.50 (s, 3, CH_3), and 2.98 ppm (s, 2, $-CH_2SO_2$); mass spectrum *m/e* (rel intensity) 200 (9), 136 (43), 121 (79), 109 (30), 107 (46), 95 (46), 93 (100), 67 (46), and 43 (65).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.92; H, 8.05; S, 16.01. Found: C, 59.99; H, 8.14; S, 15.77.

Oxidation of Camphene Sulfinate (2) to Camphene Sultone (1). A solution of 144 mg (0.72 mmol) of camphene sulfinate (**2**) in acetone was titrated with 0.30 ml (0.80 mmol) of Jones reagent.[7] After 1 hr several drops of isopropyl alcohol were added, the mixture was filtered, and the filtrate was diluted with water and extracted with ether. The ether was dried ($MgSO_4$) and removed, leaving an oil which was sublimed to give 86 mg (55%) of crystalline camphene sultone (**1**), mp 133–135°.[2]

10-Isobornyl Sulfinate Ester (7). A solution of 8.0 g (37 mmol) of 10-isobornyl sultone (**6**) in diethyl ether was added slowly to a stirred slurry of 2.88 g (74 mmol) of lithium aluminum hydride in ether. The mixture was refluxed for 45 hr and cooled, and the excess hydride was decomposed by the slow addition of saturated sodium chloride solution. The salts were separated by filtration, washed with ether, and dissolved in dilute hydrochloric acid. The acidic solution was extracted with ether. The ether extract was dried and evaporated to leave 5.26 g of crude sulfinate ester. An analytical sample of **7** was obtained by preparative TLC (silica gel PF-254, 10% ether–hexane) followed by GLC using a SE-30 column at 190°: mp 145–148°; ir (CCl_4) 8.80 ($-SO_2-$), 9.08, 10.1, and 11.65 μ; NMR (CCl_4) 0.89 and 0.92 (s, 6, CH_3), 1.0–2.25 (m, 7), 2.50 and 3.33 (AB q, 2, J = 14.2 Hz, $-CH_2SO_2-$), and 5.08 ppm (m, 1, J_{AX} = 7.5, J_{BX} = 3.8 Hz, $-CHOSO-$); mass spectrum *m/e* (rel intensity) 200 (1.4), 136 (33), 121 (72), 107 (46), 93 (100), 79 (44), 67 (40), and 41 (73).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.92; H, 8.05; S, 16.01. Found: C, 59.89; H, 8.01; S, 15.67.

GLC analysis of the material isolated from the original ether filtrate, as well as the sulfinate ester isolated from the salts as described above, indicated the formation of 70% of sulfinate ester **7**, 9% of 10-mercaptoisoborneol (**8**), and 21% of isoborneol (**19**).

10-Methylsulfonylisoborneol (9). A 4.1-g sample of a mixture of sulfinate ester **7**, sultone **6**, 10-mercaptoisoborneol (**8**), and isoborneol (**19**) was suspended in water and treated with 1.2 g of potassium hydroxide and 2.9 g of methyl iodide. The mixture was extracted after 2 hr with ether and the ether was removed to leave a small amount of oil whose ir spectrum indicated the presence of isoborneol and sultone **6**. Another 100 mg of potassium hydroxide and 3 g of methyl iodide were added to the aqueous phase, which was then stirred at ambient temperature for 24 hr and extracted with ether. The ether extract was washed with saturated sodium bisulfite and saturated salt solutions, dried, and evaporated to give 1.3 g (27%) of 10-methylsulfonylisoborneol (**9**). An analytical sample was obtained by sublimation in vacuo: mp 95–97°; ir (CCl_4) 2.8, 7.65, 8.85, 9.3, 9.5, 10.4, and 11.4 μ; NMR ($CDCl_3$) 0.84 and 1.08 (s, 6, CH_3), 1.3–2.0 (m, 7), 2.98 (s, 3, SO_2CH_3), 3.12 (s, 1, OH removed by addition of trifluoroacetic acid), 2.93 and 3.48 (AB q, 2, J = 13.5 Hz, $-CH_2SO_2$), and 4.12 ppm (broad t, 1, –CHO); mass spectrum *m/e* (rel intensity) 232 (0.1), 153 (74), 135 (83), 109 (100), 108 (100), 107 (71), 94 (49), 93 (99), and 41 (90).

Anal. Calcd for $C_{11}H_{20}O_3S$: C, 56.86; H, 8.68; S, 13.80. Found: C, 57.20; H, 8.64; S, 14.05.

10-Methylsulfonylcamphor (10). To a solution of 430 mg of 10-methylsulfonylisoborneol (**9**) in 5 ml of purified acetone was added 0.7 ml of Jones reagent.[7] The excess oxidant was destroyed with isopropyl alcohol, the solution was diluted with 15 ml of ether, and anhydrous sodium sulfate was added. The ether solution was separated and distilled in vacuo to give 425 mg of solid. Recrystallization from hexane gave 318 mg (74%) of 10-methylsulfonylcamphor (**10**): mp 79.5–80.5°; ir (CCl_4) 5.75, 7.6, and 8.8 μ; NMR (CCl_4) 0.90 and 1.08 (s, 6, CH_3), 1.3–2.7 (m, 7), 3.02 (s, 3, $-SO_2CH_3$), and 2.77 and 3.38 ppm (AB q, 2, J = 16 Hz, $-CH_2SO_2-$); mass spectrum *m/e* (rel intensity) 230 (0.6), 151 (75), 123 (49), 109 (100), 107 (30), 93 (29), 81 (80), 67 (49), 55 (36), 43 (34), and 41 (57).

Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.88; S, 13.92. Found: C, 57.08; H, 8.00; S, 13.84.

10-Mercaptoisoborneol (8). To a solution of 502 mg (2.3 mmol) of 10-isobornyl sultone (**6**) in 8 ml of dry THF was added

2.55 ml of a 1.0 *M* (2.55 mmol) solution of lithium aluminum hydride in THF. The solution was heated at reflux and aliquots were periodically withdrawn, treated with water and dilute hydrochloric acid, and extracted with ether, and the ether solution was then analyzed by GLC (SE-30 column). The yield of 10-mercaptoisoborneol rose to 40% after 44 hr. A sample of 8 isolated by GLC proved identical with an authentic sample of 8 prepared by reduction of 10-mercaptocamphor (11) as described below.

Sodium Borohydride Reduction of 10-Mercaptocamphor (11). A solution of 10 g of 10-mercaptocamphor,[12] mp 65.5–67°, and 720 mg of sodium borohydride in 50 ml of ethanol was kept at ambient temperature for 24 hr and then poured into water and extracted with ether. The ether was dried and removed to leave 9.2 g of colorless oil which slowly solidified.

A 4.1-g portion of the crude product was chromatographed on 100 g of silica gel using 5% ether–hexane as eluent. 10-Mercaptoisoborneol (8), 1.93 g, eluted first and after sublimation in vacuo showed mp 71.5–73°: ir (mull) 2.9, 3.9 μ; NMR (CCl_4) 0.83 and 1.03 (s, 6, CH_3), 1.11 (X of AMX, 1, J_{AX} = 9, J_{MX} = 6 Hz, SH), 2.25 (s, 1, OH), 2.46 and 2.79 (AM of AMX, 2, J_{AM} = 12.5 Hz, $-CH_2S$), and 3.88 ppm (broad t, 1, –CHO); mass spectrum *m/e* (rel intensity) 186 (0.5), 168 (24), 153 (7), 152 (10), 135 (32), 121 (21), 109 (27), 108 (100), 95 (58), and 93 (42).

Anal. Calcd for $C_{10}H_{18}OS$: C, 64.46; H, 9.74; S, 17.22. Found: C, 64.57; H, 9.64; S, 17.29.

After collecting a mixture of 10-mercaptoisoborneol and 10-mercaptoborneol, 350 mg of pure 10-mercaptoborneol (12) was obtained. The analytical sample was obtained by sublimation in vacuo and showed mp 83–84° (sealed capillary); ir (mull) 2.9 and 4.0 μ; NMR (CCl_4) 0.90 (s, 6, CH_3CCH_3), 2.3 (s, 1, OH which was removed upon addition of trifluoroacetic acid), 2.53 and 2.66 (m, 2, $-CH_2S$), and 4.25 ppm (m, 1, CHO); NMR (benzene) 0.71 (s, 6, CH_3CCH_3), 1.27 (m, 1, SH), 2.38 and 2.40 (AB portion of ABX, 2, $-CH_2S$), 2.57 (s, 1, OH), 4.18 ppm (m, 1, –CHO–); mass spectrum *m/e* (rel intensity) 186 (1.5), 168 (8), 153 (8), 152 (15), 135 (19), 121 (15), 109 (28), 108 (100), 95 (63), and 93 (35).

Anal. Calcd for $C_{10}H_{18}OS$: C, 64.46; H, 9.74; S, 17.22. Found: C, 64.67; H, 9.53; S, 17.12.

6-Bornyl Sulfinate Ester (14). A slurry of 278 mg (7.3 mmol) of lithium aluminum hydride in ether was added slowly to a solution of 1.58 g (7.3 mmol) of 6-bornyl sultone (13) in ether. The mixture was stirred at ambient temperature for 24 hr and then water was carefully added until the aluminum salts coagulated. The salts were removed by filtration and washed with ether. The filtrate was evaporated leaving 545 mg (34% recovery) of sultone 13.

The aluminum salts were dissolved in 10% hydrochloric acid and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated, leaving 928 mg (63%) of colorless solid. Recrystallization from hexane gave pure sulfinate ester 14: mp 191–193°; ir ($CHCl_3$) 9.0 μ; NMR (CCl_4) 0.97, 1.00, and 1.41 (s, 9, CH_3), 3.05 (d of d, 1, J = 10.7 and 3.0 Hz, $-CHSO_2-$), and 4.88 ppm (d of d, 1, J = 7.2 and 0.6 Hz, –CHO); mass spectrum *m/e* (rel intensity) 200 (28), 136 (26), 135 (37), 121 (27), 108 (28), 107 (31), 93 (100), 41 (39).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.92; H, 8.05; S, 16.01. Found: C, 60.15; H, 8.24; S, 16.16.

The results illustrated in Table I were obtained by treating 1 mmol of sultone 13 in 5 ml of THF at 0° with 1.0 and 5.0 ml of a 1.0 *M* solution of lithium aluminum hydride in ether. Aliquots were withdrawn, quenched with 5% hydrochloric acid, and extracted with ether. The ether extract was dried ($MgSO_4$), concentrated, and analyzed using an SE-30 column at 170°.

Table I
Lithium Aluminum Hydride Reduction of 6-Bornyl Sultone (13)

$LiAlH_4$, mmol	Time	% sultone 13	% sulfinate ester 14[a]
1	5 min	92	6
1	1 hr	86	12
1	6 hr	18	80
5	5 min	39	61
5	1 hr	13	86
5	5 hr	0	91

[a] Material balance shown is not 100% owing to the formation of small amounts of more highly reduced compounds.

Oxidation of 6-Bornyl Sulfinate Ester (14). A 107-mg sample of pure sulfinate ester 14 was kept overnight in acetone with an excess of chromium trioxide in sulfuric acid–water.[7] Excess reagent was destroyed with isopropyl alcohol and the mixture was diluted with water and extracted with ether. The ether was dried and removed to leave 100 mg of solid whose infrared spectrum indicated that it was mainly sultone 13 contaminated by a small amount of sulfinate ester 14.

6-*endo*-Methylsulfonylcamphor (17). A suspension of 770 mg (3.8 mmol) of 6-bornyl sulfinate ester (14) in 20 ml of water containing 700 mg of potassium hydroxide was heated for 2 hr, cooled, filtered, and then treated with 1.0 ml of methyl iodide. After stirring at ambient temperature for 24 hr, the mixture was heated to drive off excess methyl iodide, cooled, and then extracted with ether. The ether was removed to give 551 mg of crude 6-*endo*-methylsulfonylborneol (16). Two recrystallizations from hexane gave a solid, mp 85–94°, sublimation under vacuum gave a product melting over a range of 70–90°, while preparative thin layer chromatography gave a solid: mp 71–74°; ir (CCl_4) 2.9 and 8.85 μ; NMR (CCl_4) 0.95 (s, 6, CH_3CCH_3), 1.18 (s, 3, CH_3), 3.00 (s, 3, CH_3SO_2-), 3.42 (four broad lines, 1, $CHSO_2-$), 3.72 (s, 1, OH), and 3.97 ppm (four broad lines, 1, –CHO); mass spectrum *m/e* (rel intensity) 232 (0.1), 188 (1), 153 (4), 152 (3), 109 (32), 108 (100), 93 (28), and 41 (34).

6-*endo*-methylsulfonylborneol (16, 368 mg) in 20 ml of acetone was treated with 1 ml of Jones reagent.[7] After 15 min the excess chromic acid was destroyed with ethanol and the mixture was poured into water and extracted with ether. The ether was removed and the residue was recrystallized from dry methanol to give 77 mg of 6-*endo*-methylsulfonylcamphor (17): mp 209–211°; ir (mull) 5.75 and 8.8 μ; NMR ($CDCl_3$) 0.87 (s, 3, CH_3), 1.05 (s, 3, CH_3), 2.88 (s, 3, CH_3SO_2-), and 3.51 (X portion of ABX, 1, J_{AX} = 10.5, J_{BX} = 5.5 Hz, $-CHSO_2$).

Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.88. Found: C, 57.15; H, 7.99.

Lithium Aluminum Hydride Reduction of 6-Bornyl Sulfinate ester (14). To a solution of 73 mg (0.36 mmol) of 6-bornyl sulfinate ester (14) in 5 ml of dry THF was added 0.7 ml of a 1.0 *M* solution (0.7 mmol) of lithium aluminum hydride in ether. Aliquots were periodically removed from the refluxing solution, quenched with water, and acidified with 5% hydrochloric acid. The resulting solutions were saturated with sodium chloride and extracted with ether. The ether solutions were dried ($MgSO_4$), concentrated, and analyzed using a SE-30 column at 155°. The yield of 6-*endo*-mercaptoborneol (15)[3] rose to 97% within 2 hr and then dropped to 90% after 44 hr as the amount of borneol (18) increased to 10%.

Reduction of 6-Bornyl Sultone (13) with Lithium Aluminum Deuteride. A solution of 326 mg of 6-bornyl sultone in dry THF was added to a slurry of 650 mg of lithium aluminum deuteride (Alfa Inorganics) in THF. The solution was heated at reflux for 440 hr and cooled and the excess deuteride was decomposed with deuterium oxide. Dilute hydrochloric acid was added until the salts dissolved and the solution was extracted with ether. The ether was dried and removed and GLC analysis of the residue showed that it was composed of 6-*endo*-mercaptoborneol (15) and borneol (18). A pure sample of borneol was obtained by GLC using a SE-30 column at 125°. The NMR spectrum of this sample of borneol was identical with that of authentic material except it integrated for one less proton in the region 1.9–2.6 ppm. The relative abundance of the molecular ion was too low to permit an accurate determination of the deuterium content.

A 25-mg sample of the borneol obtained above was oxidized using a solution of chromium trioxide in pyridine and water. After the usual work-up a mixture of 60% camphor and 40% borneol was obtained. A pure sample of camphor was isolated by GLC using a 20% Carbowax column at 177°; the mass spectrum indicated the presence of 88% of one deuterium atom; the NMR spectrum showed a reduction in peak area in the 1.3–1.4 region.

Lithium Aluminum Hydride Reduction of Dodecyl Mercaptan. A weighed amount of dodecyl mercaptan was added to the solvent, followed by an appropriate amount of 1.0 *M* lithium aluminum hydride solution in ether. The solution was brought to reflux and aliquots were withdrawn at appropriate time intervals, quenched with 5% hydrochloric acid, and extracted with ether. The ether extract was dried, concentrated, and analyzed using a SE-30 column at 140°. The results are displayed in Table II.

Table II
Lithium Aluminum Hydride Reduction of Dodecyl Mercaptan

Solvent	Mmol $LiAlH_4$/ mmol RSH	Time, hr	% dodecane
THF	5.4	3.5	0
THF	5.4	21.0	6
THF	5.4	115	53
Dioxane	5.0	2.0	3
Dioxane	5.0	44	47
Dioxane	5.0	71	92
Dioxane	1.1	40	25
Dioxane	1.1	72	83
Dioxane	1.1	96	98

Lithium Aluminum Hydride Reduction of Decyl Dodecyl Sulfide. Approximately 20 ml of dioxane was distilled into a flask containing 1.002 g (2.93 mmol) of decyl dodecyl sulfide,[13] and then 264 mg of cyclododecane and 230 mg (6.0 mmol) of lithium aluminum hydride were added. The stirred slurry was heated at reflux and aliquots were withdrawn periodically, diluted with ether, quenched with water, and acidified with 5% hydrochloric acid. The organic products were extracted with ether and dried. The concentrated ether solution was analyzed using an SE-30 column at 130°. The yields of dodecane follow, time in hours (% dodecane): 2 (0), 15 (0.2), 82 (24), 278 (56), and 472 (64). At no time was there evidence for the presence of decyl or dodecyl mercaptan.

Registry No.—**1**, 13131-58-3; **2**, 54934-37-1; **3**, 54934-38-2; **4**, 54934-39-3; **6**, 13131-57-2; **7**, 54934-40-6; **8**, 54934-41-7; **9**, 54934-42-8; **10**, 54934-43-9; **11**, 54984-43-9; **12**, 54934-44-0; **13**, 38359-42-1; **14**, 54934-45-1; **16**, 54934-46-2; **17**, 54934-47-3; lithium aluminum hydride, 16853-85-3; sodium borohydride, 16940-66-2; dodecyl mercaptan, 112-55-0; decyl dodecyl sulfide, 54934-48-4.

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Reactions of Organolithium Compounds and Grignard Reagents with Lithium Carboxylates

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With the exception of the reaction of equivalents of phenyllithium with lithium acetate for 24 hr, which gives a mixture of acetophenone and diphenylmethylcarbinol, similar reactions involving six other lithium carboxylates give only ketones. The reactions of three lithium carboxylates with phenyllithium for only 0.5 hr give mixtures of ketones and carbinols. These latter results are explained by suggesting that even in the presence of water the unreacted phenyllithium survives for sufficiently long so that it reacts appreciably with the ketone, $RCOC_6H_5$, which arises from the hydrolysis of the intermediate, $R(C_6H_5)C(OLi)_2$. Evidence to support this argument is given. The reactions of two lithium carboxylates with three Grignard reagents give mixtures of ketones and carbinols with the latter products predominating except with methylmagnesium iodide, in which case the reverse is true.

A thorough study of the reactions of carboxylic acids and their lithium salts with phenyllithium has apparently not been reported. In 1933 Gilman and Van Ess[1] made the significant observations that the reaction of benzoic acid (1 equiv) with phenyllithium (2 equiv) gave benzophenone (37.2%) and triphenylcarbinol (14.1%) and that refluxing lithium benzoate (0.136 mol) with phenyllithium (0.1 mol) for 5.5 hr gave benzophenone (70.0%) and no triphenylcarbinol. In contrast to these results Tegnér[2] has shown that the reactions of 2 equiv of methyllithium with 1 equiv of a series of aliphatic and aromatic acids for 1 hr give the corresponding methyl ketones and no tertiary alcohols.

Braude and Coles[3] have also obtained only ketone (30–40%) by stirring a mixture of equivalents of isobutenyllithium and lithium acetate, benzoate, or crotonate for a 24-hr period. Petrov and Sokolova[4] report yields of less than 25% of ketone and no carbinol from the reactions of sodium acetate and sodium *n*-butyrate with primary Grignard reagents in ether.

The present investigation is concerned with a study of

the reactions of certain organolithium compounds and Grignard reagents with a series of lithium carboxylates. Refluxing equimolar amounts of phenyllithium and the lithium salts of a number of carboxylic acids (Table I) for 24 hr gave, upon quenching with water, high yields of ketone and usually no tertiary alcohol.

Table I
Reactions of Lithium Carboxylates with Phenyllithium for 24 Hr

Registry no.	Lithium salt[a]	Yields of products[b] % ketone	% carbinol
546-89-4	Acetate	39 (66[c])	35 (5[c])
6531-45-9	Propionate	82	0
21303-03-7	*n*-Butyrate	85	0
25179-23-1	Isobutyrate	79	0
14271-99-9	Pivalate	89[d]	0
16577-51-8	Caproate	84[e]	0
553-54-8	Benzoate	85[f]	0

[a] In each reaction, except as noted below, the lithium carboxylate (1 equiv) was added to phenyllithium (1 equiv) in ether and the mixture was refluxed for 24 hr. [b] In all cases the physical constants of the products agree with the literature values. [c] Reflux time was 72 hr. [d] Pivalic acid (8%) was recovered. [e] Caproic acid (12%) was recovered. [f] Benzoic acid (10%) was recovered.

It is suggested that the reason for obtaining only ketone in all of the reactions except that with lithium acetate for a 24-hr reaction time may be due to the stability of the dilithium salts.[1] $RR'C(OLi)_2$, which might resist further substitution with a second mole of organolithium reagent or loss of lithium oxide to give the ketone, $RR'C{=}O$, which could then react with an additional mole of organolithium reagent. The following suggestion might possibly account for the formation of a mixture of ketone (39%) and carbinol (35%) in the 24-hr lithium acetate–phenyllithium reaction. The stability of the initially formed adduct between lithium acetate and phenyllithium, $CH_3C(C_6H_5)(OLi)_2$, may be such that it decomposes to some extent during the reaction to give some free ketone, $CH_3COC_6H_5$, which reacts with more phenyllithium to give the carbinol, $(C_6H_5)_2C(CH_3)OH$. Alternatively, the steric requirements of the adduct may be sufficiently favorable so what may be described as a nucleophilic attack on carbon by the phenyllithium may occur to some extent to give the carbinol.

It was somewhat unexpected to find that the interaction of equivalents of phenyllithium and three typical lithium carboxylates, with a reflux time of only 30 min, gives mixtures of ketones and tertiary alcohols. Thus, lithium propionate gave propiophenone (40%) and diphenylethylcarbinol (25%); lithium *n*-butyrate gave *n*-butyrophenone (39%) and diphenyl-*n*-propylcarbinol (30%); and lithium benzoate gave benzophenone (8%) and triphenylcarbinol (22%). Furthermore, in the case of lithium *n*-butyrate, for example, when the reflux time is increased by increments, from 0.5 to 24 hr, increasing amounts of ketone and decreasing amounts of tertiary alcohol are obtained (Table II). It was also found that the interaction of equivalents of lithium benzoate and *n*-propyllithium for 24 hr gave only *n*-butyrophenone (85.8%) while a similar reaction for a 30-min reaction time gave a mixture of *n*-butyrophenone (11.7%) and di-*n*-propylphenylcarbinol (17.6%).

The formation of substantial amounts of carbinol during a short reaction time appears to be the result of a *slow* reaction between the lithium carboxylate and the organolithium compound combined with a *slow* hydrolysis of the reaction intermediate. It is suggested that at short reaction

Table II
Reactions of Lithium *n*-Butyrate with Phenyllithium[a] for Varying Reaction Times

Reflux time, hr	Products, % yield Ketone[b]	Carbinol[b]
0.5	39	30
1.0	42	28
2.0	46	30
3.0	61	21
4.0	70	10
5.0	79	5
10.0	90	0
24.0	85	0

[a] Equivalents of lithium *n*-butyrate and phenyllithium were used. [b] The physical constants of the *n*-butyrophenone [C. R. Hauser, W. J. Humphlett, and M. J. Weiss, *J. Am. Chem. Soc.*, **70**, 426 (1948)] and diphenyl-*n*-propylcarbinol [H. Masson, *C. R. Acad. Sci.*, **135**, 534 (1902)] agree with the literature values.

times there is considerable unreacted organolithium compound present which reacts during the hydrolysis with part of the ketone which is formed by the hydrolysis of the intermediate adduct, $RR'C(OLi)_2$.

$$RR'C(OLi)_2 \xrightarrow{H_2O} RCOR' \xrightarrow{R'Li} RR'R'C(OLi) \xrightarrow{H_2O} RR'R'COH$$

A somewhat comparable mechanism has been suggested by Jorgenson[5] in a review on the preparation of ketones from the reaction of organolithium reagents with carboxylic acids. It is of interest to note that when House and Bare[6] treated a mixture of the stereoisomeric 4-*tert*-butylcyclohexanecarboxylic acids with methyllithium and processed the reaction by removing aliquots from the mixture and adding them dropwise, with vigorous stirring, to fresh portions of ice and dilute hydrochloric acid, only 4-*tert*-butylcyclohexyl methyl ketone (94.8%) and no dimethyl-4-*tert*-butylcyclohexylcarbinol were obtained. Under less controlled hydrolytic conditions often a mixture of ketone and carbinol is obtained.[5]

To obtain evidence in support of the scheme shown above, two experiments were performed. A mixture of equivalents of lithium propionate and phenyllithium, A, was refluxed for 24 hr. Hydrolysis of such a mixture had given (see Table I) an 82% yield of propiophenone and no carbinol. In another flask, phenyllithium, B (1 equiv), was prepared. Simultaneously, rapidly and with vigorous stirring, A and B were poured down the opposite sides of a beaker containing crushed ice and water. Processing gave propiophenone (58.1%) and diphenylethylcarbinol (28.3%). In the second experiment equivalents of propiophenone, C, in an equal volume of ether and phenyllithium, B, were treated with ice and water as described above to give diphenylethylcarbinol (44.8%) and some material which appeared to be self-condensed derivatives of propiophenone. These experiments lend some support to the proposed origin of diphenylalkylcarbinols (vide supra).

It was not surprising to find that when lithium *n*-butyrate (1 equiv) and phenyllithium (2 and 3 equiv) were allowed to react for 24 hr, the yields of ketones dropped to 63.5 and 48.0% and the yields of carbinol increased to 34 and 52%, respectively, as contrasted with the yields of products, ketone (85.0%) and carbinol (0%), which were obtained when equivalents of the reagents were allowed to react for 24 hr.

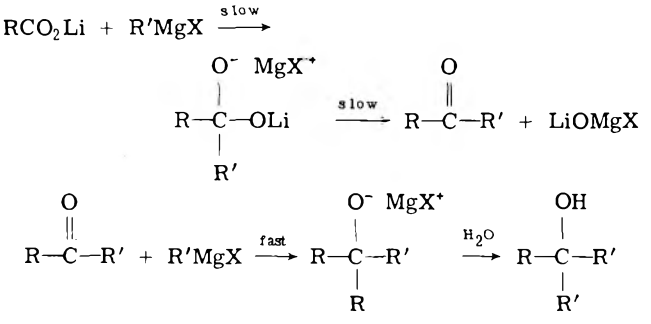
In contrast with what was observed in the reaction of the lithium carboxylates with organolithium compounds, lithi-

Table III
Reactions of Grignard Reagents with Lithium Carboxylates

Grignard reagent[a]	Products[b]	Yield, %
	Lithium *n*-Butyrate[a]	
CH_3MgI	n-$C_3H_7COCH_3$	24
	n-$C_3H_7C(CH_3)_2OH$	12
n-C_4H_9MgBr	n-$C_3H_7COC_4H_9$-n	11
	n-$C_3H_7C(n$-$C_4H_9)_2OH$	43
C_6H_5MgBr	n-$C_3H_7COC_6H_5$	7 (14[c])
	n-$C_3H_7C(C_6H_5)_2OH$	70 (58[c])
	Lithium Benzoate[a]	
CH_3MgI	$C_6H_5COCH_3$	33
	$C_6H_5C(CH_3)_2OH$	15
n-C_4H_9MgBr	$C_6H_5COC_4H_9$-n	12
	$C_6H_5C(n$-$C_4H_9)_2OH$	61
C_6H_5MgBr	$(C_6H_5)_2CO$	10
	$(C_6H_5)_3COH$	61

[a] In each reaction the lithium carboxylate (1 equiv) was slowly added to the Grignard reagent (1 equiv) and the mixture was refluxed for 24 hr. [b] The physical constants of the products agreed with the literature values. [c] This reaction was refluxed for 2.5 hr.

um salts of carboxylic acids (1 equiv) reacted exothermally with an ether solution of Grignard reagent (1 equiv) to give mixtures of both ketone and tertiary alcohol with the tertiary alcohol usually the major product, even in a 24-hr reaction time. The results obtained from the reactions of lithium n-butyrate and lithium benzoate with methyl, n-butyl, and phenylmagnesium halides are found in Table III. The results obtained in the lithium carboxylate–Grignard reagent experiments (Table III) when coupled with those in Table II suggest that in the former reactions (Table III) the formation of free ketone may occur slowly prior to the hydrolysis of the intermediate adduct, RR'C(OMgX)(OLi), and the ketone may then be rapidly converted to the halomagnesium salt of the tertiary alcohol by reaction with more Grignard reagent.



Experimental Section

Lithium Carboxylates. These were prepared by the interaction of equivalents of lithium carbonate and the appropriate carboxylic acids in aqueous solution followed by evaporation and thorough drying under vacuum, e.g., lithium isobutyrate. Anal. Calcd for $C_4H_7O_2Li$: Li, 7.38. Found: Li, 7.16.

General Procedure for the Reaction of Lithium Carboxylates with Organolithium Compounds. The dry lithium carboxylate was added all at once to the organolithium compound in ether (100 ml of ether was used per 0.1 mol of lithium reagent). The ether does not reflux during the addition of the lithium salts. The reaction mixture was then refluxed for the appropriate length of time and the reaction was then quenched by pouring the mixture onto crushed ice and water. The phases were separated and the aqueous phase was extracted with several portions of ether. The combined basic, ether phases were dried over Drierite, the solvent and low boilers were removed at atmospheric pressure, and the residue was fractionated under vacuum. The aqueous phase was acidified with concentrated hydrochloric acid and extracted with several portions of ether. The combined acidic, ether phases were processed in the same manner as the basic ether phases.

Reaction of Equivalents of Lithium Propionate and Phenyllithium for 24 and 0.5 Hr. From the interaction of phenyllithium [0.4 mol, prepared from lithium ribbon (0.8 mol, 5.6 g, in 400 ml of ether) and bromobenzene (0.4 mol, 62.8 g)] and lithium propionate (0.4 mol, 32.0 g) there was obtained, after a 24-hr reaction time, propiophenone [43.7 g, 82.0%, bp 84–85° (8 mm)] (see first reference in Table II), 2,4-dinitrophenylhydrazone mp 187.0–188.0, alone and when mixed with an authentic sample. When this reaction was repeated using phenyllithium (0.2 mol) and lithium propionate (0.2 mol) except that the reaction time was 0.5 hr, there was obtained a mixture of propiophenone [10.8 g, 40.3%, bp 104–107° (20 mm)] and diphenylethylcarbinol [5.2 g, 24.5%, bp 183–185° (21 mm), mp 93.2–94.6° (see second reference in Table II)].

Reaction of Equivalents of Lithium n-Butyrate and Phenyllithium for 0.5 and 3 Hr. From the interaction of phenyllithium (0.3 mol) and lithium n-butyrate (0.3 mol, 28.2 g) there was obtained a mixture of n-butyrophenone [17.4 g, 39.0%, bp 104–108° (11 mm) (see first reference in Table II)] and diphenyl-n-propylcarbinol [10.1 g, 29.7%, bp 176–177° (10 mm) (see second reference in Table II)]. When this reaction was repeated except that the reflux time was 3 hr, there was obtained n-butyrophenone [27.0 g, 60.6%, bp 96–98° (8 mm)] and diphenyl-n-propylcarbinol [7.2 g, 21.2%, bp 173–175° (8 mm)].[8]

Reaction of Lithium Benzoate (1 Equiv) with n-Propyllithium (1 Equiv) for 0.5 and 24 Hr. From 0.26 mol of n-propyllithium [prepared in 75% yield from lithium (0.7 mol, 4.9 g)], n-propyl bromide (0.35 mol, 43.1 g), and lithium benzoate (0.26 mol, 33.3 g), there were obtained 4.5 g (11.7%) of n-butyrophenone and 4.4 g (17.6%) of di-n-propylphenylcarbinol.

The total yields of n-butyrophenone and di-n-propylphenylcarbinol were determined by the hydroxylamine hydrochloride titration method.[7] The distilled material consisted of three fractions. The lowest boiling fraction consisted of pure ketone and the highest boiling fraction consisted of pure carbinol. Aliquots of the intermediate boiling fraction, consisting of a mixture of ketone and carbinol, were titrated with hydroxylamine hydrochloride in order to determine the ketone content. The amount of carbinol in this intermediate fraction was calculated by subtracting the amount of ketone from the total weight of the fraction. The yields of ketone and carbinol indicated above represent, within experimental error, the total amounts of ketone and carbinol obtained. The lowest boiling fraction, n-butyrophenone, bp 108.0–111.0° (14 mm), gave a 2-4-dinitrophenylhydrazone, mp 189.0–189.8°, alone and when mixed with an authentic sample.

The highest boiling fraction, which was pure di-n-propylphenylcarbinol, bp 128.0–131.0° (14 mm),[8] and did not give a positive hydroxylamine test, was dehydrated to 4-phenyl-3-hexene by refluxing a sample (1.8 g) with acetic anhydride (5 ml) and glacial acetic acid (10 ml) for 2 hr. The resulting olefin was extracted with ether and oxidized with potassium permanganate in acetone (according to the procedure of Adkins and Roebuck)[9] to give propionic acid (identified as propionamide, mp 78.0–78.5°, alone and when mixed with an authentic sample) and n-butyrophenone (2,4-dinitrophenylhydrazone, mp 189.0–189.8°, alone and when mixed with an authentic sample). In addition, 23.7 g (74.5%) of benzoic acid was recovered. When the reaction was repeated using a 24-hr reaction time there was obtained n-butyrophenone [33.0 g, 85.8%, bp 119–120° (23 mm), 2,4-dinitrophenylhydrazone, mp 89.0–189.8°].

Reaction of the 1:1 Adduct of Lithium Propionate and Phenyllithium, Phenyllithium, and Water. In flask A, lithium propionate (0.1 mol, 8.0 g) and phenyllithium (0.1 mol in 100 ml of ether) were refluxed for 24 hr. In another flask, B, phenyllithium (0.1 mol in 1.00 ml of ether) was prepared. Simultaneously and with rapid stirring the contents of flasks A and B were poured down the opposite sides of a beaker containing 250 g of crushed ice. The customary processing gave propiophenone [7.8 g, 58.1%, bp 84–85° (8 mm) (see first reference in Table II); 2,4-dinitrophenylhydrazone mp 187.0–188.0° alone and when mixed with an authentic sample] and diphenylethylcarbinol (3.0 g, 28.3%, mp 94.0–95.0°[10] alone and when mixed with an authentic sample).

Reaction of Equivalents of Propiophenone, Phenyllithium, and Water. Using a procedure similar to that described in the last experiment, phenyllithium (0.1 mol, 70 ml of 1.4 M commercial material in 30% ether and 70% benzene) and propiophenone (0.1 mol, 13.4 g in 12 ml of anhydrous ether) were added with rapid stirring to 300 g of ice and water to give diphenylethylcarbinol [9.0

g, 44.8% (8 mm), mp 94–95°[10] alone and when mixed with an authentic sample] and 5.7 g of material, bp 108–125° (20 mm), which appeared to consist of propiophenone and its self-condensed products.

Registry No.—Phenyllithium, 591-51-5; propiophenone, 93-55-0; propiophenone 2,4-dinitrophenylhydrazone, 3375-37-9; diphenylethylcarbinol, 5180-33-6; *n*-butyrophenone, 495-40-9; diphenyl-*n*-propylcarbinol, 5331-17-9; *n*-propyllithium, 2417-93-8; di-*n*-propylphenylcarbinol, 4436-96-8; methyl iodide, 74-88-4; *n*-butyl bromide, 109-65-9; phenyl bromide, 108-86-1.

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Action of Grignard Reagents on the Esters of Propiolic Acid

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When methyl propiolate (**1**) was treated with an excess of ethylmagnesium bromide, no ethane was evolved and the expected tertiary alcohol, diethylethinylcarbinol, was obtained in only 10% yield. The primary reaction product proved to be an unsaturated 3,4-epoxy ester (**2**) whose formation required two alkyl groups, *, from the Grignard reagent and a third, x, from a second mole of the original ester. Catalytic hydrogenation yielded the saturated analog (**5**) which upon mild hydrolysis underwent simultaneous loss of carbon dioxide and fissure of the epoxide ring to form an identifiable ethyl ketone (**8**). Several combinations of Grignards and esters were employed to show in each case analogous reaction products. A mechanism to account for the products obtained is presented.

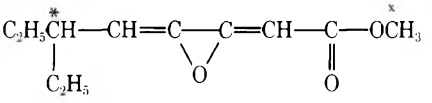
The investigation presented in this paper originated from the observation that methyl propiolate (**1**), $HC{\equiv}C-COOCH_3$, on treatment with methylmagnesium iodide in the Zerevitinov machine yielded no methane but did undergo a vigorous reaction which consumed 3 mol of Grignard reagent. The failure to form methane was particularly puzzling since the acidity of the acetylenic hydrogen is increased by its conjugation with the carbomethoxy group to such an extent that it not only forms a silver and copper salt, but also undergoes Claisen condensation with ethyl oxalate and Michael condensation with ethyl fumarate.[1]

Addition of Grignard reagents of higher molecular weight such as phenyl-, naphthyl-, or triphenylvinylmagnesium bromide[2] and the reagent prepared by the action of phenylmagnesium bromide on α-bromo-β-phenylbenzalacetophenone[3] produced immediate and vigorous reaction, but decomposition of the reaction mixtures yielded only heavy, intractable oils. Gilman and Robinson[4] reported similar difficulties when they added phenylmagnesium bromide to the ethyl ester of acetylenedicarboxylic acid.

The action of lighter Grignards such as methyl- and ethylmagnesium bromide on methyl propiolate yielded distillable oils from which definite compounds could be obtained by fractionation under vacuum. Thus, when methyl propiolate (**1**) was added to an excess of ethylmagnesium bromide, two pure liquids were isolated from the reaction mixture.

The first, a colorless, low-boiling oil, was identified as diethylethinylcarbinol through the formation of a silver salt and by catalytic hydrogenation to the known triethylcarbinol. The acetylenic alcohol was present only to the extent of 8–10% and its formation may be regarded as a secondary reaction in which the Grignard reagent undergoes the expected 1,2 addition to the ester carbonyl.

The primary reaction product **2**, a pale yellow oil, was shown by analytical methods to be dimolecular product of empirical formula $C_{11}H_{16}O_3$, containing one methoxy group. All tests for the functional groups $-HC{=}O$, $>C{=}O$, and $HC{\equiv}C-$ were negative, but catalytic hydrogenation



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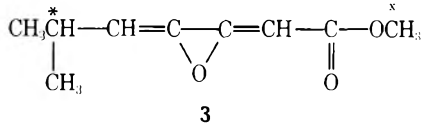

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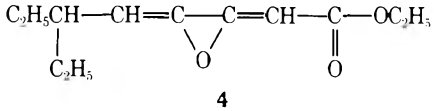

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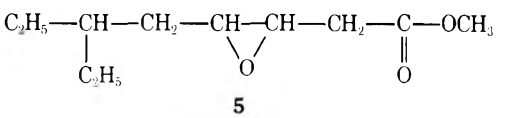
consumed 2 mol of hydrogen, indicating the presence of two double bonds or one triple bond of the type $RC{\equiv}CR$.

The reduction product **5**, a colorless oil of empirical formula $C_{11}H_{20}O_3$, distilled without decomposition under vacuum. Because of its greater physical and chemical stability it was selected to elucidate the ultimate structure of **2**. The reduction product **5** contained one methoxyl group, formed



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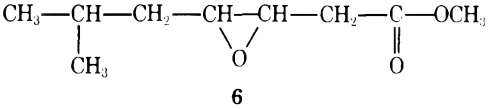

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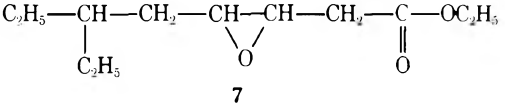

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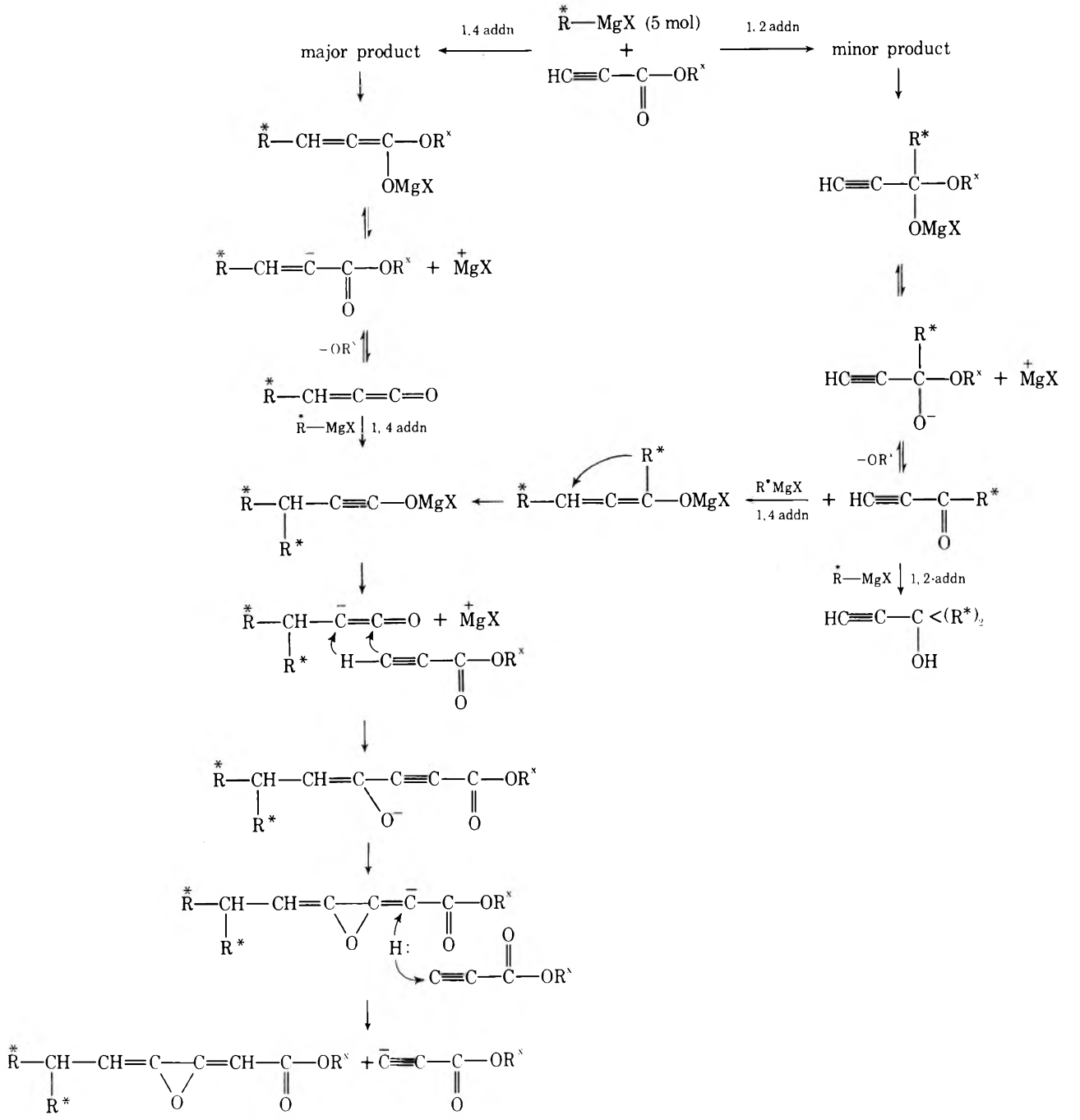
a crystalline amide, $C_{10}H_{19}O_2N$, with concentrated ammonia, and gave no test for aldehydic or ketonic carbonyl groups. In the Zerevitinov machine no gas was evolved but 2 mol of Grignard was consumed.

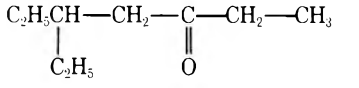
Scheme I



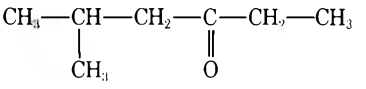
The above facts indicate strongly that two of the three oxygens were present in the form of the original ester group, which accordingly must be involved in the dimerization. The third oxygen was best represented by some form of ether linkage. On treatment with warm, 3% methyl alcoholic potassium hydroxide the ester linkage was readily saponified, but the saponification was accompanied by a simultaneous loss of carbon dioxide by the acid and fissure of the ether linkage to form a ketone, a reaction characteristic of epoxy esters. The presence of the 3,4-epoxy ring was confirmed by infrared spectra (Experimental Section). The ketone **8** was shown to be 5-ethyl-3-heptanone by comparing its semicarbazone with an authentic sample synthesized previously.[5] The formation of an ethyl ketone leads further support to the final structure as a 3,4- rather than a 2,3-epoxy ester.

Important information on the course of the reaction and the structures of the major reaction products was obtained by using several combinations of alkyl groups in the esters and Grignard reagents employed. Thus a methyl ester and an ethyl Grignard yielded **2**, two methyls yielded **3**, and two ethyls produced **4**. The above structures indicate that the two alkyls introduced at point * originate from the Grignard employed while the third, x, is from the original ester.

Catalytic hydrogenation of **2**, **3**, and **4** yields the saturated epoxy esters **5**, **6**, and **7**, which in turn can be saponified to yield one of two ethyl ketones, **8** or **9**, formed through a

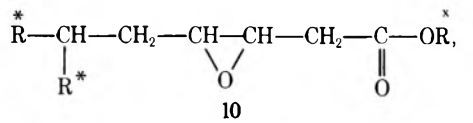


8



9

simultaneous decarboxylation of the acid and fissure of the epoxide ring. A mechanism for arriving at the general formula **10** for the epoxy esters is presented in Scheme I.



10

The 1,4 addition of the Grignard to the conjugated system in propiolic esters is not surprising. There is no hindrance at all in the 4 position and covering up the acetylenic hydrogen, HC≡C–, would account for the lack of gas (methane or ethane) in the Grignard reaction. Formation of a carbanion and loss of the ester alkoxyl would yield an allene–ketene system which could react either 1,2 or 1,4 with the Grignard reagent. Again the 1,4 addition is preferred, this time because the requirement of two Grignard alkyls on carbon 4 is met and because allenes readily rearrange to alkynes as shown. Note also that this same intermediate containing the two required alkyl groups can also be obtained from the minor reaction products by 1,4 addition of the Grignard to the ethinyl ketone followed by a 1,3 shift of the alkyl group to give the more stable alkyne.

At this point dimerization with 1 mol of the original ester would satisfy the analytical data found for the unsaturated epoxy esters. Addition of the ester to the carbanion is illustrated followed by cyclization to form the 3,4-epoxy ester. The two double bonds are conjugated and the carbanion produced can be satisfied by the acetylenic hydrogen from yet another mole of ester. This would also account for the fact that some unchanged ester may be found at the end of the reaction, even in the presence of a large excess of Grignard reagent.

Experimental Section

Propiolic Acid. The acid was prepared by treating dibromosuccinic acid[6] (500 g) dissolved in 1200 ml of hot, 95% ethanol with a solution of 550 g of KOH in 2000 ml of 95% ethanol,[7] a modification of the original procedure of Perkin and Simonsen.[8] The purified product boiled at 62° (20 mm) with a yield of 15–18 g per 100 g of dibromosuccinic acid used.

Esterification of Propiolic Acid.[9] Direct esterification of propiolic acid by the acid-catalyzed reaction between organic acid and alcohol was complicated by the reactivity of the triple bond which resulted in very low yields (below 40%). Satisfactory yields of 55–65% could be obtained, however, by treating equal weights of propiolic acid and concentrated H_2SO_4 with a large excess of the required alcohol under refluxing conditions for 1 hr. Thus, 129 g of propiolic acid added to a mixture of 129 g of concentrated H_2SO_4 in 500 ml of absolute methanol yielded 85 g (56%) of methyl propiolate (**1**), bp 100–102°.

Grignard Reaction. The usual precautions for preparing Grignard reagents were employed including an atmosphere of dry nitrogen to prevent oxidation, 5.0 mol of Grignard per mole of ester in order to ensure an excess of Grignard, and an ice bath to cool the strongly exothermic reaction with the ester. The dried ($MgSO_4$) ether extracts, highly colored owing to polymerization, were concentrated via a long fractionating column to prevent loss of the volatile acetylenic tertiary alcohols. Heating was discontinued when the temperature reacted 65°. The residue weighed 70–80 g and still contained some ether.

This crude reaction product was next subjected to slow sublimation in an all-glass apparatus connected through a series of traps to a source of high vacuum (10^{-4} mm or better). A simple system employed a 250-ml round-bottom short-necked flask for the sublimation and two or more 500-ml two-neck round-bottom short-necked flasks for the receiving traps. The former was heated with a water bath and the latter could be cooled successively with Dry Ice in acetone. The flasks were connected through their 24/40 ⅋ joints by inverted U tubes constructed of 30-mm Pyrex tubing. After several sublimations the residue contained about 15 g of black tar and the sublimate about 50 g of a pale yellow oil. Refractionation of the sublimate under vacuum at 2 mm with Mini-Lab equipment yielded 8–10 g of the acetylenic alcohol and 20–25 g of the glycidic ester plus a small amount of tar.

Catalytic Hydrogenation. General Procedure. The unsaturated materials (2.0–15.0 g) (ethinyl carbinols or unsaturated epoxy esters) were dissolved in 20–50 ml of absolute methanol containing 0.05–0.15 g of platinum oxide (Adams catalyst) and reduced (20–30 min) in a Parr low-pressure hydrogenator pressurized to 30 psi. The reaction mixture was filtered to remove the catalyst, poured into ice water to remove the methanol, extracted with ether, washed (H_2O), dried (Na_2SO_4), and repeatedly fractionated to produce colorless oils suitable for analysis.

Saponification of the 3,4-Epoxy Esters. General Procedure. The saturated 3,4-epoxy esters (5.0–10.0 g) were added to 150 ml of absolute methanol containing 6.0 g of KOH. Saponification was complete after 40 min of refluxing and a quantitative yield of K_2CO_3, formed by the loss of CO_2 from the acid, usually precipitated in the form of small white needles. The reaction mixture was poured into ice water, extracted with ether, washed (H_2O), and dried (Na_2SO_4) in the usual manner to yield the ethyl ketones as colorless oils which were carefully fractionated.

Characterization of Grignard Reaction Products. Methyl 3,4-epoxy-6-ethyl-2,4-octadienoate (**2**): bp 75–76° (2 mm); ir (CCl_4) 1740 (ester CO), 1590 (conjugated C=C), 1225 (epoxy CO), 1140, 1035 (ester CO), 870 cm^{-1} (epoxy CO).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.34; H, 8.16; OCH_3, 15.8; mol wt, 196. Found: C, 67.30; H, 8.40; OCH_3, 16.7; mol wt, 192 (benzene).

Methyl 3,4-epoxy-6-ethyloctanoate (**5**): bp 76–78° (2 mm), 125–127° (26 mm), 133–135° (38 mm); $n^{20}D$ 1.4413; d^{20}_4 0.956; ir (CCl_4) 1740 (ester CO), 1225 (epoxy CO), 1140, 1035 (ester CO), 830 cm^{-1} (epoxy CO).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 66.00; H, 10.00; OCH_3, 15.5; MD, 54.1. Found: C, 66.20; H, 10.20; OCH_3, 14.5; MD, 54.27.

Amide of **5** above, mp 152.5–153.0°.

Anal. Calcd for $C_{10}H_{19}O_2N$: C, 64.84; H, 10.34. Found: C, 64.70; H, 10.20.

5-Ethyl-3-heptanone (**8**): bp 70–72° (17 mm), 171–173° (1 atm); $n^{20}D$ 1.4240 (synthetic sample, 1.4237).

Semicarbazone of **8** above, mp 133–134°; it was identical with a synthetic sample[5] by mixture melting point.

Anal. Calcd for $C_{10}H_{21}ON_3$: C, 60.30; H, 10.60. Found: C, 60.30; H, 10.80.

Methyl 3,4-epoxy-6-methyl-2,4-heptadienoate (**3**): bp 61–63° (2 mm), 116–118° (40 mm); ir (CCl_4) 1740 (ester CO), 1610 (conjugated C=C), 1225 (epoxy CO), 1145, 1015 (ester CO), 860 cm^{-1} (epoxy CO).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.22; H, 7.14; OCH_3, 18.4; mol wt, 168. Found: C, 64.08; H, 7.28; OCH_3, 17.9; mol wt, 164 (benzene).

Methyl 3,4-epoxy-6-methylheptanoate (**6**): bp 65° (2 mm), 116–118° (40 mm); $n^{20}D$ 1.4341; d^{20}_4 0.947; ir (CCl_4) 1740 (ester CO), 1230 (epoxy CO), 1145, 1030 (ester CO), 843 cm^{-1} (epoxy CO).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.78; H, 9.30; OCH_3, 18.0 MD, 44.86. Found: C, 63.20; H, 9.60; OCH_3, 17.6; MD, 46.30.

5-Methyl-3-hexanone (**9**), bp 135–137° (1 atm).

Semicarbazone of **9** above, mp 149–150°; it was identical with a synthetic sample[5] by mixture melting point.

Ethyl 3,4-epoxy-6-ethyl-2,4-octadienoate (**4**): bp 75–76° (2 mm); ir (CCl_4) 1740 (ester CO), 1580 (conjugated C=C), 1230 (epoxy CO), 860 cm^{-1} (epoxy CO).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.60; H, 8.60; OC_2H_5, 21.2. Found: C, 68.80; H, 8.80; OC_2H_5, 19.0.

Ethyl 3,4-epoxy-6-ethyloctanoate (**7**): bp 76–78° (2 mm); ir (CCl_4) 1740 (ester CO), 1225 (epoxy CO), 1140, 1030 (ester CO), 825 cm^{-1} (epoxy CO).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.30; H, 10.40. Found: C, 67.10; H, 10.70.

The infrared spectra were obtained with a Perkin-Elmer Model 700 spectrophotometer. Samples were prepared by dissolving 100 μl in 3 ml CCl_4.

Acknowledgments. We are grateful to the National Science Foundation (Grant GY-9326) for support of this work, and to Janet Graham and Douglas Weber for technical assistance.

Registry No.—**1**, 922-67-8; **1** free acid, 471-25-0; **2**, 55058-94-1; **3**, 55058-95-2; **4**, 55058-96-3; **5**, 55058-97-4; **5** amide, 55058-98-5; **6**, 55058-99-6; **7**, 55059-00-2; **8**, 6137-18-4; **8** semicarbazone, 55059-01-3; **9**, 623-56-3; ethyl bromide, 74-96-4; dibromosuccinic acid, 526-78-3.

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(1) E. H. Ingold, *J. Chem. Soc.*, **127**, 1199 (1925).
(2) C. F. Koelsch, *J. Am. Chem. Soc.*, **54**, 2045 (1932).
(3) E. P. Kohler, *J. Am. Chem. Soc.*, **55**, 1073 (1933).
(4) H. Gilman and J. D. Robinson, *Bull. Soc. Chim. Fr.*, **45**, 636 (1929).
(5) H. S. Rhinesmith, *J. Am. Chem. Soc.*, **58**, 596 (1936).
(6) H. S. Rhinesmith, *Org. Syn.*, **18**, 17 (1938).
(7) A 165-g portion of KOH pellets will dissolve rapidly in 600 ml of ethanol if the alcohol is placed in a glass tube (2.5 ft × 55 mm) and the alkali suspended in the upper third of the liquid. The time of solution is reduced from 6 hr (in a beaker or erlenmeyer) to 30 min in the glass tube.
(8) W. H. Perkin and J. L. Simonsen, *J. Chem. Soc.*, **91**, 833 (1907).
(9) Propiolic acid has a corrosive, blistering action on the skin. The esters are powerful lachrymators. It is essential to carry out all reactions in the hood with good ventilation and to protect the eyes and hands.

A Mild and Convenient Oxidation Procedure for the Conversion of Organoboranes to the Corresponding Alcohols[1]

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Organoboranes are oxidized efficiently by trimethylamine *N*-oxide dihydrate. The reagent is exceptionally mild, permitting the oxidation of a wide variety of functionally substituted organoboranes. In every instance the yields of product alcohol are as good as or better than the yields obtained using the standard oxidation procedure.

The oxidation of organoboranes has been utilized extensively as a convenient preparation of alcohols (eq 1).[2] In

$$R_3B \xrightarrow{\text{oxidn}} 3ROH \qquad (1)$$

fact, the hydroboration–oxidation sequence is the most efficient route for the anti-Markovnikov hydration of alkenes (eq 2).

$$RCH{=}CH_2 \xrightarrow{BH_3} \xrightarrow{\text{oxidn}} RCH_2CH_2OH \qquad (2)$$

The oxidation of organoboranes has become an increasingly important reaction as the role of organoboranes in organic synthesis has expanded.[3] One of the key features of the organoboranes is that they can be prepared containing a wide variety of functional substituents. These substituents are sometimes sensitive to the oxidation reagents, hydrogen peroxide and sodium hydroxide.[4] The presence of the strong base and oxidant can lead to undesirable side reactions.

In an attempt to minimize side reactions of functionally substituted organoboranes, researchers have resorted to modifying the standard oxidation procedure. Two modifications have been successful: the simultaneous addition of the base and peroxide[5] and the use of milder bases.[6,7] In addition alternate oxidation procedures have been explored. The alternate procedures generally utilize reagents which are inconvenient to handle, difficult to obtain, or are themselves reactive toward certain functional substituents.[8–10]

One reagent has been studied that appeared to offer promise as a mild oxidizing agent, trimethylamine *N*-oxide[11,12] (eq 3). However, anhydrous amine oxides are inconvenient to prepare and the reported procedure utilizes hydrocarbon solvents, whereas most organoboranes are formed in ethereal solvents.

$$R_3B + \bar{O}\text{–}\overset{+}{N}R_3 \longrightarrow R_2B\text{–}OR + :NR_3 \qquad (3)$$

We now wish to report that the commercially available, easily handled, trimethylamine *N*-oxide dihydrate is an efficient reagent for organoborane oxidations. In addition the reagent will tolerate a wide variety of functional substituents and the reactions may be performed in any of the common organic solvents.

Results and Discussion

Temperature and Solvent Effects. Oxidations of organoboranes with trimethylamine *N*-oxide dihydrate (TAO) can be carried out in either hydrocarbon or ethereal solvents. The rate of the oxidations appears to be insensitive to the solvent utilized. This is presumably a consequence of the low solubility of TAO in all of the solvents used in the study.

Table I
Comparison of the Efficiencies of the Trimethylamine *N*-Oxide Dihydrate and Hydrogen Peroxide Oxidation Procedures[a,b]

Organoborane[c]	Registry no.	Product	Registry no.	Yield, %[d] Amine oxide	Yield, %[d] Hydrogen peroxide
Tri-*n*-hexylborane	1188-92-7	1-Hexanol[e]	111-27-3	95	95
Tri-*n*-octylborane	3248-78-0	1-Octanol[e]	111-87-5	95	95
Tri-*sec*-butylborane	1113-78-6	2-Butanol	78-92-2	94	94
Tricyclohexylborane	1088-01-3	Cyclohexanol	108-93-0	94	92
Trinorbornylborane	14289-75-9	*exo*-Norborneol	497-37-0	100	100

[a] The amine oxide procedure was carried out by refluxing 3 equiv of trimethylamine *N*-oxide with the organoborane (1 *M* in diglyme) for 2 hr. [b] The peroxide oxidations were carried out by adding 3 equiv of hydrogen peroxide (30% aqueous solution) and 1 equiv of sodium hydroxide (3 *N*) to the organoborane (1 *M* in tetrahydrofuran) and heating to 60° for 1 hr.[4] [c] The organoborane was prepared via the hydroboration of the corresponding alkene using the standard procedures outlined in ref 4. [d] Yields determined via GLC analysis. [e] Conversion based only on tri-*n*-hexylborane and tri-*n*-octylborane.

Table II
Oxidation of Tricyclohexylborane in the Presence of Added Reagents[a]

Reagent	Yield, %[b] cyclohexanol	Recovered, %[b] reagent
Benzaldehyde	94	100
Butyrophenone	94	100
Ethyl valerate	94	100
Ethyl cinnamate	94	100
Phenylethylene oxide	94	100
Benzonitrile	94	100
Thiophene	94	100
Bromohexane	94	100
3-Penten-2-one	94	95

[a] The oxidations were carried out by adding 3 equiv of trimethylamine *N*-oxide dihydrate to 10 mmol of tricyclohexylborane in diglyme (1 *M*) and heating the reaction to reflux for 2 hr.[16] [b] Determined by GLC analysis.

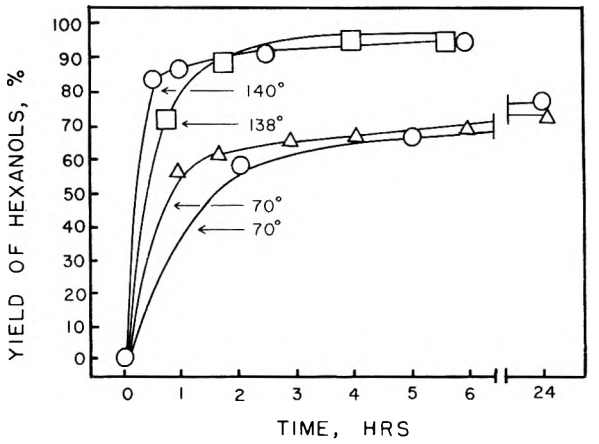


Figure 1. A comparison of the rates of oxidation of tri-*n*-hexylborane with trimethylamine *N*-oxide dihydrate at various temperatures. The reactions were carried out in a variety of solvents: ○, diglyme; □, xylene; △, THF.

The rate of the oxidation reaction is temperature dependent. The data indicate that the second and third alkyl groups are removed more slowly than the first, requiring either higher temperatures or longer reaction times.[13] The experimental results are summarized in Figure 1.

TAO permits an essentially quantitative conversion of an organoborane to corresponding alcohol. In all cases the yields of alcohols were as good as or better than the results in which the standard oxidation procedure was employed.[4] The results of a comparative study are summarized in Table I. Diglyme was employed as a solvent in the oxidations, since it is a common hydroboration solvent and permits a convenient oxidation rate.

Specificity. Trimethylamine *N*-oxide dihydrate is a remarkably mild oxidizing agent. A variety of functionality is unaffected by it under the reaction conditions employed. To demonstrate this aspect of the oxidation procedure, tricyclohexylborane was oxidized in the presence of added reagents. In nearly every case the added reagents were found to be unchanged at the end of the oxidation. The results are summarized in Table II.

TAO thus appears to be a milder oxidant than hydrogen peroxide. A series of functionally substituted alkenes was then hydroborated and oxidized using both the TAO procedure and the standard procedure.[4] In a number of these cases isomeric products are possible owing to the effect of the functional group on the direction of the hydroboration reaction.[14] Furthermore, certain of the intermediate organoboranes are prone to reactions such as cyclization.[15] The results are presented in Table III, in which only the major product is considered.

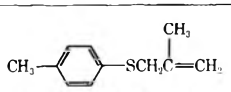
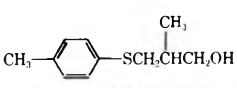
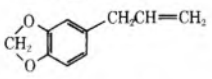
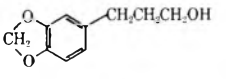
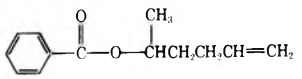
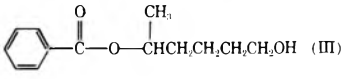
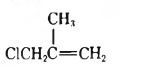
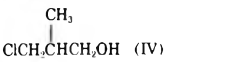
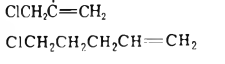
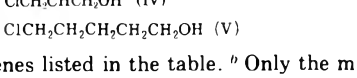
Conclusions

The use of trimethylamine *N*-oxide dihydrate as an oxidizing agent for organoboranes should be considered as a viable alternative to the standard oxidation procedure. The reagent is more convenient and far safer to handle than hydrogen peroxide. Furthermore, the yields of alcohols are at least as good as, and in some cases better than, those obtained in the peroxide procedure.

Experimental Section

Proton NMR spectra were recorded on a Varian Associates A-60 spectrometer. All chemical shifts are reported in parts per million downfield from tetramethylsilane.

Table III
Comparison of the Trimethylamine *N*-Oxide and the Hydrogen Peroxide Oxidation Procedures for a Series of Functionally Substituted Organoboranes[a]

Alkene	Registry no.	Product[b]	Yield, %[c] $(CH_3)_3\overset{+}{N}-\overset{-}{O}\cdot 2H_2O$[d]	Yield, %[c] H_2O_2–OH^-[e]
	54844-24-5	 (I)	92	83
	94-59-7	 (II)	75	75
	54844-25-6	 (III)	94	91
	563-47-3	 (IV)	67	60
	928-50-7	 (V)	95	89

[a] The organoboranes were formed via the hydroboration of the alkenes listed in the table. [b] Only the major product is indicated. [c] By GLC analysis. [d] Oxidations were carried out by adding 3 equiv of trimethylamine *N*-oxide dihydrate to 10 mmol of the organoborane in diglyme (1 *M*) and heating for 2 hr.[16] [e] Oxidations were carried out by adding 3 equiv of H_2O_2 (30%, aqueous) and 1 equiv of NaOH (3 *N*) to 10 mmol of organoborane (1 *M*) in diglyme. The reaction mixture was then heated to 60° for 1 hr.

Table IV
Hydroboration–Oxidation of Representative Alkenes. Experimental Details

Alkene	Registry no.	Quantity, g	Oxidn reflux time, hr	Product	Yield, %	Bp, °C
1-Hexene	592-41-6	2.53	3	1-Hexanol[a]	95	156
1-Octene	111-66-0	3.36	2	1-Octanol[a]	95	196
(*E*)-2-Butene	624-64-6	1.69	1	2-Butanol[b]	94	101
Cyclohexene	110-83-8	2.48	1	Cyclohexanol	94	160
Norbornene		2.72	1	*exo*-Norborneol	100	176

[a] Product contains 6% of the secondary isomer. [b] Product contains no 1-butanol.

All melting points and boiling points are uncorrected. The gas chromatography work was performed on a Varian Aerograph 90-P. The following columns were used: 5% SE-30 on Chromosorb W, 10 ft × 0.25 in.; 9% Carbowax 20M on Chromosorb W, 10 ft × 0.25 in. Commercially available samples of (*E*)-2-butene, 1-hexene, 1-octene, cyclohexene, norbornene, safrole, 3-chloro-2-methylpropene, 5-chloro-1-pentene, and trimethylamine *N*-oxide dihydrate were used without further purification (Aldrich).

Products were isolated by distillation at reduced pressures. The samples were characterized and the data compared to known values.

Oxidations. General Procedures. A. Trimethylamine *N*-Oxide Dihydrate. The organoborane (10 mmol) dissolved in 20 ml of diglyme was contained in a 50-ml, N_2-flushed flask fitted with a reflux condenser and mercury bubbler, vented to a hood. TAO (30 mmol, 3.33 g) was added all at once to this solution and the reaction mixture was gently refluxed with efficient stirring for 2 hr.[17] The reaction product was isolated by extraction. The contents of the reaction flask were transferred to a separatory funnel. The flask was rinsed with 50 ml of ether and the ether solution was added to the separatory funnel. The mixture was extracted three times with 25 ml of saturated aqueous NaCl. The ether layer was separated and dried over anhydrous magnesium sulfate, and the product was distilled.

B. Hydrogen Peroxide. The organoborane (10 mmol) dissolved in 20 ml of tetrahydrofuran was contained in a 50-ml, N_2-flushed flask fitted with a septum inlet and a reflux condenser.[18] Aqueous sodium hydroxide (10 mmol, 3.33 ml of 3 *N* solutions) was added followed by the slow addition, via syringe, of hydrogen peroxide (30 mmol, approximately 3.3 ml of a 30% aqueous solution). The reaction mixture was heated to 60° for 1 hr to ensure completion of the oxidation. The alcoholic products were isolated by saturating the mixture with sodium chloride and separating the THF layer, which was back extracted with saturated sodium chloride solution. The THF layer was dried ($MgSO_4$) and the product isolated by distillation.

Hydroboration. The hydroborations were carried out using standard procedures.[19] The procedure using BH_3–THF was as follows. The alkene (30 mmol) was dissolved in 20 ml of diglyme in a 50-ml, N_2-flushed, round-bottomed flask equipped with a septum inlet and a reflux condenser. The solution was cooled to 0° by means of an ice–water bath and the BH_3–THF (10 mmol, 5 ml of a 2 *M* solution) was added via a syringe. The hydroboration was permitted to proceed for 0.5 hr at 0° and then the mixture was allowed to warm to room temperature. The THF could be removed by distillation prior to the oxidation or during the oxidation.

Oxidations with Added Reagents. These oxidations were carried out as described above except that 10 mmol of the extra reagent was added to the reaction mixture. The percentage of added reagent (and alcohol product) was determined via gas chromatographic analyses utilizing an internal standard.

Aliphatic Alcohols. In each case 30 mmol of the alkene in 20 ml of diglyme was hydroborated with 10 mmol (5 ml of 2 *M* solution) of BH_3-THF. The resultant organoborane was oxidized with trimethylamine *N*-oxide dihydrate (30 mmol, 3.33 g) by refluxing for the indicated time. The products were analyzed by GLC and isolated by distillation.

The experimental details are summarized in Table IV.

3-*p*-Tolylthio-2-methylpropene. *p*-Tolylthiol (0.3 mmol, 24.2 g) was treated with 1 equiv of aqueous sodium hydroxide (50 ml, 6 *N*). The mixture was stirred at room temperature for 4 hr. The water was removed at room temperature under reduced pressure. The residual salt was mixed with 50 ml of methanol. 3-Chloro-2-methylpropene (0.3 mmol, 27.5 g) was added to the mixture and stirred overnight. The mixture was added to 100 ml of H_2O and the product was extracted with 3 × 50 ml of ether. The ether layer was dried over anhydrous $MgSO_4$ and the product was distilled: bp 67° (0.3 mmHg); yield 43 g, (80%); NMR (neat) δ 1.8 (s, 3, CH_3C=), 2.2 (s, 3, CH_3Ar), 3.4 (s, 2, $-CH_2S$), 4.8 (broad s, 2, H_2C=C), 7.2 ($A_2'X_2'$, 4, ArH).

Anal. Calcd for $C_{11}H_{14}S$: C, 74.09; H, 7.92; S, 17.99. Found: C, 74.20; H, 8.06; S, 18.40.

5-Benzoxy-1-hexene. 5-Hexen-2-one (0.30 mol, 30 g) was slowly added to aqueous $NaBH_4$ (0.1 mol, 1 *M*). The mixture was stirred for 1.5 hr and the product, 1-hexen-5-ol, was isolated by extraction into ether and then distilled: bp 135° (740 mmHg) [lit. bp 138–139° (752 mmHg)];[20] yield of alcohol 90% (27 g); NMR ($CDCl_3$) δ 1.2 (d, 3, $-CH_3$, J = 6 Hz), 1.5 (m, 2, $-CH_2C$=C), 2.1 (m, 2, $-CH_2-$), 3.0 (s, 1, -OH), 3.8 (sextet, 1, methine), 5.1 (m, 2, H_2C=C), 5.8 (m, complex, 1 H). The benzoate ester was prepared by adding benzoyl chloride (0.3 mol, 42 g) to 1-hexen-5-ol (0.27 mol, 27 g) dissolved in 50 ml of pyridine. The product was isolated by pouring the reaction mixture into 100 g of ice–water. The 5-benzoxy-1-hexene was extracted with 3 × 50 ml of ether. The ether layer was dried over anhydrous $MgSO_4$ and the product was distilled: bp 95° (0.5 mmHg); NMR ($CDCl_3$) δ 1.4 (d, 3, $-CH_3$, J = 6 Hz), 2.0 (m, broad, 4, $-CH_2CH_2-$), 5.2 (sextet, 1, methine), 5.1 (m, 2, H_2C=C–), δ 5.9 (m, 1, –C=CH–), 7.6 (m, 3, ArH), 8.3 (m, 2, ArH).

3-*p*-Tolythio-2-methyl-1-propanol (I). 3-*p*-Tolythio-2-methylpropene (30 mmol, 5.34 g) was hydroborated with 10 mmol of BH_3-THF at 0° for 1 hr. Oxidation was performed by refluxing the resultant organoborane with 30 mmol of TAO in diglyme for 30 min. GLC analysis (SE-30) indicated a 92% yield of I. The product was isolated by distillation: bp 112–113° (0.15 mmHg); NMR ($CDCl_3$) δ 1.0 (d, 3, $-CH_3$, J = 7 Hz), 1.9 (broad m, 1, CH), 2.3 (s, 3, $ArCH_3$), 2.9 [m (AB), 2, SCH_2], 3.0 (s, 1, -OH), 3.6 (d, 2, $-CH_2O$, J = 6 Hz), 7.3 ($A_2'X_2'$, 4, ArH).

Anal. Calcd for $C_{11}H_{16}OS$: C, 67.28; H, 8.22; S, 16.34. Found: C, 67.20; H, 8.16; S, 16.53.

3-(3,4-Methylenedioxyphenyl)-1-propanol (II). Safrole (30 mmol, 4.86 g) was hydroborated with 10 mmol of BH_3-THF at 0° for 1 hr. The resultant organoborane was oxidized by refluxing with 30 mmol of TAO in diglyme for 1 hr. GLC analysis (Carbowax) indicated a 75% yield of product II; 12% of the secondary isomer was also present. The product was isolated by distillation: bp 124–128° (2 mmHg) [lit. bp 170–172° (8 mmHg)];[21] NMR ($CDCl_3$) δ 1.8 (m, 2, $-CH_2-$), 2.7 (t, 2, $ArCH_2-$, J = 7 Hz), 3.7 (t, 2, $-CH_2O$, J = 6.5 Hz), 3.0 (s, 1, -OH), 6.0 (s, 2, OCH_2O), 6.8 (s, 3, ArH).

5-Benzoxy-1-hexanol (III). 5-Benzoxy-1-hexene (30 mmol, 6.12 g) was hydroborated with BH_3-THF at 0° for 1 hr. The resultant organoborane was oxidized by refluxing with 30 mmol of TAO in diglyme for 30 min. GLC analysis (SE-30) indicated a 95% yield of III. The product was isolated by distillation: bp 121–125° (0.05 mmHg); NMR ($CDCl_3$) δ 1.5 (broad envelope, 9, alkyl), 3.3 (s, 1, OH), 3.7 (t, 2, $-CH_2O$, $J \cong$ 6.5 Hz), 5.2 (m, 1, OCH–), 7.6 (m, 3, ArH), 8.2 (m, 2, ArH).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.05; H, 8.06.

3-Chloro-2-methyl-1-propanol (IV). 3-chloro-2-methylpropene (30 mmol, 2.72 g) was hydroborated with 10 mmol of BH_3-THF for 1 hr at 0°. The resultant organoborane was oxidized with TAO by refluxing in diglyme for 1 hr. GLC analysis (Carbowax) indicated a 67% yield of product. The product was isolated by distillation: bp 65–66° (9–10 mmHg) [lit. bp 76° (21 mmHg)];[22] NMR (neat) δ 0.9 (d, 3, $-CH_3$, J = 7 Hz), 1.9 (m, 1, –CH–), 3.5 (d, 2, $-CH_2Cl$, J = 6 Hz), 3.6 (d, 2, $-CH_2O$, J = 5.5 Hz), 4.6 (s, 1, -OH).

5-Chloro-1-pentanol (V). 5-Chloro-1-pentene (30 mmol, 3.14 g) was hydroborated with BH_3-THF at 0° for 1 hr. The resultant organoborane was oxidized by refluxing with 30 mmol of TAO in

diglyme for 1 hr. GLC analysis (SE-30) indicated a 95% yield of V. The product was isolated by distillation: bp 74° (5 mmHg) [lit. bp 121° (30 mmHg)];[23] NMR ($CDCl_3$) δ 1.6 (m, broad, 6, aliphatic), 3.6 (m, broad, 4, $-CH_2O$ and CH_2Cl), 3.9 (s, 1, OH).

Acknowledgment. We wish to thank the Research Corporation for support of this study.

Registry No.—I, 54844-22-3; II, 7031-03-0; III, 54844-23-4; IV, 10317-10-9; V, 5259-98-3; *p*-tolylthiol, 106-45-6; 5-hexen-2-one, 109-49-9; 1-hexen-5-ol, 626-94-8.

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(18) Oxidations were carried out in diglyme as well as THF. The results were identical.
(19) The hydroborations may also be carried out using the commercially available borane dimethyl sulfide complex (Aldrich).
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Mechanisms and Stereochemistry of Displacement of Methoxide Ion by Hydroxide Ion from Phosphorus in Phospholanium and Phosphorinanium Salts

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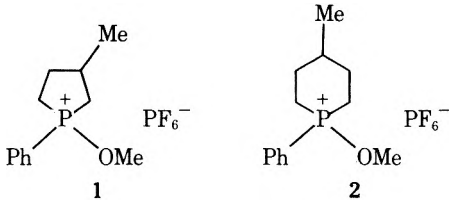
The synthesis of the cis and trans isomers of 1-methoxy-3-methyl-1-phenylphospholanium hexafluorophosphate is reported. Hydroxide displacement of methoxide from the trans isomer leads to 3-methyl-1-phenylphospholane 1-oxide with 51% retention and 49% inversion of configuration at phosphorus, while cleavage of the cis isomer gives the same product with 42% retention and 58% inversion. The cis and trans isomers of 4-methyl-1-phenylphosphorinane 1-oxide were also prepared and methylated with retention to yield the corresponding *cis*- and *trans*-1-methoxy-4-methyl-1-phenylphosphorinanium hexafluorophosphates. Alkaline cleavage of the cis and trans phosphorinanium salts leads to complete inversion of configuration as a result of nucleophilic attack at phosphorus. ^{18}O-Labeling experiments reveal that, under reaction conditions employed, nucleophilic attack at methoxy carbon occurs to the extent of 11% in the phospholanium salts and 9% in the phosphorinanium salts. The stereochemistry of nucleophilic displacement at phosphorus in both systems can be rationalized in terms of stereoelectronic vs. ring strain effects in phosphorane intermediates.

As part of a continuing study of the effect of ring size on the mechanism and stereochemistry of displacement of leaving groups from phosphorus in heterocyclic phosphonium salts,[1] we wish to report results of hydroxide ion displacement of methoxide ion from *cis*- and *trans*-1-methoxy-3-methyl-1-phenylphospholanium (1) and *cis*- and *trans*-1-methoxy-4-methyl-1-phenylphosphorinanium (2) hexafluorophosphates.



1 2

Synthesis of and Assignment of Stereochemistry to Alkoxyphosphonium Salts. These compounds were prepared by alkylation of the stereoisomerically pure phosphine oxides[1d,f] with trimethyloxonium hexafluorophosphate (eq 1). As expected, alkylation occurred with retention of configuration at phosphorus as shown previously for the phosphetane oxide system.[2] It was also possible to alkylate the oxides by use of methyl fluorosulfonate ("Magic Methyl"). ^1H NMR analysis of methoxyphosphonium fluorosulfonates formed also indicated stereospecific alkylation. However, because the fluorosulfonate salts were difficult to obtain in a pure crystalline form for the purpose of elemental analysis, trimethyloxonium hexafluorophosphate was used and found to be superior in this respect. Characteristics of these compounds are listed in Table I.

$$R_3P{=}O + (CH_3)_3O^+\ PF_6^- \longrightarrow R_3P^+OCH_3\ PF_6^- + (CH_3)_2O \quad (1)$$

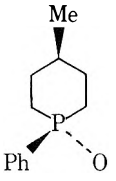
The cis and trans stereochemistry for isomers of 1 was established indirectly by an X-ray crystal structure determination.[3] The stereostructure of the isomers of 2 was assigned by ^1H NMR analysis of the oxides (3) from which they were derived, together with corroborating physical properties of the oxides. With respect to cyclohexane, the conformational preferences for methyl and phenyl[4] are such that for the 1,4-trans arrangement of these two groups

Table I
Methoxyphospholanium (1) and Methoxyphosphorinanium (2) Hexafluorophosphates[a]

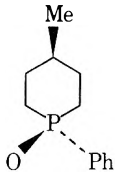
		NMR Data[c]			
		CCH_3		OCH_3	
Salt	Mp,[b] °C	δ	J_{HCCH}, Hz	δ	J_{POCH}, Hz
trans-1	50–50.5	1.22	5.2	3.80	12.0
cis-1	50–53	1.25	4.5	3.82	12.0
trans-2	122–128[d]	0.96	5.2	3.72	11.6
cis-2	118–119.5	1.37	3.0	3.59	11.4

[a] Prepared from the corresponding pure oxides by treatment with trimethyloxonium hexafluorophosphate. [b] Melting points were taken for the crude material without recrystallization but after thorough washing with ether. [c] Spectra were determined at 60 MHz in chloroform-*d* with a JEOL C-60H spectrometer. Chemical shifts are measured from Me_4Si. [d] Prior to washing with ether.

in **3b** the predominant, if not exclusive, conformer would be expected to be (e)-methyl-(e)-phenyl. At ambient tem-



3a



3b

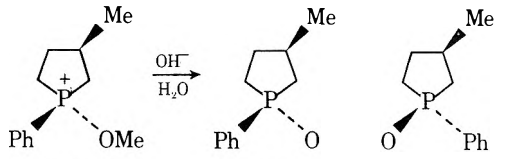
δ (CH_3), ppm	Doublet 0.89 (J = 6.0 Hz)	Unresolved doublet, 0.99 (J = 1.0 Hz)
Mp, °C	60–61	148–149
R_f (acetone, silica gel G)	0.11	0.26

perature, for example, *trans*-1-methyl-4-phenylcyclohexane is detectable only in the ee conformation. The coupling constant for $HCCH_3$ for the trans isomer is 3.5 Hz and the methyl doublet is poorly resolved.[5] *cis*-1-Methyl-4-phenylcyclohexane, on the other hand, has been determined to exist predominantly (>90%) in the (a)-methyl-(e)-phenyl conformation and the well-resolved methyl doublet displays a coupling constant of 6.9 Hz.[5] In general, protons on axial methyl groups are known to show larger coupling constants with vicinal tertiary ring protons,[5,6] and equatorial methyl protons not only exhibit smaller coupling constants with tertiary protons[5,6] but are also characteristically structureless or poorly resolved.[5,7] On this basis the lower melting isomer is assigned the structure **3a** with methyl and phenyl in axial and equatorial positions, respectively, in the predominant isomer in solution (CH_2Cl_2). The higher melting isomer is assigned the structure **3b** with both phenyl and methyl occupying equatorial positions, probably exclusively.[8] Moreover, a cis 1,4-methyl–oxygen arrangement (**3b**) might be expected to result in deshielding[9] of the methyl group, while a shielding effect on the methyl substituent might be anticipated from a cis methyl–phenyl configuration (**3a**). In this respect also the chemical shifts for **3a** and **3b** are consistent with configurational assignments.

Physical properties give additional support to the assignment of stereochemistry. It is well known that equatorially oriented polar substituents usually result in higher retention times than do polar axial groups in chromatographic separations of epimers.[5,10] Thus **3b** would be predicted to have a higher R_f number than **3a** which could be more strongly adsorbed through the conformer containing an equatorial phosphoryl oxygen. Melting point data, although not always reliable, also tend to support the assigned structure.[11]

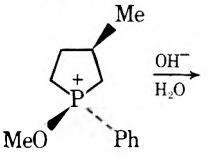
Results

Results for the aqueous hydroxide cleavage of the phospholanium isomers are given in eq 2 and 3.[12] Only one enantiomer of each salt is shown, although racemic mixtures were used in this study.



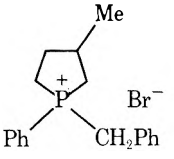
trans-1 **4a** **4b** (2)

51% 49%



cis-1 **4a**, 58% **4b**, 42% (3)

As seen from Table I, the chemical shifts of the *C*-methyl and *O*-methyl groups for *trans*-1 and *cis*-1 are virtually identical at 60 MHz. The oxides also have nearly identical shifts.[1f] Thus the oxide mixtures could neither be analyzed directly by NMR nor stereospecifically reconverted to 1 for analysis. Also decoupled ^{31}P NMR (40.5 MHz) signals for the isomeric oxides cannot be distinguished from each other in mixtures. Therefore, the oxide mixture was stereospecifically reduced to the corresponding phosphines (complete retention)[1f] which were quaternized with benzyl bromide (complete retention)[13] to yield a mixture of the diastereomeric benzylphosphonium salts (**5**).



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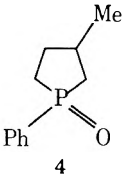
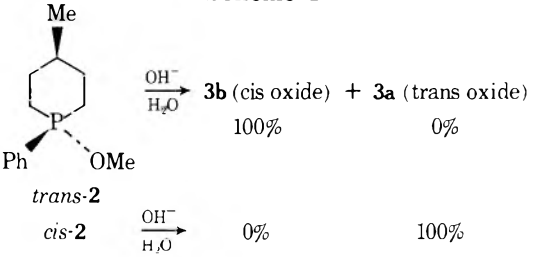


4

These mixtures in D_2O were analyzed by ^1H NMR at 220 MHz and the separated benzyl doublets integrated to give the compositions shown in eq 2 and 3.

The two phosphorinanium salts (*trans*-2 and *cis*-2), when decomposed by aqueous alkali under the same conditions as the phospholanium salts, behaved identically; i.e., within experimental error by ^1H NMR detection at the concentrations used, both experienced complete *inversion* of configuration at phosphorus as exemplified in Scheme I.

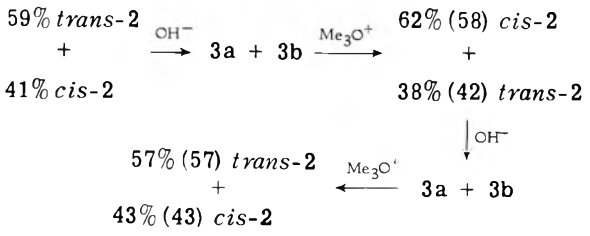
Scheme I



Analyses of the oxides were accomplished by stereospecific reconversion to the methoxyphosphonium salts **2** with trimethyloxonium hexafluorophosphate and integration of the separated *O*-methyl doublets recorded at 60 MHz (cf. Table I). These results were checked by completion of a

stereochemical cycle for a mixture of oxides as shown in Scheme II.

Scheme II

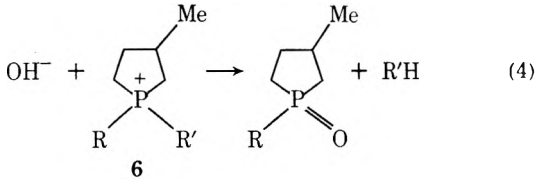


The *calculated* percent composition of **2** [assuming a 9% ^{1}H NMR detection limit for retention upon hydroxide cleavage (vide infra)], after steps 2 and 4 in Scheme II, is shown in parentheses in the scheme.

In order to determine whether any retention of configuration occurred below ^{1}H NMR detection level and, if so, to explain such retention of configuration in the cleavage of **1** and **2**, oxides **3** and **4** were enriched in ^{18}O by treatment of the respective oxides with $^{18}OH_2$ acidified with hydrogen chloride.[14] The oxides enriched in ^{18}O were methylated with trimethyloxonium hexafluorophosphate and the labeled salts cleaved with hydroxide as before. Examination of the oxides showed, after correction for natural abundance, 11.3 ± 0.5% retention of label for the base cleavage of **1** and 8.7 ± 0.5% for that of **2**.

Discussion

Cleavage of the Methoxyphospholanium Salts (1). Previous investigations into the stereochemistry of displacement of leaving groups in system **6** by hydroxide are summarized in eq 4. When the nucleophile is butoxide in



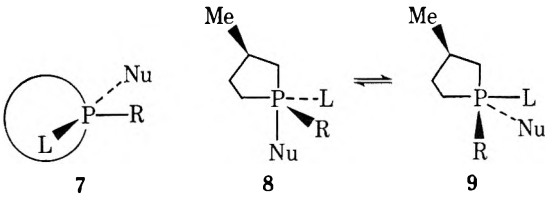
(4)

6

R = Ph; R′ = CH_2Ph; retention of configuration at phosphorus[1c,f]

R = Me; R′ = Ph; stereomutation at phosphorus[1f]

the cleavage of the 1-methyl-1-benzyl analog of **6**, predominant retention of configuration is observed,[1b] while displacement of trichlorosiloxide as leaving group by trichlorosilyl anion as nucleophile (in the reduction of **4a** by Si_2Cl_6) leads ultimately to predominant inversion of configuration.[1c] These stereochemical results have been rationalized in terms of the competition between stereoelectronic and ring strain effects involving proposed phosphorane intermediates.[15] Briefly stated, it is held that electronegative substituents have a preference for apical positions in trigonal bipyramidal phosphoranes. However, the reaction pathway involving such an intermediate may be modified in cases when two of the ligands at phosphorus are part of a four-, five-, or in some cases a six-membered ring, because of ring strain introduced by ee disposition of ring bonds (**7**). Thus only leaving groups of comparatively high electronegativity, where relief of "stereoelectronic strain" exceeds relief of "ring strain", are permitted to occupy an apical position. This then accounts for predominant inversion of configuration at phosphorus in the reduction of **4a** by Si_2Cl_6 where the leaving group is $OSiCl_3^-$. In cases of poor leaving groups (low electronegativity), as exemplified by benzyl, ring strain dictates stereochemistry of the initially



7 **8** **9**

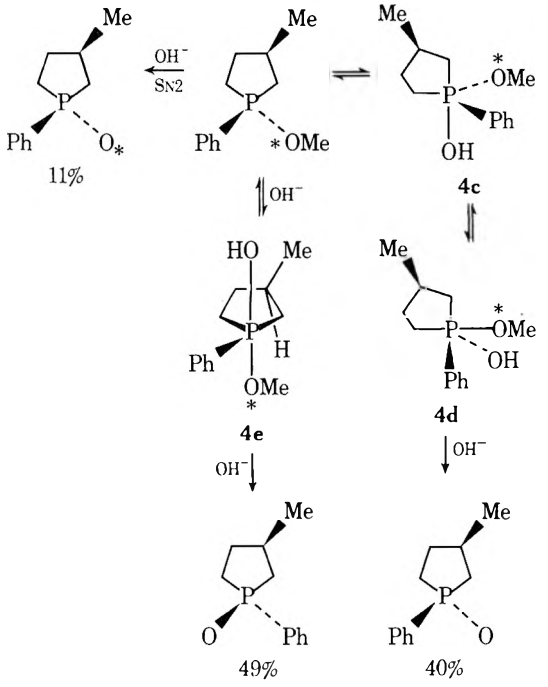
formed phosphorane as shown by structure **8** where L is benzyl and R is phenyl or methyl. Loss of benzyl may occur apically from **9** after one pseudo-rotation with no net change of configuration at phosphorus. Such is observed for aqueous alkaline cleavage of **8** (L = CH_2Ph; R = Ph or Me; Nu = OH).[1a-c,f] For a leaving group such as phenyl, which is even poorer than benzyl as demonstrated by competitive cleavage experiments,[16] the energy barriers to pseudo-rotation among phosphoranes leading to stereomutation at phosphorus, after attachment of hydroxide ion to phosphorus, is lower than the energy barrier preceding product formation. This has been observed for **8** where L = Ph, R = Me, and Nu = OH,[1f] and where a thermodynamic mixture of diastereomeric phosphine oxides has been found to be formed from the equilibrating mixture of phosphoranes.

In this work we have observed a still different type of behavior for the cleavage of a phospholanium salt as exemplified by the hydroxide decomposition of **1**. Experimental results suggest that three different reactions are occurring simultaneously in the conversion of the isomers of **1** to a mixture of the corresponding oxides. Stereoelectronic strain and ring strain are evidently of comparable magnitude where methoxide ion is a leaving group. Thus intermediates **7** and **8** (L = OMe; R = Ph; Nu = OH) are *both* viable.

The product compositions shown in eq 2 and 3 are not reasonably accounted for by complete stereochemical equilibrium through pseudo-rotation of phosphorane intermediates. Even though the cleavage results are similar for *trans*-**1** and *cis*-**1** they are nevertheless detectably different and reproducibly so. Thus pseudo-rotation, if it occurs, can only be competitive with product formation. However, competitive pseudo-rotation would not be consistent with the observation that loss of benzyl, a poorer leaving group than methoxy, from **6** by hydroxide cleavage occurs with complete retention of configuration at phosphorus.[1a-d] If the theory of stereoelectronic strain were to apply to the case of methoxyphospholanium salts one would predict with some assurance that methoxy would fall somewhere between benzyl and trichlorosiloxy in its apicophilicity relative to the intermediate phosphorane formed. This prediction is evidently borne out by our findings.

Coexistent with the duality of mechanism accompanying attack at phosphorus by hydroxide is the occurrence of nucleophilic attack at methoxy carbon as revealed by the retention of some ^{18}O label. Although a diastereomeric mixture of methoxyphospholanium salts was used because of stereomutation accompanying incorporation of label into the oxide starting material, it is reasonable to assume that nucleophilic attack at carbon should be relatively uninfluenced by the stereochemistry at the ring methyl because of its remoteness from the site of reaction. Therefore, *trans*-**1** is apparently decomposed by aqueous sodium hydroxide in the manner displayed in Scheme III for molecules of the labeled compound. Isomer *cis*-**1** similarly yields 58% inverted product, 31% retained product by attack of hydroxide at phosphorus, and 11% retained product by attack of hydroxide at carbon. It is tempting to explain the reduced amount of inversion at phosphorus for *trans*-**1** as compared to *cis*-**1** by steric interference of the ring methyl to attack by hydroxide from that side of the ring.

Scheme III

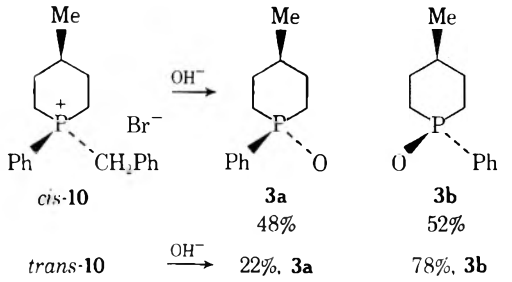


Although Scheme III shows attack opposite the 1,2 ring bond by hydroxide, attack opposite the 1,5 ring bond is also possible and would also yield product of retained configuration. These two attack routes are not strictly equivalent sterically but are expected to be very nearly so based upon models. Assuming both routes of attack to be identical, it is possible to calculate the following relative reaction rates for the three cleavage processes.

	Relative rates	
	trans-1	*cis*-1
Attack at C	1.0	1.0
Attack opposite a ring bond (retention)	1.8	1.4
Attack at P (inversion)	4.5	5.3

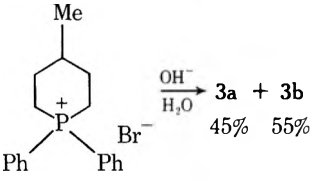
It is seen that the kinetically favored process for both compounds is inversion, with *cis*-1 more reactive in this respect than *trans*-1.

Cleavage of the Methoxyphosphorinanium Salts (2). In a previous communication[1d] we reported trans and cis isomers of **10** to undergo base cleavage with the results indicated. This evidence was interpreted[1e] as illustrating a



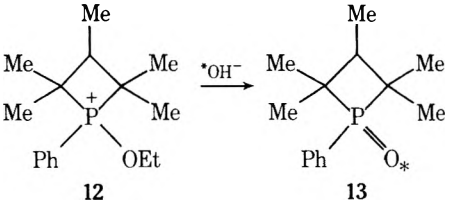
dual mechanism involving attack at phosphorus in a manner similar to that portrayed in Scheme III for methoxyphospholanium salts. That **3a** and **3b** do not result from a common intermediate is attested to by the fact that *cis*-**10** and *trans*-**10** give *different* ratios of the same products. Analogous results have been reported for a bicyclic phosphorinanium salt.[17]

It now appears that the findings shown in Scheme I are entirely consistent with hydroxide attack at phosphorus with *exclusive* inversion, the small amount of retention observed occurring *only* by SN2 attack by hydroxyl at carbon. The NMR analysis indicated a maximum limit of 9% retention for both isomers and the mass spectral determination of ^{18}O in the labeled salt and the oxide resulting from cleavage of the salt showed 8.7% retention of label. The greater apicophilicity of methoxide as compared to benzyl permits the former to occupy an apical position (relief of stereoelectronic strain) in the phosphorane of lowest energy. The stereoelectronic effect completely offsets any ring strain effect in this instance because of the increased ring size, whereas in the example of the cleavage of **10**, stereoelectronic and ring strain effects are comparable. It should be parenthetically stated that the high stereospecificity of this reaction allows convenient access to **3a**. Oxides **3a** and **3b** are obtained as a mixture by base cleavage of **11**. Pure



3b is readily obtained in good yield from this mixture by recrystallization from CCl_4. Preparation of the methoxy salt of **3b** followed by cleavage and recrystallization, then, can afford pure **3a**.

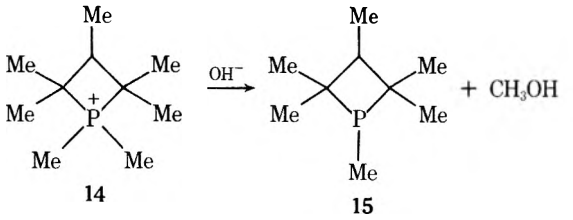
Comparison of Behavior of Phosphonium Salts of Different Ring Size. Mislow et al. have reported that hydroxide displacement of ethoxy from the cis and trans isomers of **12** takes place without any measurable accompanying attack at ethoxy carbon to give **13**.[18] However, the



error limits given for ^{18}O analysis of the hydroxide solution and the products are such that a maximum of 7.6% attack at carbon could have occurred without detection. Hydroxide attack at the *P*-methyl carbon of **14**[19] to yield **15** in 1.8% yield has also been reported. The extent of displacement at the ethoxy methylene carbon in **12**, if it occurs, is less than for **1** and **2**. The diminished (or possible absence of) attack at carbon in this case is most likely due to a combination of effects: the lowered activation energy for attack at phosphorus in the four-membered ring system as compared to the five- or six-membered systems and the lower reactivity of ethyl *vs.* methyl in SN2 reaction at carbon. The former effect is reflected in reaction rates determined by Cremer et al.,[20a] who have shown that, for base cleavage of selected benzyl salts, the phosphetanium salt reacts on the order of 10^4 times as fast as the phospholanium and 10^6 times faster than the phosphorinanium salt. The latter effect is seen, for example, in the average 30-fold greater reactivity of methyl as compared to ethyl in SN2 reactions.[20b] It might also be noted that C–O cleavage has been observed in dialkoxyphosphonium salts.[21]

In the progression stereomutation, retention, inversion, it is found that for ring systems studied which contain alkoxy substituents, retention occurs for hydroxide attack at phosphorus in the four-membered ring.[18] Both retention and inversion are observed with the five-membered ring, and inversion takes place with the six-membered ring. The

six-membered ring behaves essentially as an acyclic monoalkoxyphosphonium salt, since Mislow et al. have reported complete inversion of configuration at carbon by hydroxide cleavage of ethoxymethyl-β-naphthylphenylphosphonium nitrate.[2] Hexachlorodisilane reduction of **4a** has been reported to occur with *predominant* inversion of configuration, the lack of complete stereospecificity being attributed to $SiCl_4$-induced stereomutation at phosphorus or the operation of a dual mechanism.[1c] Our reported observation of the existence of a dual mechanism for P–O cleavage in **1** now makes plausible the dual mechanism explanation for the *small* amount of retention witnessed in the reduction of **4a**, since $OSiCl_3$ would be expected to be more apicophilic than methoxy.



14 15

Experimental Section[22]

Preparation of the Cis and Trans Isomers of 3-Methyl-1-methoxy-1-phenylphospholanium Hexafluorophosphate (1). For the preparation of the trans isomer of **1**, 2.98 g (15.3 mmol) of the phosphine oxide[1f] **4a** was dissolved in 25 ml of dry methylene chloride. This solution was added to a suspension of 3.51 g (17 mmol) of trimethyloxonium hexafluorophosphate in dry methylene chloride and the resulting mixture was stirred at room temperature overnight. Traces of insoluble residue were removed by centrifugation and the solution was evaporated to dryness in vacuo. The glassy residue crystallized upon standing and the resulting crystals were triturated with 150 ml of anhydrous ether in 10-ml portions. The crystals were then dissolved in dry methylene chloride and anhydrous ether was added until an oil separated. The oil was triturated twice with anhydrous ether, and upon drying in vacuo the oil crystallized to give 1.60 g of *trans*-**1**: mp 50–52.5°; cf. Table I for NMR data.

Anal. Calcd for $C_{12}H_{18}F_6P_2O$: C, 40.69; H, 5.12. Found: C, 40.95; H, 5.40.

The cis isomer of **1** was similarly prepared from **4b**:[1f] mp 50–53°; mixture melting point with the trans isomer of **1** gave 29–44°; cf. Table I for NMR data for *cis*-**1**.

Anal. Calcd for $C_{12}H_{18}F_6P_2O$: C, 40.69; H, 5.12. Found: C, 40.80; H, 5.39.

***cis*-4-Methyl-1-phenylphosphorinane 1-Oxide (3b).** 4-Methyl-1,1-diphenylphosphorinanium bromide[23] (**11**, 10 g, 28.6 mmol) was added to 50 ml of 5 *M* sodium hydroxide and the mixture was refluxed for 8 hr. The resulting reaction mixture was extracted twice with 20-ml portions of chloroform, and the separated aqueous layer was saturated with sodium chloride and again extracted three times with 20-ml portions of chloroform. The extracts were combined, the chloroform was distilled, and the residue was sublimed to give 5.90 g of a hygroscopic mixture of *trans*- and *cis*-4-methyl-1-phenylphosphorinane 1-oxide, mp 90.5–112°.

Anal. Calcd for $C_{12}H_{17}OP$: C, 69.21; H, 8.23. Found: C, 69.32; H, 8.21.

Chromatographic separation of this mixture on silica gel G with acetone and spot development with iodine vapors gave two spots of R_f 0.11 (**3a**) and 0.26 (**3b**). Elution of the spots and uv analysis of aqueous solutions at 218 nm (ε 8840 for both isomers) showed the cleavage mixture to be 45% **3a** and 55% **3b**.

Four recrystallizations of the cleavage mixture from 1:1 hexane–carbon tetrachloride furnished crystals: mp 147.8–148.9°; NMR (CH_2Cl_2, Me_4Si) δ 0.99 (unresolved d, 3, J = 1.0 Hz, CCH_3).

Anal. Calcd for $C_{12}H_{17}OP$; C, 69.21; H, 8.23. Found: C, 69.39; H, 8.40.

***trans*-4-Methyl-1-phenylphosphorinane 1-Oxide (3a).** A portion of the cleavage mixture was separated on Brinkmann precoated silica gel 60 F-254 preparative TLC plates with acetone. The component of R_f 0.11 was removed by chloroform extraction of the silica gel and, after evaporation of the chloroform, the residue was then distilled. The distillate of bp 146° (0.1 mm) crystallized to a hygroscopic solid upon standing: mp 60–61°; NMR (CH_2Cl_2, Me_4Si) δ 0.89 (d, 3, J = 6.0 Hz, CCH_3).

Anal. Calcd for $C_{12}H_{17}OP \cdot \frac{1}{4}H_2O$: C, 67.74; H, 8.29. Found: C, 67.93; H, 8.51.

***cis*-1-Methoxy-4-methyl-1-phenylphosphorinanium Hexafluorophosphate (2).** The same procedure was followed as for the preparation of the methoxyphospholanium salts; cf. Table I for physical properties.

Anal. Calcd for $C_{13}H_{20}F_6OP_2$: C, 42.39; H, 5.47. Found: C, 42.65; H, 5.64.

Cleavage of *trans*-1-Methoxy-3-methyl-1-phenylphospholanium Hexafluorophosphate (1). The hexafluorophosphate salt (*trans*-**1**, 1.07 g) was added to 34 ml of 0.50 *N* sodium hydroxide at room temperature with stirring, whereupon the solid dissolved. The solution was then slowly heated to reflux. The cooled reaction mixture was extracted five times with 25-ml portions of methylene chloride, the solvent was distilled from the combined extracts and the residue was distilled to give a 97% yield of 3-methyl-1-phenylphospholane 1-oxide: bp 125° (0.1 mm) (Kugelrohr) [lit. bp of trans oxide, 115–125° (0.05 mm); cis oxide, 120° (0.01 mm)].[1f] The ^{1}HNMR spectrum (60 MHz) indicated a mixture of oxides.

In order to analyze the oxide mixture it was reduced in 81% yield with phenylsilane (retention)[24] and the resulting phosphine mixture was quaternized with benzyl bromide (retention)[13] to give a mixture of the benzyl salts in 98% yield (mp 154–165°) the composition of which was determined by integration of the benzyl protons at 220 MHz: NMR (D_2O, DSS) δ 1.20 (overlapping d, CCH_3), 4.10 (overlapping d, J = 15 Hz, CH_2Ph). Integration gave 49% *trans*-**5** salt, δ 4.11 (d, J = 15 Hz, CH_2Ph), and 51% *cis*-**5** salt, δ 4.09 (d, J = 15 Hz, CH_2Ph).

Cleavage of *cis*-3-Methyl-1-methoxy-1-phenylphospholanium Hexafluorophosphate (1). The same procedure was followed as for the trans isomer with similar results except that the mixture of benzyl salts melted at 145.5–155.0° and the NMR analysis gave 42% *trans*-**5** and 58% *cis*-**5**.

Cleavage of *trans*-1-Methoxy-4-methyl-1-phenylphosphorinanium Hexafluorophosphate (2). The same procedure was followed as for *trans*-**1** above. A yield of 83% of the oxide was obtained which was methylated as described for **4a** above. The mixture was analyzed by integration of the methoxy protons (cf. Table I). The cleavage of the cis isomer and analysis of the product were similarly carried out. The reactions and analyses shown in the stereochemical cycle in Scheme II were similarly conducted. At concentrations used, it was determined that the presence of a maximum of about 9% of the minor isomer was needed before detection and integration of the methoxy peaks could be achieved.

^{18}O Labeling of 3-Methyl-1-phenylphospholane 1-Oxide. A mixture of 1.00 g of **4a**[1f] and 5 ml of unnormalized 10 atom % ^{18}O water was acidified to ca. pH 1 with hydrogen chloride and the resulting mixture was refluxed for 72 hr at 100°. Most of the water was then distilled off and the remainder was removed by azeotropic distillation with benzene. After evaporation of the benzene, the residue was distilled to yield 0.97 g of the oxide, bp 115° (3 mm) (Kugelrohr). The methoxy salt **1** was prepared and cleaved as described previously. ^{18}O content: methoxy salt, 0.452 ± 0.001 atom %; oxide **4** resulting from cleavage, 0.232 ± 0.001 atom %.

^{18}O Labeling of 4-Methyl-1-phenylphosphorinane 1-Oxide. This was accomplished by treatment of **3b** in the same fashion as above to give the oxide of bp 145° (0.08 mm) (Kugelrohr). The methoxy salt **2** was prepared and cleaved as previously described. ^{18}O content: methoxy salt, 0.422 ± 0.001 atom %; oxide resulting from cleavage, 0.223 ± 0.001 atom %.

***trans*- and *cis*-1-Benzyl-4-methyl-1-phenylphosphorinanium Bromides (10).** Phosphine oxide **3b** was reduced with phenylsilane to the corresponding *trans*-4-methyl-1-phenylphosphorinane, bp 76° (0.15mm) (Kugelrohr), and the phosphine was quaternized with benzyl bromide to give an overall yield of 86.5% of *trans*-1-benzyl-4-methyl-1-phenylphosphorinanium bromide (**10**), mp 196° (EtOH–EtOAc).

Anal. Calcd for $C_{19}H_{24}BrP$: C, 62.81; H, 6.66. Found: C, 63.09; H, 6.40.

cis-1-Benzyl-4-methyl-1-phenylphosphorinanium bromide (**10**) was prepared from phosphine oxide **3a** by the procedure described immediately above, mp 161–163° (not sharp). This salt was found to be hygroscopic.

Anal. Calcd for $C_{19}H_{24}BrP \cdot \frac{3}{4}H_2O$: C, 60.56; H, 6.82. Found: C, 60.52; H, 6.92.

Cleavage of *trans*- and *cis*-1-Benzyl-4-methyl-1-phenylphosphorinanium Bromides (10). *trans*-**10** (0.50 g) was dissolved

in 4.5 ml of 1.00 *N* NaOH and the resulting mixture was refluxed for 9 hr. The cooled reaction mixture was extracted with two 5-ml portions of chloroform, and the aqueous layer was saturated with sodium chloride and then extracted with two 5-ml portions of chloroform. The chloroform were evaporated and the residue was sublimed at 0.25 mm to yield 97.5% of a mixture of oxides (**3**), mp 73–133°.

Anal. Calcd for $C_{12}H_{17}OP$: C, 69.21; H, 8.23. Found: C, 69.47; H, 8.20.

This mixture was analyzed by TLC as described above for the cleavage products of 4-methyl-1,1-diphenylphosphorinanium bromide (**11**) and gave 78% **3b** and 22% **3a**.

The cis isomer of **10** was similarly cleaved to give a hygroscopic mixture of oxides.

Anal. Calcd for $C_{12}H_{17}OP \cdot \frac{1}{4}H_2O$: C, 67.74; H, 8.29. Found: C, 67.93; H, 8.39.

The analysis of this mixture gave 52% **3b** and 48% **3a**.

Acknowledgments. The assistance of R. H. Bowman and F. B. Burns with exploratory work on the synthesis of alkoxyphosphonium salts is gratefully recognized. Appreciation is expressed to Dr. C. G. Willson for 220-MHz spectra determinations. The author is also indebted to the National Science Foundation for support under Grants GP-7407 and GP-25479.

Registry No.—*cis*-**1**, 55043-89-5; *trans*-**1**, 55043-91-9; *cis*-**2**, 55043-93-1; *trans*-**2**, 55043-95-3; **3a**, 55043-96-4; **3b**, 55043-97-5; **4a**, 55043-98-6; **4b**, 55043-99-7; *cis*-**5**, 54932-29-5; *trans*-**5**, 55044-00-3; *cis*-**10**, 55044-01-4; *trans*-**10**, 55044-02-5; **11**, 55044-03-6; trimethyloxonium hexafluorophosphate, 12116-05-1.

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Concerning the Mechanism of the Characteristic Ring D Fragmentation of Steroids[1]

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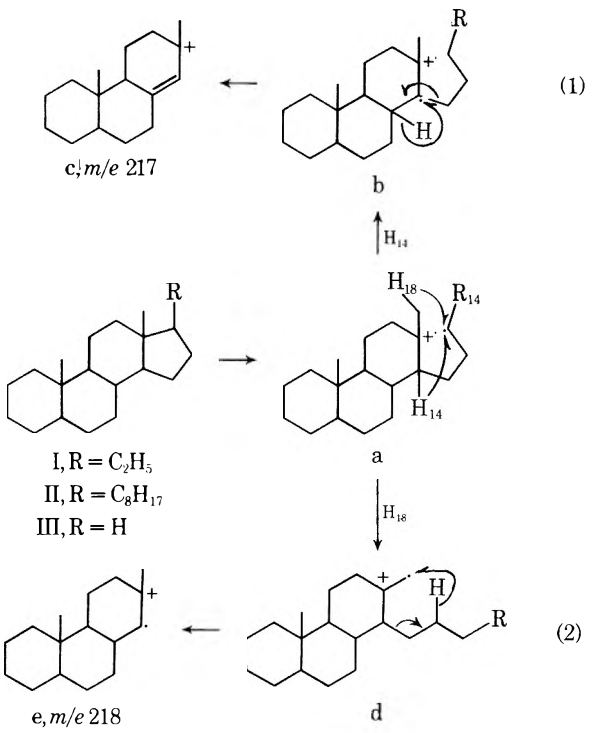
The electron impact induced fragmentations of $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene (VI) and $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (VII) were investigated. Both compounds and appropriate deuterium-labeled analogs fragmented in accord with the existing mechanistic proposal for the characteristic ring D fragmentation of steroids. First field-free region metastable intensities were consistent with structural identity among the *m/e* 217 ions from 5α-pregnane and the *D*-seco steroids, and among the *m/e* 218 ions from the same sources; widely divergent metastable intensities were observed from known isomeric ions. Evidence was obtained for significant interconversion of the molecular ions of VI and VII. The results of these experiments lend powerful support to the previously proposed ring D fragmentation mechanisms.

The most conspicuous peaks in the mass spectra of steroid hydrocarbons such as pregnane (I) or cholestane (II) appear at *m/e* 217 and 218, corresponding to the elimination of ring D and the side chain at C-17.[2] Since these fragmentations persist even in highly functionalized steroids, and since they are of obvious diagnostic importance (they define the molecular weight of the side chain at C-17), a number of investigators have attempted to determine the mechanisms by which these peaks arise. Initially, this was an area of some controversy.[3-5] The elegant and extensive deuterium-labeling experiments of Djerassi[2] provided data which permitted formulation of a plausible mechanism for the genesis of these ubiquitous peaks (Scheme I).

Initial charge localization in the C-13–C-17 bond (I → a) was postulated, since it results in the formation of a stable tertiary carbonium ion and a secondary (R = alkyl) or primary (R = H) radical site, and relieves the strain inherent in the trans hydrindan ring system. Deuterium-labeling experiments demonstrated that the genesis of the *m/e* 217 ion (c) involved transfer of the C-14 hydrogen atom to the eliminated moiety; such a process appears plausible, since it generates an ionized double bond between C-13 and

Scheme I



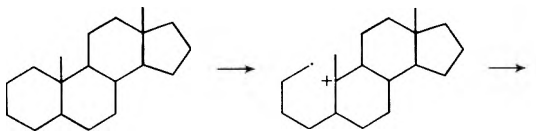
(1)

(2)

C-14, more stable than the ionized single bond at C-13–C-17. Cleavage of the C-14–C-15 bond of ion b generates *m/e* 217 (eq 1).

The formation of the *m/e* 218 ion was shown to be even more remarkable; a reciprocal hydrogen transfer from C-18 to the eliminated moiety and from C-16 to the charge retaining species was demonstrated. The mechanism depicted in eq 2 was therefore postulated; hydrogen transfer from C-18 to the C-17 radical site (a → d) appeared favorable, since it again generates an ionized double bond. Back transfer of a hydrogen atom from C-16 and cleavage of the C-14–C-15 bond generates the *m/e* 218 ion (d → e). Deuterium-labeling experiments on androstane (III),[6] *D*-homo steroids,[7] and 14α-methyl steroids[8] have been in complete accord with the above formulation. Nevertheless, several aspects of this unusual fragmentation mechanism merit further investigation.

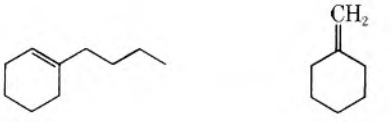
First, charge localization in the C-13–C-17 bond is an essential step in the mechanisms depicted in Scheme I. For pregnane, this appears plausible; cleavage generates a tertiary carbonium ion and a secondary radical site,[2] and relieves two skew butane interactions (C_{20}–C_{17}–C_{13}–C_{18} and C_{20}–C_{17}–C_{13}–C_{12}) and the strain inherent in a trans-fused hydrindan.[7] For many other steroids, however, the apparent site of preferred charge localization does not correspond to the most frangible bond. In androstane, for example, the predominant mode of fragmentation involves cleavage of ring A. Deuterium-labeling experiments have domonstrated that the mechanisms are directly analogous to that depicted in Scheme I;[6] initial charge localization is postulated in the C-1–C-10 bond (eq 3). Such charge localization generates a tertiary carbonium ion and a primary radical site, and relieves a single gauche butane interaction (C_1–C_{10}–C_9–C_{11}). A priori, charge localization in the C-9–C-10 bond, for example, appears more favorable; a tertiary carbonium ion and a secondary radical site are generated, and three skew butane interactions are relieved (C_1–C_{10}–C_9–C_{11}, C_1–C_{10}–C_9–C_8, C_{19}–C_{10}–C_9–C_8). It is suprising that little fragmentation appears to occur from this charge-localized species, particularly in light of the demonstrated sensitivity of charge localization of steric effects.[7]



(3)

Another aspect of the formulation of Scheme I which appears troubling is the failure of the C_{12} hydrogens to participate in these reactions. Abstraction of a C-14 hydrogen, rationalized because it generates an ionized double bond, results in the formation of *m/e* 217. Abstraction of the C-18 hydrogen, again considered propitious because it forms an ionized double bond, produces *m/e* 218. However, abstraction of a C-12 hydrogen atom also generates an ionized double bond; furthermore, the ring size involved in such a hydrogen migration is identical with that required for migration of a C-18 hydrogen. The migratory aptitude of the secondary C-12 hydrogen atoms should be larger than that of the primary C-18 hydrogens, since secondary hydrogens are more mobile than primary ones.[9] Nevertheless, deuterium-labeling experiments demonstrate that abstraction of a C-12 hydrogen is not a major pathway in the characteristic ring D cleavage.

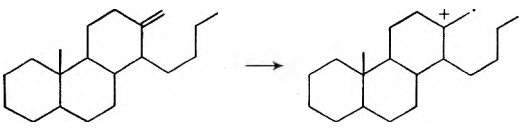
Finally, it is interesting to note that intermediate ions b and d correspond formally to ionized alkenes. Deuterium-labeling experiments[2] show clearly that these ions do not interconvert significantly before fragmentation. This observation is unexpected in light of the reports indicating that extensive double bond isomerization precedes fragmentation in structurally related alkenes such as IV and V.[10]



IV V

Because of these troubling inconsistencies and the preeminent position of this much-studied mechanism among steroid fragmentations, further investigation appeared warranted. Further, metastable data indicate that these ions are themselves precursors of many abundant low-mass ions in steroid mass spectra.[2,11] If significant structural information is to be gleaned from these low-mass ions, the structures of the precursor ions must be firmly elucidated. Thus, an investigation of the electron impact induced behavior of $\Delta^{13(18)}$-13,17-seco-*D*-homoandrostene (VI) and $\Delta^{13(14)}$-13,17-seco-*D*-homoandrostene (VII) was launched.

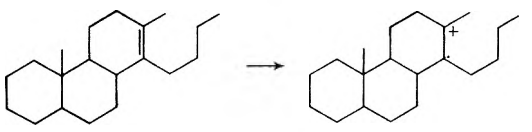
Ionization of the exocyclic alkene VI with subsequent charge localization in the functional group of lowest ionization potential[12] generates the ion d; similarly, ionization of



(4)

VI d

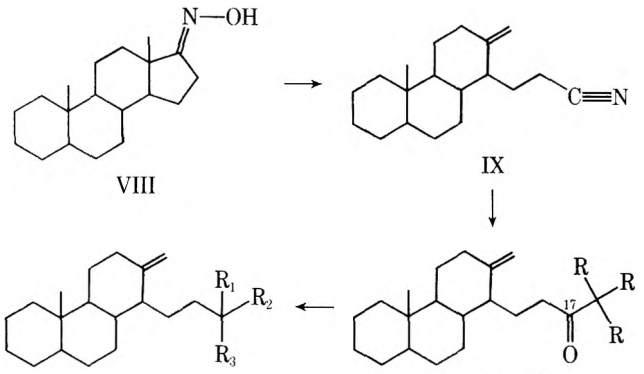
the endocyclic isomer VII generates ion b. Analysis of the mass spectra of VI and VII and appropriate deuterium-labeled analogs should establish whether these ions fragment in accord with Scheme I, and whether fragmentation pre-



(5)

VII b

Scheme II



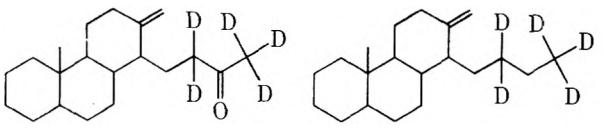
VIII IX X, R = H XIII, R = D

XI, R_1 = H; R_2 = OH; R_3 = CH_3
XII, R_1 = H; R_2 = OTs; R_3 = CH_3
VI, R_1 = R_2 = H; R_3 = CH_3
XIV, R_1 = R_2 = H; R_3 = CD_3
XV, R_1 = D; R_2 = OH; R_3 = CH_3
XVI, R_1 = D; R_2 = OTs; R_3 = CH_3
XVII, R_1 = R_2 = D; R_3 = CH_3

cedes isomerization. If these molecules do, indeed, generate *m/e* 217 and 218, metastable defocusing experiments can be utilized to ascertain whether these ions are structurally identical with those produced from authentic steroids, such as pregnane (I). In addition, since the electron impact induced behavior of alkenes remains a subject of continuing investigations,[10,13] the fragmentations of these compounds should be of intrinsic interest.

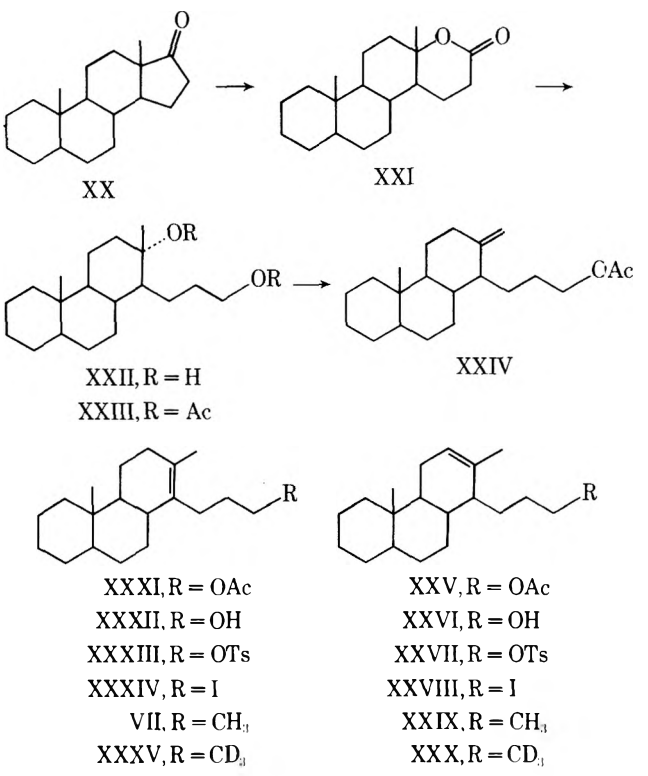
Synthesis of Labeled and Unlabeled *D*-Seco Alkenes. The synthesis of the exocyclic alkene $\Delta^{13(18)}$-13,17-seco-*D*-homoandrostene (VI) is depicted in Scheme II. Beckmann rearrangement of 5α-androstan-17-one oxime (VIII),[14] according to the procedure of Barton,[15] gave an 11% yield of the "abnormal" Beckmann product $\Delta^{13(18)}$-13,17-seco-5α-androstene-17-nitrile (IX). Treatment of the nitrile with methyllithium gave the ketone $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one (X). Lithium aluminum hydride reduction gave the corresponding alcohol, $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol (XI); conversion to the tosylate XII and further lithium aluminum hydride reduction gave the desired hydrocarbon, $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene (VI).

For the purposes of this study it became necessary to prepare derivatives deuterium labeled at C-17a, C-17, and C-16. Reaction of the nitrile IX with trideuteriomethyllithium gave the ketone $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*17a,17a,17a-d*$_3$ (XIII). Conversion to the hydrocarbon in the usual way gave $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XIV) in 63% isotopic purity. Reduction of the ketone X with lithium aluminum deuteride gave $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol-*17-d*$_1$ (XV); conversion to the tosylate XVI and reduction with lithium aluminum deuteride gave the desired hydrocarbon $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XVII, 96% d_2). Repeated base-catalyzed exchanges (D_2O–CH_3OD–K_2CO_3) of the ketone X gave the pentadeuterated ketone XVIII; conversion to the hydrocarbon XIX ($\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*16,16,17a,17a,17a-d*$_5$, 89% d_5) was accomplished in the usual way.



XVIII XIX

Scheme III



XX XXI XXII, R = H XXIII, R = Ac XXIV

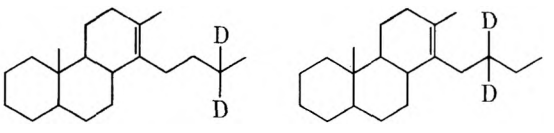
XXXI, R = OAc XXXII, R = OH XXXIII, R = OTs XXXIV, R = I VII, R = CH_3 XXXV, R = CD_3

XXV, R = OAc XXVI, R = OH XXVII, R = OTs XXVIII, R = I XXIX, R = CH_3 XXX, R = CD_3

The synthesis of $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (VII) is depicted in Scheme III. Baeyer–Villiger oxidation of 5α-androstan-17-one (XX)[16] with peroxytrifluoroacetic acid yielded 5α-androstane-13,17-seco-17-oic acid lactone (XXI);[17] lithium aluminum hydride reduction gave 13,17-seco-5α-androstan-13α,17-diol (XXII).

Pyrolysis of the diacetate XXIII gave a mixture of three alkene acetates in which the desired isomer ($\Delta^{13(14)}$-13,17-seco-5α-androstene 17-acetate, XXXI) was predominant. Thin layer chromatography on silica gel impregnated with 10% silver nitrate[18] removed the exocyclic isomer XXIV; removal of the endocyclic impurity XXV was postponed until the acetates had been converted to the hydrocarbons. Hydrolysis of the isomeric mixture of alkenes to the corresponding alcohols (XXVI and XXXII), formation of the tosylates (XXVII and XXXIII), and then treatment with sodium iodide in acetone gave the isomeric mixture of the iodides (XXVIII and XXXIV). Homologation with lithium dimethylcopper followed by thin layer chromatography on silica gel–silver nitrate gave isomerically pure $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (VII).

Preparation of $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XXXV) was accomplished by reaction of the isomeric iodide mixture with lithium perdeuteriodimethylcopper. After silica gel–silver nitrate chromatography, the desired alkene was obtained in 95% isotopic purity. Reduction of the lactone XXI with lithium aluminum deuteride gave 13,17-seco-5α-androstane-13α,17-diol-*17,17-d*$_2$. The diol was converted to $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XXXVI, 97% d_2) in the usual manner. Finally, reaction of 5α-androstane-17-one-*16,16-d*$_2$[14] according to the usual procedure gave $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*16,16-d*$_2$ (XXXVII) in 97% isotopic purity.



XXXVI XXXVII

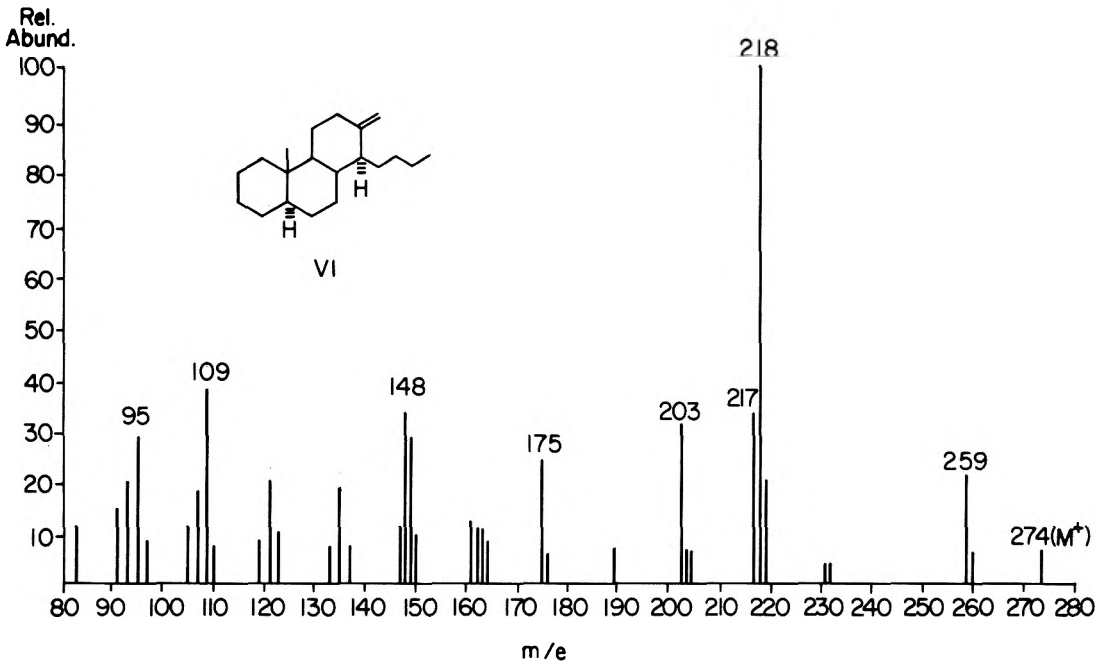


Figure 1.

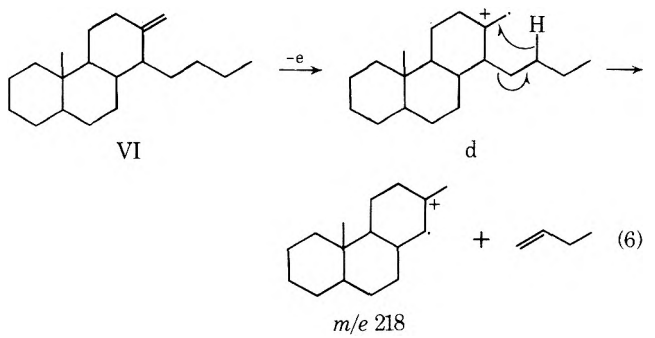
Table I
Shifts[a] of Peaks Corresponding to Ring D in $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene (VI)

Compd	Isotopic purity, %	M^+	$M - C_3H_6$	$M - C_4H_8$	$M - C_4H_9$
$-d_0$		274	232	218	217
$-17a,17a,17a-d_3$	d_3 63	277	232	218	217
$-17,17-d_2$	d_2 96	276	233	218 (80%)	217 (90%)
				219 (20%)	218 (10%)
$-16,16,17a,17a,17a-d_5$	d_5 89	279	232	219	217 (75%)
					218 (25%)

[a] Reported shifts are corrected for isotopic impurity as well as ^{13}C contributions and are greater than 95% unless otherwise indicated.

Results and Discussion

Ionization of $\Delta^{13(18)}$-13,17-seco-*D*-homoandrostene (VI) and subsequent charge localization in the carbon–carbon double bond generates ion d. The mechanism depicted in Scheme I predicts that d fragments to give an ion of *m/e* 218. Inspection of Figure 1 indicates that such behavior indeed occurs; *m/e* 218 is the base peak in the spectrum of the alkene VI. Deuterium-labeling experiments were performed in order to ascertain the mechanism of formation of *m/e* 218. The results obtained (Table I) were in full accord with the formulation of Scheme I. Labels at C-17a and C-17 were largely eliminated, while a deuterium from C-16 was transferred to the charge-retaining moiety (eq 6).



These observations clearly establish that d fragments to generate *m/e* 218; they do not, however, exclude the possibility that the *m/e* 218 ion in steroid mass spectra arises by a different mechanism and generates an isomeric *m/e* 218 ion. Metastable defocusing experiments[19,20] were therefore performed to determine whether the *m/e* 218 ion from the alkene VI and 5α-pregnane had identical structures.

Table II
Metastable Defocusing Results for the *m/e* 218 Ion

Compd	[218 → 203]/[218 → 189]	[218 → 175]/[218 → 148]	[218 → 189]/[218 → 175]
5α-Pregnane (I)	19	0.49	0.07
$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene (VI)	15	0.56	0.06
$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene (VII)	13	0.50	0.05
5α-Androstane-13,17-seco-17-oic acid lactone (XXI)	13	0.75	0.06
5α-*D*-homoandrostane	3.5	2.5	1.0

Four first field-free region metastable transitions arising from the *m/e* 218 ion were utilized in these experiments. The reactions corresponded to loss of CH_3 (218 → 203), loss of C_2H_5 (218 → 189), loss of C_3H_7 (218 → 175), and loss of C_5H_{10} (218 → 148). The intensity ratios[20] of metastables arising from the *m/e* 218 ions of 5α-pregnane, of 5α-androstane-13,17-seco-17-oic acid (eq 7), and of the exocyclic alkene VI agreed closely (Table II), consistent with their structural identity. In contrast, the ratios observed from the *m/e* 218 ion of *D*-homoandrostane were markedly different. This is not unexpected, since it has been demonstrated that these ions arise largely (ca. 70%) from ring A cleavage (eq 8).[7] The widely divergent ratios observed, however, demonstrate that the technique has utility for establishing the structure of steroid ions.

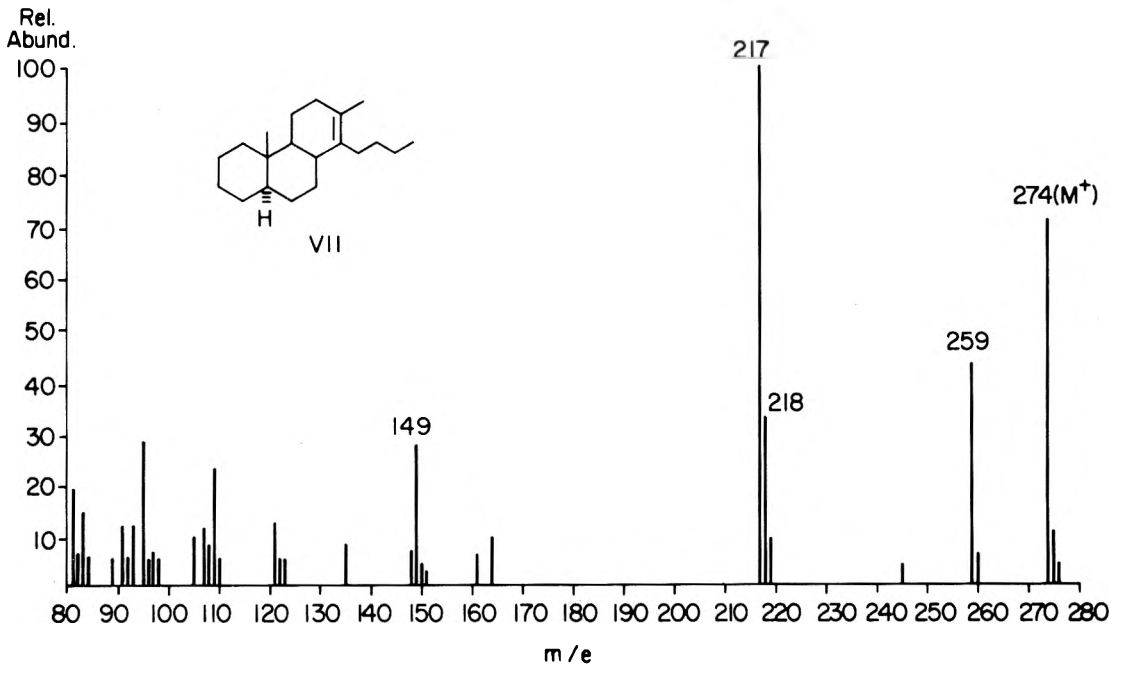


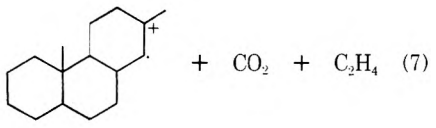
Figure 2.

Table III
Shifts[a] of Peaks Corresponding to Ring D in $\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene (VII)

Compd	Isotopic purity, %	M^+	$M - C_4H_8$	$M - C_4H_9$
$-d_0$		274	218	217
$-17a,17a,17a-d_3$	d_3 95	277	218	217
$-17,17-d_2$	d_2 97	276	218	217
$-16,16-d_2$	d_2 97	276	219	217

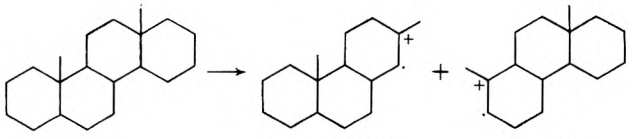
[a] Reported shifts are corrected for isotopic impurity as well as ^{13}C contributions and are greater than 95% unless otherwise indicated.

XXI



+ CO_2 + C_2H_4 (7)

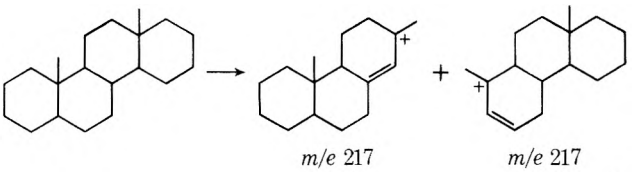
m/e 218



m/e 218 (30%) *m/e* 218 (70%)

(8)

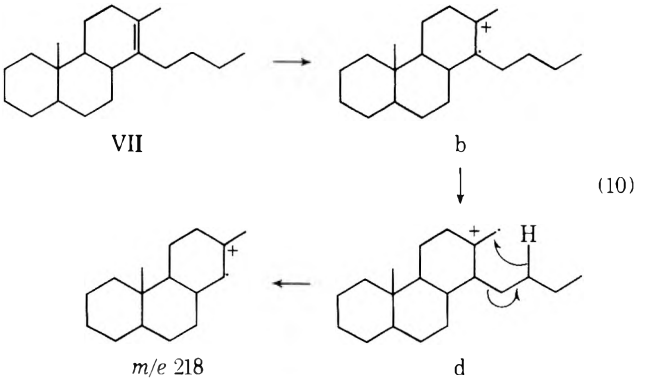
Ionization of $\Delta^{13(14)}$-13,17-seco-*D*-homoandrostene (VII) and charge localization in the carbon–carbon double bond generates b; according to Scheme I, b fragments to give *m/e* 217. Inspection of Figure 2 indicates that the base peak in the spectrum of the $\Delta^{13(14)}$ alkene is indeed at *m/e* 217. Deuterium-labeling experiments (Table III) demonstrated that labels at C-17a, C-17, and C-16 were completely eliminated, as the mechanism of Scheme I predicts. In an effort to determine whether the *m/e* 217 ion from VII and that of 5α-pregnane were identical, the intensities of two first field-free region metastables [loss of C_4H_7 (217 → 162) and loss of C_5H_8 (217 → 149)] were determined. The ratio of their intensities (Table III) was nearly identical for the *m/e* 217 ions of pregnane and of the $\Delta^{13(14)}$ alkene, consistent with their structural identity. In contrast, the intensity ratio for metastables arising from the *m/e* 217 ion of *D*-homoandrostane (known[7] to be largely isomeric, eq 9) differed by an order of magnitude, confirming the sensitivity of these ratios to steroid structure.



m/e 217 *m/e* 217

(9)

A troubling aspect of the mechanism of Scheme I is the small amount (<10%) of interconversion of ions b and d.[21] In this connection, it is interesting to note that the spectrum of the $\Delta^{13(14)}$ alkene (VII) exhibits a significant peak at *m/e* 218 (217/218 = 6.95). A priori, the *m/e* 218 ion could arise either by isomerization of b to d followed by the usual fragmentation process, or it could form through direct fragmentation of b. Considerable evidence points to its origin by the isomerization pathway. Metastable defocusing data (Table II) are consistent with structural identity between the *m/e* 218 ion of the $\Delta^{13(14)}$ alkene and that of 5α-pregnane. Further, deuterium-labeling experiments (Table III) establish that the genesis of the *m/e* 218 involves migration



VII b

(10)

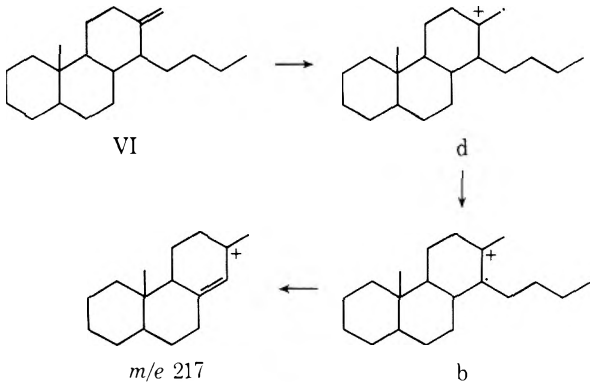
m/e 218 d

Table IV
Metastable Defocusing Results for the *m/e* 217 Ion

Compd	[217→162]/[217→149]
5α-Pregnane (I)	1.9
$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene (VI)	1.6
$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene (VII)	1.8
5α-*D*-Homoandrostane	0.11

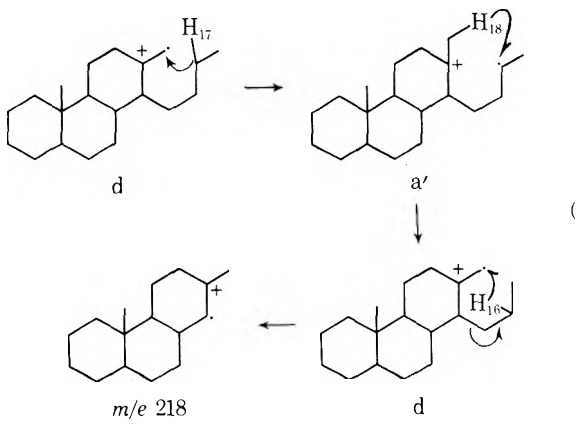
of a hydrogen from C-16, again consistent with behavior already observed for d (cf. eq 10).

Similarly, the mass spectrum of the $\Delta^{13(18)}$ alkene VI exhibits a significant peak at *m/e* 217 (217/218 = 0.34). Again, it appears likely that an isomerization reaction is occurring to produce *m/e* 217. Metastable data (Table IV) are consistent with a common structure for the *m/e* 217 ions from 5α-pregnane and from the $\Delta^{13(18)}$ alkene. Deuterium-labeling experiments (Table I) demonstrate that the genesis of the *m/e* 217 ion involves predominant expulsion of C-16, C-17, and C-17a hydrogens, consistent with behavior already described for d (cf. eq 11). Thus, the interconversion reactions b → d and d → b are more significant for the *m/e* 218 and 217 ions generated from the alkenes VI and VII than for the corresponding ions generated from intact steroids. The modest differences observed, however, are probably attributable to differences in the internal energies of the ions generated from the different sources, rather than structural differences.[22]

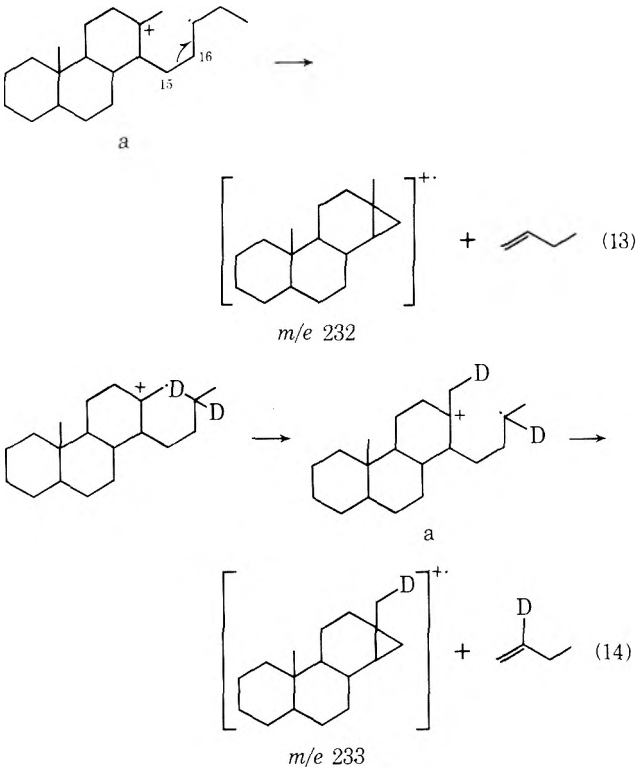


(11)

The mechanisms of the isomerization reactions remain obscure, but a related observation merits comment. The labeling data (Table I) require that the genesis of *m/e* 218 in the spectrum of $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostane (VI) always involves transfer of a hydrogen atom from C-16. Nevertheless, a 20% transfer from C-17 also occurs. An attractive rationalization of this phenomenon is depicted in eq 12. Transfer of a hydrogen atom from C-17 generates a′, analogous to the ion formed by charge localization in the C-13–C-17 bond of 5α-pregnane. Reciprocal transfer of a C-18 hydrogen regenerates d, which can fragment in the usual way to produce *m/e* 218. Supporting this hypothesis is the observation that the *m/e* 232 peak shifts cleanly to *m/e* 233 in the spectrum of the 17,17-dideuterated $\Delta^{13(18)}$ alkene. The *m/e* 232 peak in steroids such as 5α-cholestane arises via cleavage of the C-15–C-16 bond of the initially formed ion a (eq 13).[2] If the *m/e* 232 ion in the mass spectrum of the $\Delta^{13(18)}$ alkene is arising by an analogous process, a shift to *m/e* 233 is predicted on deuteration of the 17 position (eq 14). It is notable that the *m/e* 232 peak is absent from the spectrum of the $\Delta^{13(14)}$ alkene, suggesting that conversion of b to a′ does not occur.



(12)



(13)
(14)

Conclusions

The results obtained here provide strong evidence in support of the mechanism depicted in Scheme I for the characteristic ring D fragmentation of steroids. Deuterium-labeling experiments established that b and d, generated via alternative pathways, do, in fact, fragment as predicted. Metastable defocusing studies were consistent with identical structures for the *m/e* 218 ions generated from the $\Delta^{13(18)}$ alkene and from 5α-pregnane.

Evidence was obtained for a significant amount of isomerization of ions b and d, when generated by direct electron impact, and evidence for the reversibility of the initial hydrogen abstraction from C-18 (a → d) was observed.

The most useful result obtained from these studies, however, relates to the demonstrated sensitivity of metastable abundance ratios to steroid ion structure. These results suggest that the defocusing technique may have wide application to the solution of mechanistic and structural problems in steroid mass spectrometry.

Experimental Section

Melting points are uncorrected. Infrared spectra were measured on a Beckman IR-10 spectrometer in chloroform solution. NMR spectra were recorded on a Varian A-60A spectrometer or a Varian HA-100D spectrometer interfaced with a Digilab FTS-3 Fourier transform data system. All NMR spectra were run in deuteriochloroform solution with tetramethylsilane as a internal reference. Optical rotations were measured on dilute solutions in chloroform. All mass spectra were run on an AEI-MS 902 spectrometer at 70 eV

using the direct inlet procedure. Thin layer chromatography was carried out on silica gel (HF-254). All reactions were run under nitrogen unless otherwise specified.

$\Delta^{13(18)}$-13,17-Seco-5α-androstene-17-nitrile (IX). 5α-Androstan-17-one oxime[14,23] (VIII, 1.5 g, 5.17 mmol) was dissolved in 10 ml of dry pyridine. *p*-Toluenesulfonyl chloride (1.5 g, 7.84 mmol) was added and the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with 120 ml of ice water and extracted into chloroform. The extracts were washed twice with 10% hydrochloric acid to remove all the pyridine. Column chromatography on silica gel (benzene, benzene–methylene chloride) yielded 0.680 g (2.35 mmol, 45.6% yield, ~20% conversion) of 13α-amino-13,17-seco-5α-androstan-17-oic acid lactam[14] (mp 311–313°) and 0.735 g (2.61 mmol, 52.5% yield, ~20% conversion) of $\Delta^{13(18)}$-13,17-seco-5α-androstene-17-nitrile (IX):[24] mp 57–62°; ν_{max} 2248 (–C≡N) and 1647 cm^{-1} (>C=); NMR C-19 CH_3 0.70 (singlet), $-CH_2CN$ 2.35 (triplet), olefinic protons 4.52 (singlet) and 4.83 ppm (singlet); $[\alpha]^{25}D$ −34.6°. Anal. Calcd for $C_{19}H_{29}N$: mol wt, 271.2300. Found: mol wt, 271.2306.

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-one (X). $\Delta^{13(18)}$-13,17-Seco-5α-androstene-17-nitrile (IX, 148 mg, 0.545 mmol) was dissolved in 40 ml of dry ether. Methyllithium (34 mmol, Ventron, 1.8 *M* in ether) was added dropwise to the ice-cooled reaction flask. The reaction mixture was allowed to warm to room temperature over a 3-hr period, at which time it was quenched with a saturated ammonium chloride solution. The mixture was extracted with ether and washed twice with water. After drying over magnesium sulfate and purification by thin layer chromatography on silica gel (chloroform) a colorless oil, $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one, was obtained (X, 143 mg, 0.49 mmol, 90%): ν_{max} 1710 (C=O), 1640 cm^{-1} (>C=); NMR C-19 CH_3 0.71 (singlet), CH_3C=O 2.13 (singlet), $-CH_2C$=O 2.4 (multiplet), and olefinic protons at 4.5 (singlet) and 4.74 ppm (singlet); $[\alpha]^{25}D$ −25.2°. Anal. Calcd for $C_{20}H_{32}O$: mol wt, 288.2453. Found: mol wt, 288.2446.

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol (XI). Lithium aluminum hydride (100 mg, 2.62 mmol) was added to 35 ml of dry ether and the mixture was brought to reflux. $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-one (X, 45 mg, 0.155 mmol) dissolved in 20 ml of dry ether was added dropwise to the refluxing mixture. Refluxing was continued for 3 hr, at which time the mixture was quenched with a saturated ammonium chloride solution. The mixture was filtered hot to remove the lithium salts. The filtrate was then extracted with ether and washed with water. After drying over magnesium sulfate the mixture was purified by thin layer chromatography on silica gel and eluted with chloroform. This yielded 32 mg (0.109 mmol, 70%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homandrosten-17-ol (XI): ν_{max} 3610 (–OH), 1647 cm^{-1} (>C=); NMR C-19 CH_3 0.63 (singlet), olefinic protons 4.50 (singlet), 4.62 ppm (singlet). Anal. Calcd for $C_{20}H_{34}O$: mol wt, 290.2609. Found; mol wt, 290.2607.

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol Tosylate (XII). $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol (XI, 8.5 mg, 0.03 mmol) was dissolved in 3 ml of dry pyridine and cooled in ice for 0.5 hr. *p*-Toluenesulfonyl chloride (10 mg, 0.052 mmol) was then added and the reaction mixture was kept at ~10° for 24 hr. The reaction mixture was then quenched with ice–water and extracted into ether, washed twice with water, and dried over magnesium sulfate. Thin layer chromatography on silica gel (cyclohexane–toluene) yielded 10 mg (0.023 mmol, 77%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol tosylate (XII): ν_{max} 1350, 1170 ($-SO_2$), and 1647 cm^{-1} (>C=); NMR C-19 CH_3 0.60 (singlet), tolyl methyl 2.33 (singlet), aromatic protons 7.2–7.71, olefinic protons 4.30 (singlet), 4.55 ppm (singlet).

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene (VI). Lithium aluminum hydride (100 mg, 2.62 mmol) was added to 35 ml of freshly distilled tetrahydrofuran and the mixture was brought to reflux. $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol tosylate (XII, 10 mg, 0.023 mol) dissolved in 15 ml of tetrahydrofuran was added dropwise to the refluxing mixture. Refluxing was continued for 3 hr. The mixture was then quenched with a saturated ammonium chloride solution. The hot solution was filtered and the filtrate was extracted with ether and washed twice with water. After drying over magnesium sulfate, purification by chromatography on silica gel (pentane) yielded 4.62 mg (0.0168 mmol, 73%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene (VI): ν_{max} 1647 cm^{-1} (>C=); NMR C-19 CH_3 0.70 (singlet), olefinic protons at 4.55 (singlet) and 4.68 ppm (singlet); $[\alpha]^{25}D$ −15.5°. Anal. Calcd for $C_{20}H_{34}$: mol wt, 274.2660. Found: mol wt, 274.2665.

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XVII). Lithium aluminum deuteride (104 mg, 2.62 mmol) was added to 35 ml of dry ether and the mixture was brought to reflux. $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-one (X, 45 mg, 0.155 mmol) dissolved in 20 ml of dry ether was added dropwise to the refluxing mixture. Refluxing was continued for 3 hr, at which time the mixture was quenched with a saturated ammonium chloride solution. The mixture was filtered hot to remove the lithium salts and the filtrate was extracted into ether and washed with water. After drying over magnesium sulfate the mixture was thin layer chromatographed on silica gel and eluted with chloroform to give 32.6 mg (0.112 mmol, 72%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol-*17*-d_1 (XV). Its NMR and ir spectra were identical with those of the unlabeled compound XI. The $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol tosylate-*17*-d_1 (XVI) was prepared from $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol-*17*-d_1 (XV) in a manner analogous to the preparation of the unlabeled tosylate XII. Lithium aluminum deuteride (104 mg, 2.62 mmol) was added to 35 ml of freshly distilled tetrahydrofuran and the mixture was brought to reflux. $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol tosylate-*17*-d_1 (XVI, 11 mg, 0.0247 mol) dissolved in 15 ml of distilled tetrahydrofuran was added dropwise to the refluxing mixture. Refluxing was continued for 3 hr and then the mixture was quenched with a saturated ammonium chloride solution. Work-up was analogous to that of the unlabeled hydrocarbon VI. Thin layer chromatography yielded 5.35 mg (0.0193 mol, 78%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*17,17*-d_2 (XVII). The ir spectrum was identical with that of the unlabeled analog. The NMR spectrum was similar; however, the terminal side-chain methyl (C-17a) was apparent at 0.90 ppm as a broad singlet. Mass spectroscopy gave a molecular ion at *m/e* 276 (96% d_2).

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XVI). To a thoroughly dried flask was added 645 mg (92.4 mmol) of benzene-washed lithium metal cut into 1-cm pieces. The lithium was stirred in 40 ml of anhydrous ether under argon. To this mixture was added 6.9 g (47.4 mmol) of methyl iodide-d_3 dropwise.[25] The reaction mixture was refluxed for 1 hr and then stored under argon until needed. Titration showed the methyllithium-d_3 to be 0.8 *M*. $\Delta^{13(18)}$-13,17-Seco-5α-androstene-17-nitrile (IX, 148 mg, 0.545 mmol) was dissolved in 40 ml of dry ether and stirred under argon. Methyllithium-d_3 prepared as above (4.25 ml, 34 mmol) was added dropwise to the ice-cooled reaction flask. After 3 hr at room temperature the reaction was quenched with saturated ammonium chloride solution. Work-up and purification was identical with that of the unlabeled ketone X. A colorless oil, $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*17a,17a,17a-d*$_3$ was obtained (XIII, 146 mg, 0.502 mmol, 92%). Its ir spectrum was identical with that of the unlabeled ketone X and its NMR spectrum was similar except for the absence of the ketone α-methyl group at 2.13 ppm. The conversion of the $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*17a,17a,17a-d*$_3$ (XIII) to the corresponding trideuterated alcohol, tosylate, and hydrocarbon are identical with those of the unlabeled derivatives already described. The $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XIV) had ir and NMR spectra identical with that of the unlabeled hydrocarbon VI. The mass spectrum had a molecular ion at *m/e* 277 (63% d_3).

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene-*16,16,17a,17a,17a-d*$_5$ (XIX). $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-one (X, 37 mg, 0.128 mmol) was dissolved in 5 ml of methanol-d_3. Deuterium oxide (2 ml) was added and the solution was refluxed with 100 mg of anhydrous potassium carbonate. After 48 hr the procedure was repeated with fresh methanol-d_3 and deuterium oxide. Extraction into chloroform and evaporation of the solvent yielded $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*16,16,17a,17a,17a-d*$_5$ (XVIII). Its ir spectrum was identical with that of the unlabeled ketone X. Its NMR appeared identical except for the absence of all ketonic protons at 2.9 and 2.13 ppm. The mass spectrum showed a molecular ion at *m/e* 293. The conversion of the $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*16,16,17a,17a,17a-d*$_5$ (XVIII) to its corresponding alcohol, tosylate, and hydrocarbon is identical with that of the unlabeled derivatives already described. The $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*16,16,17a,17a,17a-d*$_5$ (XIX) had ir and NMR spectra identical with those of the unlabeled hydrocarbon VI. The mass spectrum had a molecular ion at *m/e* 279 (89% d_5).

5α-Androstane-13,17-seco-17-oic Acid Lactone (XXI). Hydrogen peroxide (90%, 0.5 ml, 22 mmol) was added to 3 ml of methylene chloride. Trifluoroacetic anhydride (1 ml, 5.25 mmol) was added slowly to the ice-cooled mixture. After stirring for 0.5 hr the peracid was added slowly to an ice-cooled solution of 1 g (3.65

mmol) of 5α-androsten-17-one (XX)[16] dissolved in 10 ml of methylene chloride. The reaction was allowed to proceed overnight, when the mixture was diluted with water and extracted into methylene chloride. The extracts were washed twice with a 10% sodium carbonate solution and the solvent was evaporated. Recrystallization from ethanol yielded a white, crystalline solid (mp 227–230°) of 5α-androstane-13,17-seco-17-oic acid lactone (XXI, 825 mg, 2.84 mmol, 78%).[17]

13,17-Seco-5α-androstane-13α,17-diol (XXII). Lithium aluminum hydride (200 mg, 5.24 mmol) was added to 50 ml of freshly distilled dioxane and the mixture was brought to reflux. A solution of 5α-androstane-13,17-seco-17-oic acid lactone (XXI, 825 mg, 2.84 mmol) in 50 ml of freshly distilled dioxane was added dropwise to the refluxing mixture. Refluxing was continued for 15 hr, at which time the reaction was quenched with a saturated ammonium chloride solution. The mixture was filtered to remove the lithium salts and the filtrate was extracted into chloroform, washed twice with 5% hydrochloric acid, and dried over magnesium sulfate. Recrystallization from ethanol–2% water yielded 664 mg (2.26 mmol, 80%) of white crystals of 13,17-seco-5α-androstane-13α,17-diol (XXII, mp 149.5–150.5°): ν_{max} 3600–3320 (broad, OH), 1120 (tertiary OH), 1050 cm^{-1} (primary OH); NMR C-18 CH_3 1.1 (singlet), C-19 CH_3 0.73 (singlet), C-17a CH_2OH 3.63 ppm (triplet); $[\alpha]^{25}D$ +5.17°. Anal. Calcd for $C_{19}H_{34}O_2$: mol wt, 294.2561. Found: mol wt, 294.2569.

13,17-Seco-5α-androstane 13α,17-Diacetate (XXIII). 13,17-Seco-5α-androstane-13α,17-diol (XXII, 317 mg, 1.08 mmol) was dissolved in 10 ml of dry pyridine. Acetic anhydride (500 mg, 4.8 mmol) was added and the mixture was heated at 70° for 24 hr. The reaction mixture was diluted with water and extracted into chloroform. Two washes with 5% hydrochloric acid removed the last traces of pyridine. After column chromatography on silica gel (Woelm) and elution with benzene followed by chloroform, 303 mg (0.80 mmol, 74%) of a colorless oil, 13,17-seco-5α-androstane 13α,17-diacetate (XXIII), was isolated: ν_{max} 1725 cm^{-1} (O=$COCH_3$); NMR C-18 CH_3 1.36 (singlet), C-19 CH_3 0.71 (singlet), C-13 OC(=O)CH_3 2.01 (singlet), C-17 OC(=O)CH_3 1.94 (singlet), C-17 (CH_2OC=O) 4.0 ppm (triplet); $[\alpha]^{25}D$ +20.14°. The mass spectrum gave no molecular ion but the base peak was at *m/e* 318 (M^+ − AcOH), consistent with a tertiary acetate.

$\Delta^{13(14)}$-13,17-Seco-5α-androstene 17-Acetate (XXXI). 13,17-Seco-5α-androstane 13α,17-diacetate (XXIII, 78 mg, 0.206 mmol) was placed in a sublimation tube equipped with a Dry Ice–acetone cooled cold finger. The sublimator was flushed with nitrogen and placed in an oil bath (preheated to 332°) for 10 min. The product was purified by thin layer chromatography on silica gel (chloroform) to give a mixture of three isomeric olefins. The exocyclic olefin, $\Delta^{13(18)}$-13,17-seco-5α-androstene 17-acetate (XXIV), was removed by careful chromatography on silica gel impregnated with 10% silver nitrate[18] (benzene–2.5% acetone). The remaining mixture[26] contained 43 mg (0.113 mmol, 55%) of the colorless oil $\Delta^{13(14)}$-13,17-seco-5α-androstene 17-acetate (XXXI): ν_{max} 1730 (O=CCH_3), 1660 cm^{-1} (weak, >C=C<); NMR C-18 CH_3 1.59 (singlet), C-19 CH_3 0.72 (singlet), C-17 OC(=O)CH_3 2.02 (singlet), C-17 (CH_2OC=O) 4.01 ppm (triplet). The small peak at 5.5 ppm was due to the $\Delta^{12(13)}$ double bond isomer. Anal. Calcd for $C_{21}H_{34}O_2$: mol wt, 318.2559. Found: mol wt, 318.2557.

$\Delta^{13(14)}$-13,17-Seco-5α-androsten-17-ol (XXXII). The isomeric mixture $\Delta^{13(14)}$- and $\Delta^{12(13)}$-13,17-seco-5α-androstene 17-acetate (75 mg, 0.236 mmol) was dissolved in 20 ml of methanol. Water (2 ml) and potassium hydroxide (ca. 450 mg) were added and the mixture was refluxed for 0.5 hr. The mixture was diluted with water and extracted into chloroform. After washing with 10% hydrochloric acid and drying over magnesium sulfate the mixture was purified by thin layer chromatography on silica gel (chloroform) to give 55 mg (0.199 mmol, 84%) of the isomeric $\Delta^{12(13)}$- and $\Delta^{13(14)}$-13,17-seco-5α-androsten-17-ol (XXVI and XXXII): ν_{max} 3600–3300 cm^{-1} (broad, primary –OH); NMR C-18 CH_3 1.59 (singlet), C-19 CH_3 0.73 (singlet), C-17 CH_2OH 3.6 ppm (triplet). The small peak at 5.5 ppm was due to the $\Delta^{12(13)}$ isomer (XXVI). Anal. Calcd for $C_{19}H_{32}O$: mol wt, 276.2453. Found: mol wt 276.2459.

$\Delta^{13(14)}$-13,17-Seco-5α-androsten-17-ol Tosylate (XXXIII). The isomeric mixture of $\Delta^{13(14)}$- and $\Delta^{12(13)}$-13,17-seco-5α-androsten-17-ol (XXXII and XXVI, 42 mg, 0.152 mmol) was dissolved in 10 ml of dry pyridine and chilled to 0°. The flask was then flushed with nitrogen and 100 mg (0.502 mmol) of *p*-toluenesulfonyl chloride was added. The flask was kept at 10° for 18 hr and then diluted with 120 ml of water. Extraction into chloroform was followed by two washes with 5% hydrochloric acid to remove all the pyridine. Thin layer chromatography on silica gel (chloroform) yielded 44 mg (0.102 mmol, 67%) of the isomeric $\Delta^{12(13)}$- and $\Delta^{13(14)}$-13,17-seco-5α-androsten-17-ol tosylate (XXVII and XXXIII): ν_{max} 1350, 1170 cm^{-1} (SO_2): NMR C-18 CH_3 1.57 (singlet), C-19 CH_3 0.70 (singlet), tolyl CH_3 2.44 (singlet), aromatic protons 7.20–7.71 ppm. The small peak at 5.5 ppm was due to the $\Delta^{12(13)}$ isomer.

17-Iodo-$\Delta^{13(14)}$-13,17-seco-5α-androstene (XXXIV). The isomer mixture of $\Delta^{12(13)}$- and $\Delta^{13(14)}$-13,17-seco-5α-androsten-17-ol tosylate (XXVII and XXXIII, 44 mg, 0.102 mmol) was dissolved in 10 ml of acetone. Sodium iodide (30.6 mg, 0.204 mmol) was added and the reaction flask was placed in the dark under nitrogen. After a few hours white crystals of sodium tosylate started to precipitate out. The reaction was allowed to proceed until the formation of new crystals ceased (ca. 30 hr). Dilution with water and extraction into chloroform followed by thin layer chromatography on silica gel (benzene) yielded 12 mg (0.031 mmol, 56%) of the isomeric 17-iodo-$\Delta^{12(13)}$- and -$\Delta^{13(14)}$-13,17-seco-5α-androstene (XXVIII and XXXIV): no significant ir absorptions; NMR C-18 CH_3 1.62 (singlet), C-19 CH_3 0.72 (singlet), C-17 CH_2I 3.18 ppm (triplet). Anal. Calcd for $C_{19}H_{31}I$: mol wt, 386.1474. Found: mol wt, 386.1468.

$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene (VII). Copper iodide (156 mg, 0.816 mmol, Alfa Inorganics Ultra Pure) was added to a thoroughly dried three-necked flask containing 3 ml of anhydrous ether. While this mixture was stirring at −10° (ice–acetone) 2.6 ml of methyllithium (1.63 mmoles, 0.63 *M*) in ether (prepared from 0.5 mol of lithium metal and 0.25 mol of methyl iodide)[25] was added dropwise. The first few drops of methyllithium generated a bright yellow color which became a light tan color on complete addition of the methyllithium.[27] The lithium dimethylcopper was allowed to stir for 0.5 hr at −10°, at which time 24 mg (0.0623 mmol) of the isomeric 17-iodo-$\Delta^{12(13)}$- and -$\Delta^{13(14)}$-13,17-seco-5α-androstene (XXVIII and XXXIV) dissolved in 5 ml of anhydrous ether was added dropwise. This mixture was stirred at −10° for 6 hr and then quenched with water and extracted into ether. Repeated water washes, drying over magnesium sulfate, and thin layer chromatography on silica gel (pentane) gave the isomeric mixture of $\Delta^{12(13)}$- and $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (XXIX and VII). Careful chromatography on 10% silver nitrate impregnated silica gel[18] (hexane–6.5% benzene) yielded 9.3 mg (0.034 mmol, 55%) of the pure, colorless oil $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (VII): ν_{max} 2920, 2860 (C–H), 1660 cm^{-1} (weak, >C=C<); NMR C-18 CH_3 1.62 (singlet), C-19 CH_3 0.72 ppm (singlet) (the small peak at 5.5 ppm is absent); $[\alpha]^{25}D$ −60°. Anal. Calcd for $C_{20}H_{34}$: mol wt, 274.2661. Found: mol wt, 274.2660.

$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XXXV). The isomeric mixture of 17-iodo-$\Delta^{12(13)}$- and -$\Delta^{13(14)}$-13,17-seco-5α-androstene (XXVIII and XXXIV, 24 mg, 0.0623 mmol) was treated in a similar manner as above except that methyl iodide-d_3 was substituted for methyl iodide in the preparation of the methyllithium-d_3.[25] Silica gel (pentane) thin layer chromatography followed by silica gel–10% silver nitrate[18] (hexane–6.5% benzene) thin layer chromatography yielded the isomerically pure, colorless oil $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XXXV, 10.0 mg, 0.037 mmol, 59%). Its ir and NMR spectra were identical with those of the unlabeled analog VII. Its mass spectrum had a molecular ion at *m/e* 277 (95% d_3).

$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene-*16,16-d*$_2$ (XXXVII). 5α-Androsten-17-one (XX, 921 mg, 3.35 mmol) was dissolved in 10 ml of methanol-d_1. Anhydrous potassium carbonate (200 mg) and 2 ml of deuterium oxide was added and the mixture was refluxed for 48 hr. The process was repeated with fresh methanol-d_1 and deuterium oxide. The reaction mixture was then diluted with water and extracted into chloroform. Its ir spectrum was identical with that of the unlabeled ketone XX (mp 114–116°).[16] Its NMR spectrum was similar to that of the unlabeled ketone XX except for the absence of the ketonic methylene protons at 2.28 ppm. The mass spectrum showed a molecular ion at *m/e* 276. The conversion of 5α-androstan-17-one-*16,16-d*$_2$ to the corresponding $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*16,16-d*$_2$ (XXXVII) was accomplished in the usual manner. The $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*16,16-d*$_2$ (XXXVII) had ir and NMR spectra identical with those of the unlabeled hydrocarbon VII. Its mass spectrum showed a molecular ion at *m/e* 276 (97% d_2).

$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XXXVI). 5α-Androstane-13,17-seco-17-oic acid lactone (XXI, 825 mg, 2.84 mmol) dissolved in 50 ml of freshly distilled dioxane was added dropwise to a refluxing mixture of 190 mg (5 mmol) of lithium aluminum deuteride in 50 ml of freshly distilled dioxane. The mixture was refluxed for 18 hr and then quenched with a saturated ammonium chloride solution. Filtration removed the lithium salts and

then the filtrate was extracted into chloroform. Thin layer chromatography on silica gel (chloroform) yielded 712 mg (2.41 mmol, 85%) of white crystalline 13,17-seco-5α-androstene-13α,17-diol-*17,17-d*$_2$ (mp 148–150°). Its ir spectrum was identical with that of the unlabeled diol XXII. Its NMR spectrum was similar except for the absence of the C-17 methylene protons at 3.63 ppm. The mass spectrum showed a molecular ion at *m/e* 296. The conversion of 13,17-seco-5α-androstane-13α,17-diol-*17,17-d*$_2$ to the corresponding $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XXXVI) was accomplished in the usual manner.

The $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XXXVI) had an ir spectrum identical with that of the unlabeled hydrocarbon VII. Its NMR spectrum was similar except that the terminal C-17a methyl group appeared at 0.90 ppm as a broad signal. The mass spectrum showed a molecular ion at *m/e* 276 (97% d_2).

Registry No.—VI, 54869-94-2; VII, 54869-95-3; VIII, 1035-62-7; IX, 22214-86-4; X, 54869-96-4; XI, 54869-97-5; XII, 54869-98-6; XIII, 54869-99-7; XIV, 54870-00-7; XV, 54870-01-8; XVI, 54870-02-9; XVII, 54911-57-8; XVIII, 54870-03-0; XIX, 54870-04-1; XX, 963-74-6; XXI, 2466-25-3; XXII, 54870-05-2; XXIII, 54870-06-3; XXIV, 54870-07-4; XXV, 54870-08-5; XXVI, 54870-09-6; XXVII, 54870-10-9; XXVIII, 54870-11-0; XXIX, 54870-12-1; XXXI, 54870-13-2; XXXII, 54870-14-3; XXXIII, 54870-15-4; XXXIV, 54870-16-5; XXXV, 54910-88-2; XXXVI, 54933-60-7; XXXVII, 54933-61-8; 13, 17-seco-5α-androstane-13α, 17-diol-*17, 17-d*$_2$, 54870-17-6.

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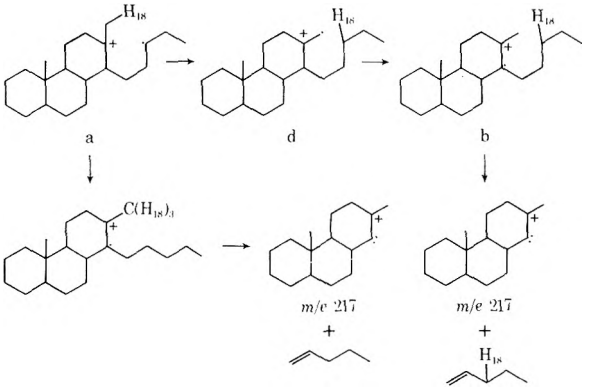
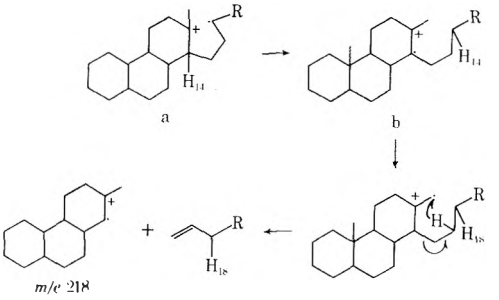


the M − C_5H_{10} peak of the 14α-deuterated compound. An apparent typographical error in Table I makes this analysis hazardous. Analogous data for 5α-cholestane (Table II) suggest that the isomerization reaction contributes 10% or less to the genesis of *m/e* 218.



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Kinetics and Mechanism of Hydrolysis of Succinimide under Highly Alkaline Medium

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The kinetic study of hydrolysis of succinimide has been done in highly alkaline medium. The hydrolysis follows an irreversible first-order consecutive reaction path of the type A → B → C where k_1 and k_2 are the pseudo-first-order rate constants for reaction A → B and B → C, respectively. The variation of k_1 and k_2 with alkali concentration was found to be in agreement with equations $k_{1(obsd)} = B_1 + B_2[OH^-]$ and $1/k_{2(obsd)} = C_1 + C_2/[OH^-]$ where B_1, B_2, C_1, and C_2 are the arbitrary constants.

In the basic hydrolysis of succinimide and substituted imides, many interesting features have been observed by a number of investigators.[1-2] The effect of various groups and associated rings on the hydrolysis of imides was studied by Sircar.[3] Prabhudas[4] studied separately the first and second stage basic hydrolysis of succinimide in 0.07143, 0.05, and 0.04286 *M* sodium hydroxide solutions using usual one-step first- and second-order rate equations at temperatures ranging from 20 to 50°. He found that the first step was about 300 times faster than the second one for this reaction. He had simply given the stoichiometry of the basic hydrolysis of succinimide and had not discussed the mechanism. In the present study, the kinetics has been done in highly alkaline medium with the aim to establish the consecutive nature as well as the mechanism of two-stage hydrolysis of succinimide. The rate constants of the consecutive steps have been evaluated using the equation of Esson as discussed by Frost and Pearson.[5]

Experimental Section

Reagents. Succinimide was prepared by the method of Clarke and Behr.[6] The stock solution of carbonate-free sodium hydroxide was prepared and diluted to the required concentrations using double distilled water. All other reagents were of reagent grade.

Kinetic Measurements. A two-necked flask containing sodium hydroxide and sodium nitrate (used to maintain the ionic strength) was thermostated in an oil bath whose temperature was maintained within ±0.1°. Succinimide solution was then added and the evolved ammonia was flushed out by passing a continuous current of nitrogen gas and was absorbed in hydrochloric acid.[7,8] The evolved ammonia at different time intervals was estimated spectrophotometrically using Nessler's reagent.[9-13] The spectrophotometric measurements were made using a Bausch and Lomb Spectronic-20. The reaction vessel was fitted with a double-walled condenser to check any evaporation.

Results and Discussion

The basic hydrolysis of succinimide follows the reaction path

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C \qquad (1)$$

where A, B, and C stand for succinimide, succinamic acid, and ammonia. For this reaction, the concentration of ammonia is related with time by the equation[5]

$$C = A_0\left[1 + \frac{1}{k_1 - k_2}(k_2 e^{-k_1 t} - k_1 e^{-k_2 t})\right] \qquad (2)$$

where k_1 and k_2 are the pseudo-first-order rate constants and A_0 is the initial concentration of succinimide. By substituting a parameter, ρ, for k_2/k_1 in eq 2, we get

$$C = A_0\left[1 + \frac{1}{1 - \rho}(\rho e^{-k_1 t} - e^{-\rho k_1 t})\right] \qquad (3)$$

Equation 3 has been solved for k_1 introducing various trial values of ρ using the Newton–Raphson method.[14] The best possible value of ρ was obtained by selecting one of those trial values for which the sum of the squares of the difference of observed and calculated values was found to be minimum. This fitting was done using a computer program developed for IBM-1130. The value of k_2 was determined from the exact value of ρ and k_1.

To study the effect of hydroxide ions, the kinetic measurements were made in sodium hydroxide solutions with concentrations ranging from 0.1 to 1.0 *M* at four different temperatures. The results are shown in Figures 1 and 2.

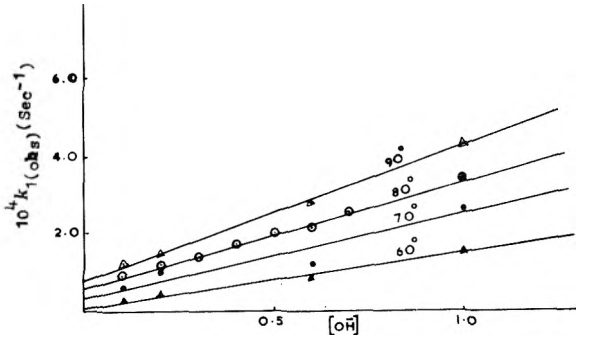


Figure 1. Effect of concentration of sodium hydroxide on pseudo-first-order rate constant for first step hydrolysis.

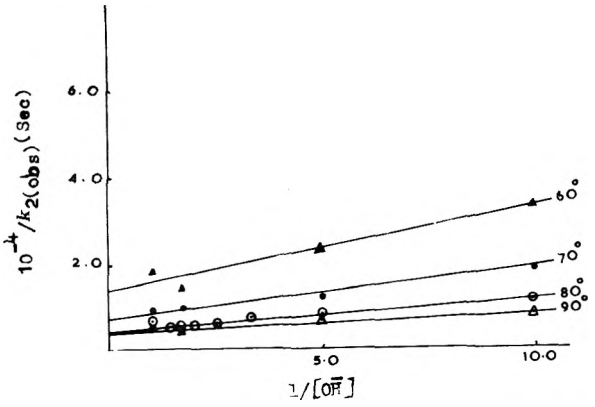


Figure 2. Effect of concentration of sodium hydroxide on pseudo-first-order rate constant for second step hydrolysis.

From these results it is clear that the variation of k_1 and k_2 with alkali concentration obeys the equations

$$k_{1(obsd)} = B_1 + B_2[OH^-] \qquad (4)$$

$$1/k_{2(obsd)} = C_1 + C_2/[OH^-] \qquad (5)$$

Table I
Linear Parameters Corresponding to $k_{1(obsd)}$ vs. $[OH^-]^a$

Temp, °C	$10^5 B_1$, sec^{-1}	$10^4 B_2$, M^{-1} sec^{-1}
60	1.544 ± 0.743[b]	1.277 ± 0.125[b]
70	3.704 ± 3.11	2.032 ± 0.524
80	6.639 ± 0.527	2.568 ± 0.118
90	8.276 ± 0.839	3.366 ± 0.141

[a] Conditions: 0.004 *M* succinimide, 1.5 *M* ionic strength. [b] Error limits are standard deviations.

Table II
Linear Parameters Corresponding to $1/k_{2(obsd)}$ vs. $1/[OH^-]^a$

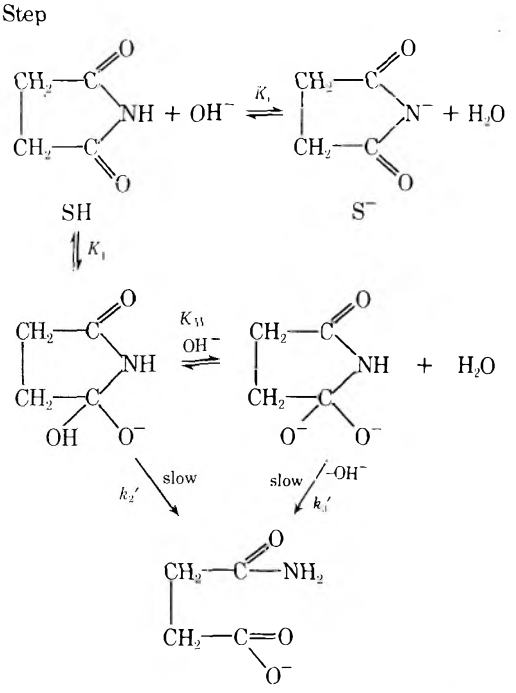
Temp, °C	$10^{-3} C_1$, sec	$10^{-2} C_2$, *M* sec
60	13.72 ± 2.45[b]	18.99 ± 4.33[b]
70	7.937 ± 0.890	9.619 ± 1.568
80	4.622 ± 0.317	6.685 ± 0.683
90	4.713 ± 0.928	3.450 ± 1.636

[a] Conditions: 0.004 *M* succinimide, 1.5 *M* ionic strength. [b] Error limits are standard deviations.

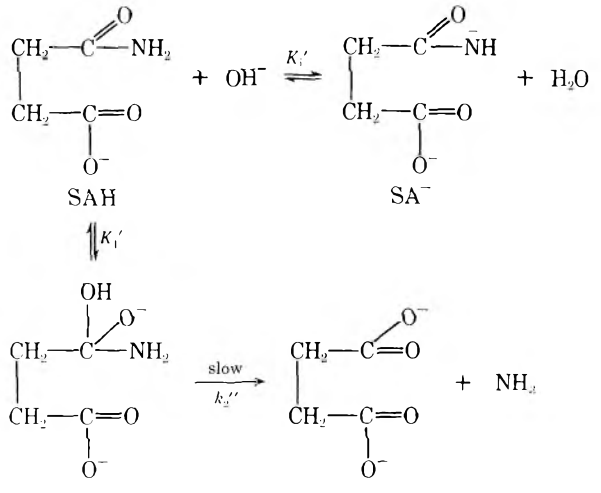
where B_1, B_2, C_1, and C_2 are arbitrary constants and have been evaluated using least-squares technique. The results are summarized in Tables I and II.

The mechanism consistent with the observed results to which we are led is as follows.

First Step



Second Step



The above mechanism is in close agreement with the results of various authors[12,15-23] on alkaline hydrolysis of monoamides, dihydropyrimidines, substituted anilides, and *N*-acylpyrroles. On the basis of this mechanism the following kinetic equations have been derived.

$$k_{1(obsd)} = \frac{K_1 k_2'[OH^-]}{1 + K[OH^-]} + \frac{K_I K_{II} k_3'[OH^-]^2}{1 + K[OH^-]} \quad (6)$$

or

$$k_{1(obsd)} = \frac{K_I k_2'}{K} + \frac{K_I K_{II} k_3'}{K}[OH^-] \quad (7)$$

because $K[OH^-] \gg 1$ in this particular case; and

$$k_{2(obsd)} = \frac{K_I' k_2''[OH^-]}{1 + K'[OH^-]} \quad (8)$$

where k_2', k_2'', and k_3' are the rate constants corresponding to rate-determining steps for the decomposition of tetrahedral intermediates to products and $K = K_i/[H_2O]$, $K' = K_i'/[H_2O]$. Equations 7 and 8 confirm the dependence of rate constants on alkali concentration and are similar to eq 4 and 5.

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Registry No.—Succinimide, 123-56-8.

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Internal Hydrogen Bonding and Positions of Protonation in the Monoprotonated Forms of Some 1,3- and 1,4-Diamines[1]

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Values of pK_1 and pK_2 have been determined for *N,N*,2-trimethyl-1,3-propanediamine, *N,N*,2,2-tetramethyl-1,3-propanediamine, *N,N,N',N'*,2,2-hexamethyl-1,3-propanediamine, *cis*- and *trans*-2-(dimethylaminomethyl)-cyclohexylamine, 3-*endo*- and 3-exo-dimethylaminomethyl-2-*endo*-norbornanamine, o-(dimethylaminomethyl)benzylamine, and o-bis(dimethylaminomethyl)benzene. The ^1H nuclear magnetic resonance chemical shifts of the *N*-methyl and certain other hydrogen atoms in these compounds were measured in the presence of increasing amounts of added strong acid. It is concluded that the monoprotonated forms of some of the diamines exist largely as cyclic internally hydrogen-bonded species, but in other cases, such as that of monoprotonated *N,N,N',N'*-tetramethyl-1,3-propanediamine, such cyclization is negligible. The largest extents of cyclization are found with the monoprotonated forms of *N,N,N',N'*,2,2-hexamethyl-1,3-propanediamine, *o*-(dimethylaminomethyl)benzylamine, and o-bis(dimethylaminomethyl)benzene, which are estimated to be 77, 93.4, and 98.6% cyclic, respectively. Also estimated are the fractions of the monoprotonated forms of the primary–tertiary diamines that are protonated at the primary and at the tertiary amino groups. These estimates and the observed overall p*K* values give estimated micro p*K* values for such specific subspecies as the tertiary-monoprotonated and primary-monoprotonated diamines.

A ^1H nuclear magnetic resonance (^1H NMR) method for determining the relative basicities of the individual amino groups of unsymmetrical diamines was described previously.[2] The micro pK_a values obtained for several ω-dimethylamino alkyl amines have since been used in studies of bifunctional catalysis of the oximation of acetone,[3] the dedeuteration of acetone-d_6,[4] and the dealdolization of diacetone alcohol[5] by the monoprotonated forms of such diamines. We have now made analogous ^1H NMR measurements and p*K* determinations on additional 1,3- and 1,4-diamines and have obtained evidence that the monoprotonated forms of some of these diamines exist to major extents as cyclic hydrogen-bonded species in which the added proton is attached to both amino groups simultaneously.

Results and Discussion

p*K* Values. Values of pK_1 (for the monoprotonated amine) and pK_2 (for the diprotonated amine) were determined at 35° in aqueous solution by potentiometric titration using the Davies equation for ionic activity coefficients[6] to obtain the values at infinite dilution. Table I contains the results obtained for nine diamines plus literature values[2,4,7,8] for five other diamines for comparison purposes. In interpreting these results it should be noted that primary amino groups attached to saturated carbon are ordinarily significantly more basic than their *N,N*-dimethyl derivatives are in aqueous solution. This generalization is supported by the pK_a values listed in Table II, most of which were obtained from the literature[4,7-11] and corrected to 35° if not determined at that temperature. The only exception to this rule that we found was with the cyclohexyl compounds, where the literature value[7] at 25° and our temperature correction gave a pK_a value of 10.48 for the conjugate acid of *N,N*-dimethylcyclohexylamine at 35°. In view of the lack of details as to how the literature p*K* value had been determined we carried out a determination at 35°. The result, which is listed in Table II, shows that the *N,N*-dimethyl derivative is a weaker base than cyclohexylamine, albeit by a smaller amount than is found with the other pairs listed.

The most anomalous of the pK_1 values for the tertiary–primary diamines is probably that for *o*-(dimethylami-

Table I
Acidity Constants for Mono- and Diprotonated 1,3- and 1,4-Diamines in Water at 35°

Diamine	pK_1	pK_2	Registry no.
$H_2NCH_2CH_2CH_2NH_2$	10.16[a]	8.17[a]	
$Me_2NCH_2CH_2CH_2NH_2$	9.91[b]	7.67[b]	
$Me_2NCH_2CHMeCH_2NH_2$	9.87	7.25	6105-72-2
$Me_2NCH_2CMe_2CH_2NH_2$	10.03	6.74	53369-71-4
$Me_2NCH_2CH_2CH_2NMe_2$	9.52[c]	7.36[c]	
$Me_2NCH_2CMe_2CH_2NMe_2$	9.84	5.99	53369-79-2
2-(Dimethylaminomethyl)cyclopentylamines, cis	~9.44[d,e]	~7.00[d,e]	
2-(Dimethylaminomethyl)cyclopentylamines, trans	9.80[d]	7.59[d]	
2-(Dimethylaminomethyl)cyclohexylamines, cis	10.02	7.08	53369-73-6
2-(Dimethylaminomethyl)cyclohexylamines, trans	10.29	6.70	53369-74-7
3-(Dimethylaminomethyl)-2-norbornamines, 3-exo-2-endo	9.92	7.61	53403-34-2
3-(Dimethylaminomethyl)-2-norbornamines, endo-endo	9.78	6.82	53369-68-9
o-$Me_2NCH_2C_6H_4CH_2NH_2$	10.07	5.86	53369-77-0
o-$C_6H_4(CH_2NMe_2)_2$	10.58	4.97	53369-80-5

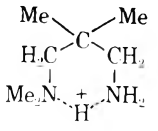
[a] Interpolated between values at 30° and 40° listed in ref 7. [b] From ref 2. [c] From ref 8. [d] From ref 4. [e] Measurements made on material containing about 81% cis and 19% trans isomer.

Table II
Acidity Constants for Primary Ammonium Ions and Their *N,N*-Dimethyl Derivatives in Water at 35° [a]

R	$pK_{RNH_3^+}$	Ref	$pK_{RNHMe_2^+}$	Ref
Me	10.31	7	9.58	7
Et	10.32	7	9.79[b]	7
n-Pr	10.24	8	9.79[b]	7
n-Bu	10.27	7	9.80	4
i-Bu	10.15	9	9.71[b]	7
t-BuCH$_2$	9.83[c]	7	9.52[b,d]	8
Cyclopentyl	10.31	9		
Cyclohexyl	10.30	9	10.24	*e*
MeOCH$_2$CH$_2$	9.09	10	8.96	4
MeO(CH$_2$)$_3$	9.83	9	9.14[b]	8
HC≡CCH$_2$	7.87	9	7.27	11
PhCH$_2$	9.00	9	8.70[b]	8
o-MeC$_6$H$_4$CH$_2$	8.90[c]	8		
2-*endo*-Norbornyl	10.03	*e*		

[a] Unless otherwise noted, these values were determined at 35° or corrected to 35° using an experimentally determined value of $\Delta H°$. [b] Corrected to 35° from 20° or 25° using a $\Delta S°$ value of −11.7 eu. The standard deviation of the 12 values of $\Delta S°$ for monoprotonated, electrically neutral tertiary amines (diamine data being statistically corrected) listed in a recent compilation[9] from this average value was 3.3 eu. [c] Corrected to 35° from 16–25° using a $\Delta S°$ value of −0.8 eu estimated from values for similar primary amines. [d] Obtained in a study in which a pK_a value for neopentylammonium ions was obtained that was about 0.4 log unit lower than that found by other workers. [e] Determined in the present investigation.

nomethyl)benzylamine. The data in Table II show that benzylammonium ion has a pK_a of only 9.00 and this value is decreased by an ortho methyl substituent. If replacing a hydrogen atom on this ortho methyl group by a dimethylamino group has the same effect on the basicity of the primary amino group that replacing a hydrogen on carbon-4 of *n*-butylamine by an amino group does,[7] the pK_a of *o*-(dimethylaminomethyl)benzylammonium ions would be about 8.7. The basicity of the tertiary amino group may be estimated analogously to be enough to make the total pK_1 of the monoprotonated diamine about 8.9. The observed value of 10.07 shows that this diamine is about 15 times as basic as would be expected from data on related compounds. Other less pronounced anomalies include the relatively large pK_1 values for the 2-(dimethylaminomethyl)-cyclohexylamines and for *N,N*,2,2-tetramethyl-1,3-propanediamine. These anomalies seem qualitatively explicable in terms of stabilization of the monoprotonated diamines by an internal hydrogen bond such as that in **1**.



1

In order to have compounds for which the interpretation of ^{1}H NMR data would be particularly simple we studied the *N',N'*-dimethyl derivatives of the primary–tertiary diamines in three of the cases in which such compounds would have two equivalent dimethylamino groups. The pK_1 values for two of these compounds, *N,N,N',N'*,2,2-hexamethyl-1,3-propanediamine and *o*-bis(dimethylaminomethyl)benzene, also point to cyclic hydrogen-bonded structures for the monoprotonated species.

^{1}H Nuclear Magnetic Resonance Measurements. The ^{1}H NMR method for estimating the relative basicities of the two amino groups in unsymmetrical diamines involves measuring the chemical shift, as a function of the extent of protonation of the diamine, of some hydrogen atom(s) in the diamine.[2] The most reliable results are expected when the hydrogen atom whose shift is being measured is much nearer one amino group than the other. In all the cases studied previously measurements were made on the *N*-methyl protons of dimethylamino substituted primary amines. For such cases we may derive eq 1, in which δ_{obsd} is

$$\delta_{obsd} = f_d\delta_d + f_m\delta_m \quad (1)$$

the observed chemical shift of the methyl protons in the solution in question, f_m is the fraction of the diamine that is monoprotonated and f_d is the fraction diprotonated in that solution, δ_d is the chemical shift in the diprotonated species, and δ_m is the chemical shift in the average monoprotonated species. If the monoprotonated species consists solely of diamine protonated only at the tertiary amino group and diamine protonated only at the primary amino group, the value of δ_m may be expressed as shown in eq 2,

$$\delta_m = f_t\delta_t + f_p\delta_p \quad (2)$$

in which f_t and f_p are the fractions of monoprotonated diamine that are tertiary protonated and primary protonated, respectively, and δ_t and δ_p are the respective chemical shifts in these two species. In eq 1 and 2 all chemical shifts are downfield from that in the unprotonated diamine. Since f_d and f_m may be calculated from the amount of strong acid used in making up the diamine solution and from the pK values for the diamine, values of δ_d and δ_m may be obtained from eq 1 (or an equivalent expression) using δ_{obsd} values for diamine solutions with various amounts of added acid. However, in order to obtain a value for f_t or f_p it is necessary to estimate δ_t and δ_p. To do this it was first assumed that δ_d is equal to $\delta_p + \delta_t$ (eq 3). This follows from the assumption that protonation of the primary amino group has the same effect on the chemical shift of the *N*-methyl hydrogen atoms when the tertiary amino group is protonated as when it is not. This assumption may be a good approximation when the molecular geometry of the diamine is not significantly affected by either monoprotonation or diprotonation. It is very similar to assuming that the chemical shift of the *N*-methyl hydrogen atoms of a symmetrical ditertiary amine is affected in the same way by protonation of the distant amino group when the nearby amino group is protonated as when the nearby amino group is not protonated. If this latter assumption is correct the chemical shift of the *N*-methyl hydrogen atoms (or any hydrogen atom) of a symmetrical diamine will be a linear function of the average extent of protonation of the diamine. If the assumption is significantly in error a plot of the chemical shift vs. the extent of protonation will show a break at 1.0 proton per molecule of diamine. Hence the validity of eq 2 was tested by making such plots for *N,N,N',N'*-tetramethylethylenediamine and *N,N,N',N'*-tetramethyl-1,3-propanediamine. The plots were both linear within the experimental error and it was concluded that the monoprotonated forms of these two diamines did not exist to a significant extent as cyclic hydrogen-bonded species and that eq 2 was probably a good approximation for the primary–tertiary diamines, at least in the cases where there were two and three methylene groups between the two amino groups.[2]

$$\delta_d = \delta_p + \delta_t \quad (3)$$

Since we concluded on the basis of pK determinations that the monoprotonated forms of o-bis(dimethylaminomethyl)benzene and *N,N,N',N'*-2,2-hexamethyl-1,3-propanediamine existed largely as species in which the added

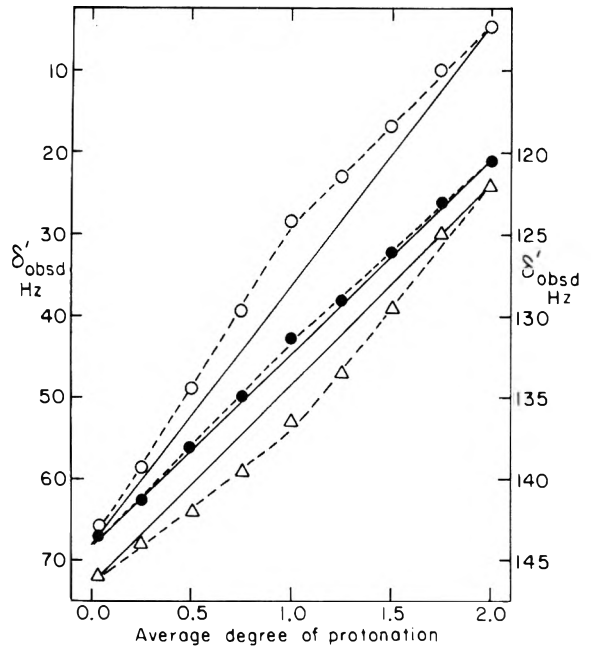


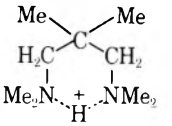
Figure 1. Plots of chemical shifts upfield from internal methanol vs. degree of protonation: O, methylene protons (shifts on left-hand scale); ●, *N*-methyl protons (shifts on left-hand scale); △, *C*-methyl protons (shifts on right-hand scale), of *N,N,N′,N′*,2,2-hexamethyl-1,3-propanediamine in aqueous solution.

proton was bonded to both amino groups simultaneously, we have studied the ^{1}H NMR spectra of these compounds as a function of the extent of protonation in aqueous solution. The latter diamine gave the more informative results. Plots of the chemical shifts of the *N*-methyl, the *C*-methyl, and the methylene hydrogen atoms vs. the average number of protons added to the diamine molecule are shown in Figure 1. Each set of data was fitted by the method of least squares to eq 4, which is a modified version of eq 1 in which

$$\delta'_{obsd} = \delta_0 - f_m\delta_m - f_d\delta_d \qquad (4)$$

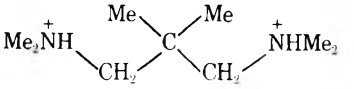
δ'_{obsd} is measured upfield from the internal standard methanol and δ_0 is the upfield chemical shift of the unprotonated diamine relative to this standard. The experimental points agree well with the dashed lines which were constructed from the optimum values of δ_0, δ_d, and δ_m obtained. The solid lines, which are straight lines connecting the ends of the dashed lines, are drawn to show how much the plots deviate from linearity. These deviations show that δ_m is more than half as large as δ_d for the *N*-methyl and methylene protons but less than half as large for the *C*-methyl protons. Neither the absolute nor the relative magnitudes of the various chemical shifts could be reproduced by calculations based on the equation of Schweizer and coworkers,[12,13] in which we took the protonated amino groups as having unit positive charges located at the nitrogen atoms and then assumed various plausible molecular geometries. Improved agreement could be obtained by assuming that the effects of the charges were attenuated to varying degrees by the dielectric constant in the vicinity, but we did not go so far as to carry out a Kirkwood–Westheimer treatment to obtain an effective dielectric constant.[14] The fact that the protonation of a tertiary amino group has a much larger effect on chemical shifts of nearby hydrogen atoms than does protonation of an analogous primary amino group[2] suggests that much of the charge on a protonated amino group is dispersed via hydrogen bonding onto surrounding water molecules. This will seriously complicate any quantitative interpretation of the effect of protonation of amino groups on chemical shifts.

The deviations from linearity in the plots in Figure 1 may be explained *qualitatively* in terms of the formation of the cyclic hydrogen-bonded monoprotonated species, **2**, in



2

which the hydrogen bond is written as symmetrical not to imply that there is necessarily only one potential energy minimum for the hydrogen atom but to reflect the fact that the hydrogen atom would be bonded equally to both nitrogen atoms on the ^{1}H NMR time scale. It is assumed that the diprotonated amine exists largely in a conformation such as **3**, in which the positively charged nitrogen atoms



3

are separated as far as possible. The *C*-methyl hydrogen atoms are seen to be much closer to the fully positively charged nitrogen atoms in **3** than they are to the half-positively charged nitrogen atoms in **2**. This explains why diprotonation changes their chemical shift more than twice as much as monoprotonation does. The *N*-methyl and the methylene hydrogen atoms, on the other hand, are at the same distance from the nearer nitrogen atom in **2** as they are in **3**, but they are much nearer the more distant nitrogen atom in **2** than in **3**.

Although we regard the p*K* data as providing convincing evidence for the cyclic hydrogen-bonded character of most of the monoprotonated form of *N,N,N′,N′*,2,2-hexamethyl-1,3-propanediamine, the deviation of the plot of the chemical shifts of the *N*-methyl protons vs. the extent of protonation (Figure 1) from linearity is relatively small. If this is generally true for the chemical shifts of the *N*-methyl protons in α,ω-bis(dimethylamino) compounds, such plots may provide little evidence as to whether the monoprotonated diamines are internally hydrogen bonded or not. In view of the evidence that the plots for other types of protons are more sensitive to internal hydrogen bonding, we have studied *N,N,N′,N′*-tetramethylethylenediamine and *N,N,N′,N′*-tetramethyl-1,3-propanediamine again, observing the chemical shifts of the *N*-methylene as well as the methyl protons. (The peak for the middle methylene group of the propanediamine derivative was too highly split to give reliable chemical shifts.) The data, which fit eq 4 well, gave the δ_d and δ_m values listed in Table III. The straightness of the plots of δ_{obsd} for the *N*-methyl hydrogen atoms vs. the extent of protonation of the diamine may be seen in the fact that the ratio of δ_d to δ_m is within the experimental uncertainty of 2.00 for both compounds. The ratio is also 2.00 for the *N*-methylene hydrogen atoms of *N,N,N′,N′*-tetramethyl-1,3-propanediamine, a fact that seems highly significant since it is only 1.64 for the *N*-methylene protons of *N,N,N′,N′*,2,2-hexamethyl-1,3-propanediamine, whose monoprotonated form is believed to be largely cyclic. We take this as strong evidence for the largely acyclic character of monoprotonated *N,N,N′,N′*-tetramethyl-1,3-propanediamine. The ratio is 2.11 for the methylene hydrogen atoms of *N,N,N′,N′*-tetramethylethylenediamine. The fact that this is larger than 2.00 rather than smaller than 2.00, as was observed for the methylene hydrogen atoms of a compound for which there is good evidence for the formation of a cyclic monoprotonated form, makes us suspicious of the hy-

Table III
Values of Parameters from Eq 4 for Diamines[a]

Diamine[b]	δ_d,[c] ppm	δ_m,[c] ppm	δ_0,[d] ppm
$Me_2NCH_2CH_2NMe_2$	0.80	0.39	1.16
$Me_2NCH_2CH_2NMe_2$	1.18	0.56	0.90
$Me_2NCH_2CH_2CH_2NMe_2$	0.76	0.38	1.18
$Me_2NCH_2CH_2CH_2NMe_2$[e]	0.94	0.47	1.04
$Me_2NCH_2CHMeCH_2NH_2$	0.78	0.27	1.20
$Me_2NCH_2CMe_2CH_2NH_2$	0.78	0.33	1.09
$Me_2NCH_2CMe_2CH_2NH_2$	0.37	0.16	2.42
$Me_2NCH_2CMe_2CH_2NMe_2$	0.79	0.42	1.14
$Me_2NCH_2CMe_2CH_2NMe_2$	1.06	0.65	1.13
$Me_2NCH_2CMe_2CH_2NMe_2$	0.41	0.16	2.44
cis-2-Me_2NCH_2-c-$C_6H_{10}NH_2$	0.77	0.38	1.16
trans-2-Me_2NCH_2-c-$C_6H_{10}NH_2$	0.76	0.29	1.19
3-*exo*-Me_2NCH_2-2-*endo*-norbornanamine	0.79	0.40	1.20
3-*endo*-Me_2NCH_2-2-*endo*-norbornanamine	0.76	0.47	1.16
o-$MeNCH_2C_6H_4CH_2NH_2$	0.68	0.18	1.12
o-$C_6H_4(CH_2NMe_2)_2$	0.67	0.32	1.14

[a] At about 37° in H_2O using a 60-MHz instrument unless otherwise noted. [b] The δ values refer to the boldfaced hydrogen atoms or methyl groups. [c] Chemical shift in the diprotonated (δ_d) or the average monoprotonated (δ_m) amine downfield from that in the unprotonated diamine. [d] Chemical shift in the unprotonated diamine upfield from internal methanol. [e] At about 31° in D_2O using a 100-MHz instrument.

pothesis that this diamine also gives a cyclic monoprotonated form. Although we cannot rule out the possibility of cyclization, we can point out that the two nitrogen atoms in an ethylenediamine derivative cannot assume positions nearly as favorable for internal hydrogen bonding as those in a 1,3-propanediamine derivative can. It therefore seems possible that this rather small deviation of the ratio from 2.00 is simply a measure of the imperfection, perhaps arising from changes in the relative populations of various types of conformers, in the ^1H NMR method for measuring micro pK values and diagnosing cyclization of monoprotonated derivatives.

The ratio of δ_d to δ_m (2.09) for the *N*-methyl hydrogen atoms of *o*-bis(dimethylaminomethyl)benzene, a compound for which there is convincing pK evidence for the formation of a cyclic monoprotonated form, is also near 2.00. The interpretation of this fact, however, is even more complicated than is interpretation of the data on aliphatic diamines, because in this case one must consider the effect of cyclization on the positions of the methyl groups relative to the aromatic ring current. We have not carried through any detailed evaluation of the ring-current effect.

Estimation of Micro pK Values. We have used both the pK data and the ^1H NMR data to estimate the relative amounts of the monoprotonated primary–tertiary diamines that exist in the primary-protonated (TPH^+), tertiary-protonated (HTP^+), and cyclic hydrogen-bonded (THP^+) forms. In doing so we estimated the pK values associated with these individual forms, that is, the micro pK values. We expressed observed pK values in terms of additive contributions of various structural features. We first dealt with the pK_a values in Table II for the conjugate acids of monoamines of the type RNH_2 and $RNMe_2$ where R is a saturated hydrocarbon group larger than methyl and the values of the sum $pK_1 + pK_2$ for those primary–tertiary diamines in Table I in which there are three carbon atoms between the amino groups. This sum is simply the negative logarithm of the equilibrium constants for the dissociation of the diprotonated diamine to the unprotonated diamine and two hydrogen ions. It has nothing to do with any monoprotonated form of the diamine and therefore its value is not influenced by the presence or absence of hydrogen bonding in the monoprotonated diamine. A least-squares treatment gave a contribution of 10.27 for an amine of the type $RCH_2CH_2NH_2$ or a cyclohexylamine or cyclopentylamine and a contribution of 10.22 for a 2-*endo*-norbornanamine. There is a contribution of −0.46 for such compounds if there is double branching at a β carbon atom or if there is a single branch that is eclipsed, or almost eclipsed, with the amino group [as in 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine or *cis*-2-(dimethylaminomethyl)cyclopentylamine]. In the absence of such branching there is a contribution of −0.20 for a single β branch unless it is held away from the amino group with a dihedral angle of at least 120° [as it is assumed to be in 3-*exo*-dimethylaminomethyl-2-*endo*-norbornanamine but not in the more flexible *trans*-2-(dimethylaminomethyl)cyclopentylamine]. There is a contribution of 9.81 for an amine of the type $RCH_2CH_2NMe_2$ to which −0.07 is added for a single β branch and −0.31 for a double β branch. (Since the α-carbon–β-carbon bond is never in a ring, no complications arise from conformational rigidity.) In addition to these contributions, which apply to both the monoamines and diamines, there is a contribution of −2.52 to the sum $pK_1 + pK_2$ arising from destabilizing interactions between the two protonated amino groups in the diprotonated diamines. To this is added another −0.49 if the charges are held near each other by eclipsing of the $C–NH_3^+$ bond with the $C–CH_2NMe_2$ bond or −0.24 if the dihedral angle between these two bonds is held at about 60° [as it is assumed to be in the case of the 2-(dimethylaminomethyl)cyclohexylamines; transformation of the trans isomer to the diaxial conformer would involve much more destabilization]. From these ten parameters the 11 relevant pK_a values from Table II and the nine $pK_1 + pK_2$ sums from Table I may be calculated with an average deviation of 0.06 and a maximum deviation of 0.19. Every parameter had to be used to calculate more than one pK value or sum.

The first seven of the parameters given in the preceding paragraph should be of use in estimating the basicities of the individual amino groups of the diamines. In addition two more parameters were used: one being the effect of an amino substituent on the pK_a of a dimethylammonio group three carbons away and the other being the effect of a dimethylamino substituent on the pK_a of an ammonio group three carbons away. Before evaluating these parameters let us note that K_1, the observed acidity constant for a monoprotonated diamine, may be expressed as shown in eq 5,

$$\frac{1}{K_1} = \frac{1}{K_{TPH}} + \frac{1}{K_{HTP}} + \frac{1}{K_{THP}} \quad (5)$$

where K_{TPH}, K_{HTP}, and K_{THP} are the acidity constants of the primary-protonated, tertiary-protonated, and cyclic hydrogen-bonded forms of the monoprotonated diamine (e.g., eq 6). The parameters in the preceding paragraph

$$K_{HTP} = \frac{[H^+][TP]}{[HTP^+]} \quad (6)$$

plus the two new parameters we are seeking will give estimates of K_{TPH} and K_{HTP}. These give us an estimated upper limit for K_1, i.e., a lower limit for pK_1. If a significant amount of the monoprotonated diamine exists in the cyclic hydrogen-bonded form the actual value of pK_1 should be larger than this estimate. In view of the evidence that *N,N,N′,N′*-tetramethyl-1,3-propanediamine does not give any significant amount of cyclic species upon monc-

Table IV
Estimated Micro pK Values for Primary–Tertiary Diamines[a]

Diamine	f_t[b]	f_c[c]	pK_{TPH}	pK_{HTP}	pK_{THP}
$Me_2NCH_2CH_2CH_2NH_2$	0.30	0	9.75	9.39	*d*
$Me_2NCH_2CHMeCH_2NH_2$	0.28	0.24	9.55	9.32	9.25
$Me_2NCH_2CMe_2CH_2NH_2$	0.11	0.71	9.29	9.08	9.88
trans-2-Me_2NCH_2-c-$C_5H_8NH_2$	0.33	~0.11	9.55	9.32	~8.83
cis-2-Me_2NCH_2-c-$C_6H_{10}NH_2$	0.20	0.46	9.55	9.32	9.68
trans-2-Me_2NCH_2-c-$C_6H_{10}NH_2$	0.11	0.71	9.55	9.32	10.14
3-*exo*-Me_2NCH_2-2-*endo*-norbornanamine	~0.25	~0.15	~9.70	~9.32	~9.09
3-*endo*-Me_2NCH_2-2-*endo*-norbornanamine	~0.35	~0.36	~9.24	~9.32	~9.34
o-$Me_2NCH_2C_6H_4CH_2NH_2$	0.022	0.934	8.71	8.41	10.04

[a] In water at 35°. [b] Fraction of monoprotonated diamine protonated at the tertiary amino group. [c] Fraction of monoprotonated diamine with a cyclic hydrogen-bonded structure. [d] No significant amount of cyclic hydrogen-bonded species formed.

protonation we tentatively assumed that the same was true for *N,N*-dimethyl-1,3-propanediamine. We further assumed that ^{1}H NMR measurements could be used as described previously to calculate the relative amounts of TPH^+ and HTP^+ present (using eq 2 with a δ_p value of 0.015 ppm).[2] That is, we accepted the previously reported pK_{TPH} and pK_{HTP} values of 9.75 and 9.39, respectively. Since the values we obtain from the parameters in the preceding paragraph are 10.27 and 9.81, this gives values of −0.52 and −0.42 for the effects of 3-dimethylamino and 3-amino substituents on the pK_a values of protonated primary amines and *N,N*-dimethylamines, respectively. These contributions were then combined with those from the preceding paragraph to calculate pK_{TPH} and pK_{HTP} values (which are listed in Table IV for all the compounds upon which ^{1}H NMR measurements were made) and then lower limits for pK_1 values for each of the primary–tertiary diamines with three carbon atoms between the amino groups that are listed in Table I. This lower limit was larger than the experimental pK_1 value only in the case of *cis*-2-(dimethylamino)cyclopentylamine, where it was larger by 0.17. However, since this is the amine for which the experimental pK values are probably least reliable and for which one of the poorer correlations of pK_1 + pK_2 values had been obtained, we regarded the overall agreement as satisfactory. The other seven diamines were all more basic than indicated by the estimated lower limits for pK_1, presumably because of the formation of various amounts of the cyclic hydrogen-bonded form of the monoprotonated diamine. The estimated values of K_{TPH} and K_{HTP} were used in eq 5 with the experimental values of K_1 to obtain the values of pK_{THP} listed in Table IV. From the pK values, f_t and f_c (the fraction of the monoprotonated diamine that exists in the cyclic hydrogen-bonded form), which are equal to K_1/K_{HTP} and K_1/K_{THP}, respectively, were calculated.

The values of f_c and pK_{THP} for *trans*-2-(dimethylaminomethyl)cyclopentylamine and 3-*exo*-dimethylaminomethyl-2-*endo*-norbornanamine are probably rather unreliable because they were obtained from estimated lower limits for pK_1 that differed from the experimental pK_1 values by only 0.05 and 0.07, respectively. In addition, the estimated pK_1 values for the norbornanamines were based in part on parameters that also appeared in the calculation of pK_1 for relatively few other compounds. This decreases the estimated reliability of the results obtained for these compounds. In spite of such reasons for doubt, the relative values of f_c listed in Table IV are on the whole rather plausible. For the three acyclic diamines the increase in f_c that accompanies methylation of the β carbon atom may be explained in the same way as the "*gem*-dimethyl effect", which has been found to encourage many cyclization reactions.[15] For the five compounds in which the H_2NC–CCH_2NMe_2 bond is part of a ring, the two smallest f_c values are for the two diamines in which the dihedral angle is about 120° such that the two amino groups are so far apart that hydrogen bonding between them is difficult. (We would have expected hydrogen bonding to be easier with the more flexible cyclopentane derivative but are not sure that either f_c value is really significantly different from zero.) The next smallest f_c value is for the endo-endo norbornyl compound, in which the dihedral angle must be near 0°. Use of molecular models shows that with such a dihedral angle it is impossible to achieve simultaneously an optimum nitrogen–nitrogen distance (which we take to be in the range 2.5–3.0 Å) and optimum C–N–N angles (which we take to be around 109°) for a cyclic hydrogen-bonded species. The two largest f_c values for cyclic diamines are for the cyclohexyl compounds, where the dihedral angle is about 60°, which is fairly nearly optimum for formation of a cyclic hydrogen-bonded species. The fact that f_c is larger for the trans than for the cis isomer may result from axial–axial interactions in the cyclic hydrogen-bonded form of monoprotonated *cis*-2-(dimethylaminomethyl)cyclohexylamine. (These cyclized monoprotonated diamines bear a certain resemblance to the decalins, where the trans is significantly more stable than the cis isomer.)

The pK_{TPH} and pK_{HTP} values for *o*-(dimethylaminomethyl)benzylamine were estimated as described previously. These and the experimental value of pK_1 give an f_c value of 0.934, which shows a greater extent of cyclization of the monoprotonated diamine than for any of the other primary-tertiary diamines studied. Analogous calculations on *o*-bis(dimethylaminomethyl)benzene, however, give an even larger f_c value, 0.986. The f_c value obtained for *N,N,N′,N′*,2,2-hexamethyl-1,3-propanediamine is 0.77.

In aqueous solution, where the amine and ammonio groups have the alternative of hydrogen bonding to water, the tendency for cyclization is much smaller than it is in the gas phase, where 1,3-propanediamine has been found to have a proton affinity[16] about 19 kcal/mol larger than that for a similar monoamino compound such as *n*-butylamine.[17] Even in solution a much larger tendency toward cyclization has been observed with the monoprotonated form of 1,8-bis(dimethylamino)naphthalene, whose pK_1

value of 12.34 shows that it is more than 800,000 times as basic as any of the less N-methylated derivatives of 1,8-diaminonaphthalene.[18]

Experimental Section

Chemicals. The synthesis and properties of the *N,N*,2-trimethyl-1,3-propanediamine, *N,N*,2,2-tetramethyl-1,3-propanediamine, *N,N,N',N'*,2,2-hexamethyl-1,3-propanediamine, *cis*- and *trans*-2-(dimethylaminomethyl)cyclohexylamine, the 3-dimethylaminomethyl-2-norbornanamines, *o*-(dimethylaminomethyl)benzylamine, and *o*-bis(dimethylaminomethyl)benzene used have been described recently.[19] The other compounds were commercial products.

p*K* Determinations. The diamines and *N,N*-dimethylcyclohexylamine were titrated with standard 0.10 *M* hydrochloric acid in aqueous solution at 35.0 ± 0.5° using a Radiometer Model 26 pH meter and type G202B and K401 glass and reference electrodes. The pH values were read to 0.001 from the meter after the stirrer had been turned off. Values obtained when 0.2–0.8 and 1.2–1.8 equiv of acid had been added were used in a computer program[20] that obtained the p*K* values that minimized the sums of the squares of the deviations of the calculated from the observed pH values, of which there were usually about 25. In no case was the standard deviation as large as 0.040. The 20-, 25-, or 30-ml samples of 0.020 ± 0.005 *M* amine solutions titrated gave ionic strengths in the range 0.003–0.016 during the first half of the titration, which largely determined the value of pK_1, and 0.013–0.045 during the second half, which largely determined pK_2. The pH was taken to be $-\log a_{H^+}$ and ionic activity coefficients were calculated from the Davies equation.[6]

The p*K* for 2-*endo*-norbornanamine was determined analogously except that 0.040 *M* amine hydrochloride was titrated with 0.10 *M* sodium hydroxide.

^{1}H Nuclear Magnetic Resonance Measurements. All ^{1}H NMR measurements were made at about 37° in H_2O using a Varian A-60A spectrometer except in the case of the measurements on the methylene protons of *N,N,N',N'*-tetramethyl-1,3-propanediamine, which were made in D_2O at about 31° using a JEOL JNM-MH-100 instrument to minimize complications arising from spin–spin splitting and overlap with other peaks. All the amines were studied at a total concentration of 0.1 *M* except in the case of *o*-bis(dimethylaminomethyl)benzene, 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine, and the methylene proton study of *N,N,N',N'*-tetramethyl-1,3-propanediamine, where concentrations of 0.04–0.05 *M* were used. In the case of the 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine 20% methanol was added to increase the solubility of the amine. In all other cases 0.1–0.5 *M* methanol was used as an internal reference. The concentrations of the three forms of the diamines present were calculated from the concentrations of amine and hydrochloric or perchloric acid used to make up the solutions and the p*K* values at 35°. This resulted in values of f_m and f_d that were combined with the δ'_{obsd} values to calculate the values of δ_0, δ_m, and δ_d shown in Table III by the method of least squares.

Calculation of Micro p*K* Values for Primary–Tertiary Diamines. These calculations may be illustrated by the case of *trans*-2-(dimethylaminomethyl)cyclohexylamine. For pK_{TPH} we start with the p*K* of 10.27 for a cyclohexylamine (or $RCH_2CH_2NH_2$). A contribution of −0.20 is added because the primary amino group has a single β branch (not held away with a dihedral angle of 120° or more). Finally, −0.52 is added for the effect of the dimethylamino substituent three carbons away from the primary amino group. For pK_{HTP} the uncorrected value is 9.81, −0.07 is added because of the single branch β to the dimethylamino group, and −0.42 is added because of the primary amino group three carbon atoms away. The resulting pK_{TPH} and pK_{HTP} values of 9.55 and 9.32, respectively, and the experimentally determined value 10.29 for pK_1 (from Table I) give *K* values that leave K_{THP} as the only unknown in eq 5. The value 10.14 thus obtained for pK_{THP} is then used to calculate f_c, which may be seen to be equal to K_1/K_{THP}. Similarly, f_t is equal to K_1/K_{HTP} and f_p to K_1/K_{TPH}.

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(1) This investigation was supported in part by Public Health Service Grant GM 18593 from the National Institute of General Medical Sciences.
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9,9′-Dianthrylmethane Derivatives. Conjugate Rearrangements and Photocyclizations

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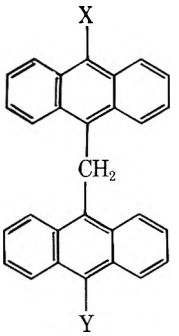
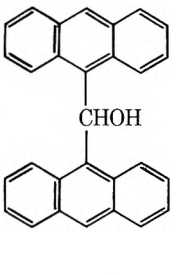
Attempted preparation of di-9-anthrylmethane and its brominated derivatives led to the discovery of incorrect structural assignments in previous work. The successful preparation of 9,9′-dianthrylmethane derivatives is reported, and the photocyclization of some of them is described.

It was earlier reported from this laboratory that 9,9′-dianthrylmethane (**1a**) had been prepared by catalytic hydrogenolysis of 9,9′-dianthrylcarbinol (**2**) using 5% palladium on carbon in ethanol.[1] The preparation has since been found unreproducible (yields of zero to 9%) and alternatives have therefore been sought. A satisfactory two-step procedure has been found, the first step being reduction of **2** with a 2:1 mixture of aluminum chloride and lithium aluminum hydride in ether to give **3a**, an isomer of **1a**, in 94% yield, and the second step being the isomerization of **3a** to



1a, X = Y = Br
b, X = H; Y = Br
c, X = Y = Br
d, X = Y = Cl



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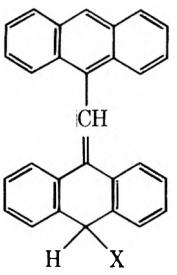
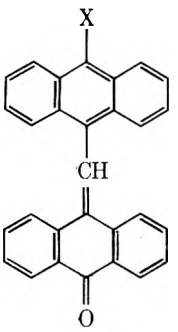


3a, X = H
b, X = OC_2H_5
c, X = Cl



4, X = Br
5, X = H

1a in 94% yield with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol or potassium hydroxide in refluxing isoamyl alcohol.[2]

Unfortunately, neither **1a** nor **3a** as prepared by the present method is the same as the substance previously assigned structure **1a**. The respective melting points are 315–317°, 189–191° dec, and 382–384° dec. The infrared spectra are all distinctly different. Both **1a** and **3a** (present report) show parent mass peaks at *m/e* 368. **1a** shows an anthracene chromophore in the uv with nearly twice the intensity of that in **3a**: for **1a**, λ_{max} 339 nm (ϵ 4400), 357 (8500), 376 (15,000), and 396 (17,000); for **3b**, λ_{max} 338 nm (sh) (ϵ 2700), 357 (5500), 375 (8900), and 394 (9500). The ^{1}H NMR spectrum of **1a** shows two two-proton singlets, at δ 5.60 (for $-CH_2-$) and 8.04 (for the 10 and 10′ positions). The ^{1}H NMR spectrum of **3a** shows a two-proton singlet at δ 4.19 (for $-CH_2-$) and two one-proton singlets at δ 7.68 and 8.39 (assigned respectively to the central vinyl proton and the 10-anthryl proton). These data appear consistent only with the structures assigned.[3]

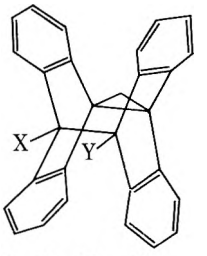
Two other examples of the facile formation of the 9-(9-anthrylmethylidene)-9,10-dihydroanthracene system were discovered during attempts to prepare **1a**. In the first, **2** reacted with zinc chloride in ethanol to give ether **3b** under conditions where triphenylcarbinol gives triphenylmethane.[4] In the second, **2** reacted with thionyl chloride and pyridine in benzene to give chloride **3c**. The structures of **3b** and **3c** are assigned primarily from the ^{1}H NMR spectra, which show singlets for the vinyl proton at about δ 7.7, as in **3a**, and which show appropriately downshifted methine protons α to ethoxy and chlorine at δ 5.62 and 6.13, respectively, to be compared with the methylene signal at δ 4.19 in **3a**. For comparison, the corresponding signals in fluorene, 9-methoxyfluorene, and 9-chlorofluorene are at δ 3.90, 5.59, and 5.80, respectively.[5]

Our particular reason for repeating the earlier preparation of **1a** was to reinvestigate the bromination of that hydrocarbon.[1] It had been reported that monobromo compound **1b** was easily formed, while dibromination, to form **1c**, was much slower. Since the wrong compound was brominated in that study, the result is not necessarily a surprising one. In fact, it has now been shown that **1a** is readily dibrominated with bromine in carbon tetrachloride to form **1c** in 22% yield. No **1b** was found, but a 22% yield of bromo ketone **4** was isolated, presumably arising from an air oxidation. Compound **4** was independently prepared by reaction of ketone **5** with cupric bromide in refluxing chlorobenzene, and **5** was in turn prepared by the permanganate oxidation of **3a** (39% yield, along with 53% of anthraquinone). Comparison of infrared and NMR spectra revealed that the substance assigned structure **1a** in the earlier report was probably an impure form of **4**.

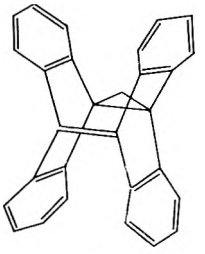
10-Bromo-9,9′-dianthrylmethane (**1b**) was not obtained by bromination of **1a**, but was independently prepared by coupling of 9-bromo-10-lithioanthracene with 9-chloromethylanthracene. Bromination of **1b** in carbon tetrachloride yielded 43% dibromide **1c** and 3% ketone **4**.

Also prepared in the present study was the dichlorodianthrylmethane **1d**, from reaction of 9-chloroanthracene with paraformaldehyde and hydrogen chloride in acetic acid (42% yield). A similar preparation of **1c** gave only a 10% yield.

Having the authentic dianthrylmethanes **1a–d**, it was next desirable to reinvestigate their photocyclization reactions, which had previously[1] been examined on the wrong compounds. It was found that **1a** and **1b** in benzene solution readily underwent photocyclization to the typical anthracene photodimer structures, **6a** and **6b**. These were col-



6a, X = Y = H
b, X = H; Y = Br



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orless solids which reverted to **1a** and **1b** upon melting or refluxing in benzene. The uv spectra show only the typical o-xylene chromophores.[6] Substances **1c** and **1d** did not yield photoproducts, which is in accord with the fact that no dianthracene with vicinal bridgehead halogens has been reported.

Compound **6b** is of special interest as a possible precursor of the bridgehead alkene **7**. In fact, dehydrohalogenation with *tert*-butoxide, trapping of **7** with azide ion, and regeneration of **7** through the elegant procedure of Greene[7] did yield a colorless solid having the expected molecular weight (mass spectrum). It will be the subject of a future report.

Experimental Section

All melting points were determined on a Buchi melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 521 grating Infracord or on a Beckman IR12 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on Varian T-60, A-60A, HA-100, or HR-220 instruments. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane used as internal standard and assigned the value δ 0 ppm. Ultraviolet (uv) spectra were recorded on a Cary 14 or Beckman DB spectrophotometer. Mass spectra were run on a Varian MAT CH-5 spectrometer. Microanalyses were performed by Mr. J. Nemeth and his associates.

All chemicals and solvents were reagent grade unless otherwise noted and were used without further purification except as noted.

10-Ethoxy-9-(9-anthrylmethylidene)-9,10-dihydroanthra-

cene (3b). A mixture of 0.78 g (0.00203 mol) of 9,9′-dianthrylcarbinol (2)[1] and 2.77 g (0.0203 mol) of zinc chloride in 15 ml (0.256 mol) of absolute ethanol was magnetically stirred and heated at reflux for 1.5 hr. The mixture was cooled and 12 ml of aqueous hydrochloric acid (1:5) was added to remove any solid zinc chloride. The organic material was extracted with diethyl ether, the extract was washed with water, dried ($MgSO_4$), and filtered, and the solvent was removed to give 0.762 g of a yellow oil. Separation on a silica gel column with 1:1 benzene–hexane gave 0.6 g (72%) of a yellow solid, mp 149–151°. Recrystallization from benzene–hexane gave 0.45 g (54%) of yellow crystals of **3b:** mp 150.5–151.5°; ir (KBr) 3050 (m), 2975 (m), 2890 (m), 1620 (w), 1480 (m), 1455 (m), 1440 (m), 1120 (m), 1070 (s), 780 (m), 760 (s), 730 cm^{-1} (s); NMR ($CDCl_3$) δ 1.34 (t, 3, J = 6 Hz, $-CH_2CH_3$), 3.61 (q, 2, J = 6 Hz, $-CH_2CH_3$), 5.62 (s, 1, 10 proton of 9,10-dihydroanthracene ring), 6.32–6.59 (m, 2, aromatic protons), 6.75–7.62 (m, 10, aromatic protons), 7.72 (s, 1, vinyl proton), 7.80–8.14 (m, 4, aromatic protons), 8.29 (s, 1, 10 proton of anthracene nucleus).

Anal. Calcd for $C_{31}H_{24}O$: C, 90.26; H, 5.86. Found: C, 90.30; H, 5.84.

10-Chloro-9-(9-anthrylmethylidene)-9,10-dihydroanthracene (3c). A solution of 2.0 g (0.0052 mol) of 9,9′-dianthrylcarbinol (2) in 100 ml of warm benzene was added dropwise over 30 min to a stirred solution of 1.66 g (0.014 mol) of thionyl chloride and 3 drops of pyridine in 25 ml of benzene. The mixture was stirred at room temperature for 2 hr and then reluxed for 40 min. The solvent and thionyl chloride were removed in vacuo from the cooled mixture to give a yellow oil. Crystallization with hexane and recrystallization from benzene–hexane gave 1.06 g (51%) of a yellow solid: mp 196–198° dec (lit.[8] mp 190–192°); ir (KBr) 3050 (m), 1620 (m), 1470 (m), 1450 (m), 1440 (m), 885 (m), 840 (m), 785 (m), 770 (s), 635 cm^{-1} (m); NMR ($CDCl_3$) δ 6.13 (s, 1, 10 proton of the 9,10-dihydroanthracene nucleus), 6.30–6.58 (m, 2, aromatic protons), 6.68–7.73 (m, 10, aromatic protons), 7.78 (s, 1, vinyl proton), 7.87–8.25 (m, 4, aromatic protons), 8.28 (s, 1, 10 proton of anthracene nucleus).

9-(9-Anthrylmethylidene)-9,10-dihydroanthracene (3a). To a magnetically stirred suspension of 0.2 g (0.0052 mol) of lithium aluminum hydride in 10 ml of dry ether was added a solution of 1.41 g (0.0106 mol) of aluminum chloride in 15 ml of dry ether. Dry ether (15 ml) was added to the flask and a Soxhlet thimble containing 1.0 g (0.0026 mol) of 9,9′-dianthrylcarbinol (2) was placed in the extraction apparatus. The stirred mixture was heated to reflux (50–54°) for 10 hr, or until the carbinol had been introduced into the reaction flask. Ethyl acetate was added dropwise to destroy excess reagent and the mixture was poured into 30 ml of 20% sulfuric acid. The mixture was filtered, the layers were separated, the water layer was washed once with ether, the ether layer was washed twice with water, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo to give 0.9 g (94%) of a yellow solid, mp 183–188° dec. Two recrystallizations from ethanol–benzene gave 0.64 g (80%) of a yellow solid: mp 189–191° dec; ir (KBr) 3050 (m), 3020 (m), 2930 (w), 2850 (w), 2180 (w), 1620 (w), 1475 (m), 1455 (ms), 1440 (w), 1345 (m), 880 (ms), 845 (m), 780 (s), 730 (s), 710 cm^{-1} (m); 100-MHz NMR (CCl_4) δ 4.19 (s, 2, $-CH_2-$), 6.34–6.62 (m, 2, aromatic protons), 6.92 [doublet (J = 2 Hz) of triplets (J = 7 Hz), 1, aromatic proton)], 7.18–7.58 (m, 8, aromatic protons), 7.68 (s, 1, vinyl proton), 7.94–8.28 (m, 5, aromatic protons), 8.39 (s, 1, meso proton on anthracene nucleus); uv ($CHCl_3$) 259 nm (ϵ 84,000), 338 sh (2500), 354 (4900), 372 (7500), 391 (7900); mass spectrum (70 eV) m/e (rel intensity) 369 (29), 368 (100), 367 (26), 365 (13), 363 (12), 353 (12), 339 (11), 289 (13), 191 (11), 190 (10), 189 (17), 184 (13), 177 (5), 176 (11).

Anal. Calcd for $C_{29}H_{20}$: C, 94.53; H, 5.47. Found: C, 94.63; H, 5.54.

In a few runs an insoluble yellow solid which did not melt below 360° was isolated. Combustion of the material left a white solid which gave a positive test for the aluminum ion when treated with aluminon reagent.[9]

9,9′-Dianthrylmethane (1a) from Reduction of 3c. A solution of 0.91 g (0.0023 mol) of **3c** in 30 ml of dry tetrahydrofuran was added dropwise over 15 min to a magnetically stirred solution of 0.1 g (0.0029 mol) of lithium aluminum hydride in 10 ml of dry tetrahydrofuran at room temperature. The mixture was stirred and heated at reflux for 45 min, then cooled to room temperature, and wet tetrahydrofuran and ethyl acetate were added until foaming stopped. The solution was filtered and the gray precipitate was washed with tetrahydrofuran and toluene. To the filtrate was added 250 ml of toluene, the solution was dried ($MgSO_4$) and filtered and the solvents were removed in vacuo to give 0.814 g of a yellow solid. The yellow solid was partially dissolved in diethyl ether to give a greenish-yellow solution plus a bright yellow precipitate. The solid was washed with ether and benzene until the filtrate showed no color. The filtrate was evaporated to give 0.617 g (73%) of a yellow solid, mp 181–186° dec. The solid was recrystallized from ethanol–benzene to give 0.43 g (51%) of a yellow solid, mp 188–190° dec, shown by ir (KBr) and melting point comparison with an authentic sample to be the hydrocarbon **3a.**

The bright yellow precipitate isolated in the filtration (0.16 g, 19%) melted at 313–316°. The solid was recrystallized several times from benzene or tetrahydrofuran to give bright yellow needles of 9,9′-dianthrylmethane (**1a**): mp 315–317°; ir (KBr) 3050 (m), 1620 (m), 1520 (m), 1445 (w), 1340 (m), 955 (m), 880 (s), 870 (m), 735 (s), 725 (s), 530 (m), 495 cm^{-1} (m); 220-MHz NMR (CCl_4) (200 250-sec scans, computer averaged, 81°) δ 5.60 (s, 2, $-CH_2-$), 6.95 (m, 8, aromatic protons), 7.65 (d, 4, aromatic protons), 7.94 (d, 4, aromatic protons), 8.04 (s, 2, 10-protons); uv ($CHCl_3$) 254 nm sh (ϵ 84,000), 260 (92,000), 322 sh (1900), 336 (4400), 353 (8500), 372 (15,000), 394 (17,000); mass spectrum (70 eV) m/e (rel intensity) 369 (31), 368 (100), 367 (23), 353 (18), 352 (10), 291 (8), 290 (7), 289 (10), 191 (31), 190 (22), 189 (39), 184 (12), 177 (9), 176 (14).

Anal. Calcd for $C_{29}H_{20}$: C, 94.53; H, 5.47. Found: C, 94.30; H, 5.55.

9,9′-Dianthrylmethane (1a) from Isomerization of 3a. A mixture of 4.26 g (0.109 g-atom) of freshly cut potassium in 60 ml of dry *tert*-butyl alcohol (freshly distilled from sodium) was refluxed under nitrogen for about 4 hr until all the potassium dissolved. Addition of 0.568 g (0.00154 mol) of hydrocarbon **3a** to the refluxing solution resulted in almost immediate formation of an insoluble, highly fluorescent, yellow solid. The mixture was refluxed for 48 hr.

The mixture was cooled to room temperature and 10 ml of wet *tert*-butyl alcohol was added to the mixture, followed by 10 ml of water. The mixture was filtered through a sintered glass funnel and the precipitate was washed with water and ether several times. The precipitate was dried in vacuo to give 0.159 g (91.5%) of 9,9′-dianthrylmethane (**1a**), mp 312–316°. Recrystallization from tetrahydrofuran gave yellow needles, mp 315–317°. The ir (KBr) spectrum matched that of **1a** formed in the preceding method.

The isomerization was also successfully performed in a 10% solution of KOH in isoamyl alcohol at reflux for 1.5 hr to give a 93% yield, mp 312–314°, or 73%, mp 313–315° after recrystallization from toluene.

10-(9-Anthrylmethylidene)anthrone (5). A mixture of 0.7 g (0.0019 mol) of hydrocarbon **3a** and 8.0 g (0.0564 mol) of sodium permanganate in 150 ml of dioxane and 100 ml of water was mechanically stirred at 48–51° for 4 hr. The mixture was cooled to 25° and filtered. The solid manganese dioxide was washed several times with benzene and ether and then extracted with benzene in a Soxhlet extractor for 4 hr. The organic layers were combined and after separation the water layer was extracted with benzene, the combined organic layers were dried ($MgSO_4$) and filtered, and the solvents were removed to give a mixture of orange and yellow solids.

Ether extraction of the mixture afforded an orange solution and left a light yellow solid. The yellow solid was shown to be 0.424 g (53.2% based on 2 mol/1 mol of **3a**) of anthraquinone, mp 285–287° (lit.[10] mp 286°). The ir (KBr) spectrum matched that recorded for anthraquinone.[11]

The ether extract yielded 0.29 g (39.3%) of the ketone **5:** mp 253–255° dec; 100-MHz NMR ($CDCl_3$) δ 6.60–6.76 (m, 2), 7.05–8.41 (several complex multiplets, 15), 8.43 (s, 1, meso proton of anthracene nucleus); ir (KBr) 3050 (m), 1660 (s), 1600 (s), 1475 (m) 1460 (w), 1440 (w), 1315 (s), 1270 (m), 935 (m), 775 (s), 735 (s), 675 cm^{-1} (m); uv ($CHCl_3$) 252 nm sh (ϵ 52,000), 259 (65,000), 356 (4500), 373 (4800), 391 (5000); mass spectrum (70 eV) m/e (rel intensity) 383 (32), 382 (100), 381 (20), 354 (9), 353 (27), 352 (19), 351 (14), 350 (19), 191 (11), 190 (6), 177 (5), 176 (17), 175 (32), 168 (12), 32 (14), 31 (17), 28 (23).

Anal. Calcd for $C_{29}H_{18}O$; C, 91.07; H, 4.74. Found: C, 90.76; H, 4.79.

10-(10-Bromo-9-anthrylmethylidene)anthrone (4). A mixture of 0.1 g (0.00026 mol) of **5** and 0.08 g (0.00036 mol) of cupric bromide in 7 ml of chlorobenzene was magnetically stirred at reflux for 18 hr. The mixture was cooled to room temperature and filtered to give a red filtrate and gray precipitate. The solvent was removed in vacuo from the filtrate to give a dark oil.

A solution of the oil in benzene was applied to a column containing 35 g of silica gel and the mixture was eluted with benzene to give 80.7 mg of an orange-yellow solid, mp 202–206° dec. The solid

was washed with carbon tetrachloride and filtered to give 37 mg (31%) of a gold solid. Recrystallization from ethanol–water gave orange crystals: mp 220–222°; ir (KBr) 3060 (w), 1660 (s), 1600 (m), 1470 (w), 1460 (w), 1435 (w), 1310 (s), 1280 (m), 1165 (w), 920 (w), 900 (w), 770 (m), 755 (m), 730 (w), 680 cm^{-1} (w); 220-MHz NMR ($CDCl_3$) δ 6.65 (m, 1.3), 7.05–7.80 (several complex multiplets, 8.0), 7.80–8.60 (several complex multiplets, 7.7); mass spectrum (70 eV) *m/e* (rel intensity) 462 (100), 460 (98.9), 434 (2.1), 433 (4.8), 432 (2.9), 431 (3.9), 383 (10.1), 382 (34.6), 381 (39.9), 380 (13.3), 354 (7.6), 353 (7.6), 352 (34.7), 351 (26.4), 350 (39.8), 349 (4.9), 348 (10.8), 191 (19.5), 190 (11.2), 176 (18.0), 175 (36.2), 168 (12.0), 162 (9.1).

Anal. Calcd for $C_{29}H_{17}BrO$: C, 75.50; H, 3.71; Br, 17.32. Found: C, 75.52; H, 3.66; Br, 17.08.

10,10′-Dibromo-9,9′-dianthrylmethane (1c). A magnetically stirred suspension of 1.96 g (0.0053 mol) of 9,9′-dianthrylmethane (**1a**) in 60 ml of carbon tetrachloride was brought to reflux. At reflux a solution of 1.75 g (0.0109 mol) of bromine in 25 ml of carbon tetrachloride was added dropwise during 30 min, after addition of one to two crystals of iodine. The mixture was stirred at reflux for 4 days and then cooled to room temperature and filtered to give a red filtrate and a yellow precipitate. The precipitate was washed with carbon tetrachloride, benzene, and finally ether. Recrystallization from toluene gave 0.60 g (22%) of fluffy, yellow crystals of **1c**: mp 295–305° (turned brown, did not melt below 400°); ir (KBr) 3070 (w), 3030 (w), 1620 (w), 1520 (w), 1440 (w), 1325 (m), 895 (s), 740 cm^{-1} (s); 220-MHz NMR (CCl_4) (250 250-sec scans, computer averaged, 88°) δ 5.75 (s, 2, $-CH_2-$), 7.12 (m, 4, aromatic protons), 7.35 (m, 4, aromatic protons), 8.06 (d, 4, aromatic protons), 8.48 (d, 4, aromatic protons); uv ($CHCl_3$) 267 nm (ϵ 62,400), 346 (2400), 366 (4500), 388 (7600), 411 (10,000); mass spectrum (70 eV) *m/e* (rel intensity) 529 (2), 528 (5.5) ($C_{29}H_{18}{}^{81}Br_2$), 527 (4), 526 ($C_{29}H_{18}{}^{79}Br^{81}Br$) (11), 525 (2), 524 (5.6) ($C_{29}H_{18}{}^{79}Br_2$), 448 (13), 447 (36.5), 446 (14), 445 (38), 367 (15.5), 366 (38), 365 (33), 364 (12), 363 (19), 289 (4), 272 (1), 271 (5), 270 (2), 269 (7), 259 (1), 258 (3.5), 257 (1), 256 (3), 190 (11), 189 (32), 178 (8), 177 (9), 176 (10), 175 (42), 174 (28), 65 (100).

Anal. Calcd for $C_{29}H_{18}{}^{79}Br_2$: mol wt, 523.9775. Found: mol wt, 523.9772 (mass spectrum). Calcd for $C_{29}H_{18}Br_2$: C, 66.19; H, 3.44; Br, 31.37. Found: C, 66.38; H, 3.36; Br, 30.36.

The solvents were removed in vacuo from the filtrate to give a yellow oil. The oil was dissolved in toluene and the solution was applied to a column of 250 g of silica gel in 1:1 toluene–hexane. Elution with 1:1 toluene–hexane yielded 0.54 g (22%) of orange crystals of bromo ketone **4**, mp 200–215° dec. The ir (KBr) spectrum matched that of an authentic sample. A second band gave 0.17 g of a yellow solid which decomposed at 228–235° to a black oil.

10,10′-Dichloro-9,9′-dianthrylmethane (1d). A suspension of 9.0 g (0.042 mol) of 9-chloroanthracene in 45 ml of glacial acetic acid plus 0.9 g (0.03 mol) of paraformaldehyde in 18 ml of glacial acetic acid (brought into solution by bubbling with hydrogen chloride gas until clear) was magnetically stirred and heated at 75–80° for 6.5 hr. The mixture was cooled to room temperature and filtered. The precipitate was washed with acetic acid, water, benzene, and ether to give 5.28 g (57.5%) of a yellow solid, mp 322–325° dec. The solid was recrystallized from toluene to give 3.81 g (41.5%) of a bright yellow solid (**1d**): mp 335–337° dec; ir (KBr) 3030 (w), 1615 (m), 1520 (w), 1440 (m), 1430 (w), 1330 (s), 1250 (w), 1020 (w), 920 (s), 745 (s), 710 cm^{-1} (m); mass spectrum (70 eV) *m/e* (rel intensity) 440 (9), 438 (42), 436 (60), 404 (16), 403 (39), 401 (100), 400 (40), 399 (12), 367 (22), 366 (41), 365 (43), 227 (13), 225 (40), 224 (12), 214 (5), 212 (15), 200 (21), 190 (23), 189 (88), 176 (27), 175 (21).

Anal. Calcd for $C_{29}H_{18}Cl_2$: C, 79.64; H, 4.15. Found: C, 79.38; H, 4.13.

10-Bromo-9,9′-dianthrylmethane (1b). A flask equipped with a rubber septum inlet, condenser, dropping funnel, argon atmosphere system, and magnetic stirrer was charged with 14.92 g (0.044 mol) of 9,10-dibromoanthracene and flushed with argon overnight. By syringe, 60 ml of dry ether was added to the flask and then 44 ml (0.044 mol) of 1.4 *M* phenyllithium was added to the stirred suspension. The mixture was stirred at room temperature for 20 min.

A solution of 9.95 g (0.044 mol) of 9-chloromethylanthracene in 185 ml of dry benzene was then added dropwise to the stirred mixture over 3.5 hr. The resulting mixture was stirred overnight and then diethyl ether and water were added. The precipitate was filtered and washed with water and ether to give an orange filtrate plus 19.40 g of a lemon-yellow, fluorescent precipitate. Dissolution of 4.0 g of the precipitate in toluene and filtration gave 0.77 g of an insoluble white solid which was soluble in water. Removal of the solvent from the filtrate gave 3.2 g (80%) of a bright, fluorescent yellow solid, mp 282–283° dec. Recrystallization from benzene or toluene gave yellow crystals of **1b**: mp 286–289° dec; ir (KBr) 3080 (w), 3040 (w), 1620 (m), 1520 (m), 1440 (m), 1425 (w), 1330 (m), 1320 (m), 1245 (w), 1150 (w), 1025 (w), 895 (s), 870 (s), 745 (s), 720 (s), 705 cm^{-1} (m); 100-MHz NMR (benzene-d_6) δ 5.52 (s, $-CH_2-$), 7.0 (large solvent peak covering part of aromatic absorptions), 7.5–8.5 (several multiplets which integrate for five protons vs. two protons for the absorption at δ 5.52); uv ($CHCl_3$) 258 nm (ϵ 83,000), 320 sh (1700), 337 sh (3800), 354 (7200), 364 sh (9300), 372 (11,200), 382 (14,000), 392 (12,000), 404 (15,500); mass spectrum (70 eV) *m/e* (rel intensity) 449 (21), 448 (65), 447 (24), 446 (64), 369 (8), 368 (37), 367 (100), 366 (16), 365 (21), 363 (14), 290 (6), 289 (12), 191 (16), 190 (14), 189 (44), 183 (18), 177 (11), 176 (26).

Anal. Calcd for $C_{29}H_{19}Br$: C, 77.86; H, 4.28. Found: 77.81; H, 4.22.

Bromination of 10-Bromo-9,9′-dianthrylmethane (1b). A suspension of 1.0 g (0.00224 mol) of 10-bromo-9,9′-dianthrylmethane (**1b**) and one crystal of iodine in 30 ml of dry carbon tetrachloride was magnetically stirred at reflux under argon. To the stirred suspension at reflux was added a solution of 0.36 g (0.00224 mol) of bromine in 15 ml of carbon tetrachloride over 45 min. The mixture was then stirred at reflux for 2 days, cooled to room temperature, and filtered. The precipitate was washed with carbon tetrachloride, 10% sodium bisulfite, acetone, and finally ether and sucked dry to give 0.64 g (54.5%) of a yellow solid which darkened at 290–295° but did not melt below 360°. The solid was recrystallized from toluene to give 0.5 g (43%) of the dibromo compound **1c**, which darkened at 280–290° and did not melt below 360°. The ir (KBr) spectrum matched the spectrum of **1c** as described above.

The solvent was removed from the filtrate to give a mixture of colored products as evidenced by thin layer chromatography on silica gel with benzene as the mobile phase. The mixture was dissolved in benzene and applied to a column containing 100 g of silica gel in benzene. Elution with benzene gave four bands which were collected.

The third component eluted proved to be 0.031 g (3%) of the ketone **4** as shown by ir (KBr) and mass spectral comparison with the known spectra.

Photocyclization of 9,9′-Dianthrylmethane (1a). A solution of 0.407 g (0.0011 mol) of 9,9′-dianthrylmethane (**1a**) in 3250 ml of benzene (all benzene for the photolysis reactions was washed with sulfuric and water and distilled from calcium hydride) was placed in a 5-l. flask fitted with a quartz immersion well designed to accomodate a 450-W Hanovia mercury lamp. The magnetically stirred solution was boiled under nitrogen and bubbled with dry nitrogen to remove oxygen. The solution was cooled to room temperature and the stirred solution was irradiated for 17 hr. The solvent was removed in vacuo to leave a pale brown solid. Addition of hexane followed by filtration left 0.261 g (63.8%) of a beige solid which turned to a yellow solid at 180–210° and melted at 308–317°. Recrystallization of the solid from benzene–hexane gave 0.156 g (38%) of a white solid (**6a**) which turned fluorescent yellow at 180–210° and melted at 311–313° (remelt 311–313°): ir (KBr) 3060 (w), 3040 (w), 3010 (w), 2920 (w), 1600 (w), 1470 (m), 1450 (s), 1245 (w), 1130 (m), 765 (s), 745 (w), 675 (m), 640 (m), 595 (m), 500 cm^{-1} (m); 220-MHz NMR ($CDCl_3$) δ 2.78 (s, 2, $-CH_2-$), 4.62 (s, 2, bridgehead protons), 6.74–7.05 (two multiplets, 16, aromatic protons); uv ($CHCl_3$) 272 nm (ϵ 3000), 281 (2000); mass spectrum (70 eV) essentially the same as that of 9,9′-dianthrylmethane (**1a**).

Anal. Calcd for $C_{29}H_{20}$: C, 94.53; H, 5.47. Found: C, 94.62; H, 5.52.

Photocyclization of 10-Bromo-9,9′-dianthrylmethane (1b). A suspension of 2.00 g of 10-bromo-9,9′-dianthrylmethane (**1b**) in 3225 ml of benzene was stirred under reflux for 10 min under argon. Benzene (150 ml) was distilled off under argon and the solution was cooled to room temperature and sealed under argon. The solution was irradiated with a 450-W Hanovia mercury lamp (Pyrex filter) for 19 hr at 40°. Removal of the solvent in vacuo left a brown solid. Addition of 300 ml of ether and filtration gave a creamy white solid which was washed with ether and cold benzene to give 1.50 g (75%) of a creamy white solid (**6b**), which turned orange at about 150°, then fluorescent yellow around 200° and melted at 270–272° dec: ir (KBr) 3070 (m), 3040 (w), 3020 (w), 1475 (m), 1460 (s), 1285 (w), 1155 (w), 1145 (w), 890 (w), 798 (m), 773 (s), 750 (m), 685 (s), 650 (s), 620 (m), 520 cm^{-1} (m); 100-MHz NMR ($CDCl_3$) δ 2.74 (s, 2, $-CH_2-$), 5.30 (s, 1, bridgehead proton), 6.60–6.95 (m, 12, aromatic protons), 6.85–7.15 (m, 2, aromatic pro-

tons), 7.65–7.88 (m, 2 aromatic protons); mass spectrum (70 eV) *m/e* (rel intensity) 449 (3.4), 448 (10), 447 (4.5), 446 (10), 369 (31), 368 (100), 376 (50), 366 (11), 365 (12), 363 (12), 353 (29), 352 (20), 351 (15), 291 (10), 290 (9), 289 (11), 191 (29), 190 (25), 189 (48), 184 (15), 183 (11), 182 (13), 175 (27), 164 (10); uv ($CHCl_3$) 271 nm (ε 3340), 281 (2180). Recrystallization from benzene–hexane gave an analytical sample.

Anal. Calcd for $C_{29}H_{19}Br$: C, 77.86. Found: C, 77.60; H, 4.47; Br, 17.76.

Removal of solvents from the filtrate and addition of small amounts of cold ether and benzene followed by filtration and benzene and ether washings gave an additional 0.25 g (12.5%) of product, mp 259–262° dec. The total yield of **6b** was 1.75 g (87.5%).

Registry No.—**1a**, 15080-14-5; **1b**, 15156-60-2; **1c**, 15080-12-3; **1d**, 55043-36-2; **2**, 15080-13-4; **3a**, 55043-37-3; **3b**, 55043-38-4; **3c**, 55043-39-5; **4**, 55043-40-8; **5**, 55043-41-9; **6a**, 55043-42-0; **6b**, 55043-43-1; anthraquinone, 84-65-1; 9,10-dibromoanthracene, 523-27-3; 9-chloroanthracine 716-53-0; 9-chloromethylanthracene, 24463-19-2; bromine, 7726-95-6.

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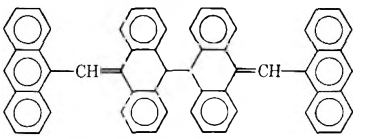
(3) The structure of the substance of mp 382–395° dec previously assigned structure **1a**[1] has been briefly reinvestigated. The observations that its infrared spectrum closely resembles that of **3a** between 1400 and 1500 cm^{-1}, that its mass spectrum shows the highest mass at *m/e* 367 instead of 368, and that its uv spectrum is essentially the same as that of **3a** with nearly the same extinction coefficients on a weight basis, suggest a dimeric structure $C_{58}H_{38}$ as follows.



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Polyphenolic Acids of *Lithospermum ruderale* Dougl. ex Lehm. (Boraginaceae). 1. Isolation and Structure Determination of Lithospermic Acid[1a]

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A structure is proposed for lithospermic acid ($C_{27}H_{22}O_{12}$, **1a**), the major polyphenolic acid of *Lithospermum ruderale* and several other plant species of the families, Boraginaceae and Labiatae. Chromatography on Sephadex of aqueous extracts of the plant yields the dipotassium salt of **1a**, together with salts of lesser constituents which include (*R*)-3-(3,4-dihydroxyphenyl)lactic acid (**2a**), 2-(3,4-dihydroxyphenyl)-3-carboxy-4-(2-carboxy-*trans*-vinyl)-7-hydroxycoumaran (**3a**), and rosmarinic acid (**4a**). Structures were deduced from spectral studies of the salts, the free acids, and also the methylated derivatives produced by the action of diazomethane on the free acids or dimethyl sulfate on the salts.

This paper describes our isolation of lithospermic acid, $C_{27}H_{22}O_{12}$, the principal polyphenolic acid constituent of roots of the plant *Lithospermum ruderale* Dougl. ex Lehm. (Boraginaceae; common names, gromwell, puccoon) and the structure elucidation of this acid and of three closely related plant constituents.

Interest in the chemical constituents of *Lithospermum ruderale* was stimulated by the report in 1941 of Train et al.[2] that certain Indians of Nevada use the plant to make a contraceptive tea. Extracts from at least six species of the genus *Lithospermum* have been found to inactivate gonadotropins.[3] The most readily cultivated of these species, *Lithospermum officinale* L., long known in European herbal medicine,[4,5] has been shown to produce a pituitary hormone blocking effect[5] both in vitro and in vivo.

The plants *Lycopus europaeus* and *Lycopus virginicus*, although members of the family Labiatae, were reported to have antihormonal activities remarkably similar to those of *Lithospermum* species.[6]

Lithospermic acid[7] has been implicated[8,9] in the hormonal inhibitory mechanisms, presumably as the chemical precursor of the active inhibitory substances produced by oxidative processes involving air- or enzyme-catalyzed reactions. It has been recognized[9–11] as a constituent of *Lycopus europaeus*, *Lycopus virginicus*, *Lithospermum ruderale*, *Lithospermum officinale*, and *Symphytum officinale* (common name, comfrey). More recently, *Anchusa officinalis* and *Echium vulgare* were added to the growing number of Boraginaceae which have antigonadotropic activity in animals and also contain lithospermic acid.[12] Reviews of contraceptive plant species have been published.[13,14]

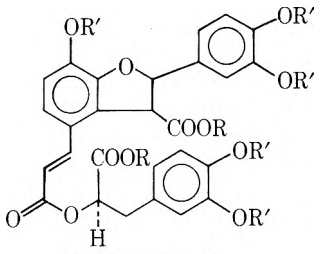
von Seemann and Grant[15] isolated fractions of *Lithospermum ruderale* as amorphous powders having antigonadotropic activity. They characterized the materials as polyphenolic acid salts, possibly flavanoids, which gave reactions characteristic of phlobatannins, and observed that the active principle(s) in the plant extract could be precipitated by acids and redissolved at pH above 5. A number of phytochemical investigations failed to identify the specific antihormonal compound(s) of *Lithospermum* species.[16]

In 1963, Johnson et al.[7] reported the isolation of a polyphenolic acid from roots of *Lithospermum ruderale* which they named lithospermic acid and assigned the structure of 2-hydroxy-2,4-bis(3,4-dihydroxyphenyl)butenoic acid, $C_{16}H_{14}O_7$. The amorphous, water-soluble acid was said to melt at 130–131° and the structure was supported by analyses for several crystalline derivatives, including a "pen-

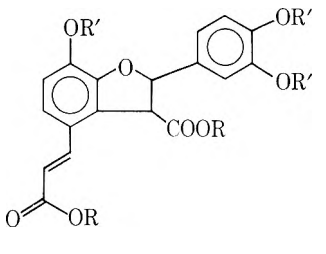
tamethyl" derivative. Schmiechen and Gibian[17] described the synthesis of the *O*-methyl derivative corresponding to the racemate of the proposed lithospermic acid structure. Since their pentamethyl compound behaved very differently than the derivative of natural lithospermic acid, it was concluded that the proposed structure was not correct. The same conclusion was reached by Wagner et al.,[9] who isolated lithospermic acid from *Lycopus europaeus* and *Symphytum officinale*, prepared several of the derivatives reported by Johnson et al., and made a direct comparison with a specimen of the acid supplied by those workers.

Since we had achieved some concentration of inhibiting constituents of *L. ruderale*[1f] in earlier column chromatography on cellulose, we evolved a more effective separation procedure involving extracts of the root on columns of Sephadex. On elution with water, polymeric materials, followed by carbohydrates, preceded the polyphenolic carboxylate salts responsible for the antihormonal effects. One chromatographic fraction contained almost exclusively the salts of lithospermic acid in quantities up to 3% of the weight of the dry roots.

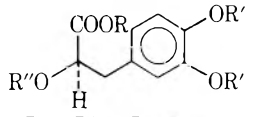
From a study of the salts, the liberated carboxylic acid, and methylated derivatives, we have deduced that lithospermic acid, the principal polyphenolic acid, is a dicarboxylic acid having structure **1a.** In addition, *L. ruderale* contains lesser quantities of the two formal hydrolysis products of **1a,** (*R*)-3-(3,4-dihydroxyphenyl)lactic acid (**2a**) and 2-(3,4-dihydroxyphenyl)-3-carboxy-4-(2-carboxy-*trans*-vinyl)-7-hydroxycoumaran (**3a**). Also found in the plant was the caffeyl ester of (*R*)-**2a,** rosmarinic acid (**4a**).



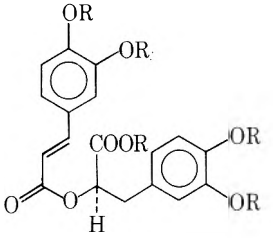
1a, R = R′ = H
b. R = Me, R′ = H
c. R = R′ = Me



3a, R = R′ = H
b. R = Me, R′ = H
c. R = R′ = Me



2a, R = R′ = R″ = H
b. R = Me; R′ = R″ = H
c. R = R′ = Me; R″ = H
d. R = R′ = Me; R″ = Ac
e. R = R″ = H; R′ = Me



4a, R = H
b, R = Me

Fractionation of Polyphenolic Acids. The polyphenolic acids of *Lithospermum ruderale* have been found in roots, leaves, seeds, and stems in varying amounts, and are extractable with water as nearly neutral salts over a range of pH, and as the free carboxylic acids at pH 2. In practice, the roots are a much better source of these materials owing to the ease with which the extracts may be handled. The direct extraction of powdered root materials with water under an inert atmosphere gives a solution (pH ~7) containing up to 40% of the dry weight of the plant material. If these solutions are allowed to stand in air, they darken and begin to deposit amorphous materials in a few hours. If such solutions are lyophilized immediately, however, the resulting dry powders may be stored without significant change for years.

Table I
Separation of Whole Root Extracts of *L. ruderale* on Sephadex G-50

Group[a]	Fractions	Appearance of lyophilized powder	Wt, g	Percent
Insoluble pellet		Removed by centrifugation	0.69	3.5
A	1–6	Light yellow	0.73	3.6
B	7–8	Brown, crisp	0.73	3.6
C	9–12	Brown, crisp	7.77	38.9
D	13–14	Dark brown, crisp	4.30	21.5
E	15	Medium brown, fluffy	1.41	7.1
F	16–22 (–28)	Light yellow, fluffy	3.27	16.4
Remaining on column			1.10	5.5
Total weight of extract powder			20.0[b]	100

[a] Representative samples of groups A–E were assayed by ^{13}C NMR, and the following conclusions were drawn. That portion of A soluble at pH 8.2 and groups B–D are almost exclusively carbohydrates. The principal carbohydrate in group C is sucrose. Group E contains carbohydrates similar to group D and in addition some polyphenols. A chemical separation of group E resulted in Ea, Eb, and Ec, the last consisting of the water-soluble carbohydrate. Ea consists of polyphenolate salts whose parent acids are precipitated in aqueous acid; it appears to be oligomeric material with very broad carbon resonances corresponding in chemical shift to the resonances observed for **1a**. Fraction Eb contains an unknown ester carboxylate salt, ca. 5% of salts of **3a**, and a trace of salts of **1a**. [b] This weight of lyophilized powder represents the total weight extracted in three extractions of approximately 50 g of finely ground plant roots.

After much preliminary exploratory work,[1] we found that reconstituted aqueous extracts could be efficiently separated by chromatography on Sephadex G-50 and G-25 with water as an eluent. While these adsorbents allow enzymes and carbohydrates to pass rapidly through, they selectively adsorb the polyphenolic carboxylates. Smaller carbohydrates pass through in intermediate fractions. When eluted, the polyphenolic carboxylic acid salts are stable in aqueous solution, apparently as a result of having been separated efficiently from plant enzymes which can catalyze their chemical transformation.[9]

The progress of the chromatographic separation on Sephadex G-50 (Table I) was readily observed in a series of colored bands which reproducibly formed on the column. The fractions containing the catechol acids (groups E and F) were identified by the precipitates formed with lead acetate or ferric chloride solutions. Group F of Table I is of particular interest as a source of lithospermic acid. It was further fractionated on Sephadex G-25 into five fractions which are summarized in Table II. Group E was separated by chemical methods into three subfractions (Table I, footnote *a*). The segregation of these fractions was routinely carried out after lyophilization. To aid this process, spot tests on filter paper and infrared spectroscopy (Table II) were found to be useful criteria. The use of ^{13}C NMR gives, however, the clearest fingerprints of the components present in the individual fractions (see footnote *a*, Tables I and II).

The reported[15] insolubility of biologically active constituents of *Lithospermum ruderale* in water at low pH was followed up by acidification of group E material (Table I), centrifugation of the precipitated material, dissolution of the separated solid in water at pH 5.8, and lyophilization to give Ea as a powder. The acidified aqueous filtrate was extracted with ethyl acetate to give a product containing principally an unidentified ester carboxylic acid. This lat-

Table II
Fractionation of Polyphenolic Acid Salts (Group F, Table I) on Sephadex G-25

Fraction[a]	Wt, g	Percent	Carbonyl absorption in infrared, λ (μ)[b]		
F-1	3.92	19.5	5.78 (s)	5.97 (w)	6.28 (s)
F-2	3.27	16.3	5.78 (s)	5.95 (m)	6.28 (vs)
F-3	8.72	43.5		5.91 (m)	6.28 (vs)
F-4	1.20	6.0		5.91 (m)	6.28 (vs)
F-5	0.15	0.7			
Remaining on column	2.80	13.9			
	20.1	100			

[a] ^{13}C NMR analysis of representative samples of fractions F1–F4 allowed the following conclusions. Fraction F1 was very similar to group E material. Fraction F2 was quite complex but contained up to ca. 30% of salts of **1a** and ca. 10% of **3a**. Fraction F3 contained salts chiefly of **1a** admixed with ca. 10% of **3a**. Fraction F4 contained principally salts of **1a**, but it also contained up to ca. 20% of salts of **4a** and some carbohydrate (15%). [b] Relative intensities: vs, very strong; s, strong; m, medium; w, weak.

ter was dissolved in water, neutralized with base, and lyophilized to give fraction Eb. Ec consisted of the plant material still remaining in solution (carbohydrate).

Since the biological actions affecting pituitary hormones have always been associated with the phenolic fractions of the plant, both in our own[1b-f] and others' reports,[8,9] and not at all with the large carbohydrate fractions, our attention has been directed to the identification of the constituents of fractions E and F. Experiments with animals involving these plant fractions will be reported elsewhere.

Characterization of Lithospermic Acid. Fraction F3, which represents approximately 3% of the dry root weight of *Lithospermum ruderale*, consists principally of the dipotassium salt of **1a**. While the organic anion is not exclusively that of **1a**, the contaminants, **3a** (ca. 10%) and **4a** (<2%), do not interfere with the interpretation of ir and NMR data. The liberation of lithospermic acid from its salts is readily accomplished by acidification, and the very water-soluble **1a** is readily extracted into ethyl acetate. To aid in the interpretation of the spectral properties of **1a**, authentic rosmarinic acid (**4a**) was isolated by the procedure[18a] of Scarpati and Oriente from *Rosmarinus officinalis*.[18b,c]

The published[7,9] infrared spectra for lithospermic acid are virtually identical with the ir spectrum (KBr) of our fraction F3 except that the carbonyl region of the latter is split, revealing the internal α,β-unsaturated ester band at 5.91 μ, while the two carboxylate anions have their stretching bands centered at 6.28 and 7.3 μ. The infrared spectrum of sodium rosmarinate shows the α,β-unsaturated ester band also at 5.91 μ, indicating the structural similarity of **1a** and **4a**. In addition, the rest of the ir spectrum of Na-**4a** is virtually identical with that of F3. Further evidence for the structural similarity of **1a** and **4a** was obtained from NMR measurements.

The carbonyl region of the ^{13}C NMR spectrum of Na-**4a** (in D_2O) showed an α,β-unsaturated ester carbon at 168.6 ppm and a carboxylate anion at 177.2 ppm. The spectrum of F3 showed a similar ester carbon at 168.3 ppm and carboxylate anions at 176.9 and 178.8 ppm, the latter arising from C-19 (see the numbering system in Table III). That the second carboxylate peak is C-19 rather than C-9 (as would be required by the alternative structure having the dihydroxyphenyllactate group esterified to C-19) was further established by observing that the carboxylate resonance of several model cinnamate salts falls in the range of 175.3–176.3 ppm.[19] A full analysis of the ^{13}C NMR spectrum of **1a**, **4a**, and the model compounds will be published.[20]

The striking similarity of the ^1H NMR spectra of lithospermic acid (**1a**) and rosmarinic acid (**4a**) in Table III is immediately apparent. Each molecule contains two benzene rings bearing three protons in a 1,2,4 relationship. This arrangement gives rise to the distinctive ^1H NMR coupling pattern of two doublets and one doublet of doublets for each ring. The resonances were assigned to specific hydrogens on the basis of known ring coupling constants ($J_{ortho} \simeq 8$, $J_{meta} \simeq 2$, $J_{para} \simeq 0$ Hz) and on their relative chemical shifts. The chemical shifts of H-5, -13, -16, and -17 remained almost the same for both compounds. The two protons H-2 and H-6 in **4a** ortho to the unsaturated side chain and deshielded by its anisotropy are in **1a** diminished to only one (further) deshielded proton, H-6, with a simplified coupling pattern. This indicates that C-2 is the site of fusion of the additional C_6–C_3 biogenetic unit in **1a**. The protons H-23, -26, and -27 fall at intermediate chemical shifts in **1a**. The only ambiguity in these data arises from the almost equal chemical shifts and coupling constants of H-13 and H-23 in **1a**, which do not allow them to be differentiated.

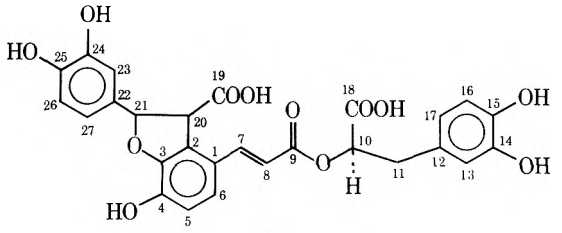
The aryllactate side chain (H-10 and 11) exhibited similar ABX coupling patterns in compounds **1a** and **4a**, differing only in the overlapping of two of the eight lines in the AB portion of the spectrum of **1a** due to a smaller $\Delta\delta_{AB}$. The chemical shift of H-10 in esters **1a** and **4a** is a full 0.7 ppm deshielded from the chemical shift of the analogous proton in the free aryllactic acid, **2a**. This difference allows the ready observation of the presence of **2a** as a contaminant of **1a** or **4a**.

The unique coupling constant of 4.8 Hz for H-20 and H-21 on the coumaran ring appears in both **1a** and salt F3. Early workers pointed out that the proton coupling constant in a 2,3-disubstituted coumaran (dihydrobenzo[*b*]furan) ring is dependent not only on the configuration of the protons but also on the nature of the other substituents at those positions.[21] A more reliable criterion for the assignment of stereochemistry in 3-substituted 2-arylcoumarans, where the 3 substituent contains hydrogen, is the shielding (cis) or lack of shielding (trans) of the protons in the 3 substituent by the aromatic ring.[22]

Esterification of **1a** with MeOH–2,2-dimethoxypropane–HCl gave a mixture in approximately 3:1 ratio of two dimethyl esters, **1b** and **3b**, which were soluble in dilute aqueous bicarbonate (apparently through phenolic ionization). Diester **3b**, which apparently arose from transesterification of **1b** with the methanol solvent, was identified by its NMR spectrum in the mixture and by its parent ion in the mass spectrum.

The ^1H NMR spectrum (acetone-d_6) showed three new methyl resonances at δ 3.72, 3.69, and 3.65. From the intensities of these resonances, it was judged that the major diester, **1b**, has resonances at δ 3.69 and 3.65, while the minor diester, **3b**, has resonances at δ 3.72 and 3.69 (overlapped by **1b**). Since none of these resonances is markedly

Table III
^{1}H NMR Spectra (220 MHz) of Lithospermic Acid and Rosmarinic Acid in Acetone-d_6[a]



1a

Proton[b]	Lithospermic acid (1a) δ (multiplicity, J, Hz)	Rosmarinic acid (4a) δ (multiplicity, J, Hz)
H-11 (2 H)	3.03 (2 q, 5, 8, 14)	3.03 (2 q, 5, 8, 14)
H-20	4.47 (d, 4.8)	
H-10	5.15 (dd, 5, 8)	5.17 (dd, 5, 8)
H-21	5.94 (d, 4.8)	
H-8	6.32 (d, 16)	6.23 (d, 16)
H-17	6.61 (dd, 2, 8)	6.60 (dd, 2, 8)
H-16	6.69 (d, 8)	6.69 (d, 8)
H-27	6.72 (dd, 2, 8)	
H-26	6.77 (d, 8)	
H-23	6.81[c] (d, 2)	
H-13	6.82[c] (d, 2)	6.79 (d, 2)
H-5	6.83 (d, 8)	6.79 (d, 8)
H-6	7.21 (d, 8)	6.96 (dd, 2, 8)
H-2		7.09 (d, 2)
H-7	7.80 (d, 16)	7.50 (d, 16)

[a] The use of deuterioacetone as a ^{1}H NMR solvent is important in obtaining the resolution of the aromatic resonances. The ^{1}H NMR spectrum of the salt **1a** (fraction F3) in D_2O shows a much more compact aromatic proton region in which not even H-6 is resolved. [b] The 18 carbon atoms shared in common in the structure of acids **1a** and **4a** are numbered in a consecutive sequence of 1–18; atoms numbered 19–27 represent the additional phenylpropanoid unit contained in lithospermic acid which is condensed as shown in the formula. [c] Overlapping resonances; assignments may be reversed.

shielded, we have assigned a trans configuration to the methoxycarbonyl and the aryl substituents on the coumaran ring in **1b** and thus in **1a.** The absolute configurations of the asymmetric carbons in the coumaran nucleus have not yet been determined.

The ultraviolet spectra of the free lithospermic acid were in general agreement with those already published,[7,9] and consistent with the presence of conjugated unsaturation of the type contained in **1a.** Quantitative data are presented in the Experimental Section. Ultraviolet spectra for the salts of **1a** showed the same major features with some variations in detail.

Further information about the configuration and composition of the polyphenolic acids was obtained on fully methylated derivatives. The total absence of O-methylated compounds in the aqueous extracts of *L. ruderale* (by ^{1}H and ^{13}C NMR criteria) makes it clear that all of the methyl groups subsequently found in the methylated derivatives were experimentally introduced into unmethylated natural products.

Methylation of Polyphenolic Acids with Diazomethane. At the same time that the separations on Sephadex (Tables I and II) were being carried out, an alternative isolation of the polyphenolic acids was undertaken by a modification of a published procedure.[7] Root powders of *L. ruderale* were extracted with aqueous HCl, and the dissolved polyphenolic carboxylic acids were taken up in organic solvents. Ethyl acetate was found to be a much more efficient solvent than ether[7] for the removal of polyphenolic acids from aqueous solution.

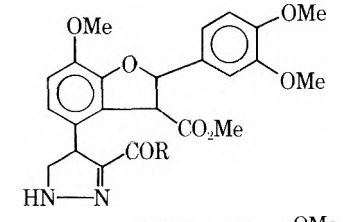
The extracted solutions of these acids were permethylated with excess diazomethane. A complicating reaction in the use of diazomethane was subsequently shown to be the cycloaddition of this reagent to the olefinic bond of the substituted cinnamic esters in these mixtures. The cinnamates were principally transformed into the corresponding pyrazoline derivatives.[26–29] The chemical changes were accompanied by changes in the ultraviolet absorption spectra—in particular, decreases in absorption above 300 nm. In spite of the formation of nitrogen heterocycles, this procedure yielded valuable early indications of the nature of the polyphenolic acids present in the plant.

The aryllactic acid **2a** was converted by diazomethane into methyl (*R*)-3-(3,4-dimethoxyphenyl)lactate [(*R*)-**2c**], which was isolated in 3% yield by repeated column chromatography. The identity of (*R*)-**2c** was established by spectral comparison with synthetic (*RS*)-**2c.** Subsequently, the absolute configuration was established to be *R* by the undepressed melting point of the ester mixed with an authentic sample[18b] of (*R*)-**2c** prepared as a derivative following the saponification of rosmarinic acid.

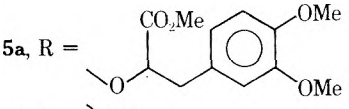
Methyl aryllactate (*R*)-**2c** was acetylated to (*R*)-**2d,** and the acetyl derivative was hydrolyzed to the aryllactic acid (*R*)-**2e.** Resolution of (*RS*)-**2e** to give (*R*)-**2e** was accomplished. The CD spectra of (*R*)-**2c** and (*R*)-**2e** are comparable in sign and intensity but opposite in sign to spectra of (*S*)-3,4-dihydroxyphenylalanine (L-dopa), (*S*)-3-phenyllactic acid,[30] and methyl (*S*)-3-phenyllactate.[30] The CD spectrum of (*R*)-**2c** from *L. ruderale* is identical with that of the authentic sample[18b] in confirmation of the previous assignment.[18c]

In the chromatographic separations used to fractionate diazomethane-methylated polyphenolic acids, the methyl aryllactate (*R*)-**2c** was eluted from a Florisil column with benzene–ether mixtures. About 70% of the methylated product, the material containing nitrogen heterocyclic derivatives, was more strongly held on the column and was eluted with ether–ethyl acetate mixtures. These latter materials were rechromatographed and were characterized by osmometric molecular weights (mol wt) in the range of 500–1200.

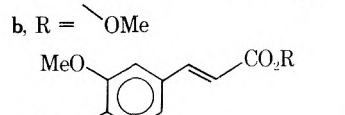
Mass spectra of these fractions show parent ions at *m/e* 470 and 472 for which the pyrazoline structures **5b** and **6a** can be written. These are the products expected from **3a** and **4a** under the reaction conditions. At higher temperatures in the mass spectrum, a major ion at *m/e* 650 was observed, apparently formed from the molecular ion of **5a** (*m/e* 678) by loss of nitrogen.[27]



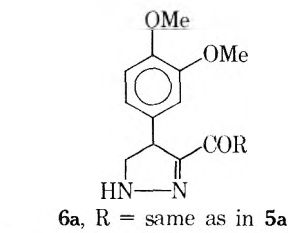
5a, R =



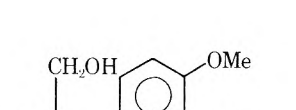
b, R =



7a, R = H
b, R = Me



6a, R = same as in **5a**
b, R = same as in **5b**



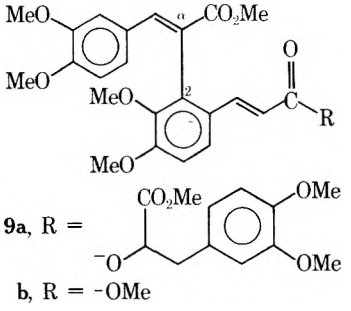
(*R*)-**8**

As a model for the diazomethane cycloadditions, the reaction of methyl 3,4-dimethoxycinnamate (**7b**) with diazomethane was observed to give in 65% yield a crystalline pyrazoline derivative, **6b**. The reaction of pentamethyl rosmarinate (**4b**) with diazomethane gave the pyrazoline **6a** (*m/e* 472) and further transformation products.[31]

Saponification of the complex permethylated product mixture, separation of the acids, remethylation of the acids with diazomethane, and separation by chromatography yielded additional amounts of (*R*)-**2c**. Treatment of the complex mixture with lithium aluminum hydride produced (*R*)-3-(3,4-dimethoxyphenyl)-1,2-propanediol [(*R*)-**8**], which was crystallized after chromatography. For identification, (*RS*)-**8** was synthesized by reduction of (*RS*)-**2c**.

Since **2c** and diol **8** have the same origin, their absolute configurations should be the same. The CD spectrum of a solution of **8** and $Ni(acac)_2$ in CCl_4 has a positive induced exciton-split type Cotton effect centered at 306 nm [λ° ($\Delta\epsilon^\circ$) 316 (+3.6) and 297 (−3.6)], establishing the absolute configuration as *R*.[33] Moreover, the ^1L_b and ^1L_a bands of (*R*)-**8** are both positive, while in (*S*)-3-phenyl-2-amino-1-propanol both of these bands are negative.[30]

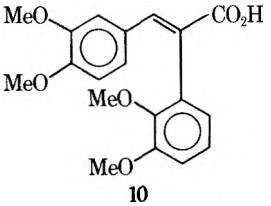
Base-Catalyzed Methylation of Fraction F3. In another procedure, fraction F3 (Table II) was permethylated in refluxing acetone with dimethyl sulfate and potassium carbonate, and the neutral methylated material was chromatographed on a series of columns (either Florisil or nearly neutral alumina), with benzene–ether–ethyl acetate as increasingly polar eluting solvents. Fractions were monitored by TLC. One compound, $C_{35}H_{38}O_{12}$, was found repeatedly in the middle fractions and accounted for ca. 25% of the weight of methylated products. This substance gave clean mass spectral and ^1H NMR data, from which the structure **9a** was deduced.



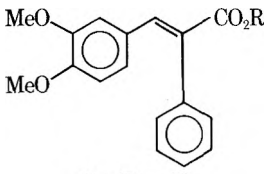
From the ^1H NMR spectrum it is concluded that **9a** is an octamethyl derivative, where a heptamethyl derivative would be expected from the uncomplicated methylation of **1a**. Thus, one additional oxygen function which was not already present as a phenol or a carboxyl group in **1a** must have been methylated under these basic conditions. The anomaly is explained as a consequence of base-catalyzed opening of the coumaran ring in **1a**, initiated by abstraction of H-20 (cf. Table III), which generates concomitantly a new phenolic function (susceptible to methylation) and a new *trans*-caffeyl functional unit. Since opening of the coumaran ring is formally an isomerization, we shall refer to **9a** as octamethyl isolithospermate. The sequence of the methylation reactions under basic conditions is not known, but it seems likely that the ring-opening reaction occurs late in the sequence. Certainly esterification of carboxylate C-19 precedes abstraction of the α hydrogen, H-20.

Accompanying **9a**, and present chiefly in chromatographic fractions immediately preceding it, were minor amounts of several other derivatives of **1a** and **3a**. These included the heptamethyl derivative, **1c**, and two derivatives, **3c** and **9b**, lacking the aryllactate group (the latter being replaced with the methyl ester function). Also present in very minor amounts was pentamethyl rosmarinate (**4b**). The presence of all of these compounds was first revealed by mass spectra; confirmatory ^1H NMR spectra were subsequently obtained for **4b** and **9b**.

To aid in the interpretation of the array of spectral data obtained from chromatographically similar methylated derivatives, the synthesis of several model compounds proved expedient: 3,4-dimethoxycinnamic acid (**7a**), its methyl ester **7b**, and the aryllactates (*RS*)-**2c**, (*RS*)-**2e**, and (*RS*)-**4b**. The latter was synthesized by the reaction of **7a** with *p*-toluenesulfonyl chloride in pyridine, followed by the addition of (*RS*)-**2c**. Two further model compounds, **10** and **11a**, were prepared by the Perkin condensation of appropriately substituted phenylacetic acids with 3,4-dimethoxybenzaldehyde.[34] The ethyl ester **11b** was prepared from the acid **11a**.



10

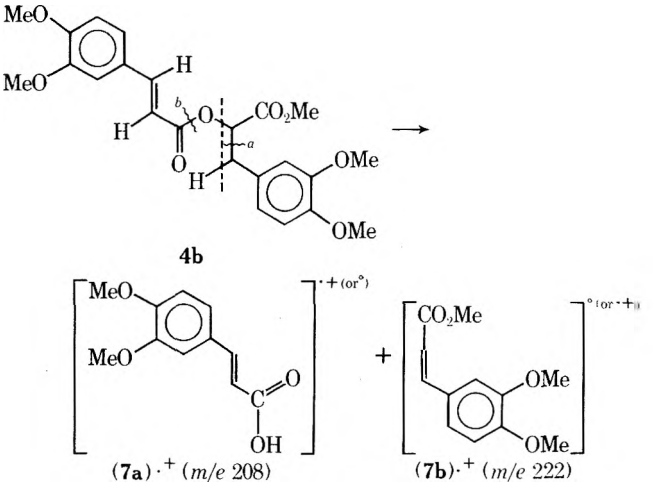


11a, R = H
b, R = Et

Mass Spectra. Table IV shows the fragmentation patterns of the five model compounds, **4b**, **7a**, **7b**, **2e**, and **2c**.

For pentamethyl rosmarinate (**4b**), two strong ion intensities in the mass spectrum arise from a McLafferty rearrangement of the molecular ion (*m/e* 430) into two fragments, *m/e* 222 and 208, according to Scheme I. Other

Scheme I
Mass Spectral Fragmentation of Pentamethyl Rosmarinate (4b)



major fragmentation pathways include cleavage at bond a to yield the dimethoxybenzyl cation at *m/e* 151 and possible cleavage at bond b to produce the acylonium ion at *m/e* 191. Alternatively, the latter ion could arise from further cleavage of (**7a**)·+ and (**7b**)·+ as is observed in the mass spectra of their parent compounds (Table IV).

The base peaks of the mass spectrum of octamethyl isolithospermate (**9a**) shown in Table V are produced in a direct cleavage of the molecular ion to give the 3,4-dimethoxybenzyl cation (*m/e* 151) and in a McLafferty rearrangement to give the methyl 3,4-dimethoxycinnamate ion, (**7b**)·+ (*m/e* 222). These same two ions were the dominant ones in the mass spectrum of pentamethyl rosmarinate (**4b**), confirming that **9a** is an *O*-acyl derivative of methyl 3-(3,4-dimethoxyphenyl)lactate (**2c**). The McLafferty rear-

Table IV
Mass Spectra of Model Compounds

Ion m/e	Rel intensities at 70 eV for model compounds[a,b] 4b	7a[c]	7b[d]	2e	2c
430	4.3				
399	0.6				
240	<1				10.2
226	0			13.7	0
222	100		100	0	1.3
208	23	100	2.0	0.6	0.6
207	4.6	0	16	0	0
191	25	4.9	47	0	0
181	1.7	0	0	1.3	2.6
165	1.1	4.3	1.3	0.5	0.6
163	8.2	3.5	9.4	0	0
151	56	0	0	100	100

[a] Determined in a Varian MAT-CH-7 mass spectrometer. [b] Intensities expressed as percentage of the strongest ion intensity. [c] Also observed: m/e 193 (19). [d] For complete mass spectrum, see ref 35.

Table V
Mass Spectrum of Octamethyl Isolithospermate (9a)

Ion[a] m/e	Rel abundance,[b] %	Mass found[c]	Mass calcd	Molecular formula
650	35	650.251	650.236	$C_{35}H_{38}O_{12}$
428	31	428.143	428.147	$C_{23}H_{24}O_8$
410	3			
396	4			
382	13			
368	9			
351	38	351.121	351.123	$C_{21}H_{19}O_5$
222	100	222.089	222.089	$C_{12}H_{14}O_4$
151	100	151.076	151.076	$C_9H_{11}O_2$

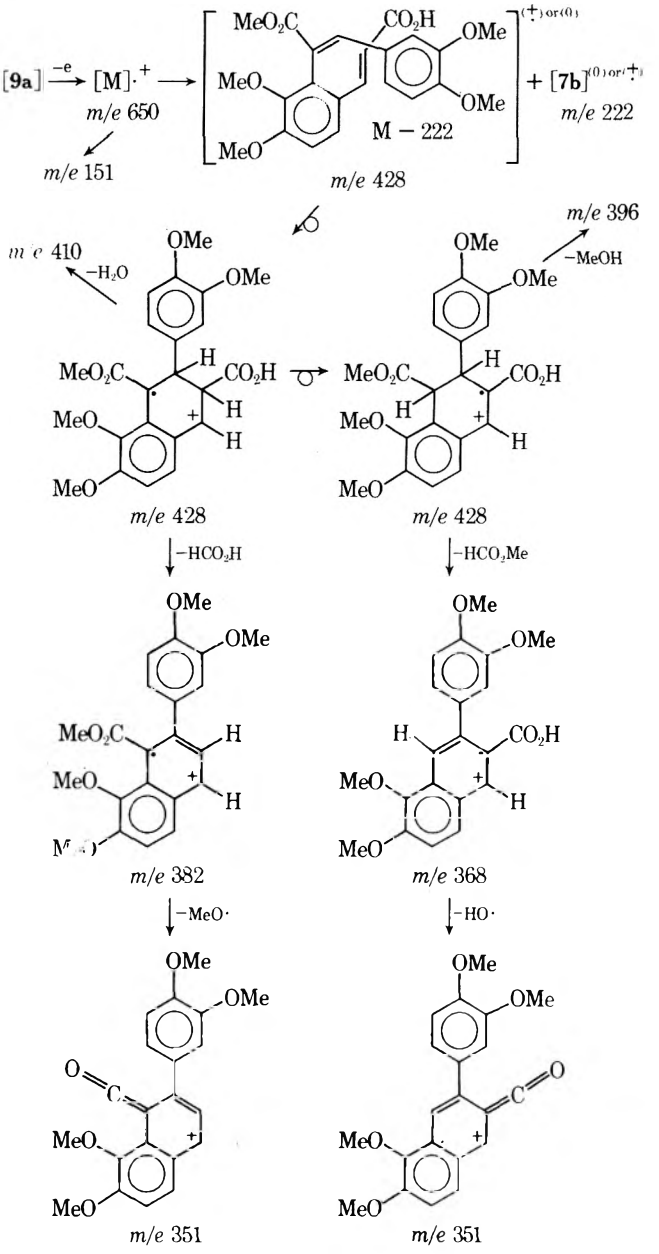
[a] Also observed: m/e 337 (4), 324 (5), 323 (4), 309 (6), 298 (8), 246 (7), 191 (10), 181 (20). [b] Determined in a Varian CH-7 mass spectrometer. [c] Determined in an AEI MS-9 mass spectrometer by peak matching technique.

rangement of the parent ion (m/e 650) also gives the m/e ion 428 (metastable ion at m/e 282), which decays through a series of ions to a stabilized ion at m/e 351. Possible structures for these ions are presented in Scheme II.

The apparent loss of the elements of HCOOMe and of HCOOH is a characteristic feature of the spectrum of **9a** which is not observed in the model compounds, and is best explained by the postulated cyclization of two ortho-situated unsaturated side chains to form a six-membered ring which can extrude small substituents to achieve additional stabilization. Such an interaction of side chains can only occur with the ortho placement of the vinyl groups of **9a,** and is one piece of evidence in the assignment of the 2,α-bicaffeate structure to **9a.** An alternative 5,α structure would be ruled out by this logic, as well as from the ^{1}H NMR data.

One chromatographic fraction of methylated derivatives (31 mg out of 5.8 g taken for the separation) consisted of an almost equal mixture of **4b** and **9b.** The NMR peaks of **9b** (reported in Table VI) in the spectrum of this sample were readily distinguished from those of **4b.** The mass spectrum of this mixture showed, in addition to the characteristic ions of **4b** [m/e 430, 222 (100), and 208], the molecular ion of **9b** [m/e 442 (33)] and two principal daughter ions [m/e 382 (19) and 351 (40)] in good agreement with the expected fragmentation of **9b** by the same pathway as **9a** (cf. Scheme II).

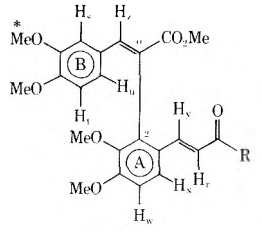
Scheme II
Fragmentation Patterns in the Mass Spectrum of Octamethyl Isolithospermate (9a)



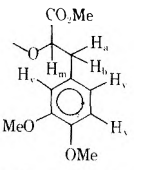
^{1}H NMR Spectra. The ^{1}H NMR spectra of octamethyl isolithospermate (**9a**) and the hexamethyl 2,α-bicaffeate (**9b**) are summarized in Table VI and compared with the two synthetic model compounds, **10** and **11b.** The methoxy region of **9a,** reproduced in Figure 1, shows eight distinct *O*-methyl groups, six of which appear as doubled resonances. We attribute the doubling of these resonances to restricted rotation about the bond joining the 2,α positions of the bicaffeyl subunit.[36] If an approximately equal distribution of two rotational forms exists about this bond, the presence of the asymmetric center in the aryllactyl ester portion of the molecule would mean that **9a** is a mixture of nearly equal amounts of two diastereoisomers. The doubling of the methyl hydrogen resonances disappears upon full catalytic hydrogenation of the olefinic unsaturation. It is also not characteristic of **9b,** which lacks the aryllactate asymmetric center and would therefore be a simple racemic pair as a consequence of the restricted rotation.

That the caffeyl moiety containing phenyl ring B in esters **9a** and **9b** has the stereochemistry of an α-phenyl-*trans*-cinnamic ester (i.e., that the phenyl rings A and B

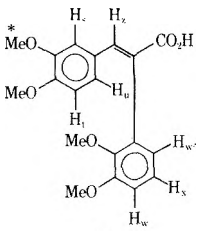
Table VI
^{1}H NMR (HR-220) Spectra of Compounds 9a, 9b, 10, and 11b in $CDCl_3$



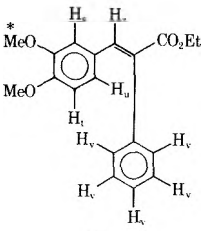
9b. R = OMe



9a. R = aryllactate



10



11b

Proton	δ^a (multiplicity, J)	δ^b (multiplicity, J, $\Delta\delta$)	δ^c (multiplicity, J)	δ^d (multiplicity, J)
H_a, H_b		3.02 (m, 2 H)		
H_m		5.21 (4d, 5, 7, 3)		
*Me	3.41 (s)	3.42 (2 s, 0, 3)	3.39 (s)	3.29 (s)
H_r	6.17 (d, 16)	6.20 (2 d, 16, 1)		
H_s	6.39 (d, 2)	6.39 (2 d, 2, 4)	6.50 (d, 2)	6.30 (d, 2)
H_t	6.65 (d, 8)	6.65 (d, 8, 0)	6.66 (d, 8)	6.61 (d, 8)
H_u	Obscured by compound 4b	Included in H_v multiplet	6.83 (dd, 2, 8)	6.75 (dd, 2, 8)
H_v		6.59–6.80 (m, 4 H)		7.14–7.36 (m, 5 H)
H_w	6.93 (d, 8)	6.93 (d, 8, 0)	6.71 (dd, 2, 8)	
$H_{w'}$		—	6.90 (dd, 2, 8)	
H_x	7.44 (d, 8)	7.45 (d, 8, 0)	7.03 (t, 8)	
H_y	7.48 (d, 16)	7.54 (2 d, 16, 1)		
H_z	7.93 (s)	7.93 (2 s, 0, 1)	7.85 (s)	7.71 (s)
$CHCl_3$	7.22 (internal)	7.21	7.20	

[a] Other OMe singlet resonances: δ 3.59, 3.64, 3.71, and 3.77; one OMe resonance obscured by compound **4b**. [b] Other OMe resonances, cf. Figure 1; δ 3.62 (d, $\Delta\delta$ = 3 Hz), 3.67 (d, $\Delta\delta$ = 3 Hz), 3.72 (d, $\Delta\delta$ = 1.5 Hz), 3.79 (d, $\Delta\delta$ = 1.5 Hz), 3.81 (s), 3.83 (d, $\Delta\delta$ = 3 Hz), 3.90 (s). [c] Other OMe singlet resonances: δ 3.69, 3.77, and 3.81. [d] Other resonances: δ 1.27 (t, J = 7 Hz, CH_2CH_3), 3.72 (s, OCH_3), 4.17 (q, J = 7 Hz, CH_2CH_3).

and the connecting double bond comprise a *cis*-stilbene subunit) is established by the chemical shift of vinyl hydrogen H_z in these compounds as compared with the vinyl proton in model compounds **10** and **11b**. Not only has the α-phenyl-*trans*-cinnamic stereochemistry been established as being more thermodynamically stable than the cis,[34b,37] but the chemical shifts of the vinyl hydrogen have been well documented as an unambiguous means of distinguishing the trans from the cis series.[29]

An additional effect of the trans stereochemistry of the caffeate subunit created by the opening of the original coumaran ring is the marked shielding of the ortho H_s and the meta CH_3O resonances in ring B. In the four compounds in Table VI, H_s is shielded by 0.5–0.7 ppm compared with the corresponding proton in **4b** (H-2; cf. Experimental Section). Similarly, the meta *CH_3O group in ring B experiences a shielding of 0.4–0.6 ppm with reference to a comparable CH_3O in **4b**.

The two ortho hydrogens on ring A (H_x and H_w) exhibit a 0.5-ppm difference in their chemical shifts in both compounds **9a** and **9b**. This difference is due in part to the deshielding of H_x by the anisotropic effect of the unsaturated substituent ortho to it on the ring. The identity of the unsaturated group which deshields H_x was revealed by the following hydrogenation experiment.

Octamethyl isolithospermate (**9a**) rapidly consumed 1 mol of hydrogen in ethyl acetate at room temperature over 10% palladium on carbon catalyst, and only quite slowly consumed a second mole of hydrogen. A mass spectrum of the product of such a hydrogenated reaction mixture which had not yet absorbed 2 mol revealed that a mixture of dihydro-**9a** and tetrahydro-**9a** had been produced (*m/e* 652:654 = 3:2). The ^{1}H NMR spectrum of this mixed product showed that, as expected, the trisubstituted double bond conjugated with ring B was the more slowly hydrogenated, since the protons H_z (δ 7.85) and H_s (δ 6.42) and the shielded meta methoxyl group (starred in Table VI) in dihydro-**9a** were clearly visible in the ^{1}H NMR spectrum, while the aromatic hydrogens in phenyl ring A (H_x and H_w) had shifted completely into the aromatic multiplet at δ 6.6–6.9. The conclusion is that the disubstituted double bond which is rapidly and fully hydrogenated must be located ortho to H_x. That H_x and H_w are ortho to each other follows from their coupling constants.

Relationship of Lithospermum Constituents to Known Plant Principles. Since the discovery of rosmarinic acid (**4a**) in 1958,[18bc] that compound has become recognized as one of the most widely distributed naturally occurring derivatives of caffeic acid.[12,38-41] Its biogenesis has been recently studied.[42]

The structure which we have proposed for lithospermic acid, **1a**, incorporates a molecule of rosmarinic acid to which is condensed a third catecholpropanoid unit. The coexistence of **1a** and **4a** in *Lithosperum ruderale* suggests that **4a** may be a precursor of **1a**.

The condensation of two *p*-hydroxyphenylpropenoid units to give a 2-aryl-3-substituted coumaran nucleus is a well-documented process in plant biochemistry. In the laboratory, models of this reaction are found in the oxidative coupling of isoeugenol[21] to dehydrodiisoeugenol (**12a**) and of coniferyl alcohol[43] to **12b**. These condensations have been cited as models of reactions which occur in lignin formation. Typically, the coumarans produced in this way have the trans arrangement of the 2,3 substituents on the 2,3-dihydrobenzo[*b*]furan nucleus.[24,44,45]

Similar self-condensations of cinnamic acid derivatives have also been observed to occur through both chemical and enzymatic oxidative coupling reactions. Ferulic acid ethyl ester has yielded coumaran **12c**,[46] and a complex amide of *p*-coumaric acid has been similarly dimerized to

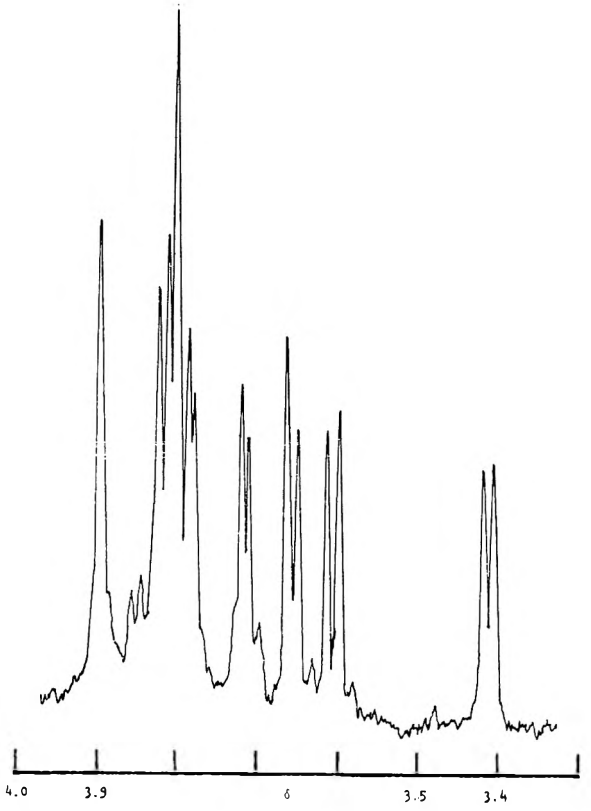
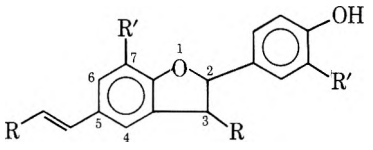


Figure 1. Proton resonances (220 MHz) of the *O*-methyl groups in octamethyl isolithospermate (**9a**).

hordatine A (aglucone) (**12d**), a member of the family of optically active antifungal factors isolated from barley coleoptiles.[47]



12a, R = Me; R′ = OMe
b, R = CH_2OH; R′ = OMe
c, R = CO_2Et; R′ = OMe
d, R = CONHR″; R′ = H

In all of the above oxidative dimerizations, the coumaran produced has its unsaturated side chain attached at C-5. This is in agreement with the radical coupling mechanisms by which the reactions are envisioned to proceed. Only a phenolic function para to a vinyl group is mechanistically suited to undergo this type of coumaran formation.

If lithospermic acid is formed by conjugation of a catecholpropanoid unit with rosmarinic acid, then the formation of the coumaran nucleus must in this case involve the 3-hydroxy (meta) group of the rosmarinate unit and formation of the new carbon–carbon bond occurs at the open ortho position, resulting in the placement of the unsaturated side chain on C-4 of the product coumaran. Data from ^1H NMR, ^{13}C NMR, and mass spectra are all consistent with the assignment of the 2,3,4,7-tetrasubstituted coumaran structure to lithospermic acid. Thus, the latter appears to be a unique example of a class of natural coumaran derivatives for which previous oxidative coupling mechanisms involving *p*-hydroxystyrene derivatives cannot be readily adapted.

The ability of lithospermic acid to inhibit or block the action of pituitary peptide hormones has been reported to require[8,9] its prior oxidation by air or phenoloxidases. The nature of the oxidation and the mechanism(s) of hormone blocking are still unknown. One must consider the possibility that *o*-benzoquinones may be implicated. The oxidative coupling of two or more lithospermate units would be a facile process, and probably occurs. We have observed that plant fractions E and F1 (Tables I and II) contain oligomeric materials which are insoluble in water at low pH but spectroscopically similar to lithospermic acid. Further chemical studies are being directed to these materials, which have shown inhibitory responses in animal endocrine experiments.

Experimental Section

General. Melting points were taken in open glass capillaries in a Mel-Temp apparatus and are uncorrected. Analyses were carried out by Alfred Bernhardt, Max Planck Institut, Mülheim (Ruhr), Germany, or Midwest Microlab Inc., Indianapolis, Ind. Infrared (ir) spectra were measured on Perkin-Elmer Infracord Models 137B or 137G. Ultraviolet (uv) and circular dichroism (CD) spectra were recorded with a Durrum–Jasco ORD/UV/CD-5 incorporating the SS-10 modification. Uv data are represented as λ_{max} (ϵ), sh = shoulder, and i = inflection. CD data are represented as λ_{max} ($\Delta\epsilon$) where $\Delta\epsilon = [\theta]/3300$. ^1H NMR spectra were recorded on Varian HR-220, HA-100, A-60, and EM-360 spectrometers. Mass spectra (MS) were obtained at 70 eV on a Varian MAT CH-7 mass spectrometer. Absolute masses were determined on a AEI MS-9 mass spectrometer. Optical rotations were measured with a Rudolph polarimeter, Model 80, in a 2-dm cell. Osmometric molecular weights were determined in a Mechrolab Model 301A vapor pressure osmometer in boiling benzene. Anhydrous $MgSO_4$ was routinely used as a drying agent.

Extraction of Water-Soluble Constituents of *Lithospermum ruderale* Roots. Roots of *L. ruderale* Dougl. ex Lehm. were collected by Mr. J. H. Coleman near Missoula, Mont., in the summer of 1959 and air dried. The woody roots were brushed free of soil and were ground in a Wiley Laboratory mill using a 2-mm mesh sieve. In a typical extraction, 100 g of the powder was stirred vigorously with 1 l. of distilled water under N_2 for 30 min, then filtered through a heavy cotton towel in a Büchner funnel. The solid cake was stirred vigorously with two additional 1-l. portions of water for 30 min each and filtered as before. Since the dark brown, opaque filtrates clogged ordinary filters, each of the three solutions (812, 881, and 943 ml, respectively) was clarified by centrifugation at 2800 rpm for 20 min at 7°. The water was removed by lyophilization during 3 days, and the dried powder preparations weighed 25, 11, and 4 g, respectively.

The powders have a flaky, gold-bronze appearance and a crisp, friable texture. They may be stored indefinitely in a thoroughly dry state and can be almost completely redissolved in water. Reconstituted solutions should, in general, be centrifuged to ensure adequate flow rates through any chromatographic medium.

Separation of Root Extracts on Sephadex G-50. A quantity of 20.0 g of lyophilized root-extract powder was dissolved in 100 ml of deoxygenated, distilled water and centrifuged for 1 hr at 35,000 rpm, and the supernatant solution was transferred to a chromatographic column (5.5 × 78 cm) containing 200 g of coarse grade Sephadex G-50 packed and washed according to the manufacturer's directions. The pellet removed by centrifugation weighed 0.7 g. Elution with water was followed by the development of colored bands; the first solute appeared after 540 ml of water, after which fractions of ca. 100 ml were collected, combined, and lyophilized.

The reproducibly colored bands were taken as the principal criterion for the combination of fractions into groups A–F. Treatment of aliquots of the solutions with neutral lead acetate or 1% aqueous ferric chloride gave voluminous precipitates (brown or green) only with groups E and F. After lyophilization, ir (KBr) spectra show significant aromatic ring stretching bands (6.6–6.8 μ) for groups A, E, and F, but not for groups B, C, and D. Of all the groups, only A would not readily redissolve in water; however, much of the group A material could be dissolved at pH 8.2.

Fractionation of Polyphenolic Acid Salts on Sephadex G-25. Group F material (20.1 g) was dissolved in 400 ml of water and chromatographed on 1 kg of Sephadex G-25-course prepared in a 8.5 × 80 cm glass column according to the manufacturer's directions. Portions of 100 ml were collected and lyophilized directly. Fractions F1–F5 were segregated on the basis of TLC on silica gel with *tert*-butyl alcohol–acetic acid–water (3:1:1) and filter paper

spot tests. In both assays, fractions F2 and F3 gave a blue-white fluorescence under uv light which became blue-green after exposure to ammonia vapors. Fractions F1, F4, and F5 appeared yellow under uv light with or without ammonia. Fraction F2 was distinguished from F3 by the absence of the 5.78-μ band in the ir spectrum of the latter (cf. Table II). Fraction F3 was further characterized as follows: uv (MeOH) (ϵ calcd using mol wt 614) 335 nm (sh, 12,700), 309 (14,500), 289 (14,800), 254 (16,400), 230 (i, 22,000); ^{1}H NMR (100 MHz, D_2O, internal acetone δ 2.23) δ 3.11 (m, 2 H, H-11), 4.25 (d, J = 4.8 Hz, H-20), 4.7–5.2 (HOD and H-10), 5.86 (d, J = 4.8 Hz, H-21), 6.22 (d, J = 16 Hz, H-8), 6.7–7.1 (m, 8 H, aromatic), 7.61 (d, J = 16 Hz, H-7).

Anal. Calcd for $C_{27}H_{20}K_2O_{12}\cdot H_2O$: C, 51.26; H, 3.51; K, 12.36; O, 32.87. Found: C, 51.47, 51.68; H, 4.19, 3.96; K, 10.1, 10.1; O, 34.1, 34.0.

Fractionation of Group E. Group E powder (2.13 g) was dissolved in 100 ml of water (pH 6.0), and the pH was lowered to 2 by the dropwise addition of 2 *N* HCl. Below pH 4, a precipitate appeared. This precipitate was collected by centrifugation and was resuspended in 75 ml of water with vigorous stirring (pH 3). The pH of the solution was adjusted to 5.6 by the addition of 1.49 ml of 1 *N* KOH. Lyophilization gave 523 mg of a dark brown powder (fraction Ea).

The supernatant from the centrifugation was acidified further (pH 1.5) and extracted with four 60-ml portions of ethyl acetate. The dried extract was concentrated to an oil which was redissolved in 40 ml of water to give a solution of pH 2.7. The pH was adjusted to 5.8 by the addition of 1.78 ml of 1 *N* KOH, and the solution was lyophilized to give 566 mg of a brown powder (fraction Eb): ir (KBr) 5.76 (s, ester C=O), 6.3 μ (vs, CO_2^-). Neutralization and lyophilization of the aqueous solution remaining after the ethyl acetate extraction gave lumpy brown material containing much KCl (fraction Ec).

Liberation of Compound 1a from F3. A solution of F3 (350 mg) in 20 ml of water (pH 4.9) was acidified to pH 1.6 with 1 ml of 2 *N* HCl. A few milligrams of a red-brown precipitate were removed by filtration. The clear brown solution was extracted with four 20-ml portions of ethyl acetate, and the extract was dried and concentrated to a brown film. The film was twice dissolved in 5 ml of MeCN and stripped to leave 290 mg of crude **1a** containing a little residual MeCN (^{1}H NMR in Table III). The sample was dissolved in 4 ml of water and lyophilized to an off-white, amorphous powder: uv (MeOH) (ϵ calcd using mol wt 538) 335 nm (sh, 12,000), 310 (14,600), 289 (14,700), 255 (15,700), 225–230 (i, 24,000).

Esterification of 1a. To a solution of 90 mg of **1a** in 2 ml of MeOH and 2 ml of 2,2-dimethoxypropane was added 4 drops of concentrated HCl, and the solution was stirred at room temperature for 3 days. The solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed three times each with water and dilute $NaHCO_3$. The bright yellow bicarbonate washed solution was immediately added to 2 *N* HCl and the gummy precipitate was mostly dissolved during three extractions with CH_2Cl_2. Concentration of the solvent gave a mixture of **1b** and **3b** (ca. 3:1, 50 mg) which would not redissolve in CH_2Cl_2: ^{1}H NMR (100 MHz, acetone-d_6) for **1b** (partial) δ 3.65 and 3.69 (2 s, 6 H, CO_2CH_3), 4.50 (d, J = 5 Hz, H-20), 5.15 (2 d, J = 6, 7 Hz, H-10), 5.92 (d, J = 5 Hz, H-21), 6.29 (d, J = 16 Hz, H-8), 7.22 (d, J = 8 Hz, H-6), 7.74 (d, J = 16 Hz, H-7); for **3b** (partial) 3.69 and 3.72 (2 s, 6 H, CO_2CH_3), 4.48 (d, J = 5 Hz, H-20), 5.89 (d, J = 5 Hz, H-21), 6.28 (d, J = 16 Hz, H-8), 7.20 (d, J = 8 Hz, H-6), 7.70 (d, J = 16 Hz, H-7).

Polyphenolic Acids. A. Direct Isolation from Roots. Whole root powder (100 g) was vigorously stirred with 400 ml of 0.5 *N* HCl at room temperature for 20 min. The root cake was filtered on cotton cloth and saved for separate extraction. The clear filtrate was extracted with six portions of 100 ml each of peroxide-free ethyl ether. From the dried ether extracts, removal of the solvent left 1.86 g of friable brown material (fraction I). The aqueous solution was then extracted with five portions of 100 ml each of ethyl acetate, from which removal of the solvent left 1.19 g of straw-colored product (fraction II). The root cake was also stirred with 200 ml of ethyl acetate for 15 min and filtered; a second similar extraction with ethyl acetate was combined with the first. Removal of the solvent from the combined root cake extracts left a dark brown, friable material weighing 3.33 g (fraction III).

B. Methylation with Diazomethane. Fraction I (1.26 g) in 15 ml of ether and 15 ml of MeOH was treated with ethereal diazomethane prepared[48a] from 5.0 g of *N*-methylnitrosourea and was allowed to stand at room temperature for 3.5 hr. Excess diazomethane was destroyed with dilute HCl. The entire mixture was washed with 1 *N* NaOH, and ethyl acetate was added to dissolve some suspended solid. The dried organic solution yielded 1.12 g of friable, brown, methylated product.

In a similar way and in similar proportions but with a 20-hr reaction time, fractions II and III materials yielded 4.09 g of neutral product. In a larger run, 21.4 g of neutral methylated product was obtained from 22.2 g of combined extract fractions II and III.

C. Separation of (*R*)-2c. On a column (3 × 78 cm) containing 300 g of Florisil (60–100 mesh) packed in benzene was placed 26.0 g of combined neutral products from the methylation of polyphenolic acids II and III. Elution with solvent mixtures of steadily increasing polarity (benzene–ether–ethyl acetate) allowed nearly quantitative recovery of methylated materials.

The initial materials eluted with benzene (1.6 g) were not further investigated, but the subsequent 6.6 g eluted with ether (and increasing amounts of ethyl acetate in ether) gave, after four further column separations, 0.836 g of a viscous liquid. Distillation at 100–140° (bath) (0.02 mm) and two recrystallizations from MeOH gave 0.318 g of (*R*)-**2c**, mp 66°, $[\alpha]^{22}D$ −19.6° (c 0.9, 95% EtOH). Admixture with authentic[18c] (*R*)-**2c** showed no depression of melting point: ir, same as literature;[18c] uv (hexane) 280 nm (ϵ 2800), 231 (8650), 200 (78,000); CD (MeOH) 288 (+0.025), 276 (−0.120), 231 (−2.23), 214 (−1.93), 200 (ca. +9); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.96 (d, $\Delta\delta$ = 6.5 Hz) and 2.99 (d, $\Delta\delta$ = 4.5 Hz) (J_{gem} unobserved, 2 H, $ArCH_2$), 3.76 (s, CO_2CH_3), 3.84 [s, 6 H, $Ar(OCH_3)_2$], 4.40 (2 d, J = 4.5, 6.5 Hz, 1 H, CHOH), 6.76 (s, C_6H_3).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71; O, 33.30; $3CH_3O$, 38.75; mol wt, 240.3. Found: C, 60.06; H, 6.41; O, 33.13; CH_3O, 38.28; mol wt, 241.

Further elution of the initial chromatography column with ether and ethyl acetate brought off a 12.7-g fraction (mol wt 1055), 50% of the material recovered, and two subsequent fractions totaling 4.7 g.

D. Characterization of Pyrazolines. The major (12.7 g) fraction from the preceding chromatogram was rechromatographed on Florisil; elution with benzene and ether brought off only traces of free **2c**. Subsequent elution with ethyl acetate gave the major fraction, 8.0 g (mol wt 854). The mass spectrum of this material changed significantly as the inlet probe temperature of the CH-7 instrument was increased. At all probe temperatures (137–207°) an ion *m/e* 240 (4.2–5.8) corresponding to **2c** and ions *m/e* 222 (38–51), 181 (11–38), and 151 (100) were present. At 160–170° parent ions *m/e* 470 (2.9–4.8) and 472 (0.7–0.8) corresponding to **5b** and **6a** were observed. The former showed a fragment ion *m/e* 411 (2.8–4.7), metastable *m/e* 359.5 (calcd for 470 → 411: *m/e* 359.5), while the latter showed a fragment ion *m/e* 250 (5.1–8.9, M − 222, McLafferty). At temperatures of 171–207° the mass spectrum showed a weak parent ion corresponding to **5a**, *m/e* 678 (0.6–0) with fragment ions *m/e* 650 (11–1.2), 636 (0–2.7), 618 (0.5–3.1), 590 (1.2–6.4), and 351 (24–32). The large fragment ions correspond to the loss of 28 (N_2), 42 (CH_2N_2?), 60 (N_2 and MeOH, the latter loss occurring by the opening of the coumaran ring with reclosure to a lactone), and 88 (N_2, MeOH, and C=O; or N_2 and HCOOMe). All of these large fragment ions show McLafferty rearrangements to ions at F − 222.

E. Saponification of Pyrazolines. A 2.0-g portion of the rechromatographed fraction (mol wt 854) was refluxed with 2.0 g of KOH in 20 ml of 50% aqueous EtOH under N_2 for 15 hr. After removal of the EtOH under reduced pressure, the alkaline solution was extracted with ethyl acetate, acidified with dilute HCl, and reextracted with ethyl acetate. The acids were reesterified with diazomethane and worked up to yield 1.29 g of neutral product. Chromatography on Florisil and distillation of the early chromatography fractions as before gave, after one recrystallization from ether, 340 mg of (*R*)-**2c**, mp 62–63°. Later chromatographic fractions were examined by MS and were found to contain some **5b** (*m/e* 470.175; exact mass calcd for $C_{26}H_{26}N_2O_8$, 470.169), **6b** (*m/e* 264, etc.), and other products. Hydrolyzable adducts **5a** and **6a** were not observed.

F. Reduction of Pyrazolines. Another portion of the rechromatographed fraction (mol wt 854, 2.0 g) was treated with 0.5 g of $LiAlH_4$ in 25 ml of THF. After an initial vigorous reaction, the solution was refluxed for 5 hr. The cooled reaction mixture was cautiously treated with ethyl acetate, water, and dilute HCl. The aqueous solution was extracted with three portions of ethyl acetate. The dried extract yielded 2.1 g of brown liquid on concentration. Chromatography on Florisil and elution with benzene–ether gave early fractions which crystallized from ligroin–ether. Four recrystallizations from benzene–ether gave shining needles of (*R*)-**8**: mp 86.5–87°; ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.66 (d, J = 7 Hz,

$ArCH_2$), 3.02 (s, broad, 2 OH, moves with D_2O), 3.55 (m, 3 H, $OCHCH_2O$), 3.84 [s, 6 H, $Ar(OCH_3)_2$], 6.76 (s, C_6H_3).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.06; H, 7.38.

Acetylation of (*R*)-2c. (*R*)-**2c** (60 mg) was treated in 1 ml of pyridine and 2 ml of ether with 0.25 ml of acetyl chloride and 0.30 ml of acetic anhydride, at first in an ice bath, then at room temperature for 5 hr. The product was washed until neutral and distilled at 120–130° (bath) (0.02 mm) to yield 54.3 mg of viscous liquid (*R*)-**2d:** ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.08 (s, $COCH_3$), 3.02 (d, $\Delta\delta$ = 2 Hz) and 3.13 (s) (J_{gem} unobserved, 2 H, $ArCH_2$), 3.72 (s, CO_2CH_3), 3.86 (s, 6 H, $ArOCH_3$), 5.20 (2 d, J = 6, 8 Hz, 1 H, CHOAc), 6.76 (s, C_6H_3).

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 60.11; H, 6.43.

Saponification of (*R*)-2d. (*R*)-**2d** (56 mg) was heated under reflux in an N_2 atmosphere for 2 hr with 140 mg of KOH in 2 ml of 95% EtOH. The mixture was acidified with 2 *N* HCl and extracted with ethyl acetate, yielding 44.8 mg of brown gum. Treatment in MeOH with charcoal and passage through a short column of alumina, followed by crystallization from benzene–hexane, yielded **2e** in two crystalline forms: long, colorless needles, mp 93–93.5°, and cotton-like material, mp 101.5–102.5°. After standing for 10 years, the long needles melted at 101.5–102.5°. The mixture melting point with synthetic (*R*)-**2e** was undepressed with both samples.

Methyl 3-(3,4-Dimethoxyphenyl)lactate [(*RS*)-2c]. Methyl 3-(3,4-dimethoxyphenyl)glycidate[49] (34 g, mp 63–64°) was hydrogenated in 300 ml of ethyl acetate over 1.6 g of 5% palladium on carbon at 3 atm. After 3 hr the solution was filtered and concentrated to an oil. The oil was dissolved in 50 ml of ethyl acetate–hexane (3:2), and it crystallized slowly after seeding [with crystals of (*RS*)-**2c** obtained by methylation of acid (*RS*)-**2e** with diazomethane] to give 24.3 g (70%) of (*RS*)-**2c:** mp 46.5–48° (lit.[18c] mp 54–55°); ir and ^{1}H NMR same as those of (*R*)-**2c.**

Methyl 2-Acetoxy-3-(3,4-dimethoxyphenyl)propanoate [(*RS*)-2d]. Crude (*RS*)-**2c** from the hydrogenation of 12.2 g of methyl 3-(3,4-dimethoxyphenyl)glycidate was dissolved in 15 ml of pyridine and 15 ml of acetic anhydride was added with chilling. After standing overnight the solution was concentrated at 10 mm, and the residue was dissolved in ether and washed with 2 *N* HCl, water, saturated $NaHCO_3$, and water. The oil obtained after drying and concentration of the solution crystallized from 18 ml of MeOH to give 11.1 g (73%) of (*RS*)-**2d:** mp 57–58°; ^{1}H NMR same as that of (*R*)-**2d;** MS *m/e* (rel intensity) 282 (18), 251 (1), 222 (100), 207 (6), 191 (11), 181 (3), 151 (89); exact mass, 282.1102 (calcd for $C_{14}H_{18}O_6$, 282.1105).

3-(3,4-Dimethoxyphenyl)lactic Acid [(*RS*)-2e]. Crude (*RS*)-**2c** (25 g) was dissolved in 50 ml of chilled MeOH, and a solution of 5.8 g of NaOH in 100 ml of water was added portionwise with stirring. After being stirred overnight at room temperature, the solution was concentrated under reduced pressure, and more water was added. The alkaline solution was washed twice with CH_2Cl_2, acidified to pH 1 with concentrated HCl, and extracted three times with ethyl acetate. The solvent was removed, and the solid product was taken up in a minimum of boiling MeCN. On cooling, (*RS*)-**2e** precipitated in large crystals (13 g, 57%): mp 121–123° (lit.[18c] mp 123–124°); ^{1}H NMR (100 MHz, $CDCl_3$) δ 3.02 (octet) [2.97 (d, $\Delta\delta$ = 7 Hz) and 3.07 (d, $\Delta\delta$ = 4 Hz), J_{gem} = 14 Hz, 2 H, $ArCH_2$], 3.82 (s, 6 H, $ArOCH_3$), 4.45 (2 d, J = 4, 7 Hz, CHOH), 6.77 (s, C_6H_3).

Resolution of 2e. A solution of 5.2 g of (*RS*)-**2e** in 105 ml of warm MeCN was treated with 2.8 g of (−)-α-methylbenzylamine (Aldrich). After chilling and rewarming of the solution, crystallization ensued to give 3 g of the salt, mp 137–141°. Five recrystallizations from MeCN gave 2.03 g of constant-melting crystals, mp 143–145.5°, $[\alpha]^{26}D$ + 29.4° (c 2.0, MeOH).

The salt (178 mg) was dissolved in dilute HCl, and the solution was extracted four times with ethyl acetate. After drying, the solvent was removed and the residue was solidified. The chilling of a toluene solution gave cottony crystals of (*R*)-**2e:** mp 102–103°; $[\alpha]^{26}D$ +29.0° (c 1.3, $CHCl_3$); uv (MeOH) 285 nm (ϵ 2590), 279 (3100), 230 (10,500); CD (MeOH) 287 (+0.04), 271 (−0.04), 233 (−1.90), 214 (−1.23), 196 (ca. +14).

Pentamethyl Rosmarinate [(*RS*)-4b]. A solution of 5.22 g (25.1 mmol) of **7a** and 6.08 g (31.9 mmol) of *p*-toluenesulfonyl chloride in 60 ml of dry pyridine under N_2 was warmed to 80°. The solution colored red-orange on warming, and an orange acylpyridinium salt precipitated while the temperature was maintained for 3 hr. The thick slurry was cooled and 0.46 g (6.8 mmol) of imidazole was added. After 30 min the temperature was 30°; 4.80 g (20 mmol) of (*RS*)-**2c** in 15 ml of pyridine was added. After stirring for 19 hr the solution was poured into 250 ml of 2 *N* HCl. The mixture was extracted four times with ether. The ether layer was washed with 2 *N* HCl and water, and was dried, filtered, and concentrated to give 8.7 g of brown oil. Crystallization from ether–isopropyl ether during 2 days gave 5.48 g of **4b,** mp 81–82.5°. A second crop from ether (0.99 g) brought the overall yield to 77%. Three recrystallizations from ethyl acetate–hexane gave an analytical sample: mp 82–83°; ir (KBr) 5.77, 5.84 (C=O), 6.15 μ (C=C); uv (MeOH) 325 nm (ϵ 22,900), 296 (16,700), 286 (16,100), 260 (5200), 233 (22,000), 217 (21,600); ^{1}H NMR (220 MHz, $CDCl_3$) δ 3.15 (m, CH_2), 3.72, 3.82, and 3.83 (3 s, 9 H, OCH_3), 3.88 (s, 6 H, OCH_3), 5.34 (2 d, J = 5, 8 Hz, CH), 6.30 (d, J = 16 Hz, H-8), 6.72–6.80 (m, H-13, -16, -17), 6.83 (d, J = 8 Hz, H-5), 7.01 (d, J = 2 Hz, H-2), 7.06 (dd, J = 2, 8 Hz, H-6), 7.62 (d, J = 16 Hz, H-7).

Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 64.31; H, 6.17.

3-Methoxycarbonyl-4-(3,4-dimethoxyphenyl)-2-pyrazoline (6b). To a chilled solution of 16 g (67 mmol) of **7b** in 100 ml of ether was added 175 ml of ca. 0.1 *M* ethereal diazomethane[48b] in portions in an ice bath. The reaction flask, fitted with a drying tube, was allowed to stand at 0° for 2 hr, and was stored at room temperature for 12 hr. The excess diazomethane was destroyed by the dropwise addition of 12% acetic acid in ether. The white precipitate was filtered to give 11.6 g (65%) of **6b:** mp 111–114°; ir (KBr) 2.95 (s, NH), 5.86 (s, C=O), 6.42 μ (m); uv (MeOH) 287 nm (ϵ 11,700), 248 (2300), 225 (10,000); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.83 (s, CO_2CH_3), 3.96 (s, 6 H, $ArOCH_3$), 3.9–4.6 (m, 4 H, $CHCH_2$, NH), 6.90 (s, C_6H_3); MS *m/e* (rel intensity) 264 (81), 236 (16), 205 (16), 204 (31), 177 (26), 176 (100); exact mass, 264.1117 (calcd for $C_{13}H_{16}N_2O_4$, 264.1110).

3-(3,4-Dimethoxyphenyl)-1,2-propanediol [(*RS*)-8]. A solution of 0.5 g of (*RS*)-**2c** in 18 ml of ether was added dropwise to 0.20 g of $LiAlH_4$ in 7 ml of ether and the slurry was refluxed for 2 hr. The reaction mixture was decomposed with wet $(NH_4)_2SO_4$ and water, concentrated, extracted three times with ethyl acetate, and concentrated to 0.33 g of a viscous liquid. Distillation at 145–155° (bath) (0.03 mm) gave a liquid which was chromatographed on alumina (III) with ether–ethyl acetate–EtOH. Crystals from later chromatographic fractions gave on recrystallization from benzene–ether (*RS*)-**8,** mp 63–64°, ir and ^{1}H NMR identical with those of (*R*)-**8.**

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.25; H, 8.01.

Base-Catalyzed Methylation of F3. Five grams of F3 was stirred at reflux in 600 ml of dry acetone with 21 ml of freshly distilled dimethyl sulfate and 35 g of anhydrous K_2CO_3. After 18 hr the solid F3 had nearly all dissolved, and the solution was filtered. The solid was washed with acetone, and the combined filtrate was concentrated. The resulting oil was agitated with water at room temperature for several hours and extracted with ethyl acetate. The extract was washed with $NaHCO_3$ solution and with water, dried, and then evaporated under reduced pressure to a neutral oil (5.8 g). Chromatographic fractionation on Florisil (50 g) with benzene–ether–ethyl acetate as eluents was followed by refractionation on both Florisil and alumina (II) columns. Substance **9a** was found in many of the fractions. A sample of ca. 90% purity by ^{1}H NMR criteria had the following spectral properties: ir (KBr) 5.69 (m) and 5.85 (s, ester C=O), 6.12 μ (w, C=C); uv (MeOH) (ϵ calcd using mol wt 650) 315 nm (29,200), 288 (sh, 23,500), 263 (11,100), 233 (31,500); ^{1}H NMR, see Table VI.

The material, a mixture of disastereomers, is not crystalline, but forms a flaky solid on being freed from solvent.

Anal. Calcd for $C_{35}H_{38}O_{12}$: C, 64.61; H, 5.89; O, 29.51; mol wt, 650.7. Found: C, 65.34; H, 5.73; O, 29.02; mol wt, 623, 650.

α-(2,3-Dimethoxyphenyl)-*trans*-3,4-dimethoxycinnamic Acid (10). A solution of 6.33 g (32.6 mmol) of 2,3-dimethoxyphenylacetic acid and 5.34 g (32.2 mmol) of 3,4-dimethoxybenzaldehyde in 12 ml of acetic anhydride–triethylamine (2:1) was refluxed for 7 hr. The reaction mixture was hydrolyzed with water and concentrated HCl and was extracted thoroughly with CH_2Cl_2. The combined organic extracts were washed three times with 2 *N* NaOH and the basic solution was washed twice with CH_2Cl_2. Acidification and reextraction into CH_2Cl_2 gave after drying and concentration an oil which crystallized spontaneously. Recrystallization from 50 ml of MeCN gave, on chilling overnight and partial evaporation of the solvent, two crops of **10,** 3.52 g (31%), mp 186–190°. Several other runs of this condensation in more dilute solutions of acetic anhydride gave significantly lower yields of **10.** Three recrystallizations from MeCN gave the analytical sample: mp 189–191°; uv (MeOH) 315 nm (ϵ 18,000), 288 (16,700), 218 (sh, 27,000).

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.26; H, 5.86. Found: C, 66.33; H, 5.86.

α-Phenyl-*trans*-3,4-dimethoxycinnamic Acid (11a). After being refluxed (ca. 160°) for 15 hr, a solution of 33 g (0.02 mol) of 3,4-dimethoxybenzaldehyde and 40 g (0.29 mol) of phenylacetic acid in 125 ml of acetic anhydride–triethylamine (4:1) was cooled to 90° while 100 ml of water was added slowly at that temperature.[34a] The mixture was cooled slowly to room temperature, and the precipitate was filtered and washed twice with 80% acetic acid. The crude product was boiled in acetic acid (in which it was only slightly soluble), filtered, and washed with MeCN to give after air drying 36 g (60%) of **11a:** mp 229–231° (lit.[50] mp 228°); uv (MeOH) 315 nm (ε 18,000), 293 (15,300), 238 (sh, 13,500), 213 (sh, 21,600).

Ethyl α-Phenyl-*trans*-3,4-dimethoxycinnamate (11b). A mixture of 2.04 g (7.2 mmol) of acid **11a** in 3.5 ml of thionyl chloride and 15 ml of $CHCl_3$ was refluxed until all of the solid had dissolved (3 hr). The volatiles were removed under reduced pressure, and 5 ml of EtOH was added. After the exothermic reaction, the solution was filtered, chilled, and scratched to give **11b,** 1.68 g (75%), in two crops: mp 86–87.5°; ir (melt) 5.86 (C=O), 6.19 μ (C=C); exact mass, 312.138 (calcd for $C_{19}H_{20}O_4$, 312.1361).

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Registry No.—**1a,** 54814-35-6; **1b,** 54844-34-7; (*R*)-**2c,** 54814-41-4; (*R,S*)-**2c,** 54910-31-5; (*R*)-**2d,** 54910-35-9; (*RS*)-**2d,** 54814-42-5; (*R*)-**2e,** 54844-37-0; (*RS*)-**2e,** 54910-33-7; (*R*)-**2e** α-methylbenzylamine, 54844-38-1; **3b,** 54814-36-7; **4a,** 20283-92-5; (*R*)-**4b,** 54814-43-6; (*RS*)-**4b,** 54910-34-8; **6b,** 54814-37-8; **7a,** 14737-89-4; **7b,** 30461-77-9; (*R*)-**8,** 54910-32-6; (*RS*)-**8,** 54844-36-9; **9a,** 54844-35-8; **9b,** 54814-38-9; **10,** 54814-39-0; **11a,** 36854-32-7; **11b,** 54814-40-3; methyl 3,4-(dimethoxyphenyl)glycidate, 39829-15-7; (−)-α-methylbenzylamine, 2627-86-3; *p*-toluenesulfonyl chloride, 98-59-9; 2,3-dimethoxyphenylacetic acid, 90-53-9; 3,4-dimethoxybenzaldehyde, 120-14-9; benzeneacetic acid, 103-82-2.

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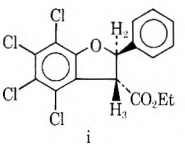
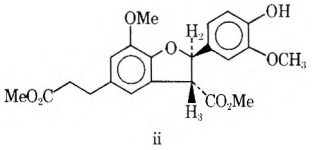
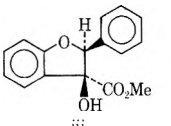


i



ii

was based on the lack of strong shielding of either methoxycarbonyl group, δ 3.67 and 3.80 ($CHCl_3$).[24] In an analysis of the ^1H NMR spectrum of a diastereomeric mixture of iii and iv,[25] the *O*-methyl resonance



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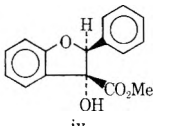

iv

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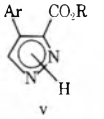
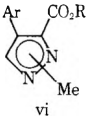


v



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Structure Determination of the *N*-Methyl Isomers of 5-Amino-3,4-dicyanopyrazole and Certain Related Pyrazolo[3,4-*d*]pyrimidines

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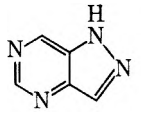
The position of N substitution of certain substituted 4-aminopyrazolo[3,4-*d*]pyrimidine derivatives has been studied by chemical and spectroscopic techniques and has resulted in the assignment of structures to the pyrazole precursors of these compounds. The more abundant pyrazole resulting from treatment of tetracyanoethylene with methylhydrazine [identical with the single pyrazole isomer originally isolated by the same condensation procedure, C. L. Dickinson, J. K. Williams, and B. C. McKusick, *J. Org. Chem.*, **29**, 1915 (1964), which was not characterized definitively with respect to the position of the N substituent] has thus been assigned as 3-amino-4,5-dicyano-1-methylpyrazole on the basis of its conversion to a pyrazolo[3,4-*d*]pyrimidine identical with authentic 4-amino-2-methylpyrazolo[3,4-*d*]pyrmidine, rather than with the authentic 1-methyl isomer. The assigned structure has been verified by X-ray crystallographic determination of 3-amino-4,5-dicyano-1-methylpyrazole. Because 3-amino-4,5-dicyano-1-methylpyrazole would not be expected to be the more abundant pyrazole on the basis of previous work, a mechanism is proposed which accounts for its formation. Also studied was the position of tautomeric equilibrium in 3-amino-4,5-dicyanopyrazole. A consideration of the ^{13}C NMR spectrum of 3-amino-4,5-dicyanopyrazole, relative to those of 5-amino-3,4-dicyano-1-methylpyrazole and 3-amino-4,5-dicyano-1-methylpyrazole, as well as the *N*-acetyl derivatives of all three, indicated that the major tautomer was 5-amino-3,4-dicyano-1*H*-pyrazole. A comparison of the ultraviolet spectrum of this pyrazole with those of the two methylated isomers led to the same conclusion.

The considerable biological and medicinal activities of substituted pyrazolo[4,3-*d*]pyrimidines (**1**) and pyrazolo[3,4-*d*]pyrimidines (**2**) as adenine analogs and antagonists has



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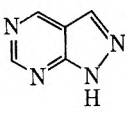


2

contributed to the interest in the pyrazoles from which they are derived synthetically. Of special concern for many years has been a description of the position of N substitution in such pyrazoles. This information is usually not available by simple consideration of the reaction scheme by which a pyrazole is synthesized and appropriate methods for differentiation between such isomeric species are frequently less than obvious.

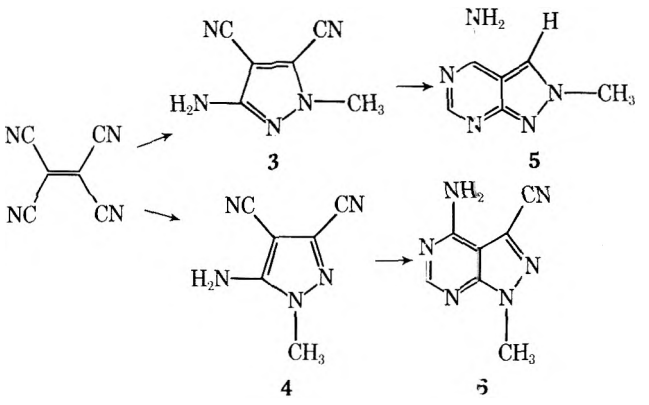
The question of the position of tautomeric equilibrium in pyrazoles which are not N substituted (e.g., **14a** ⇌ **14b**) has also been the subject of several studies,[1-3] as has the existence of individual tautomers as discrete substances.[4,5] Although the position of tautomeric equilibrium has been determined for several compounds by the use of molecular refractions or NMR spectroscopy, and the use of ultraviolet spectroscopy could be envisioned along similar lines, there is no well-established general method for such determinations.

This report is concerned with the chemical and spectroscopic determination of the position of N substitution in the isomeric N-methylated 5-amino-3,4-dicyanopyrazoles and compounds derived therefrom, as well as with the position of tautomeric equilibrium in these pyrazoles.

Results and Discussion

The difficulty in assigning correct structures to N-1- or N-2-substituted pyrazolo[3,4-*d*]pyrimidines can be attributed directly to the lack of available structural information concerning their pyrazole precursors. Substantial effort was expended in early studies in an attempt to prepare and characterize pyrazoles of authentic structure, including methods involving ring closures,[6,7] alkylations,[8,9] and selective dealkylations.[8,10,11] Subsequent studies, however, have rendered questionable many of the preparations of "authentic" samples. In addition, although at least three NMR studies have dealt with the problem of differentiating between isomeric pyrazoles,[2,3,12] the reported methods are not applicable in the present case.

A consideration of the mechanistic routes suggested in the literature for the formation of related pyrazoles illustrates the source of structural ambiguity in the formation of **3** and **4** from methylhydrazine and tetracyanoethylene. One might, for example, envision formation of the compound assigned structure **3** by conjugate addition of the more nucleophilic substituted nitrogen of methylhydrazine

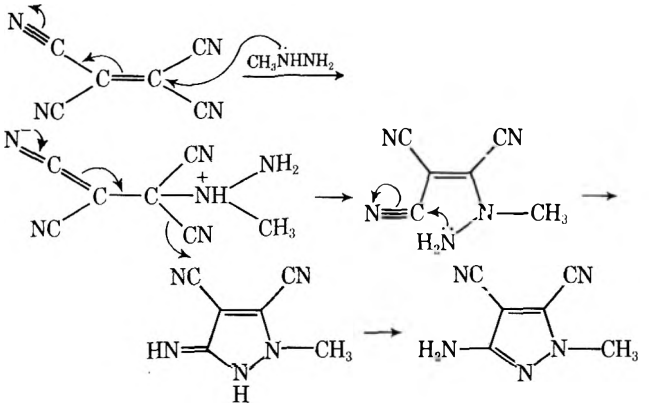


3 5

4 5

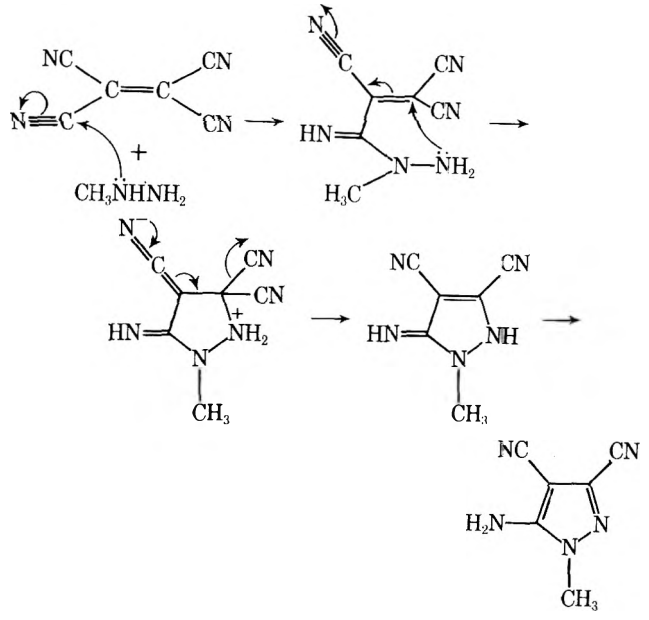
to tetracyanoethylene, followed by addition of the unsubstituted nitrogen of the hydrazine to a cyano group, affording the observed major isomer (Scheme I). Alternatively,

Scheme I



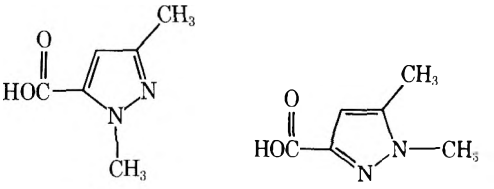
addition of the substituted nitrogen of methylhydrazine to the cyano group might occur first, followed by conjugate addition of the unsubstituted nitrogen to the intermediate olefin to afford pyrazole **4** (Scheme II).

Scheme II



Moreover, although the substituted nitrogen atom in alkylhydrazines might be considered the better nucleophile in such additions,[13] it is also the more hindered nitrogen and reports have appeared in which the reaction products seem to be derived exclusively from initial nucleophilic attack by the unsubstituted nitrogen of methylhydrazine.[14-16] Since nucleophilic attack by the unsubstituted nitrogen atom according to Scheme I or II would afford the isomer opposite to that indicated in each case, the observed 2:1 ratio of **3**:**4** could ostensibly be due to a combination of initial nucleophilic 1,2 and 1,4 addition by a single nitrogen in methylhydrazine, or to nucleophilic attack by either nitrogen of methylhydrazine in a single type (1,2 or 1,4) of addition, or to some combination of these.

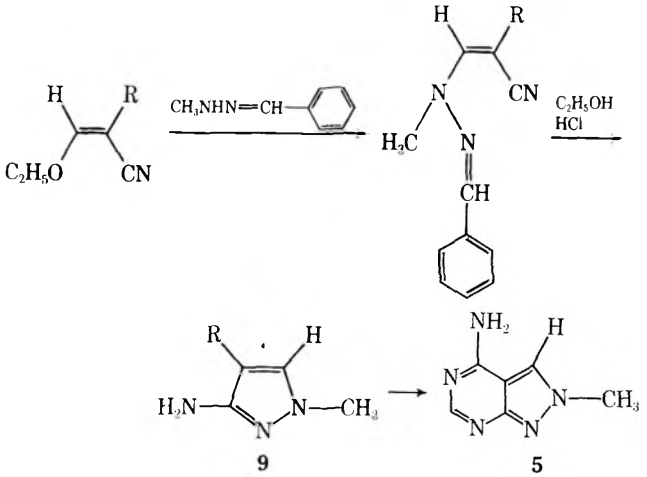
One of the earliest verified[2] examples of differentiation between two isomeric pyrazoles was recorded by von Auwers and Hollmann.[6,11] They were able to assign structures to 1,3-dimethylpyrazole-5-carboxylic acid (**7**) and 1,5-dimethylpyrazole-3-carboxylic acid (**8**) by virtue of the fact



7 8

that only one of the two respective 4-bromo derivatives could be esterified. That derivative was concluded to be related to compound **8**. In the present case, it was found that treatment of pyrazole **3** or 5-amino-3,4-dicyanopyrazole with acetic anhydride or pivaloyl chloride in pyridine at room temperature afforded the corresponding *N*-acetyl or *N*-pivaloyl derivatives in reasonable yield. Pyrazole **4** would not form the corresponding derivatives under the same conditions, but did form them at 50–60°. By analogy with the work of von Auwers and Hollmann,[6,11] this would suggest that the structural assignments for **3** and **4** should be 3-amino-4,5-dicyano-1-methylpyrazole and 5-amino-3,4-dicyano-1-methylpyrazole, respectively, since the amino group in the latter would be expected to be more hindered and therefore less reactive.

Schmidt and his coworkers[14,15] studied the reaction of ethyl ethoxymethylenecyanoacetate with the benzylidene adduct of methylhydrazine. This condensation must necessarily proceed by initial nucleophilic attack of the methyl-substituted nitrogen in methylhydrazine. Indeed, the initial adduct resulting from 1,4 addition was isolated and characterized, then shown to form 3-amino-4-carboethoxy-1-methylpyrazole (**9a**) when treated with ethanolic hydrochloric acid. The same reaction was carried out with ethoxymethylenemalononitrile to afford authentic 3-



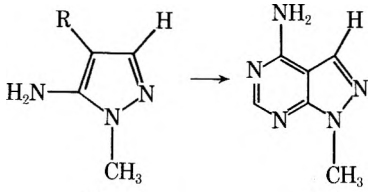
9 5

amino-4-cyano-1-methylpyrazole (**9b**). Analogous reaction utilizing methylhydrazine afforded, in each case, the isomeric pyrazoles, assumed to be 5-amino-4-carboethoxy-1-

Table I
Ultraviolet Spectra of Methylated 4-Aminopyrazolo[3,4-*d*]pyrimidines

Compd	λmax Acid	λmax Neutral	λmax Base
5[a]	268	289, 280 (sh), 266 (sh)	288, 281 (sh), 267 (sh)
4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine[b]	259	277, 268, 261	275, 262
4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine[b]	268	287, 270 (sh)	287

[a] Spectrum recorded in absolute ethanol. [b] Reference 18.



10 11

a, R = $COOC_2H_5$
b, R = CN

methylpyrazole (**10a**) and 5-amino-4-cyano-1-methylpyrazole (**10b**), respectively. Cyclizations of **9b** and **10b** were carried out[14,16] to afford authentic samples of 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine (**5**) and 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine (**11**), respectively. Montgomery et al.[17] have also reported the syntheses of the 1- and 2-β-D-ribofuranosyl derivatives of 4-aminopyrazolo[3,4-*d*]pyrimidine, which were assigned structures by comparison of their ultraviolet spectra with those of **5** and **11**.[18]

Treatment of tetracyanoethylene with methylhydrazine was reported to afford one *N*-methylpyrazole.[13] In our hands, the reaction afforded both possible *N*-methyl isomers, with the major product (53%) being the same as that reported in the literature. The two isomers were separated by chromatography on silica gel and the minor isomer was treated successively with triethyl orthoformate and ammonia,[19] thus effecting conversion to 4-amino-3-cyano-1-methylpyrazolo[3,4-*d*]pyrimidine (**6**). Similar ring closure of the more abundant pyrazole afforded a compound whose elemental analysis was consistent with the formula $C_7H_6N_6 \cdot C_2H_5OH$. The absence of a nitrile absorption in the infrared spectrum and the presence of a peak at *m/e* 220 in the mass spectrum suggested that this compound may have been ethyl 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine 3-carboximidate rather than 4-amino-3-cyano-2-methylpyrazolo[3,4-*d*]pyrimidine itself. This species was treated with aqueous sodium hydroxide to afford the corresponding 3-carboxylate, which was then fused to effect decarboxylation, thus yielding 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine (**5**). The ultraviolet spectrum of **5** was compared with those reported for authentic samples of 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine[16] and 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine.[14] As shown in Table I, the ultraviolet spectrum of **5** closely resembled that of the compound believed to be authentic 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine, rather than that of the authentic 1-methyl isomer. This may be more fully appreciated by a comparison of the ultraviolet spectrum of **5** with those of ribonucleoside analogs **12** and **13** (Figure 1), which were originally prepared by Montgomery et al.[17] and assigned structures by correlation of their ultraviolet spectra with

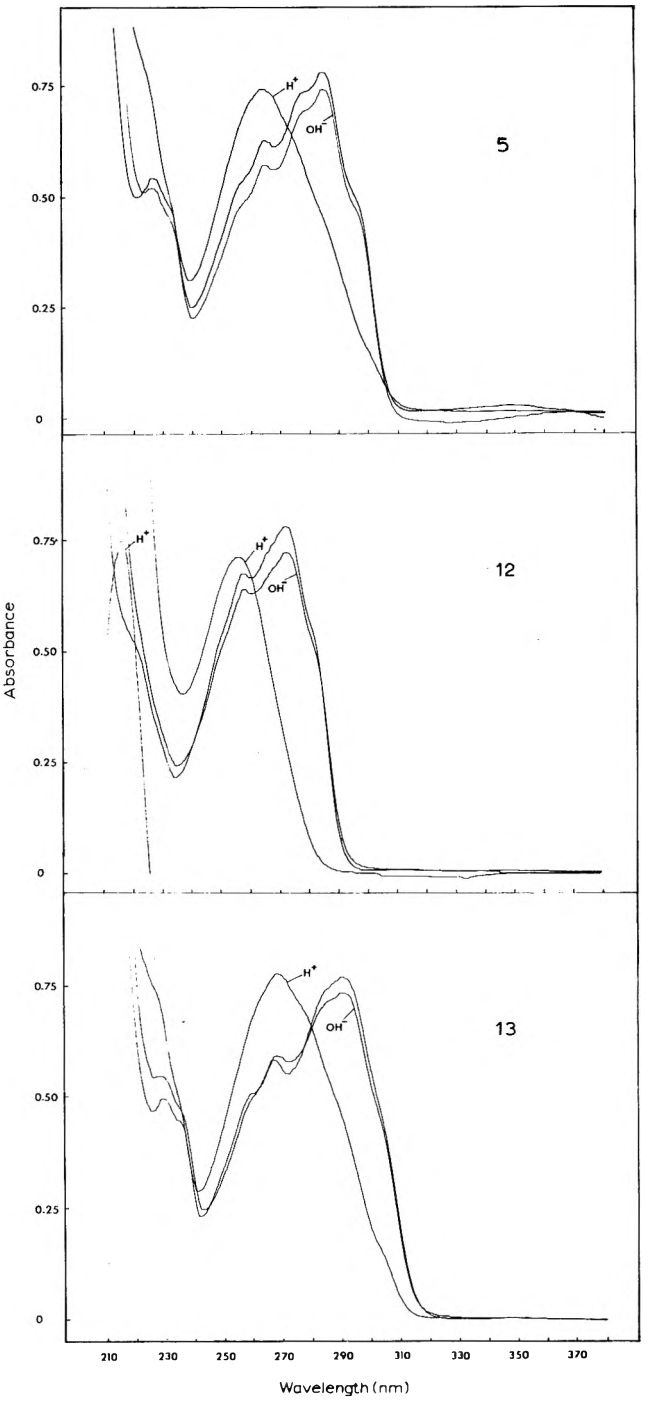
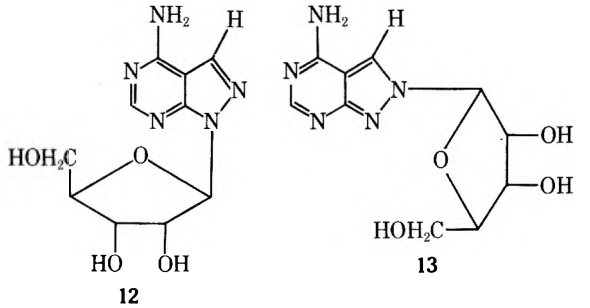


Figure 1. Comparison of the ultraviolet spectra of 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine (**5**), 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**12**) and 4-amino-2-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**13**) in water at pH 1, 7, and 12.



12 13

those of authentic **5** and **11**.[20] This suggested strongly that the compound assigned structure **5** was best represented as 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine and that **3** was

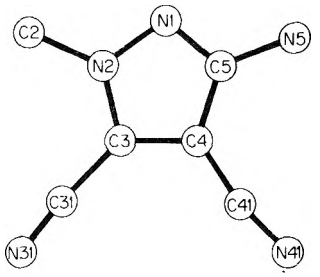


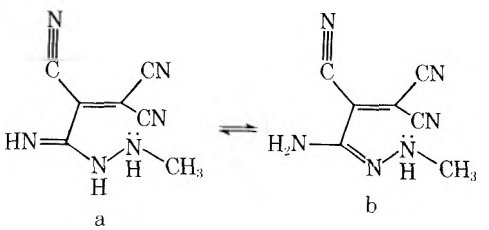
Figure 2. Relative positions of the nonhydrogen atoms in compound **3**, as determined by X-ray structure analysis.

3-amino-4,5-dicyano-1-methylpyrazole. The less abundant pyrazole was therefore assigned as 5-amino-3,4-dicyano-1-methylpyrazole (**4**) and its corresponding cyclized derivative **6** as **4**-amino-3-cyano-1-methylpyrazolo[3,4-*d*]pyrimidine.[25]

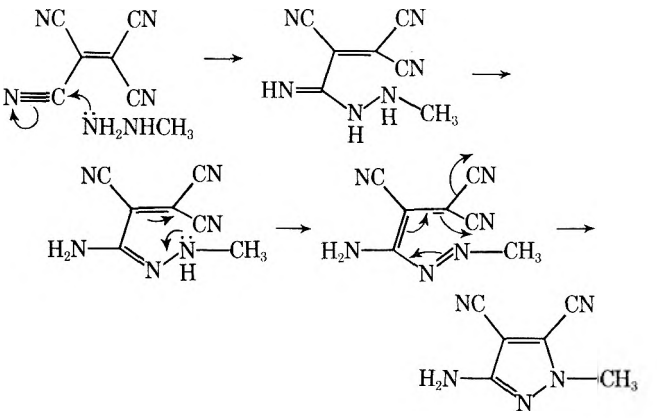
To verify the structures determined for the isomeric N-methylated pyrazoles, an X-ray structure analysis was carried out on the lower melting isomer of *N*-methyl-5-amino-3,4-dicyanopyrazole, which was identical with that isolated previously by Dickinson et al.[13] The X-ray structure determination indicated that the compound was 3-amino-4,5-dicyano-1-methylpyrazole (Figure 2), in agreement with the results obtained from chemical and spectroscopic studies.[27]

Previous studies of the condensation of monoalkyl and aryl hydrazines with ethoxymethylenemalonitrile and ethyl ethoxymethylenecyanoacetate indicated in each case the formation of pyrazoles identical with those which would form if the condensation were initiated by conjugate addition of the unsubstituted nitrogen of the alkyl or aryl hydrazine.[14-16] These findings were inconsistent with the prediction that alkyl and aryl hydrazines should afford pyrazoles of opposite N substitution, derived from initial conjugate addition by the more nucleophilic substituted and unsubstituted nitrogens, respectively.[13] The latter prediction finds superficial support in the present case, since the formation of 3-amino-4,5-dicyano-1-methylpyrazole (**3**) as the major condensation product of tetracyanoethylene and methylhydrazine would not be expected by analogy with the work of Schmidt et al.[14,15] and Cheng and Robins.[16]

However, the formation of **3** according to Scheme I, as indicated by Dickinson et al.,[13] would seem even less favorable than the corresponding additions of methylhydrazine to ethyl ethoxymethylenecyanoacetate and ethoxymethylenemalonitrile in the sense that the latter two involve additions to less hindered, more polarized double bonds and afford intermediate anions which are less electron deficient. That the additions of methylhydrazine to ethyl ethoxymethylenecyanoacetate and ethoxymethylenemalonitrile do not proceed via initial conjugate addition of the substituted nitrogen would seem to exclude the possibility that the less favorable addition to tetracyanoethylene can occur in this sense. The formation of compound **3** might also be thought to proceed by 1,2 addition of the unsubstituted nitrogen of methyl hydrazine to afford species a followed by cyclization via conjugate addition. Although this scheme is certainly plausible, the conjugate addition must

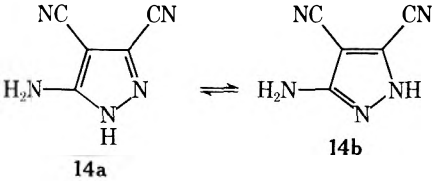


Scheme III

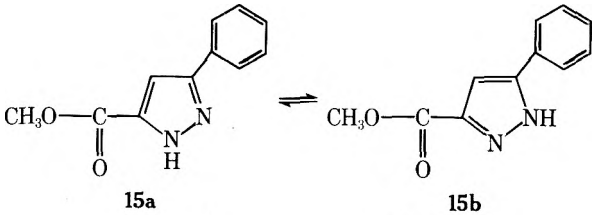


take place in the less favorable sense and the nucleophilicity of the methylated nitrogen is diminished by whatever tautomerization occurs between forms a and b. What may represent a more reasonable pathway to explain the formation of **3** is outlined in Scheme III, in which the condensation is initiated by 1,2 addition of the unsubstituted nitrogen of methylhydrazine to tetracyanoethylene.

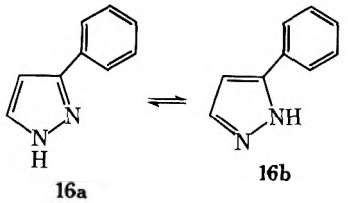
Also of interest for many years has been a description of the relationship between pyrazole tautomers (e.g., **14a** and **14b**). In the early literature, unsuccessful attempts to isolate individual tautomers were reported and these prompted the conclusion that the two forms were indistinguishable. In spite of the work of von Auwers,[1] which indicated that **15a** and **16a** were the predominant tautomeric species



14a **14b**



15a **15b**



16a **16b**

and that the 3 and 5 positions were therefore not equivalent, the belief that pyrazoles were properly represented as species in which the nitrogens were identical continued for some time. Hayes and Hunter,[4] e.g., indicated that pyrazoles existed as aggregates over which individual N-bound hydrogen atoms were delocalized and Hunter[5] later formulated this principle in general terms as "mesohydric tautomerism". Although evidence does exist for intermolecular hydrogen bonding in pyrazoles,[2,4] such bonds would not be symmetrical with respect to the heteroatoms to which they are attached so that the existence of distinct tautomers is possible.

The study of pyrazole tautomerism might in principle be facilitated by the use of ultraviolet spectroscopy, providing only that the particular isomers of interest have distinctly

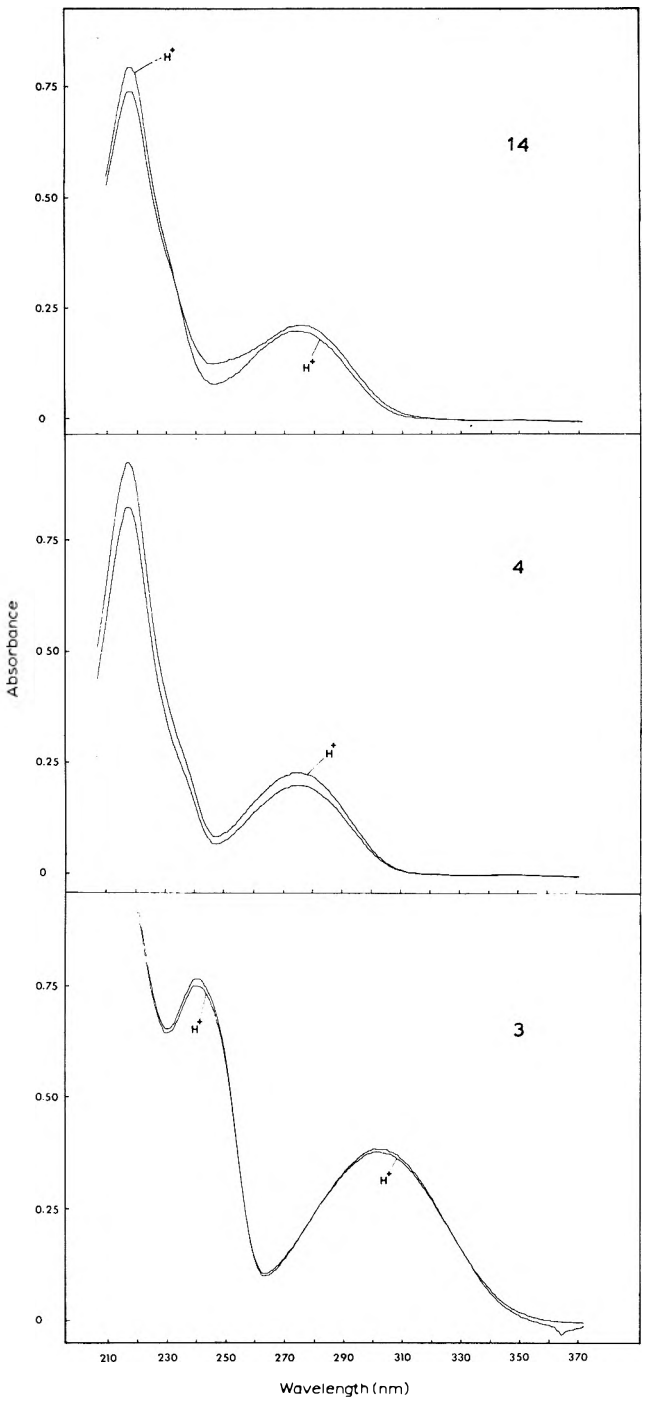


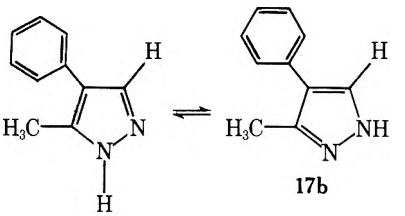
Figure 3. Ultraviolet spectra of 5-amino-3,4-dicyanopyrazole (**14**), 5-amino-3,4-dicyano-1-methylpyrazole (**4**), and 3-amino-4,5-dicyano-1-methylpyrazole (**3**). The spectra were determined in aqueous acid, pH 1, and in 0.01 *M* phosphate buffer, pH 6.7.

different spectra. Unfortunately, the differences between such isomers have sometimes been inadequate.[2] It has also been shown that proton magnetic resonance spectroscopy can be utilized to identify the major tautomeric species. Habraken and Moore,[2] e.g., showed that the chemical shift differences between the 3(5)-H proton absorption and those due to methyl and phenyl resonances in **17** were closer in magnitude to the corresponding chemical shift differences in **18** than to those in **19**, thus providing evidence that **17a** was the major tautomeric form of **17**. The original assignment of tautomeric preference to several 3(5)-phenylpyrazoles by von Auwers[1] was based on the molecular refractions of these pyrazoles as compared with those derived from the two N-alkylated derivatives of each 3(5)-phenylpyrazole.

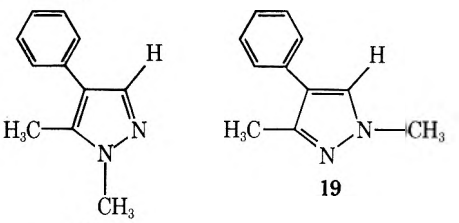
Table II
Carbon-13 Chemical Shifts

	Compd					
Carbon atom	14	4	3	20	21	22
C-3	128.3	126.5	120.6	128.7	128.3	120.6
C-4	78.5	78.9	84.6	86.7	94.1	92.1
C-5	156.3	155.1	160.3	146.6	145.3	147.3
CN	115.6[b]	115.1[b]	111.6[b]	114.1[b]	113.4[b]	108.3[b]
CN	115.6[b]	115.1[b]	114.8[b]	115.1[b]	114.3[b]	110.8[b]
NCH_3		38.8	41.9		40.9	39.6
$CO^{13}CH_3$				26.0	25.9	22.3
CO				172.5	172.0	168.8

[a] Downfield from tetramethylsilane. [b] No attempt was made to assign these resonances to a specific CN group.



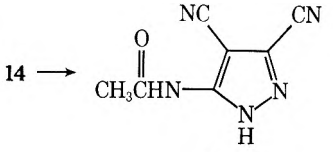
17a **17b**



18 **19**

In the present case the study of the tautomeric equilibrium was facilitated by the characteristic chromophores associated with the methylated pyrazoles **3** and **4**. As shown in Figure 3, the ultraviolet spectra of **14** and **4** were essentially identical in the position and intensity of absorption maxima at pH 1 and 6.7, while that of **3** was different from **14** and **4** at both measured pH values. The similarity of the spectra of **14** and **4** suggested that the major tautomeric form of **14** was **14a**.

Also considered in this context were the ^{13}C NMR spectra of compounds **3**, **4**, **14**, and **20–22**. The obvious similarity of the spectra of pyrazoles **14** and **4** and their acetylated derivatives **20** and **21** (Figure 4, Table II), as compared



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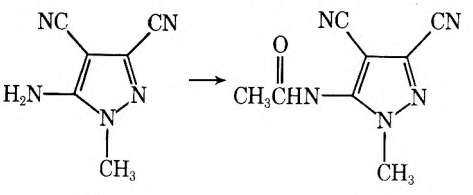
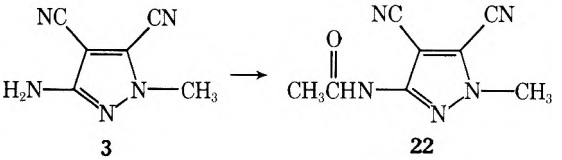


4 **21**



3 **22**

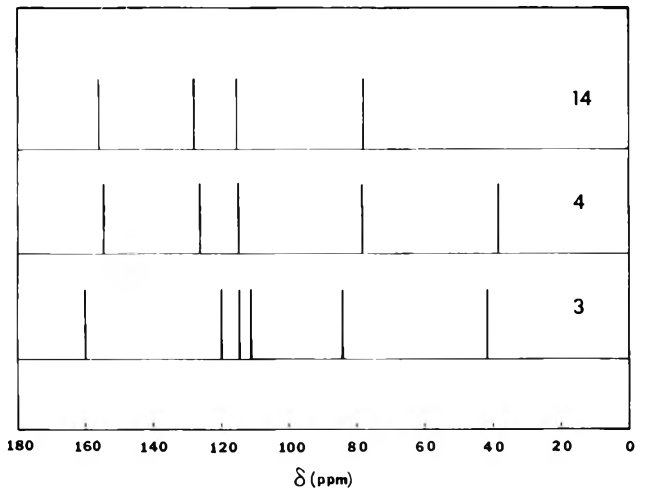


Figure 4. [^{13}C] NMR spectra of 5-amino-3,4-dicyanopyrazole (**14**), 5-amino-3,4-dicyano-1-methylpyrazole (**4**), and 3-amino-4,5-dicyano-1-methylpyrazole (**3**). The chemical shifts are given with respect to external TMS. Positive values represent decreased shieldings.

with the spectra of **3** and **22**, respectively, supported the hypothesis that **14a** was the major tautomer. The similarity of the spectra, of course, must necessarily be regarded in light of the spectral change which one would expect to accompany the formal N-methylation of a pyrazole.[28] For the unsubstituted pyrazole case, "methylation" changed the chemical shifts of carbons 3, 4, and 5 by a total of 9.4 ppm in absolute terms. This compared somewhat more favorably with the observed absolute change in chemical shifts accompanying the formal methylation of **14** to give **4** (3.4 ppm, 4.4 ppm with the cyano groups) than for absolute change associated with the formal conversion of **14** to **3** (17.8 ppm, 22.6 ppm with the cyano groups) and suggested that pyrazole **4** was structurally related to the major tautomer of **14**. A more definitive result was obtained corresponding to the formal methylation of **20** to yield **21** (9.1 ppm, 10.6 ppm with the cyano groups) and **22** (14.2 ppm, 24.3 ppm with the cyano groups), suggesting that **21** was structurally related to the major tautomer of **14**.

The known chemical shift differences of C-3, C-4, and C-5 in the spectra of pyrazole and 1-methylpyrazole may also be used to calculate the spectra of **4** and **3** from the recorded spectrum of **14**. Representation of the major tautomer as **14a** afforded calculated C-3, C-4, and C-5 values for **4** of 133.2, 79.0, and 152.3 ppm (Table II), based on the expected chemical shift differences[28] of 4.9, 0.5, and −4.0 ppm, respectively. This would imply that carbons 3, 4, and 5 in compound **3** must be related to carbons 5, 4, and 3 in the major tautomer, so that the calculated values of C-3, C-4, and C-5 for **3** (numbered as in **3**) would be 124.3, 79.0, and 161.2 ppm, based on expected respective shifts of −4.0, 0.5, and 4.9 ppm. The total difference between these six values and the observed values was 19.8 ppm. If, on the other hand, it was assumed that **14b** was the major tautomer, the total difference between the observed and calculated values of the six chemical shifts in **4** and **3** was 34.6 ppm. The better agreement between observed and calculated spectra in the former case again suggested that **14a** was the major tautomer. The same calculations, when carried out on the acetyl derivative **20**, afforded a value of 28.1 ppm on the assumption that the *N*-acetyl derivative of **14a** was the major tautomer and 39.3 ppm if the other tautomer was assumed to predominate, consistent with the results obtained for compounds **14**, **4**, and **3**.

Elguero et al.[29] have recently reported on the ^{13}C NMR spectra of a number of azoles, including several pyrazoles, and concluded that the ^{13}C chemical shifts were of limited value in ascertaining the position of tautomeric equilibrium. Interestingly, when the additivity relationship presented here for such determinations was applied to the data reported by Elguero et al.,[29] a definite tautomeric preference was indicated, e.g., for 3(5)-methylpyrazole, 3(5)-phenylpyrazole, and 3(5)-methyl-5(3)-phenylpyrazole. The first two were predicted to exist as the 3-substituted 1*H*-pyrazoles and the third as 3-phenyl-5-methyl-1*H*-pyrazole. Although no independent verification can be made of the assignment of tautomeric preference to 3(5)-methylpyrazole, the latter two assignments are consistent with those made by von Auwers,[1] who reached the same conclusion by a study of the molecular refractions of these two compounds and their *N*-methyl and *N*-ethyl derivatives.

Experimental Section

Ultraviolet spectra were recorded on a Cary 15 uv spectrophotometer; measurements in ethanol at low or high pH were taken after the addition of 1 *N* aqueous HCl or 4 *N* aqueous NaOH, respectively. Infrared spectra were recorded on a Perkin-Elmer 457A spectrophotometer and mass spectra on a Perkin-Elmer Hitachi RMU-6 spectrometer using a direct inlet. Melting points were determined on a Thomas-Hoover apparatus and are corrected. Elemental analyses were determined by Chemalytics, Inc., or by Scandinavian Microanalytical Laboratory.

^{1}H NMR spectra were recorded on a Varian Associates T-60 NMR spectrometer. The carbon-13 NMR spectra of **1**–**6** were obtained at 22.63 MHz using a Bruker HFX-90 interfaced with a Digilab FTS/NMR-3 data system. Either DMSO or DMF was employed as the solvent and the reference.[30] The chemical shifts reported in Table I are in parts per million with respect to external tetramethylsilane (TMS) and were converted from the original data using $\delta_{DMSO} = 40.4$ or $\delta_{DMF} = 162.4$. Positive values represent decreased shieldings.

X-Ray Structure Analysis. A sample suitable for X-ray structure analysis, identical with the pyrazole originally isolated from the condensation of tetracyanoethylene with methylhydrazine,[13] was obtained by crystallization of the lower melting *N*-methylpyrazole from 50% aqueous methanol. Preliminary film data indicated the systematic absences $h0l$, $l = 2n + 1$, and $0k0$, $k = 2n + 1$; hence the space group was $P2_1/c$. The cell constants, determined from 12 medium angle reflections measured on a Picker automatic diffractometer with nickel filtered Cu Kα ($\lambda = 1.5418$ Å) radiation, were found to be $a = 6.199 \pm 0.003$ Å, $b = 15.168 \pm 0.005$ Å, $c = 7.646 \pm 0.003$ Å, and $\beta = 91.95 \pm 0.04°$. Complete three-dimensional intensity data were collected on the diffractometer up to a 2θ of 128°, employing the θ–2θ scan technique. A total of 1062 independent reflections were recorded of which 920 were considered observed [$I > 1.5\ \sigma(I)$] and were used in the structure analysis. The structure was solved by employing a combination of direct methods, trial and error, and difference Fourier techniques. The *R* value after block-diagonal least-squares refinement using anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms was 0.07. The X-ray structure conforms to the chemical structure 3-amino-4,5-dicyano-1-methylpyrazole.

3-Amino-4,5-dicyano-1-methylpyrazole (3) and 5-Amino-3,4-dicyano-1-methylpyrazole (4). To a solution of 4.03 g (85.4 mmol) of methylhydrazine in 160 ml of water was added 10.93 g (87.6 mmol) of tetracyanoethylene in one portion. The resulting suspension was stirred at 0° for 1 hr and then heated on a steam bath for 45 min. The cooled solution was refrigerated for several hours and the precipitated solid was separated by filtration and air dried. The crude product, containing both **3** and **4**, was purified by chromatography on silica gel (3 × 9.5 cm) and elution with 9:1 chloroform–ethyl acetate to remove the major isomer (**3**) and then with ethyl acetate to remove the more polar isomer (**4**). The major isomer, mp 133–134°, was further purified by crystallization from water to afford **3** as colorless needles: yield 6.66 g (53%); mp 135–135.5° (lit.[13] mp 131.5–133°); λ_{max} (EtOH) (pH 1) 302 nm (ϵ 4700) and 239 (9300), λ_{min} 264 (800) and 229 (8100); λ_{max} (EtOH) (pH 7) 302 (4700) and 239 (9300), λ_{min} 263 (800) and 229 (8300); λ_{max} (EtOH) (pH 11) 298 (3700) and 240 (8400), λ_{min} 267 (2200) and 231 (7700); MS *m/e* 147, 122, 121, 120, 119, 104, 77, and 76; ir (Nujol) 3440, 3350, 3220, 2955, 2920, 2850, 2245, 2225, 1630, 1550, and 1520 cm^{-1}.

The more polar isomer, mp 238–242°, was further purified by preparative TLC on silica gel, elution with ethyl acetate, and finally by crystallization from ethanol and from ethyl acetate to afford **4** as colorless crystals: yield 3.38 g (27%); mp 244–247° (lit.[13] mp 243–245°); λ_{max} (EtOH) (pH 1) 275 nm (ϵ 4800) and 218 (21,000), λ_{min} 246 (2000); λ_{max} (EtOH) (pH 7) 274 (4600) and 218 (21,000), λ_{min} 247 (1700); λ_{max} (EtOH) (pH 11) 275 (4400), λ_{min} 257 (2700); MS *m/e* 147, 121, 120, 119, 104, 77, and 76; ir (Nujol) 3400, 3340, 3255, 3220, 2960, 2920, 2850, 2255, 2230, 1650, 1585, and 1510 cm^{-1}.

Anal. Calcd for $C_6H_5N_5$: C, 48.97; H, 3.42. Found: C, 48.76; H, 3.58.

4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine (5). A solution of 1.62 g (10.9 mmol) of 3-amino-4,5-dicyano-1-methylpyrazole (**3**) in 17 ml of triethyl orthoformate was heated to reflux for 7 hr. Excess orthoformate was removed under diminished pressure and the crystalline residue was dissolved in 35 ml of absolute ethanol and added dropwise at room temperature to a stirred solution of ethanol previously saturated with ammonia. The reaction mixture was stirred for 24 hr and the white precipitate which formed in quantitative yield was filtered: mp 238–242° dec; λ_{max} (EtOH) (pH 1) 295 nm, 281 (sh), and 248, λ_{min} 256 and 236; λ_{max} (EtOH) (pH 7) 308, 280, 269, and 252, λ_{min} 286, 275, 266, and 239; λ_{max} (EtOH) (pH 10) 305, 279, and 248, λ_{min} 285, 276, and 241 (Figure 2); MS *m/e* 220, 174, 158, 147, and 146; ir (Nujol) 3170, 1690, 1640, 1590, 1530, and 1480 cm^{-1}.

Anal. Calcd for $C_7H_6N_6 \cdot C_2H_5OH$: C, 49.07; H, 5.49. Found: C, 49.03; H, 5.15.

A suspension of this material (84 mg, 0.49 mmol) in 6 ml of 5% sodium hydroxide solution was warmed to 50° for 4 hr. Filtration afforded a clear solution which was acidified with dilute hydrochloric acid. After a few hours 4-amino-3-carboxy-2-methylpyrazolo[3,4-*d*]pyrimidine separated as colorless crystals: yield 73 mg (90%); mp > 300°; λ_{max} (EtOH) (pH 1) 313 nm, 302, 280 (sh), and 244, λ_{min} 310, 258 and 227; λ_{max} (EtOH) (pH 7) 297 (sh), 290, 280 (sh), and 240, λ_{min} 255 and 229, λ_{max} (EtOH) (pH 10) 302, 270 (sh), and 243, λ_{min} 258 and 233 (Figure 2); MS *m/e* 193, 149, 133, and 122.

Anal. Calcd for $C_7H_7N_5O_2 \cdot H_2O$: C, 39.80; H, 4.29. Found: C, 40.15; H, 4.35.

A portion of the carboxylic acid was pyrolyzed to afford a dark brown residue which was triturated with hot water, treated with charcoal to afford a clear solution, and then concentrated to give a white solid in 43% yield: mp >300° dec; λ_{max} (EtOH) (pH 1) 268 nm, λ_{min} 242; λ_{max} (EtOH) (pH 10) 288, 281 (sh), and 267 (sh), λ_{min} 242; MS *m/e* 149, 122, 107, 104, and 94.

4-Amino-3-cyano-1-methylpyrazolo[3,4-*d*]pyrimidine (6). Compound **6** was synthesized from 5-amino-3,4-dicyano-1-methylpyrazole and triethyl orthoformate by analogy with the synthesis of **5:** yield 75%; mp 309–312°; λ_{max} (EtOH) (pH 1) 286 nm (sh), 276 (ϵ 9900), 270 (sh), 241 (sh), 235 (12,000), and 228 (sh), λ_{min} 250 (5900) and 218 (10,800), λ_{max} (EtOH) (pH 7) 293 (sh), 286 (12,600), 241 (sh), and 237 (9700), λ_{min} 252 (4300) and 226 (7500); λ_{max} (EtOH) (pH 10) 292 (sh), 283 (11,100), and 243 (10,300), λ_{min} 258 (6700) and 226 (8100) (Figure 2); ir (Nujol) 3435, 3320, 3060, 2920, 2235, 1665, 1590, 1530, and 1515 cm^{-1}.

Anal. Calcd for $C_7H_6N_6$: C, 48.25; H, 3.47. Found: C, 48.34; H, 3.19.

5-Acetamido-3,4-dicyanopyrazole (20). To a solution of 400 mg (3.0 mmol) of 5-amino-3,4-dicyanopyrazole (**14**)[13] in 10 ml of pyridine was added 8.6 ml of acetic anhydride. The reaction mixture was maintained at room temperature for 16 hr, then concentrated under diminished pressure to afford a solid residue which was crystallized from ethanol (decolorization) to give colorless crystals of **20:** yield 364 mg (69%); mp 266.5–267° dec (lit.[13] mp 250° dec); λ_{max} (EtOH) (pH 1) 243 nm and 215, λ_{min} 231; λ_{max} (EtOH) (pH 7) 243 and 216, λ_{min} 230; ir (Nujol) 3270, 3120, 3070, 2960, 2920, 2855, 2250, 1710, 1705, 1685, and 1590 cm^{-1}.

5-Acetamido-3,4-dicyano-1-methylpyrazole (21). To a solution of 147 mg (1.0 mmol) of 5-amino-3,4-dicyano-1-methylpyrazole (**4**)[13] in 3.4 ml of pyridine was added 2.8 ml of acetic anhydride. The reaction mixture was maintained at room temperature for 24 hr, which afforded no change, and then at 50° for 14 hr. The solution was concentrated under diminished pressure to give a yellow solid which was decolorized with charcoal and then purified by chromatography on silica gel and crystallization from ethanol to afford **21** as colorless crystals: yield 127 mg (67%, 84% based on consumed starting material); mp 167°; λ_{max} (EtOH) (pH 10) 258 nm, λ_{min} 250 nm; MS *m/e* 189, 174, 161, 148, 147, and 146; ir (Nujol) 3180, 2960, 2920, 2850, 2245, 1685, and 1545 cm^{-1}.

Anal. Calcd for $C_8H_7N_5O$: C, 50.79; H, 3.73. Found: C, 50.53; H, 3.64.

The isomeric 3-acetamido-4,5-dicyano-1-methylpyrazole (**22**) was obtained from 3-amino-4,5-dicyano-1-methylpyrazole (**3**) as above, except that the reaction mixture was maintained at room temperature for 24 hr or at 60° for 5 hr. The product was obtained as colorless crystals from ethanol (decolorization): yield 41%; mp 172–173°; λ_{max} (EtOH) (pH 1) 271 nm and 223, λ_{min} 257; λ_{max} (EtOH) (pH 7) 271 and 223, λ_{min} 257; λ_{max} (EtOH) (pH 10) 305 and 237, λ_{min} 283 and 231; ir (Nujol) 3200, 2960, 2920, 2850, 2235, 1725, 1675, 1585, and 1510 cm^{-1}.

3,4-Dicyano-5-trimethylacetamidopyrazole. A solution of 408 mg (3.06 mmol) of 5-amino-3,4-dicyanopyrazole[13] in 10 ml of pyridine was added dropwise to a cooled, stirred solution of 406 mg (3.35 mmol) of pivaloyl chloride in 5 ml of pyridine. The combined solution was stirred at room temperature for 14 hr and then concentrated under diminished pressure to afford a yellow, crystalline product which was recrystallized from ethanol (decolorization) to give colorless crystals of the pivaloyl derivative: yield 380 mg (66%); mp 199–199.5°; λ_{max} (EtOH) (pH 1) 298 nm, 262 (sh), and 256, λ_{min} 272 and 239; λ_{max} (EtOH) (pH 7) 298, 262 (sh), and 256, λ_{min} 272 and 239; λ_{max} (EtOH) (pH 10) 277 and 246, λ_{min} 264 and 236; ir (Nujol) 3440, 3310, 3235, 3160, 2960, 2920, 2855, 2235, 2230, 1725, 1715, 1635, 1550, and 1505 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10. Found: C, 55.23; H, 4.93.

3,4-Dicyano-1-methyl-5-trimethylacetamidopyrazole. To a solution containing 179 mg (1.22 mmol) of 5-amino-3,4-dicyano-1-methylpyrazole (**4**) in 5 ml of pyridine was added dropwise a solution containing 202 mg (1.66 mmol) of pivaloyl chloride in 3 ml of pyridine. The reaction mixture was warmed to 50° for 3 hr, which afforded no change, and then to 60° for 13 hr. The solution was concentrated under diminished pressure to afford a residue which was crystallized from ethanol (decolorization) to afford 67 mg of **4.** The mother liquors were purified by preparative silica TLC and elution with ethyl acetate, to afford an additional 20 mg of **4** as well as the desired product, which gave colorless crystals from ethanol: yield 87 mg (31%, 60% based on consumed **4**); mp 174.5–176°; λ_{max} (EtOH) (pH 10) 262 nm, λ_{min} 252; MS *m/e* 231, 230, 217, 216, 203, 202, 188, 187, 174, 173, 172, 148, 147, and 146; NMR (DMSO-d_6) δ 1.33 (s, 9 H) and 3.80 (s, 3 H).

The isomeric 4,5-dicyano-1-methyl-3-trimethylacetamidopyrazole was obtained from 3-amino-4,5-dicyano-1-methylpyrazole (**3**) as above, except that the reaction mixture was maintained at room temperature for 14 hr. The product was obtained as white crystals after recrystallization from ethanol (decolorization): yield 80%; mp 174.5–175°; λ_{max} (EtOH) (pH 1) 265 nm and 222, λ_{min} 258; λ_{max} (EtOH) (pH 7) 265 and 222, λ_{min} 258; MS *m/e* 231, 217, 216, 203, 189, 188, 174, 160, 148, 147, and 146; NMR (DMSO-d_6) δ 1.25 (s, 9 H) and 4.00 (s, 3 H).

Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67. Found: C, 56.96; H, 5.63.

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Registry No.—3, 54385-48-7; **4,** 50680-85-8; **5,** 21230-48-8; **6,** 42204-41-1; **12,** 3258-05-7; **13,** 3258-06-8; **14,** 54385-49-8; **20,** 54385-50-1; **21,** 54385-51-2; **22,** 54385-52-3; methylhydrazine, 60-34-4; tetracyanoethylene, 670-54-2; triethyl orthoformate, 122-51-0; ethyl 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine 3-carboximidate, 54385-53-4; 4-amino-3-carboxy-2-methylpyrazolo[3,4-*d*]pyrimidine, 54385-54-5 3,4-dicyano-5-trimethylacetamidopyrazole, 54385-55-6; pivaloyl chloride, 3282-30-2; 3,4-dicyano-1-methyl-5-trimethylacetamidopyrazole, 54385-56-7; 4,5-dicyano-1-methyl-3-trimethylacetamidopyrazole, 54385-57-8.

Supplementary Material Available. A table of atomic positional coordinates for compound **3** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all

of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1815.

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(21) Although the compound presumed to be 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine has been shown to be a substrate for certain adenosine-utilizing enzymes, e.g., adenosine deaminase[22] and adenosine kinase,[23] the isomeric ribofuranoside has not been tested for comparative purposes. Since it has been shown that isoadenosine [6-amino-3-(β-D-ribofuranosyl)purine] is a (weak) substrate for adenosine deaminase[24] and adenosine kinase,[23] it was obviously important to compare the activities of isomers **12** and **13** in bioassays before using the results to assign structures.
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A Chemical and Carbon-13 Nuclear Magnetic Resonance Reinvestigation of the *N*-Methyl Isomers Obtained by Direct Methylation of 5-Amino-3,4-dicyanopyrazole and the Synthesis of Certain Pyrazolo[3,4-*d*]pyrimidines[1]

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A reinvestigation of the structural assignments for the isomeric *N*-1- and *N*-2-methyl derivatives of 5-amino-3,4-dicyanopyrazole (1), obtained by direct methylation, according to the published procedure, has been accomplished. The higher melting isomer (**2**, mp 243–245°) was annulated to give 4-amino-3-cyano-1-methylpyrazolo[3,4-*d*]pyrimidine (**4**) and alkaline peroxide converted **4** into 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide (**7a**). Hydrolysis of the cyano group of **4** under more vigorous conditions gave 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid (**7b**), which was subsequently decarboxylated in hot sulfolane to afford 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine (**7c**) of established structure. This established the structure of the *N*-methylpyrazole (mp 243–245°) as 5-amino-3,4-dicyano-1-methylpyrazole (**2**) and reversed the structural assignment previously reported for **2**. A similar reaction sequence converted the lower melting isomer (**3**, mp 128–130°) into 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine (**8d**) and established the structure of **3** as 5-amino-3,4-dicyano-2-methylpyrazole. ^{13}C NMR spectroscopy has furnished additional corroboration for these structural reassignments.

We have been involved for some time in the synthesis of nucleosides which are related to the naturally occurring pyrazolo[4,3-*d*]pyrimidine nucleosides[2] formycin and formycin B and the pyrrolo[2,3-*d*]pyrimidine nucleosides[3a] tubercidin, toyocamycin, and sangivamycin. The significant antitumor activity reported[3b] for these nucleoside antibiotic analogs (vide supra) prompted us to extend our investigation into the pyrazolo[3,4-*d*]pyrimidine area. It was during this phase of our research that we synthesized a ribofuranosyl derivative of 4-amino-3-cyanopyrazolo[3,4-*d*]pyrimidine (**12**).[4] This required the preparation of the *N*-1- and *N*-2-methyl derivatives of 4-amino-3-cyanopyrazolo[3,4-*d*]pyrimidine (**12**) so that an unequivocal assignment for the site of ribosylation could be made on the basis of uv spectral data.[5,6] However, a survey of the literature revealed that these *N*-methyl derivatives of **12** had not yet been reported. The most obvious approach to the synthesis of these desired model methyl compounds appeared to be a ring closure of the known[7] *N*-1- and *N*-2-methyl derivatives[8] of 5-amino-3,4-dicyanopyrazole (**2** and **3**, respectively). However, assignments[7] for the actual sites of methylation for **2** and **3** were found on closer examination to be equivocal and this prompted us to initiate the present study which was designed to unequivocally establish the actual sites of methylation.[5]

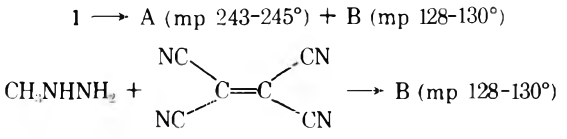
It was reported that the reaction of methylhydrazine with tetracyanoethylene gave a single *N*-methyl derivative of 5-amino-3,4-dicyanopyrazole which was reported[7] to be the *N*-1-methyl derivative **2**. On the other hand, reaction of 5-amino-3,4-dicyanopyrazole (1) with dimethyl sulfate was

found[7] to yield two *N*-methyl derivatives, a lower melting isomer (128–130°) that was identical with the product obtained from the reaction between methylhydrazine and tetracyanoethylene (assigned[9] structure **2**) and a higher melting isomer (mp 243–245°) which was assigned the structure 5-amino-3,4-dicyano-2-methylpyrazole (**3**).

It is of considerable interest that a series of *N*-methyl-4-alkylaminopyrazolo[3,4-*d*]pyrimidines was recently prepared[10] using the *N*-methylpyrazole derivative obtained from the reaction between methylhydrazine and tetracyanoethylene as the starting material. The authors of this work also assigned[10] the position of attachment of the methyl groups as being at N-1 on the basis of the previous report.[7]

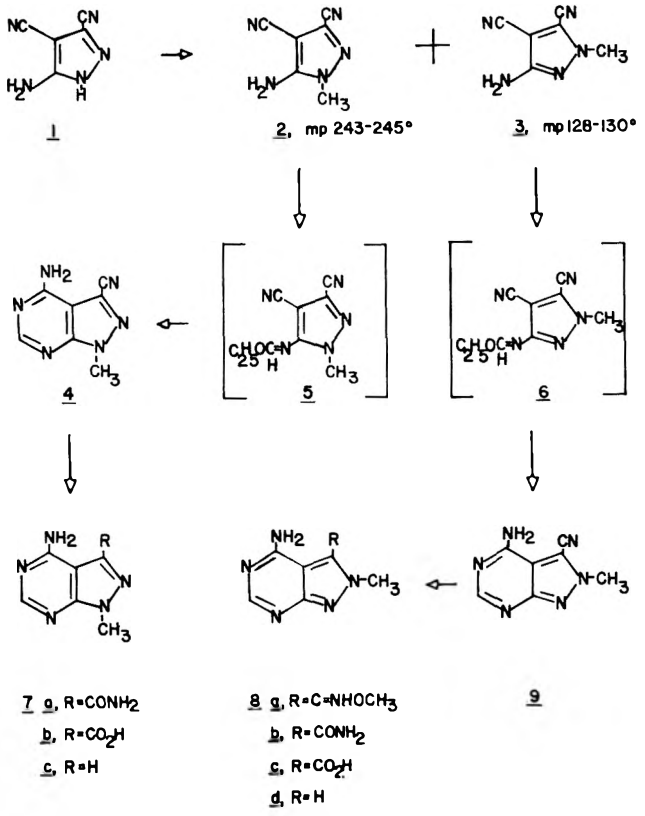
We have synthesized the isomeric *N*-methyl-5-amino-3,4-dicyanopyrazoles according to published procedures[7] and have established, through a series of chemical conversions, that the original structural assignments are incorrect and should be reversed. These structural reassignments have been corroborated by carbon-13 nuclear magnetic resonance spectroscopy.

Chemical Evidence for Structure Assignments. Reaction of 5-amino-3,4-dicyanopyrazole (**1**) with dimethyl sulfate and aqueous sodium hydroxide yielded a mixture of isomers that were separated by fractional crystallization. The higher melting isomer (**2**) (vide infra) had mp 243–245° (47% yield) and the lower melting isomer (**3**) had mp 128–130° (8% yield). The lower melting isomer was found



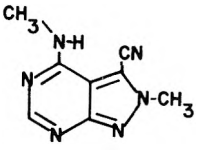
to be identical with the product obtained on reaction of methylhydrazine with tetracyanoethylene as had been previously reported.[7]

Reaction of the higher melting isomer (**2**) with diethoxymethyl acetate yielded a syrupy ethoxymethylene derivative (**5**) which was ring closed during treatment with



methanolic ammonia to yield a compound for which we assigned the structure 4-amino-3-cyano-1-methylpyrazolo[3,4-*d*]pyrimidine (**4**) on the basis of the following: treatment of **4** with ammonium hydroxide and hydrogen peroxide resulted in the formation of the carboxamide **7a** (72% yield); alkaline hydrolysis of **4**, under more vigorous conditions, gave a good yield of the carboxylic acid **7b** which was subsequently decarboxylated in hot (215–220°) sulfolane[11] to provide pure 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine (**7c**), mp 267–269°. The ir, ^{1}H NMR, and uv spectral data for **7c** were identical with those of an authentic sample of **7c** prepared by a different route[12] and a mixture melting point was undepressed.

The corresponding series of 2-methyl compounds was prepared for comparative purposes. Treatment of the lower melting isomer (**3**, mp 128–130°) with hot diethoxymethyl acetate furnished the crystalline ethoxymethylene derivative **6** with mp 98–100.5°, which was the same melting point as that previously reported[10] for the ethoxymethylene derivative of the other isomer "1-methyl-5-amino-3,4-dicyanopyrazole". Reaction of **3** with *N*-methylformamide at reflux temperature yielded a compound for which we have unequivocally assigned the structure 3-cyano-2-methyl-4-methylaminopyrazolo[3,4-*d*]pyrimidine (**10**). It is



10

of interest that **10** has a uv spectrum[13] and melting point identical with those previously reported[10] for "3-cyano-1-methyl-4-methylaminopyrazolo[3,4-*d*]pyrimidine". It was found that brief (1 hr or less) treatment of the ethoxymethylene derivative **6** with methanolic ammonia did not result in the formation of 4-amino-3-cyano-2-methylpyrazolo[3,4-*d*]pyrimidine (**9**) as we had expected on the basis of obtaining **4** from **5** under similar reaction conditions. Instead, a product was isolated whose elemental analysis indicated that we had obtained the desired heterocycle (**9**) plus 1 mol of methanol (by solvation or covalently bound). The ^{1}H NMR spectrum contained peaks at δ 3.94 and 4.25 (singlets) which were assigned to methyl groups. In addition, the ir spectrum revealed the absence of a band in the 2237–2222-cm^{-1} region, which was additional substantiation that a reaction had occurred at the cyano group. On the basis of the above data, this compound was assigned the structure methyl 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-formimidate (**8a**). This prompted us to modify our reaction conditions and it was subsequently found that 4-amino-3-cyano-2-methylpyrazolo[3,4-*d*]pyrimidine (**9**) could be formed in high yield by treating the crystalline ethoxymethylene derivative (**6**) with liquid ammonia at room temperature for 16 hr. As would be expected from the above observation, the cyano group of 4-amino-3-cyano-2-methylpyrazolo[3,4-*d*]pyrimidine (**9**) was very reactive and a facile conversion of **9** to the corresponding carboxamide (**8b**) was observed on treatment with alkaline hydrogen peroxide. Hydrolysis of the cyano group with aqueous sodium hydroxide proceeded smoothly [ca. five times faster than the corresponding 1-methyl isomer (**4**)] to give a high yield (91%) of the carboxylic acid **8c**. Decarboxylation of **8c** in hot sulfolane was very rapid [approximately 25 times faster than the decarboxylation of 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid (**7b**)] and provided a 41% yield of 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine (**8d**), mp 346–348° dec. It was subsequently found that a

better yield of **8d** could be obtained by sublimation[14] of **8c**. A comparison (uv, ir, mixture melting point) of **8d** with an authentic sample[15] of 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine established that they were identical. This conversion of **2** and **3** to compounds of unequivocal structure (**7c** and **8d**, respectively) has unequivocally established the

Table I
Uv Spectral Data for Certain Pyrazoles and Pyrazolo[3,4-*d*]pyrimidines

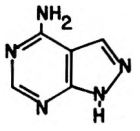
		pH 1		Methanol		pH 11	
No.	Compd	λ_{max}	λ_{min}	λ_{max}	λ_{min}	λ_{max}	λ_{min}
1	5-Amino-3,4-dicyanopyrazole	273.0 (5.10)[a]	246.0 (2.74)	273.5 (3.83)	246.5 (2.56)	276.5 (6.76) 245.0 (10.6)	264.5 (6.22) 235.0 (9.31)
2	5-Amino-3,4-dicyano-1-methylpyrazole	275.0 (5.02)	248.5 (2.28)	275.5 (5.07)	247.0 (2.16)	275.0 (4.90)	248.5 (2.54)
3	5-Amino-3,4-dicyano-2-methylpyrazole	300.0 (4.66) 238.0 (9.77)	262.0 (1.73) 229.0 (8.76)	310.0 (4.86) 240.0 (10.1)	265.0 (1.05) 231.0 (9.10)		
12	4-Amino-3-cyanopyrazolo[3,4-*d*]pyrimidine	271.0[b] 264.5 (10.0) 236.0[b] 230.5[b]	246.0 (7.03)	287.0[b] 279.0 (10.6) 238.0[b]	248.0 (4.56)	294.5 (10.5) 288.5[b] 242.0 (14.4)	260.0 (6.89) 233.0 (11.5)
4	4-Amino-3-cyano-1-methylpyrazolo[3,4-*d*]-pyrimidine	267.5 (12.5) 233.5 (19.0) 227.0 (19.0)	249.0 (8.41) 230.5 (1.84) 221.5 (16.9)	294.0[b] 284.5 (14.4) 242.0[b] 237.0 (11.7)	251.5 (5.43) 226.0 (9.66)	293.0[b] 285.0 (14.5) 242.5[b] 237.5 (12.1)	252.0 (6.04) 229.5 (9.21)
9	4-Amino-3-cyano-2-methylpyrazolo[3,4-*d*]-pyrimidine	309.5[b] 296.5 (12.7) 273.5[b] 265.5[b] 241.5 (12.7) 236.0[b]	254.0 (8.34) 225.5 (11.3)	308.5 (11.2) 277.0[b] 267.5 (7.36) 248.0 (10.1)	282.5 (6.51) 260.0 (7.00) 238.0 (9.52)	304.5 (10.5) 275.0 (6.85) 266.5 (6.81) 246.0 (9.54)	281.5 (6.24) 271.0 (6.44) 257.5 (6.15) 236.0 (8.65)
10	3-Cyano-2-methyl-4-methylaminopyrazolo-[3,4-*d*]pyrimidine	316.0[b] 305.5 (13.5) 298.5 (13.2) 248.0 (8.85) 232.5[b]	300.0 (13.0) 258.0 (7.90) 237.5 (8.66)	316.0[c] (10.7) 254.0[c] (9.04) 230.0[b,c]	284.5 (5.20) 243.5 (7.46)	312.5 (10.6) 278.0[b] 268.5[b] 253.5 (8.80) 234.0[b]	284.5 (5.27) 242.0 (7.22)
7a	4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide	265.0 (9.11) 229.0 (15.0)	252.5 (8.06)	282.5 (9.21) 239.5 (11.1)	256.5 (6.53)	283.5 (9.12) 242.0 (9.60)	258.0 (5.95) 222.0 (4.04)
8b	4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide	279.0 (7.55) 233.0 (7.34)	251.5 (4.23)	300.0 (7.99) 244.0 (6.68)	260.5 (4.84) 237.0 (6.34)	296.0 (8.30) 239.0 (6.34)	258.0 (5.00) 235.0 (6.28)
8a	Methyl 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-formimidate	279.5 (10.1) 242.5 (8.65)	255.5 (6.95) 228.0 (7.42)	305.0 (9.69) 253.0 (8.00)	266.5 (6.60) 238.0 (6.10)	302.5 (9.74) 247.0 (8.14)	276.0[b] 260.0 (6.18) 235.5 (7.11)
7b	4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid	265.5 (10.5) 231.5 (15.5)	250.5 (8.34) 222.5 (14.2)	292.0[b] 282.0 (11.4) 277.0[b] 236.0 (10.4)	252.5 (6.60) 236.0 (9.38)	292.0[b] 282.5 (11.1) 276.5[b] 238.0 (10.2)	252.5 (6.21) 230.5 (8.61)
8c	4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid	278.0 (10.5) 242.0[b] 235.5 (11.8) 287.0[b]	252.0 (7.34) 223.5 (10.0)	298.0[b] 290.0 (10.3) 279.0[b] 240.0 (10.4)	256.0 (7.21) 228.0 (9.34)	298.0 (10.7) 290.5[b] 277.5[b] 267.0[b] 242.5 (8.73)	257.5 (6.04) 231.5 (6.99)
11	4-Aminopyrazolo-[3,4-*d*]pyrimidine	258.0 (11.3)	238.5 (6.80)	281.0[b] 271.5 (11.3) 260.0[b]	235.0 (4.21)	280.0[b] 263.0 (10.6)	239.5 (6.93)
7c	4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine	258.0 (10.5)	240.5 (7.00)	286.5[b] 276.5 (11.2) 272.0[b] 260.5 (10.2)	265.0 (9.44) 239.0 (4.25)	286.0[b] 276.5 (11.2) 260.0 (11.1)	266.0 (10.4) 239.0 (5.32)
8d	4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine	266.5 (11.7)	241.0 (4.81)	298.0[b] 288.0 (12.9) 281.0[b] 267.0 (8.70) 259.5[b] 235.0[b] 230.0 (7.88)	270.0 (8.62) 242.5 (2.89) 224.5 (6.99)	296.0[b] 286.5 (12.5) 279.0[b] 266.5 (9.34) 258.0[b] 233.0[b]	269.5 (9.16) 241.5 (3.70)

[a] Values in parentheses are $\epsilon \times 10^{-3}$. [b] Shoulder. [c] Sample dissolved in ethanol.

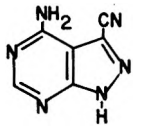
structures for all compounds reported herein and has also established that the previous structural assignments[7,10] for certain compounds were in error.

From the uv absorption data (Table I) for the methylated pyrazoles and pyrazolo[3,4-*d*]pyrimidines, it is seen that for each pair of isomeric compounds (at all pH ranges) the *N*-2-methyl isomer shows its principal absorption maximum at a longer wavelength than the *N*-1-isomer. This relationship has been reported[16] for various N-substituted pyrazolo[3,4-*d*]pyrimidines. This trend appears to be general for the pyrazolo[3,4-*d*]pyrimidines and is most likely due to the different type of electronic structures for the two isomers. However, in the case of the N-substituted pyrazoles this difference needs further substantiation which precludes the use of this trend as a basis for the unequivocal assignment of the site of N-alkylation.

For comparison purposes, the uv spectral data for 5-amino-3,4-dicyanopyrazole (**1**), 4-aminopyrazolo[3,4-*d*]pyrimidine (**11**), and 4-amino-3-cyanopyrazolo[3,4-*d*]pyrimidine (**12**) have been included in Table I. It is of consider-



11



12

able interest that the positions of uv maxima (pH 1 and methanol spectra) for **1, 11,** and **12** are very similar to the values shown for the corresponding *N*-1-methyl derivatives (**2, 7c,** and **4,** respectively) and very dissimilar for the corresponding *N*-2-methyl derivatives (**3, 8d,** and **9,** respectively). Since the uv spectral data for the unsubstituted heterocycles more closely resemble the spectral data for the *N*-1-methyl derivatives this would strongly suggest that the nonalkylated heterocycles exist predominantly in the tautomeric forms shown. ^{13}C NMR spectroscopy also provides data to support this assumption (vide infra).

Structure Assignments Based on ^{13}C NMR Spectral Data. In order to supplement and corroborate the structural assignments based on chemical evidence and presented in the previous section, carbon-13 nuclear magnetic resonance (^{13}C NMR) spectral data was obtained on compounds **4, 7c, 9, 8d, 11,** and **12.** The value of ^{13}C NMR spectroscopy in elucidating molecular structure is well known[17] and previous studies carried out in this laboratory,[18-25] as well as others,[26] have demonstrated the value of ^{13}C NMR as a tool in determining the site of N substitution in nitrogen heterocycles. If one compares the ^{13}C NMR spectral data of a nitrogen heterocycle with a N-alkylated derivative of this heterocycle (where the N substitution is methyl or β-D-ribofuranosyl), chemical shift changes are observed which reflect the replacement of a proton by a substituent on a specific nitrogen atom with the concomitant absence of tautomeric structures. While the magnitude of the N-substituent parameters is affected by the nature of the substituent (i.e., H, CH_3, or ribose),[25] the authors are aware of no case where the carbon adjacent (α) to the site of N substitution fails to move upfield or, conversely, fails to move downfield when the substituent is removed.[27] Rapid proton exchange among the various tautomeric species complicates the structural analysis but tautomeric populations have now been derived for a number of species including 26 derivatives of purines and pyrrolo[2,3-*d*]pyrimidines.[25a]

In order to independently verify the structures of **4** and **9** we also examined **12** and compared the ^{13}C NMR spectral data of these three compounds with **7c, 8d,** and 4-aminopyrazolo[3,4-*d*]pyrimidine (**11**). The structures for **7c, 8d,** and **11** have been reliably determined by chemical techniques.

Table II
Carbon-13 Chemical Shifts[a] for Derivatives of 4-Aminopyrazolo[3,4-*d*]pyrimidine

Compd[b]	Carbon position						
	C-3	C-3a	C-4	C-6	C-7a	CN	CH_3
4-APP riboside[c]	133.41	100.61	158.16	156.21	154.14		
11	132.33	99.65	158.18	154.70	154.70		
7c	132.23	100.05	158.33	155.24	153.01		32.38
8d	124.91	102.23	159.28	155.61	160.17		39.45
12	115.55	100.45	156.99	156.32	155.10	113.17	
4	115.14	100.75	157.19	156.50	153.42	112.38	33.78
9	106.62	104.14	157.69	156.40	159.48	109.21	39.54

[a] Taken with respect to external Me_4Si. Chemical shift values were measured relative to internal dioxane and converted to the Me_4Si scale using $\delta_{Me_4Si} = \delta_{dioxane} - 17.5 \times 10^{-4}T(°C) - 66.32$ ppm. [b] Samples were dissolved in HMPT (200 mg/3.0 ml solvent except **8d**, where the solution was 84 mg/3.0 ml). [c] See ref 23.

Table III
Changes[a] in the Carbon-13 Chemical Shifts ($\Delta\delta$)[b] for Certain Pyrazolo[3,4-*d*]pyrimidines

Compds compared		Δδ					
i	j	C-3	C-3a	C-4	C-6	C-7a	CN
11	**7c**	0.10	−0.40	−0.15	−0.54	1.69	
11	**8d**	7.42	−2.58	−1.10	−0.91	−5.47	
12	**4**	0.41	−0.30	−0.20	−0.18	1.68	+0.79
12	**9**	8.93[c] (6.55)[d]	−3.69	−0.70	−0.08	−4.38	+3.96[c] (6.34)[d]
11	**12**	16.78	0.80	1.19	−1.62	−0.40	

[a] Negative numbers represent shift changes (in parts per million) to lower field as compared to the chemical shifts observed for the corresponding positions in the reference compound. [b] $\Delta\delta = \delta C_i - \delta C_j$. [c] Preferred assignment. [d] Parenthetical numbers are the values obtained if the chemical shift values for C-3 and CN (of **12**) are reversed.

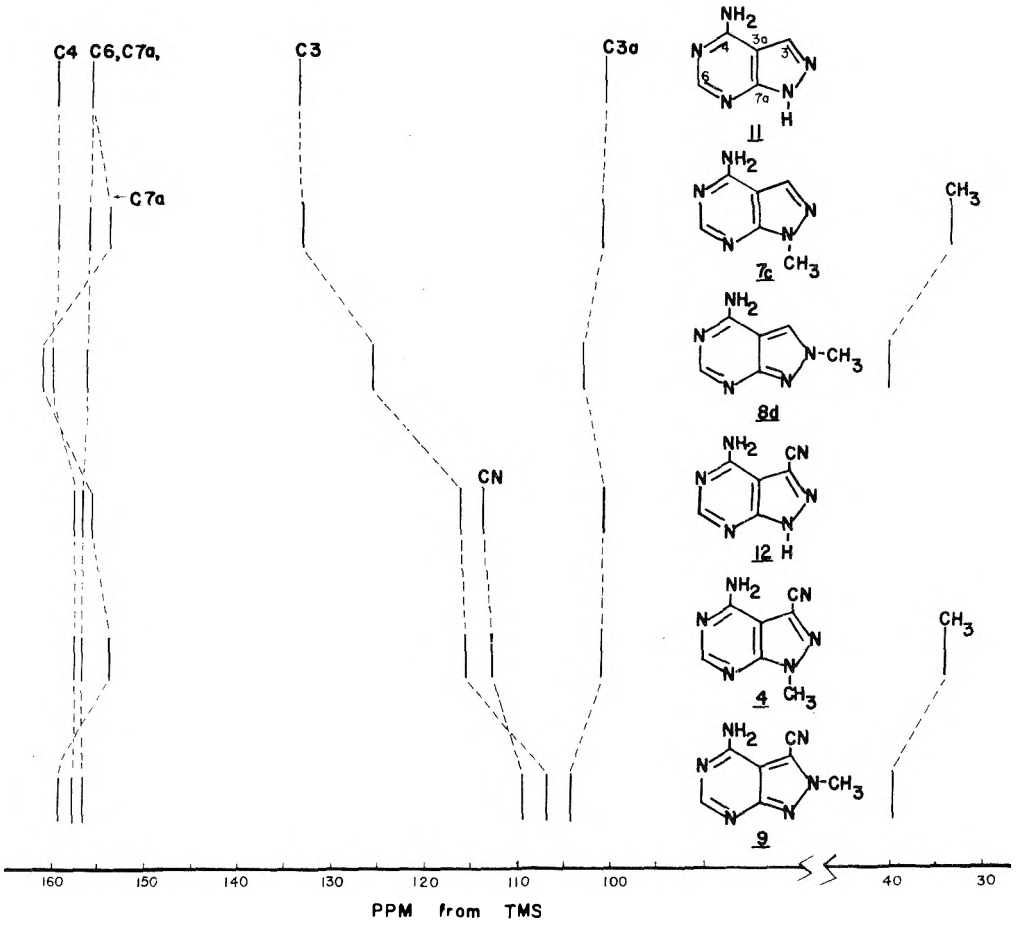


Figure 1. Carbon-13 resonance patterns for certain pyrazolo[3,4-*d*]pyrimidines.

The chemical shifts of **11** are given in Table II and the shift assignments were made by a comparison of the shift values for **11** with the shift values observed for 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (4-APP riboside).[23] It is interesting to note that C-6 has moved 1.5 ppm upfield in **11** (compared to 4-APP riboside) and is accidentally degenerate with **7a** (verified by off-resonance decoupling). The *N*-1-methyl derivative of **11** (**7c**) exhibits only minor chemical shift variations when compared to **11** (and 4-APP riboside) as shown in the correlation diagram (Figure 1). The chemical shifts of the compound identified as **8d** exhibits two major chemical shift variations when compared to the chemical shifts of **11**. The shift changes $\Delta\delta$ ($\delta C_i - \delta C_j$) given in Table III at C-3 and C-7a are in opposite directions and are consistent with addition of an α-substituent shift at C-3 and removal of the α-substituent effect at C-7a. While the magnitudes of the shift changes noted for C-3 and C-7a in Table III (7.42 and −5.47 ppm, respectively) are not identical with the +9.64 ppm α shift observed in simple five-member heterocycles,[20] the values are qualitatively correct. By comparing the data for **7c** and **8d** with that of **11**, one can readily conclude that the structure assignments are correct, since a reversal in structures would cause the resonance positions of C-3 and C-7a to move in opposite directions to that observed in the data.

Similar comparisons can be made among **12, 4,** and **9.** The resonance positions of C-4, C-6, C-7a, and C-3a in **12** were determined by off-resonance decoupling (C-6) and with the aid of the correlation diagram. The assignments of C-3 and the cyanocarbon resonance positions could not be determined unequivocally and may be reversed. However, when comparing the proton coupled and decoupled spectra of **12,** one observes that one of the resonance lines of the pair in question is little affected while the other is significantly broadened and decreases substantially in intensity when the proton decoupler is turned off. The resonance position exhibiting broadening is thus tentatively assigned to C-3, since long-range proton–carbon coupling (two-bond and three-bond coupling from the labile proton) is more likely to occur at C-3 than at the cyano carbon. It is also noted that C-3 in **12** is shifted 16.78 ppm to higher field than the corresponding position in **11.** This shift change is consistent with the 16.4 ppm upfield shift for the C-1 carbon in benzonitrile[28] (as compared to the resonance peak observed for benzene) and is further evidence that the resonance peaks for C-3 and –CN of **12** are correctly assigned.

The resonance positions in **4** exhibit little variation from **12** and the differences, $\Delta\delta$, given in Table III are quite similar, position for position, for the **7c, 11** and the **4, 12** pairs of compounds. The variations in the resonance positions of **9** as compared to **12** can also be compared to the variations observed for the 8d, 11 pair (given in Table III). Once again the $\Delta\delta$ values are comparable between the **8d, 11** and the **9, 12** pairs. As observed in the known structures **11** and **8d,** comparison of **9** and **12** indicates that the methyl resides at N-2, since C-3 is shifted upfield 8.93 ppm and C-7a moves 4.38 ppm to lower field. The same qualitative results are obtained even if the shift assignments at C-3 and CN are reversed. Hence, the ^{13}C NMR spectral data confirms the chemical evidence for the structures assigned to **4** and **9.**

In Figure 1, one observes that resonance peaks for the methyl carbons fall into two patterns. The methyl carbons, of the two *N*-1-methyl species, are separated by 1.4 ppm and are found upfield from the methyl carbons of the *N*-2-methyl derivatives which vary by only 0.1 ppm in their resonance positions. The variation in methyl chemical shifts apparently reflects the difference in resonance structures of the N-1 and N-2 methylated compounds, and these reso-

nance effects are transferred in part to the exocyclic group. It is also interesting to note that the resonance peak for the nitrile carbon moves upfield 0.79 and 3.96 ppm in **4** and **9**, respectively, as compared to the nitrile carbon of **12**. The chemical shift change of the nitrile carbon of **9** may likewise reflect the differences between the resonance structures of **4** and **9**.

Conclusions

The work presented herein has established on the basis of new chemical evidence and ^{13}C NMR spectral data that the original structural assignments for **2** and **3** were reversed. This dual approach has proven to be very useful in complex structure characterization studies in this and other laboratories and promises to become even more important in the future as the powerful ^{13}C NMR techniques become more widely used.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained with a Varian A-60 spectrometer with DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) as internal standard and the chemical shifts are expressed as δ, parts per million, from DSS with DMSO-d_6 as solvent. Carbon-13 nuclear magnetic resonance spectra were obtained with a Varian XL-100-15 spectrometer equipped with a 620-F computer. The infrared spectra were determined, utilizing pressed KBr disks, with a Beckman IR-8 spectrophotometer; absorptions are given in reciprocal centimeters and are strong absorptions unless otherwise noted. Ultraviolet spectra were recorded with a Beckman DK-2 spectrophotometer and absorptions are expressed in nanometers. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo., and M-H-W Laboratories, Garden City, Mich.

5-Amino-3,4-dicyano-1-methylpyrazole (2) and 5-Amino-3,4-dicyano-2-methylpyrazole (3). 5-Amino-3,4-dicyanopyrazole[7] (**1**, 66.5 g, 0.50 mol) was added with stirring to a solution of sodium hydroxide (23.0 g, 0.580 mol) in water (100 ml) to effect a clear solution. Dimethyl sulfate (85 g, 0.67 mol) was added immediately after **1** had completely dissolved. The reaction mixture was stirred at room temperature for 15 min, and the solid that had separated was collected by filtration, washed with cold water (2 × 20 ml), and dried (25°, 0.5 Torr), yield 45.0 g. The dry material (45 g) was added to ethanol (200 ml), the mixture was heated at reflux temperature, and the undissolved solid was removed from the hot mixture by filtration. The filter cake was recrystallized from dioxane to obtain 5-amino-3,4-dicyano-1-methylpyrazole (**2**) as colorless needles: mp 241–244° [lit.[7] mp 243–245°]; yield 35.0 g (47.5%); ir[29] 3448, 3378, 3247 (NH); 2242 (C≡N); 1647, 1658, 1650, 1433 cm^{-1} (NH and C=N); ^1H NMR[30] δ 3.59 (s, 3 H, CH_3), 7.06 (s, 2 H, NH_2).

The ethanol filtrate, from above, deposited more solid upon standing (25°, 1 hr) which was collected by filtration and washed with a small amount of cold water. The air-dried filter cake was recrystallized from ethanol to obtain 5-amino-3,4-dicyano-2-methylpyrazole (**3**) as needles: mp 128–130° [lit.[7] mp 128–130°]; yield 6.0 g (8.2%); ir 3472, 3367 (NH); 2232 (C≡N); 1621, 1546, 1517 cm^{-1} (NH and C=N); ^1H NMR δ 3.78 (s, 3 H, CH_3), 6.14 (s, 2 H, NH_2).

5-Amino-3,4-dicyano-2-methylpyrazole (3). Tetracyanoethylene (12.8 g, 0.1 mol) was added slowly to a solution of methyl hydrazine (4.6 g, 0.1 mol) in water (200 ml) at 0° with efficient stirring. After the addition was completed, the reaction mixture was stirred for 1 hr at 0° and then heated at reflux temperature for 15 min. The brown reaction solution was allowed to stand at 5° for 8 hr and the crystalline solid that separated was collected by filtration and washed several times with ice-cold water. The residue was air dried and then recrystallized from ethanol as needles to yield 7.0 g (47.6%) of **3**, mp 130–131°. A mixture melting point of this product with the sample of **3** obtained from the methylation of 5-amino-3,4-dicyanopyrazole was undepressed and their uv spectra were found to be identical.

4-Amino-3-cyano-1-methylpyrazolo[3,4-*d*]pyrimidine (4). 5-Amino-3,4-dicyano-1-methylpyrazole (**2**, mp 243–245°, 4.0 g) was heated in diethoxymethyl acetate (25 ml) for 2.5 hr at reflux temperature and under anhydrous conditions. The pale orange solution was evaporated (bath temperature 50°) under reduced pressure to a syrup. The syrup was dissolved in dry toluene (50 ml) and again evaporated in vacuo to a syrup. This process was repeated four times to provide the dry, syrupy 5-ethoxymethylene derivative (**5**). This syrup was dissolved in 200 ml of methanolic ammonia (methanol saturated with ammonia at 0°) and allowed to stand for 18 hr at room temperature. The solid that had separated was collected by filtration, washed with cold (10°) methanol (2 × 10 ml), and recrystallized from dimethylformamide as microneedles to yield 3.5 g (74.0%) of **4**: mp 312° dec; ir 3472, 3356 (w) (NH); 2242 (w) (C≡N); 1621, 1538 cm^{-1} (NH, C=N, and C=C).

Anal. Calcd for $C_7H_6N_6$: C, 48.28; H, 3.44; N, 48.28. Found: C, 47.88; H, 3.67; N, 48.24.

Methyl 4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-formimidate (8a). 5-Amino-3,4-dicyano-2-methylpyrazole (**3**, mp 128–130°, 6.0 g) was heated in diethoxymethyl acetate (30 ml) at reflux temperature for 3 hr with exclusion of moisture. The dark brown solution was evaporated in vacuo (bath temperature 50°) to a syrup. The syrup was dissolved in dry toluene (50 ml) and again evaporated in vacuo to dryness. This procedure was repeated four times to furnish the crystalline 5-ethoxymethylene derivative[31] (**6**), which was dissolved in 300 ml of methanolic ammonia and allowed to stand at room temperature for 18 hr. The solid that had separated was collected by filtration and washed with cold (0°) methanol (2 × 10 ml) and the filter cake was recrystallized from aqueous ethanol as long, colorless needles to yield 5.70 g (80%) of **8a**: mp 280° dec; ir 3195 (NH); 1645, 1590, 1527, 1481 (NH, C=N, and C=C); ^1H NMR δ 3.94 (s, 3 H, NCH_3), 4.25 (s, 3 H, OCH_3), 7.55 (br s, 2 H, $-NH_2$), 8.20 (s, 1 H, H_6), 9.06 (s, 1 H, C=NH).

Anal. Calcd for $C_8H_{10}N_6O$: C, 46.60; H, 4.85; N, 40.78. Found: C, 46.77; H, 4.82; N, 41.02.

4-Amino-3-cyano-2-methylpyrazolo[3,4-*d*]pyrimidine (9). The crude, crystalline 5-ethoxymethylene derivative, **6** (prepared from 6.0 g of **3**) was dissolved in liquid ammonia (100 ml) and the reaction mixture was allowed to stand at room temperature for 16 hr in a sealed stainless steel reaction vessel. The reaction mixture was then evaporated to dryness in vacuo and the solid was recrystallized from dimethylformamide as pale yellow microneedles to yield 5.0 g (70.5%) of **9**: mp 280° dec; ir 3472 (w), 3356 (NH); 2247 (m) (C≡N); 1621, 1538 cm^{-1} (NH, C=N, C=C); ^1H NMR δ 4.75 (s, 3 H, CH_3), 7.56 (br s, 2 H, NH_2), 8.34 (s, 1 H, H_6).

Anal. Calcd for $C_7H_6N_6$: C, 48.28; H, 3.44; N, 48.28. Found: C, 48.42; H, 3.52; N, 48.40.

4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide (7a). Hydrogen peroxide (4.0 ml of 30% solution) was added in one portion to a stirred suspension of **4** (1 g) in concentrated aqueous ammonia (20 ml, room temperature). Stirring was continued for 2.5 hr, during which time **4** went into solution (0.5 hr), and this was soon followed by the appearance of a new white solid (1 hr). After 2 hr the solid was collected by filtration, washed well with cold water, and then air dried. The solid was recrystallized from methanol to yield 0.8 g (72.7%) of **7a** as colorless needles: mp 350° dec; ir 3390, 3247 (NH); 1639, 1616, 1580, 1471 cm^{-1} (C=O, NH, C=N, C=C).

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.16; N, 43.75. Found: C, 43.90; H, 4.51, N, 43.60.

4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide (8b). Hydrogen peroxide (4 ml of 30% solution) was added in one portion to a stirred suspension of **9** (1.0 g) in concentrated aqueous ammonium hydroxide (20 ml, room temperature). After 1 hr the reaction mixture became clear and then a solid began to separate from solution. After 4 hr the solid was collected by filtration, washed thoroughly with cold water, and then recrystallized from methanol to yield 0.5 g (45.3%) of **8b** as needles: mp 310° dec; ir 3390, 3012 (NH); 1592, 1473 cm^{-1} (C=O, NH, C=N, C=C); ^1H NMR δ 4.27 (s, 3 H, CH_3), 7.61 (br s, 2 H, NH_2), 8.43 (s, 1 H, H_6), 8.44 (br s, 2 H, $CONH_2$).

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.16; N, 43.75. Found: C, 43.60, H, 4.32; N, 43.50.

4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic Acid (7b). Aqueous sodium hydroxide (3.52 ml of 1.25 *M* solution, 4.4 mmol) was added to a suspension of **4** (700 mg, 4 mmol) in 15 ml of water and the suspension was heated at reflux temperature for 5 days (ammonia evolution ceased during this time). The solution was cooled to room temperature and 100 mg of white solid (mp >360°, insoluble in hot water) was removed by filtration. The clear filtrate was acidified by the addition of 4.32 ml of 1.02 *M* aqueous hydrochloric acid. A gelatinous precipitate formed that turned to a white powder on further stirring. The solid (610 mg, 78%) was redissolved (25°) in aqueous sodium hydroxide (3.52 ml of 1.25 *M* solution) and then reprecipitated by the addition of

aqueous hydrochloric acid (4.32 ml of 1.02 *M* solution). The white solid was collected by filtration and washed with cold (0°) water (3 × 5 ml) to yield 570 mg (73.4%) of **7b**: mp 336° dec (and sublimes); ir 3356 (NH); 2703–2439 (OH); 1701 (C=O); 1603, 1548 (w), 1513 cm^{-1} (w) (NH, C=N, C=C).

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.53; H, 3.65; N, 36.26. Found: C, 43.31; H, 3.93; N, 35.96.

4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic Acid Hemihydrate (8c). When **9** (700 mg, 4 mmol) was treated as above, solution occurred in 3 min followed by the formation of a white precipitate in 5 min more which in turn soon dissolved. Ammonia evolution could no longer be detected after 36 hr at reflux temperature. Filtration was followed by the addition of aqueous hydrochloric acid, which caused 730 mg (91%) of **8c** to precipitate in the form of a white solid. A portion of the solid was dissolved in aqueous base and reprecipitated with aqueous acid to afford an analytical sample: mp 320–333° (bubbling, darkening at melting point with a change in crystalline form at 266°); ir 3846–2083 (NH, OH); 1695, 1634 (NH, C=N, C=C).

Anal. Calcd for $C_7H_7N_5O_2 \cdot 0.5H_2O$: C, 41.57; H, 3.99; N, 34.64. Found: C, 41.71; H, 4.11; N, 34.39.

4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine (7c). Dry nitrogen was passed through a suspension of **7b** (193 mg, 1 mmol) in dry, redistilled sulfolane (15 ml) for 0.5 hr. The flask containing the suspension was then lowered into a Woods metal bath preheated to 215–220° and the carbon dioxide evolution was monitored (CO_2 was led through a connecting tube to an inverted graduated cylinder, filled with water, for monitoring purposes). One-third of the carbon dioxide (7.6 ml) was evolved in ca. 25 min with the reaction being complete in ca. 100 min. No appreciable carbon dioxide evolution was observed at temperatures below 210°. Excess sulfolane was removed by vacuum distillation (0.1 Torr, oil bath at 70°). The semisolid residue was triturated with 40 ml of a 1:1 (v/v) methylene chloride–diethyl ether mixture, and then recrystallized from water (3 ml) to yield 80 mg (56%) of **7c**, mp 267–269°[c]. A mixture melting point with an authentic sample[12] of **7c** (mp 266–268°) was undepressed. The ir, uv, and ^1H NMR spectra obtained for our product were superimposable with those obtained for an authentic sample of **7c**: ir 3300 (m), 3086 (NH); 1669, 1595, 1570, 1495 (w) (NH, C=N, C=C); 1319 (m), 1190 (w), 1016 (w), 917 (m), 789 (m), 714 cm^{-1} (m).

4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine (8d). Method 1. Sublimation (235°, 0.3 mm) of **8c** (300 mg, 1.56 mmol) yielded 190 mg (82%) of **8d**, mp 341–343° (vigorous dec, darkens at 330°). One recrystallization of **8d** from water raised the melting point to 346–348° (vigorous dec) and a mixture melting point with an authentic sample[15] of 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine showed no depression. The ir and uv spectra obtained for our product were identical with those obtained for the authentic sample: ir 3311, 3030 (NH); 1661 (w), 1608, 1531 (NH, C=N, C=C); 1412 (w), 1342 (m), 1242, 1176 (m), 1034 (m), 990 (m), 909 (m), 872 (w), 791 cm^{-1}.

Method 2. 4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid (**8c**, 100 mg, 0.52 mmol) was decarboxylated in 4 ml of sulfolane at ca. 215° as described for the preparation of **7c**. Carbon dioxide evolution was complete (14 ml) in 3 min with one-third of the gas being evolved in less than 1 min. The usual work-up followed by recrystallization from water (3 ml) yielded 31.9 mg (41%) of pure **8d**.

Acknowledgments. We wish to thank P. Schmidt and S. M. Hecht for kindly supplying samples of **8d** and **10**, respectively.

Registry No.—**1**, 54385-49-8; **2**, 50680-85-8; **3**, 54385-48-7; **4**, 42204-41-1; **7a**, 54814-48-1; **7b**, 54814-49-2; **7c**, 5334-99-6; **8a**, 54814-50-5; **8b**, 54814-51-6; **8c**, 54385-54-5; **8d**, 21230-48-8; **9**, 54814-52-7; **10**, 54814-53-8; **11**, 2380-63-4; **12**, 6826-96-6; 4-APP riboside, 58-61-7; tetracyanoethylene, 670-54-2; methyl hydrazine, 60-34-4; diethoxymethyl acetate, 14036-06-7.

References and Notes

(1) We wish to acknowledge support for this work by means of a grant from Research Resources, National Institutes of Health (RR-0574) and a research contract from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare (NO1-CM-23710 and NO1-CM-43806).
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(6) Proof of structure for the nucleoside was subsequently made by a conversion to 4-amino-1-(β-D-ribofuranosyi)pyrazolo[3,4-*d*]pyrimidine [G. R. Revankar and L. B. Townsend, *J. Chem. Soc. C*, 2440 (1971)] which did not require the use of model methyl compounds.
(7) C. L. Dickenson, J. K. Williams, and B. C. McKusick, *J. Org. Chem.*, **29**, 1915 (1964).
(8) Although the nomenclature is not systematic, the N-methylated pyrazoles will be named as 1- or 2-methyl derivatives of 5-amino-3,4-dicyanopyrazole in order to simplify the discussion.
(9) The authors[7] presented a very unclear and confusing account of their research. At one point they rationalized that the initial attack on tetracyanoethylene by methyl hydrazine would involve "the nitrogen to which the methyl is attached" to yield 1-methyl-5-amino-3,4-dicyanopyrazole (**2**) and they listed **2** in a table as being the product from this reaction. Yet at another point, in their discussion on the products from the methylation of 5-amino-3,4-dicyanopyrazole, they appear to reverse this structural assignment.
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(12) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).
(13) An authentic sample of **10**, provided by Dr. S. M. Hecht, proved to be essentially identical in all respects with the product we obtained using his published procedure. It should be noted, however, that owing to what we would assume to be a printing error in the original publication,[10] our uv spectral data (pH 11, 253 nm) for **10** (see Table I) are different from the values (pH 12, 262 nm) previously reported for **10**.
(14) It has been previously shown that 4-aminopyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid is decarboxylated during sublimation; see E. C. Taylor and A. Abul-Husn, *J. Org. Chem.*, **31**, 342 (1966).
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(26) G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. P. Schweizer, *J. Am. Chem. Soc.*, **94**, 5894 (1972).
(27) At first glance, it would appear that this statement is contradicted by the work of J. Elguero, C. Marzin, and J. D. Roberts, *J. Org. Chem.*, **39**, 357 (1974). These authors studied pyrrole, pyrazole, imidazole, *s*-triazole, *v*-triazole, tetrazole, and their *N*-methyl analogs. When comparing the free base and the *N*-methyl base, downfield shifts were noted for both α and β carbons in pyrrole and imidazole. These results, however, simply reflect the differences in absolute magnitude of the proton and methyl substituent parameters (see ref 25a). The problem is further complicated by inclusion of the various tautomeric structures which exist in the di-, tri-, and tetrazoles for which insufficient data has been obtained to adequately paramaterize the substituent effects. However, a close examination of the data presented by Elguero et al. clearly demonstrates that N-substitution, whether by a proton or a methyl group, consistently produces an upfield α shift. While β shifts undoubtedly occur also, their magnitude is such (−1 to −2 ppm) as to be obscured by structural changes and variations in the H/methyl substituent effects.
(28) L. B. Johnson and W. C. Jankowsky, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972, Spectrum No. 226.
(29) Notation: w = weak; m = medium.
(30) Notation: s = singlet; br s = broad singlet.
(31) The solid could be recrystallized from toluene to yield colorless crystals (80%), mp 98–100.5° (lit.[10] mp 98–99°).

Total Synthesis of Eremophilone

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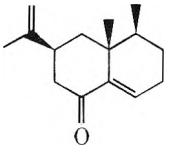
A stereoselective total synthesis of (±)-eremophilone (1) is reported starting from the known 7-epinootkatone. The synthetic sequence involves reductive deconjugation of 7-epinootkatone to homoallylic alcohol **10**. Dehydration of **10** by pyrolysis of its acetate gives triene **18**, which can be selectively epoxidized at the more substituted double bond to give **19**. Mild acid catalyzed rearrangement of this allylic epoxide is effected with lithium perchlorate in refluxing benzene, and, after base-catalyzed equilibration of the enone system, a 1:1 mixture of eremophilone and its β,γ-unsaturated isomer, itself a natural product, is produced.

Eremophilone (1) occupies a prominent place in sesquiterpene chemistry both because of the long and intricate history of its structure elucidation, and because of the considerable challenge it has provided to synthetic organic chemists.[2] Eremophilone was isolated in 1932 from the wood oil of *Eremophila mitchelli*, a shrub indigenous to Australia, by the great terpene chemist J. L. Simonsen.[3] Although they proposed an incorrect structure in their initial paper, Simonsen and his colleagues continued a series of researches through the 1930's.[4] At the suggestion of Robert Robinson, Simonsen proposed the correct structure in 1939,[5] and eremophilone thus became the first sesquiterpene found in nature whose structure does not obey the biogenetic isoprene rule. Further proof of the correctness of the nonisoprenoid structure of eremophilone was added over the next two decades,[6-8] culminating in 1959 with determination of both the relative and the absolute configuration.[9-12]



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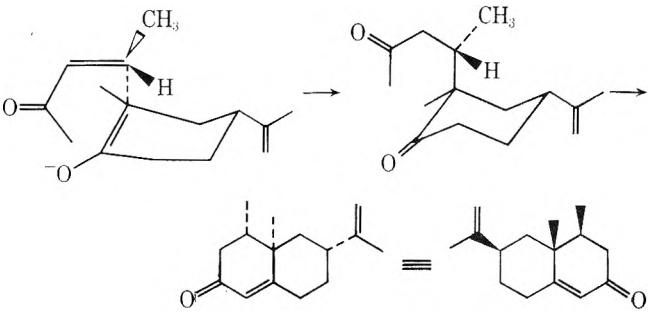
Total synthesis of eremophilone required a further wait of 15 years until Ziegler published his successful, though nonstereoselective, route in early 1974.[13] We wish now to report a second, stereoselective, total synthesis of eremophilone.

General Considerations. The most obvious problems one would expect to encounter in a synthesis of eremophilone are stereochemical.[14] One expected difficulty is in establishing the required cis relationship of the vicinal methyl groups, and another is in establishing the isopropenyl group in the thermodynamically less favorable stereochemistry (axial in the chair–chair conformer). Both of these stereochemical problems can be overcome immediately, however, if one chooses as starting material the Robinson annelation product of 2-penten-3-one with 4-isopropenyl-2-methylcyclohexanone. Van der Gen and his colleagues have studied this reaction in considerable detail, and have demonstrated conclusively that the product dimethylisopropenylhexahydronaphthalenone has the desired all-cis stereochemistry (7-epinootkatone).[15] This result is understandable if the initial Michael addition occurs axially to the methylisopropenylcyclohexanone, and if the pentenone is oriented so as to minimize steric interference (i.e., vinyl methyl away from ring) and to maximize electrostatic attractions (pentenone carbonyl near enolate oxygen).[15-17]

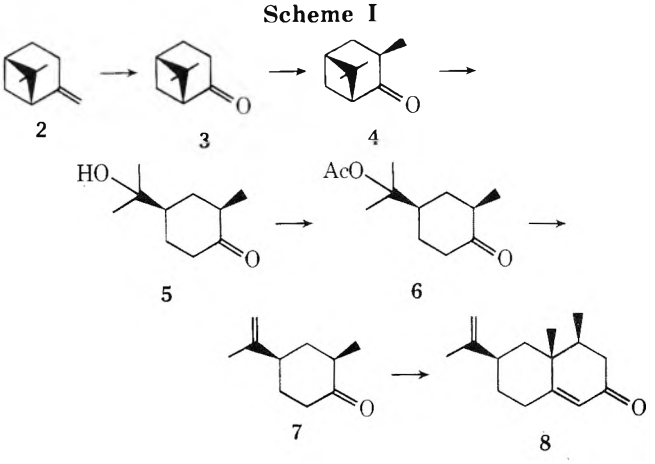
With 7-epinootkatone in hand, the problem of eremophilone synthesis is then reduced to one of functional group interchange.



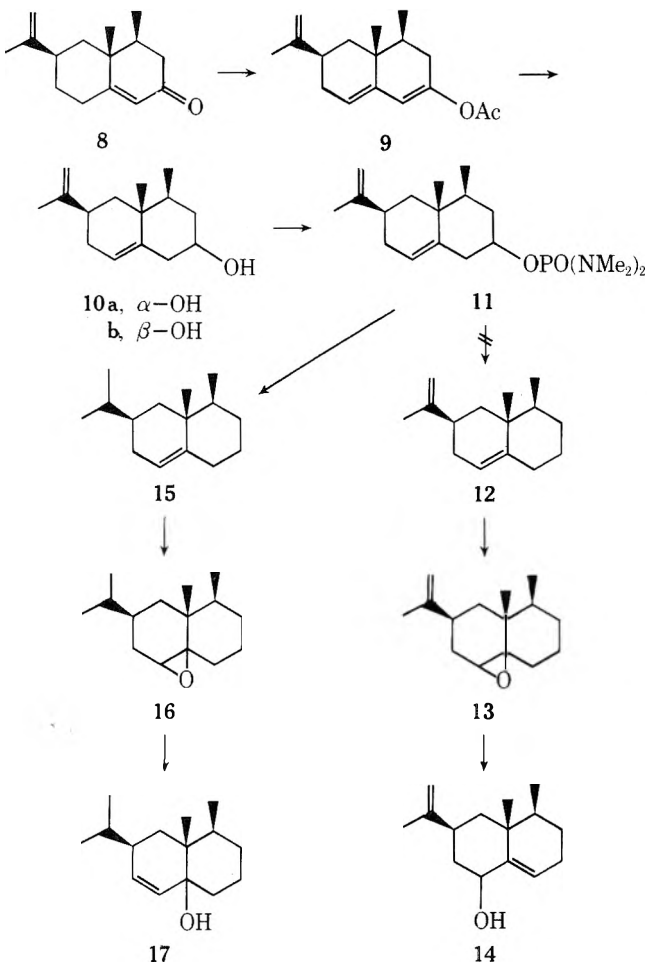
Results and Discussion

7-Epinootkatone (8) was synthesized from (−)-β-pinene by a modification of Van der Gen's procedure as outlined in Scheme I. Thus β-pinene was ozonized to nopinone (**3**, 75%), which was selectively monomethylated in 95% yield by treatment with 1.1 equiv of lithium diisopropylamide in tetrahydrofuran at −78°, followed by quenching of the enolate with methyl iodide. Methylnopinone (4) was then opened by treatment with aqueous sulfuric acid to give racemic hydroxy ketone **5** (75%). Although we encountered considerable difficulty in acetylating this tertiary alcohol with acetic anhydride using literature conditions,[15] we found that 4-*N*,*N*-dimethylaminopyridine strongly catalyzed the reaction,[18] and we isolated keto acetate **6** in 95% yield. Pyrolysis of this acetate in a stream of nitrogen at 600° gave 4-isopropenyl-2-methylcyclohexanone (45% overall from β-pinene). Careful reaction of **7** with 2-penten-3-one in the presence of sodium amide in liquid ammonia then gave 7-epinootkatone. In our hands, annelation precisely according to Van der Gen's detailed experimental procedure gave a rather poor yield of product. If, however, we modified the work-up to substitute a chromatographic isolation rather than a distillation, a considerably increased yield of 7-epinootkatone could be isolated (50% based on recovered starting material).

Scheme I



Scheme II

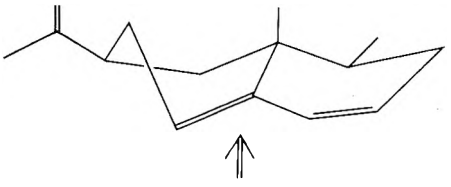


Our original plan for effecting the enone transposition necessary to convert 7-epinootkatone into eremophilone was to first deconjugate and then remove the carbonyl group to generate diene **12.** Selective epoxidation of the trisubstituted double bond should lead to epoxy olefin **13,** which we hoped to be able to rearrange to allylic alcohol **14** on treatment with strong base. Oxidation would then give eremophilone. Both Rickborn[19] and Crandall[20] have studied the base-induced rearrangement of epoxides and have found that the reaction proceeds by syn elimination. In our case, however, two different syn eliminations are possible, and no suitable examples have been reported to allow us to predict one path or the other. Presumably, the epoxide bond which breaks is the one which has the better overlap with a neighboring syn proton. Models of epoxide **13,** however, do not allow a clear prediction to be made in this case. We were hopeful, nonetheless, that epoxide **13** might rearrange by breaking the weaker, tertiary, C–O bond rather than the secondary bond. Our plan is summarized in Scheme II.

7-Epinootkatone was therefore enol acetylated and reduced with sodium borohydride according to the usual conditions[21] to give diene alcohol **10** (88%) as a 1:2 mixture of **10a** and **10b.** Although separation of these alcohols could be accomplished by high-pressure liquid chromatography on Porosil A,[22] we normally used the mixture for our further reactions. Alcohol **10** was then converted to its *N,N,N′,N′*-tetramethylphosphoroamidate, which we attempted to hydrogenolyze with lithium in ethylamine according to Ireland's procedure.[23] The sole reaction product, however, was monoolefin **15.** Evidently reduction of the isolated isopropenyl double bond occurs at a rate similar to that of phosphorodiamidate hydrogenolysis. Rather than immediately turn our attention to solving this problem, we decided to epoxidize olefin **15** and use it as a near-perfect model to study the projected base-induced epoxide opening. When epoxide **16** was prepared and treated with lithium di-*n*-propylamide in THF, however, epoxide opening occurred exclusively in the wrong sense to give tertiary alcohol **17** rather than the desired secondary alcohol. Spectral identification of the product was unequivocal (absence of OCH protons, presence of two vinyl protons in the NMR). We experimented briefly with the use of other bases (e.g., magnesium diisopropylamide) hoping that the reaction might take a different course in the presence of a Lewis acid cation, since the transition state might now be expected to have considerable carbonium ion character, thus favoring breakage of the tertiary C–O bond. These experiments were unsuccessful, however.

An alternate method of enone transposition was therefore necessary, and the homoallylic alcohol **10** which we had already obtained seemed a useful starting material, since the annular double bond is correctly disposed to allow functionalization of the proper positions. We therefore dehydrated **10** by pyrolysis of the corresponding acetate (760°, 51%) and isolated the sensitive triene **18.** The conjugated nature of the two annular double bonds follows from the uv spectrum [λ_{max} 237 nm (ϵ 14,200)]. It was our intention to selectively epoxidize the trisubstituted double bond. Acid-catalyzed rearrangement should then generate a β,γ-unsaturated ketone, which would isomerize to eremophilone.

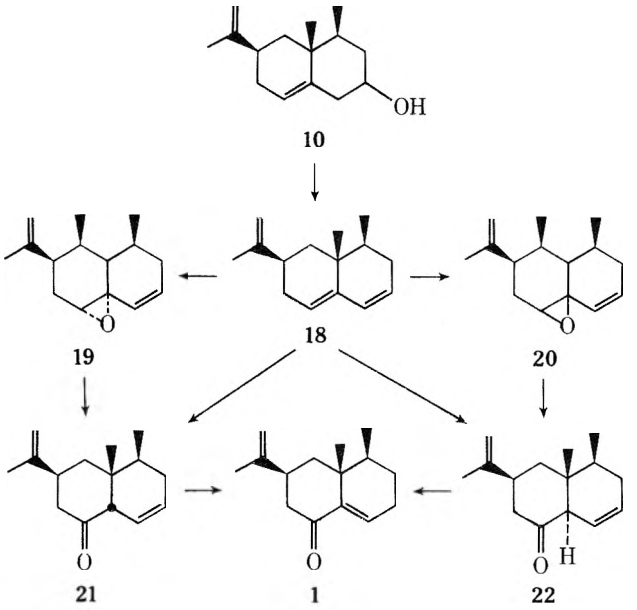
In practice, epoxidation of triene **18** with 1 equiv of *m*-chloroperbenzoic acid at 0° in a methylene chloride–0.5 *M* sodium bicarbonate two-phase system gave a complex mixture of products along with recovered starting material. High-pressure liquid chromatography on Porosil A[22] separated the product mixture into its components, among which we could identify the two epoxides **19** (21%) and **20** (7%) and the two β,γ-unsaturated ketones **21** (16%) and **22** (5%). Fortunately, all four (49% total yield) are useful for the synthesis of eremophilone. Evidently the desired epoxides are partially rearranged even under the mild conditions used in their formation. From Dreiding models of triene **18,** it is clear that peracid should approach the triene preferentially from the less hindered α face, leading to **19** as the major product.



Acid rearrangement would then occur with a 1,2-proton migration across the β face leading to β,γ-unsaturated ketone **21.** When we treated the two isolated epoxides **19** and **20** with lithium perchlorate in refluxing benzene,[24] rearrangement occurred in near-quantitative yield to give the two β,γ-unsaturated ketones **21** and **22,** respectively. From a preparative standpoint, it was simplest to treat the crude epoxidation product with lithium perchlorate directly. After so doing, a 3:1 mixture of ketones **21** and **22** could be isolated in 45% yield. Ketone **21,** the major epoxidation–rearrangement product, is itself a natural product isolation in 1969 from *Eremophila mitchelli.*[25] Our synthetic sequence, which presumably results in a cis ring fusion for the major isomer, thus further defines the ring junction stereochemistry of this minor sesquiterpene.

The total synthesis of eremophilone was completed by

Scheme III



conjugation of ketones **21** and **22** with dilute sodium methoxide in methanol at room temperature. Our synthetic eremophilone was identical with the natural product in all respects, including ir, NMR, and mass spectra. Transformations leading to eremophilone are summarized in Scheme III. Although one might expect a priori that this synthesis would result in optically active product, since (+)-β-pinene was used as starting material, this was not the case. Van der Gen has shown[15] that the acid-catalyzed opening of methylnopinone occurs with complete racemization; thus (±)-eremophilone results.

Experimental Section

(+) 3-Methylnopinone (4). To a solution of lithium diisopropylamide, prepared by treating 15 ml of freshly distilled diisopropylamine in 100 ml of dry tetrahydrofuran (THF) with *n*-BuLi (40 ml of 1.98 *M* solution) at −78°, was added a solution of (+)-nopinone[15] (10.0 g, 0.072 mol) in 10 ml of THF. After 30 min of stirring to form the enolate, the solution was warmed to 0° and 14 ml of methyl iodide was added. After stirring for an additional 2 hr, the reaction mixture was diluted with water and extracted with ether. The combined ethereal extracts were washed with dilute HCl and with saturated brine, then filtered, dried (Na_2SO_4), and concentrated to give a pale yellow oil [10.4 g, 95%, bp 50° (2 mm)] whose physical properties correspond to those reported.[15]

4-(1′-Acetoxyisopropyl)-2-methylcyclohexanone (6). 3-Methylnopinone was treated with aqueous sulfuric acid exactly as reported[15] to give 4-(1′-hydroxyisopropyl)-2-methylcyclohexanone (**5**) in 75% yield. Hydroxy ketone **5** (4.6 g, 0.027 mol), 4-*N*,*N*-dimethylaminopyridine (0.8 g), and acetic anhydride (8 ml) were dissolved in 25 ml of freshly distilled triethylamine, and the solution was stirred at room temperature for 7 hr. Methanol (10 ml) was then added to remove excess anhydride, and the mixture was then concentrated at the rotary evaporator. The residue was taken up in ether, then washed with water, dilute HCl, dilute sodium bicarbonate, and saturated brine. The ethereal solution was then dried (Na_2SO_4), filtered, and concentrated to give keto acetate **6** as a pale yellow oil with physical properties identical with those reported[15] (5.4 g, 95%).

7-Epinootkatone (8). Keto acetate **6** was pyrolyzed at 575° as reported[15] to give 2-methyl-4-isopropenylcyclohexanone (**7**, 80%), and this material was treated with 2-penten-3-one using van der Gen's conditions. Thus a solution of **7** (4.0 g, 0.026 mol) in 10 ml of dry dimethoxyethane containing 10 mg of triphenylmethane indicator was added over 30 min to a solution of sodium amide in 150 ml of dry liquid ammonia (0.7 g of sodium, 0.030 mol). After 30 min of stirring, an additional 30 ml of dry dimethoxyethane was added, and the ammonia was allowed to evaporate. A solution of 2-penten-3-one (2.6 g, 0.030 mol) in 20 ml of dry dimethoxyethane was slowly added, and the solution was stirred overnight at ice temperature. The reaction mixture was then diluted with water and extracted with ether. The ethereal extracts were dried (Na_2SO_4), filtered, and concentrated to a residue which was dissolved in 50 ml of methanolic sodium hydroxide and refluxed for 7 hr. After dilution with water, this solution was extracted with ether. These extracts were washed with water and with brine, then dried (Na_2SO_4), filtered, and concentrated. High-pressure liquid chromatography (HPLC) on Porasil A[22] (16 ft × 0.25 in.) gave 2.8 g (50%) of 7-epinootkatone whose physical properties correspond to those reported.[15]

Enol Acetate 9. A solution of 7-epinootkatone (**8**, 6.47 g, 29.7 mmol) in 50 ml of dry THF was added to a degreased suspension of sodium hydride (2.43 g of 57% dispersion in mineral oil, 38.0 mmol) in 100 ml of dry THF. Hexamethylphosphoramide (100 ml) was added, and the reaction mixture was stirred for 4 hr under nitrogen at room temperature. Acetic anhydride (6.05 g, 0.059 mol) in 50 ml of THF was added, and the mixture was stirred for an additional 30 min, then diluted with water and extracted with ether. The ether extracts were combined, washed with saturated brine, dried (Na_2SO_4), filtered, and concentrated to yield enol acetate **9** (7.72 g, 100%): ir (neat) 1765 cm^{-1}; NMR (CCl_4) δ 0.92 (d, 3 H, J = 6 Hz), 0.97 (s, 3 H), 1.76 (s, 3 H), 2.13 (s, 3 H), 4.74 (s, 2 H), 5.70 (broad s, 2 H). This material was used without further purification.

Homoallylic Alcohol 10. Enol acetate **9** (7.72 g, 0.0297 mol) was dissolved in 100 ml of ethanol and, after cooling to 0°, was added to a solution of sodium borohydride (3.84 g, 0.081 mol) in 200 ml of ethanol. The solution was stirred overnight at 0°, then heated to reflux, and 100 ml of 5% aqueous sodium hydroxide was added. After concentration at the rotary evaporator, the residue was acidified with dilute HCl and extracted with ether. The ether extracts were combined, washed with water and with brine, then dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue on 350 g of silica gel gave alcohol **10** (6.95 g, 88%) as a 1:2 mixture of **10a** and **10b** after elution with 20:1 hexane–ethyl acetate. Alcohol **10b** had the following properties: ir (neat) 3380 cm^{-1}; NMR (CCl_4) δ 0.88 (d, 3 H, J = 6 Hz), 0.93 (s, 3 H), 1.73 (s, 3 H), 4.67 (s, 2 H), 5.42 broad s, 1 H); mass spectrum *m/e* (rel intensity) 220 (P^+, 7.6).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.81; H, 11.16.

Triene 18. Homoallylic alcohol **10** (4.16 g, 0.0189 mol), acetic anhydride (5.74 g, 0.054 mol), and 4-*N*,*N*-dimethylaminopyridine (5 mg) were dissolved in 30 ml of triethylamine, and the resulting solution was stirred for 2 days at room temperature. Methanol (10 ml) was then added, and, after 30 min of stirring, the reaction mixture was concentrated at the rotary evaporator. The residue was taken up in ether, and the ether solution was washed with dilute HCl, with dilute bicarbonate, and with brine, then dried (Na_2SO_4) and concentrated. The residue was chromatographed on 200 g of silica gel to give the desired acetate (2.69 g, 60%) along with recovered starting material (1.83 g, 45%). The desired acetate had the following spectral properties: ir (neat) 1730 cm^{-1}; NMR (CCl_4) δ 0.87 (d, 3 H, J = 6 Hz), 0.96 (s, 3 H), 1.75 (s, 3 H), 1.98 (s, 3 H), 4.75 (s, 2 H), 5.55 (m, 1 H).

This acetate, corresponding to **10** (0.84 g, 0.0032 mol), was dissolved in 6 ml of benzene and slowly passed into a quartz pyrolysis tube which was heated to 760° and swept by a stream of nitrogen as carrier gas (150 ml/min). Upon cooling, the column was rinsed with ether, and the ethereal pyrolysate solution was washed with dilute bicarbonate and with brine, then dried (Na_2SO_4), and concentrated. The residue was then subjected to HPLC on Porasil A[22] (16 ft × 0.25 in.). After elution of triene **18** (300 mg), a small amount of recovered starting material was eluted (70 mg). Triene **18** had the following properties: ir (neat) 882 cm^{-1}; uv λ_{max} 229 nm (ε 15,200), 237 (14,200), 243 (10,000); NMR (CCl_4) δ 0.85 (d, 3 H, J = 6 Hz), 0.90 (s, 3 H), 1.76 (s, 3 H), 4.78 (s, 2 H), 5.44 (m, 1 H), 5.57 (m, 2 H); mass spectrum *m/e* (rel intensity) 202 (P^+, 22), 119 (100).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.16; H, 10.85.

Epoxide 19. Triene **18** (350 mg, 1.73 mmol) was dissolved in 10 ml of methylene chloride and added to 10 ml of 0.5 *M* sodium bicarbonate at 0°. *m*-Chloroperbenzoic acid (350 mg, 1.75 mmol) in 25 ml of methylene chloride was slowly added and the reaction mixture was stirred for 2 hr at 0°. The organic phase was then separated, washed with dilute bicarbonate and with brine, then dried (Na_2SO_4), filtered, and concentrated. HPLC on Porasil A[22] then gave, in order of elution, recovered triene **18** (80 mg, 0.40 mmol); epoxide **19** (60 mg, 21% based on recovered material); epoxide **20** (20 mg, 7%); ketone **21** (47 mg, 16%); ketone **22** (15 mg, 5%). Epox-

ide **19** had the following spectral properties: ir (neat) 880 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, J = 6 Hz), 1.27 (s, 3 H), 1.72 (s, 3 H), 4.70 (s, 2 H), 5.60 (m, 2 H); mass spectrum m/e (rel intensity) 218 (P^+, 6), 91 (100).

β,γ-Unsaturated Ketone 21. Epoxide **19** (140 mg, 0.64 mmol) was dissolved in 30 ml of dry benzene and refluxed with 70 mg of dry, powdered $LiClO_4$ under nitrogen for 1 hr. After cooling, the reaction mixture was diluted with ether, and the solution was washed with water and with brine, then dried (Na_2SO_4), filtered, and concentrated. HPLC on Porasil A[22] gave recovered epoxide **19** (23 mg, 0.11 mmol) and β,γ-unsaturated ketone **21** (112 mg, 96% based on recovered epoxide): ir (neat) 1710, 885 cm^{-1}; NMR (CCl_4) δ 0.85 (d, 3 H, J = 6 Hz), 0.98 (s, 3 H), 1.78 (s, 3 H), 4.80 (s, 2 H), 5.70 (m, 2 H); mass spectrum m/e (rel intensity) 218 (P^+, 16), 93 (100).

The infrared and NMR spectra of this synthetic material were identical with those of the natural product.[26]

Eremophilone (1). A 3:1 mixture of the unsaturated ketones **21** and **22** (110 mg, 0.50 mmol) was dissolved in 20 ml of methanol to which a trace of sodium had been added, and the reaction mixture was refluxed for 30 min to isomerize the double bond. Ether was added, and the solutioniwasiwashed with dilute HCl and with brine, then dried ($MgSO_4$), filtered, and concentrated. HPLC of the residue on Porosil A gave **21** (43 mg, 39%) and eremophilone (**1**, 45 mg, 41%). Synthetic eremophilone had the following physical properties: ir (CCl_4) 1685, 1620, 885 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, J = 6 Hz), 0.97 (s, 3 H), 1.75 (s, 3 H), 4.75 (s, 2 H), 6.48 (t, 1 H); mass spectrum m/e (rel intensity) 218 (P^+, 71), 108 (100). The infrared and NMR spectra of this synthetic material are identical with those of the natural product.[26]

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.46; H, 10.37.

Registry No.—**1**, 53797-64-1; **4**, 27040-88-6; **5**, 34182-10-0; **6**, 34181-38-9; **8**, 38906-83-1; **9**, 54798-77-5; **10a**, 54798-78-6; **10a** acetate, 54798-79-7; **10b**, 54798-80-0; **10b** acetate, 54798-81-1; **18**, 54868-33-6; **19**, 54798-82-2; **20**, 54831-49-1; **21**, 54831-50-4; **22**, 54868-34-7; lithium diisopropylamide, 4111-54-0; (+)-nopinone, 473-60-9.

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Notes

Interconversion of Eremophilone and Isoeremophilone and Related Reactions

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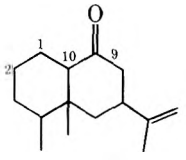
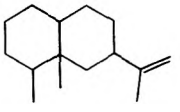
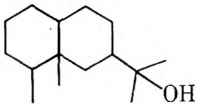
Eremophilone (1), probably the best known sesquiterpene because of its unique nonisoprenoid structure,[2,3] has only recently been synthesized,[4] culminating over 40 years of fascinating chemistry. A few years ago we demonstrated the cooccurrence of the β,γ-unsaturated isomer of eremophilone, $7\alpha(H)$-eremophila-1,11-dien-9-one (2), in the ether extract of the wood of *Eremophila mitchelli*.[5] We now report the efficient conversion of natural eremophilone into $7\alpha(H)$-eremophila-1,11-dien-9-one by alkaline deconjugation using potassium *tert*-butoxide. Thus, an eremophilone-rich (92% eremophilone, 5% $7\alpha(H)$-eremophila-1,11-dien-9-one) mixture, on stirring for 1 hr at room temperature with 5.6 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol, gave, after quenching with water, a mixture containing 88% $7\alpha(H)$-eremophila-1,11-dien-9-one and 6% eremophilone. It is interesting that the equilibrium composition of a mixture of ketones 1 and 2 comprises approximately a 1:1 ratio of the two rather than a great preponderance of the α,β-unsaturated ketone as might have been expected. The apparent decreased stability of 1 must arise from the increased steric interaction of the C-4 and C-5 methyl groups in 1 as compared to 2. As previously mentioned, this presumably is responsible for the deshielding (~0.1 ppm) of the C-4 methyl group in 1 relative to the corresponding methyl group in 2.[5]



1, $\Delta^{1(10)}$
2, $\Delta^{1(2)}$
5, $10\beta(H)$



3, $\Delta^{1(10)}$
4, $\Delta^{9(10)}$



6, $\Delta^{1(10)}$
7, $\Delta^{9(10)}$

When eremophilone was reduced with lithium aluminum hydride in the presence of aluminum chloride (1:2 molar ratio of $LiAlH_4$ to $AlCl_3$) in ether, a complex mixture of products was obtained, which was separated by chromatography on alumina into a hydrocarbon fraction (42% by weight) and a ketone fraction (58%). The hydrocarbon fraction was composed of two major components (50 and 30%, respectively, by GLC), which were collected by preparative GLC. The major hydrocarbon (>98% pure by GLC) appeared similar to eremophilene on cursory inspection (ir, NMR), but direct comparison with an authentic sample of eremophilene (3) showed that, in fact, the two hydrocarbons differed by GLC and in their ir, NMR, and mass spectra.[6] However, under identical conditions both this hydrocarbon and eremophilene were reduced to the same saturated hydrocarbon, eremophilane. On the basis of its NMR spectrum, in particular the appearance of olefinic protons at δ 5.40 (1, m) and δ 4.78 (2 H, br s), its nonidentity with eremophilene (3), and its method of preparation, this product has been assigned the structure $7\alpha(H)$-eremophila-9,11-diene (4). Owing to insufficient material, the second hydrocarbon has not been fully characterized, but it is not identical with eremophilene and appears to be a rearranged product. It has been reported that a 1:2 ratio of $LiAlH_4$ to $AlCl_3$ leads to preferential shifting of the double bond to the original carbonyl carbon.[8]

The above-mentioned ketone fraction consisted predominantly of one substance (70% by GLC) which was collected by preparative GLC and shown to be identical with *cis*-dihydroeremophilone (5) by GLC and ir, NMR, and ORD spectral comparisons. The conjugate reduction of α,β-unsaturated carbonyls with mixed hydrides has previously been reported and appears to be sensitive to the $LiAlH_4$ to $AlCl_3$ ratio.[9] Attempts to convert eremophilone into eremophilene via reduction of the thioketal or by Wolff–Kishner reduction met with no success. Likewise, plans to convert eremophilone into valencene were frustrated when preferential oxidation of the isopropenyl group by the Lemieux von Rudloff reagent or by osmium tetroxide failed.

On treatment with *m*-chloroperbenzoic acid, eremophilone gave eremophilone 11-oxide, obtained in pure form (>95% by GLC) by chromatography on neutral alumina. Reduction of this oxide with lithium aluminum hydride in ether gave a complex mixture, the GLC of which showed two major components (50 and 30%, respectively). On further reduction with lithium aluminum hydride–aluminum chloride, as described above, this mixture gave a complex mixture containing only one major component (52% by GLC). Chromatography on alumina gave a pure product (>97% by GLC), similar to but distinctly different by ir and NMR from eremoligenol (6).[10] In view of its spectral properties, in particular the appearance in the NMR of a single olefinic proton at δ 5.40, similarity to eremoligenol, and the above-mentioned results, this product has been assigned the structure $7\alpha(H)$-eremophila-9-en-11-ol (7).

Experimental Section[11]

$7\alpha(H)$-Eremophila-1,11-dien-9-one (2). Forty milligrams of an eremophilone-rich mixture (92% eremophilone, 5% $7\alpha(H)$-eremophila-1,11-dien-9-one by GLC) in 2 ml of dry *tert*-butyl alcohol was added to a solution prepared by adding 40 mg of potassium to 25 ml of dry *tert*-butyl alcohol.[12] After stirring at room temperature in a nitrogen atmosphere for 1 hr, 100 ml of water was added and the solution was extracted with ether. Washing with water, drying (sodium sulfate), and removal of the ether gave 37 mg of a pale yellow oil, which on GLC analysis (3% SE-30) showed 88% $7\alpha(H)$-eremophila-1,11-dien-9-one identified by ir, NMR, and ORD comparisons with an authentic sample.

Equilibration of 1 and 2. In an attempt to establish the equilibrium between 1 and 2, 10 mg of a mixture of eremophilone and isoeremophilone (57:43) was added to 2 ml of ethanol, and to this 2 ml of 0.5 *N* hydrochloric acid was added and the solution was allowed to stand in a nitrogen atmosphere at room temperature. Periodic analysis by GLC (3% SE-30) showed essentially no change in composition of the mixture, even after 24 hr. In another experiment, to 10 mg of the above-mentioned eremophilone–isoeremophilone mixture in 2 ml of methanol was added a solution containing 1 mg of sodium methoxide in 2 ml of methanol in a nitrogen atmosphere. After 1 hr at room temperature there was no change in the mixture composition. Likewise, there was no change after 2 hr of reflux. Use of more concentrated base and more drastic conditions resulted in the destruction of 1.

Reduction of Eremophilone with $LiAlH_4$–$AlCl_3$. To 0.152 g of lithium aluminum hydride in 20 ml of dry ethyl ether was added 1.06 g of anhydrous aluminum chloride followed by 0.218 g of ere-

mophilone in 5 ml of dry ether. The reaction mixture was stirred for 1 hr at room temperature, refluxed for 2 hr, then cooled in an ice bath and cold water was added until no further reaction occurred. After filtration, the solution was extracted with ether and the latter extract was washed with aqueous bicarbonate, then brine and finally dried and concentrated to give 0.179 g of a pale yellow, mobile liquid. Chromatography of the latter on 10 g of activity I neutral alumina gave 0.074 g of a hydrocarbon fraction in the petroleum ether eluent and 0.102 g of a ketone fraction in the ethyl ether eluent. GLC analysis (5% Carbowax column) of the hydrocarbon fraction showed two major components (50 and 30%, respectively), while GLC analysis of the ketone fraction (3% SE-30) showed one major component (70%). Preparative GLC (5% Ucon polar) gave 7α(*H*)-eremophila-9,11-diene (**4**) as the major component (>98% purity by GLC): ν_{max} (CCl_4) 1640, 882 cm^{-1}; δ (CCl_4) 0.94 (3 H, d, J = 6 Hz), 1.03 (3 H, s), 1.82 (3 H, s), 4.78 (2 H, br s), 5.40 (1 H, m); ORD (c 0.06, CH_3OH), plain negative curve $[\phi]_{589}$ −80.2°; mol wt by mass spectrometry (peak-to-peak distance measurement using 1,2-dichlorooctafluorocyclohexene-1 as reference) 204.186 (calcd for $C_{15}H_{24}$, 204.188).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.00; H, 11.90.

A comparison of the ir and NMR spectra of 7α(*H*)-eremophila-9-11-diene (**4**) with those of eremophilene (**3**) showed that they were not identical and a direct comparison with an authentic sample of eremophilene by GLC showed their nonidentity (5% Carbowax column).[6] However, hydrogenation (Pt, EtOH) of both dienes gave the same saturated hydrocarbon as determined by GLC (5% Carbowax column) and mass spectral analysis. The major component of the ketone fraction was collected by preparative GLC (3% SE-30 column) and was identified as *cis*-dihydroeremophilone[7] by GLC, ir, ORD, and NMR: δ (CCl_4) 0.93 (d, J = 5 Hz), 1.15 (3 H, s), 1.87 (3 H, s), 4.85 (2 H, br s).

7α(*H*)-Eremophil-9-en-11-ol (7). To 0.436 g of eremophilone (containing ~15% isoeremophilone) in 15 ml of anhydrous ether, 0.406 g of *m*-chloroperbenzoic acid (85% active) was added and the solution was stirred at room temperature for 24 hr. After addition of water, the solution was extracted with ether and the combined ether extracts were washed with aqueous sodium bicarbonate, then brine and finally concentrated to give 0.45 g of a colorless liquid. GLC analysis (3% SE-30 column) showed one major peak (80%). No starting material remained. Chromatography on neutral alumina (activity II–III) gave eremophilone 11-oxide (95% purity by GLC) in the benzene eluent: δ (CCl_4) 0.97 (3 H, s), 0.99 (3 H, d, J = 5.5 Hz), 1.27 (3 H, s), 6.46 (1 H, t, J = 3.8 Hz); complete disappearance of band at 896 cm^{-1} in ir.

To 50 mg of lithium aluminum hydride in 20 ml of anhydrous ether was added a solution of 400 mg of eremophilone 11-oxide in 5 ml of dry ether and the solution was stirred at room temperature for 1 hr and then refluxed for 2 hr. The solution was then cooled, moist ether was added, and, after filtration, the ether layer was dried and concentrated to give 0.375 g of a colorless, viscous liquid, the GLC (3% SE-30) of which showed a complex mixture containing two major components (50:30). This crude product (0.242 g) was dissolved in 10 ml of anhydrous ether containing 0.133 g of anhydrous aluminum chloride and this was added to a solution of 0.076 g of lithium aluminum hydride and 0.399 g of anhydrous aluminum chloride in 15 ml of anhydrous ether. The reaction mixture was stirred at room temperature for 1 hr and then refluxed for 2 hr. After the usual work-up, 0.201 g of a viscous liquid was obtained, the GLC (3% SE-30) of which showed a complex mixture with one component (51%). Chromatography on 10 g of neutral alumina (activity II–III) gave in the benzene–ether (96:4) eluent 16 mg of 7α(*H*)-eremophil-9-en-11-ol (**7**, 97% by GLC on 3% SE-30 and 15% Carbowax 2014 columns). This product was not identical, by ir and NMR comparisons, with eremoligenol (**6**):[10] ν_{max} (CCl_4) 3600, 3460, 1665 cm^{-1}; δ (CCl_4) 0.93 (unresolved doublet, $J \simeq 6$ Hz), 1.04 (3 H, s), 1.22 (3 H, s), 1.27 (3 H, s), 5.40 (1 H, m); mol wt by mass spectrometry (peak-to-peak distance measurement using 1,2-dichlorooctafluorocyclohexene-1) 222.187 (calcd for $C_{15}H_{26}O$, 222.198).

Registry No.—**1**, 562-23-2; **2**, 22489-11-8; **4**, 54868-40-5; **5**, 54814-46-9; **7**, 54832-19-8; eremophilone 11-oxide, 54814-47-0; $LiAlH_4$, 16853-85-3.

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(9) H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, Calif., 1972, p 91.
(10) We thank Dr. H. Ishii (Shionogi Research Laboratory, Osaka, Japan) for copies of the ir and NMR spectra of eremoligenol. Unfortunately, an authentic sample was no longer available (Oct 18, 1968).
(11) Ir spectra were recorded with a Perkin-Elmer 237B spectrophotometer, NMR spectra were obtained with a Varian A-60 spectrometer, and mass spectra were obtained using a Varian M-66 mass spectrometer. GLC analyses were performed using a F & M biomedical gas chromatograph, Model 400.
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A New Mild Conversion of Ketones to the Corresponding Methylene Derivatives

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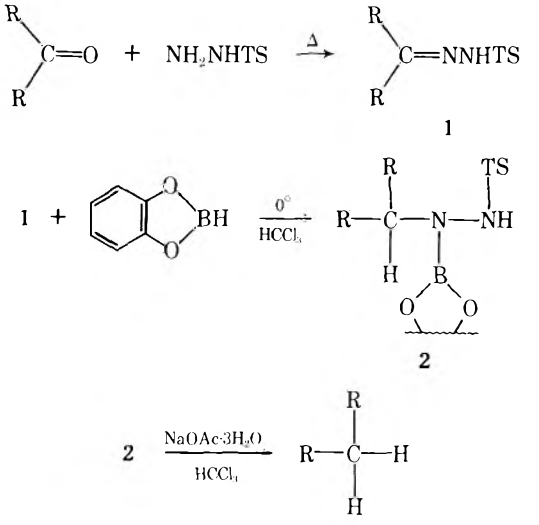
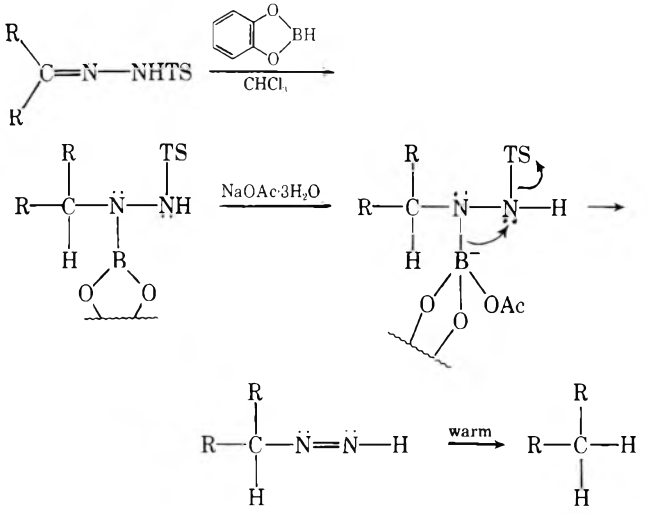
We wish to report a new, mild conversion of ketones to the corresponding methylene derivatives. The conversion involves the reduction of tosylhydrazones with catecholborane followed by decomposition of the reduction product (Scheme I).

Scheme I



The conversion of carbonyl compounds to their corresponding methylene derivatives is one of the key transformations in organic synthesis. Not surprisingly, a great deal of literature exists concerning this transformation.[1] The reduction procedures that are generally employed utilize strong acids or bases which preclude the presence of sensitive functional substituents.[2] The more recently reported reduction procedures involve the less reactive hydride reagents and carbonyl derivatives.[3,4] However, these new procedures involve the utilization of large excesses of hydride.[3] We felt that the reduction of tosylhydrazones with catecholborane would be an ideal way to achieve the reduction of carbonyl compounds. The tosylhydrazones are readily prepared, requiring no acid or base catalysis.[3a] Furthermore, the use of the mild, commercially available (Aldrich) catecholborane negates the need for excess hydride, which

Scheme II



should permit the reduction of functionally substituted carbonyl compounds.[5,6]

A reasonable mechanism for the reduction is outlined in Scheme II and is based on analogy to known reactions. Thus, it has long been recognized that organoboranes which contain an electronegative substituent β to the boron atom are prone to elimination, especially in the presence of nucleophiles.[7,8] Furthermore, diazenes are unstable and decompose to yield alkanes in the presence of proton sources.[9,10]

The reaction appears to be a general one, producing good yields of the reduction products. It depends only on the availability and stability of the tosylhydrazone derivative. Owing to the mildness of the reaction, we feel that it should be applicable to a variety of substituted ketones.[5]

Our results are summarized in Table I.

Table I
Conversion of Ketones to the Corresponding Methylene Derivatives[a]

Ketone[a]	Registry no.	Product[b]	Registry no.	Yield, %[c]
2-Octanone	111-13-7	Octane	111-65-9	91 (81)[d]
Isophorone	78-59-1	3,5,5-Trimethylcyclohexene[e]	933-12-0	41
Cyclohexanone	108-94-1	Cyclohexane	110-82-7	92
2-Methylcyclohexanone	583-60-8	Methylcyclohexane	108-87-2	64
Norbornanone	497-38-1	Norbornane	279-23-2	63

[a] The ketones were first converted to the corresponding tosylhydrazones. [b] Products exhibited physical and spectral parameters in agreement with those of authentic samples. [c] GLC analysis. [d] Isolated yield. [e] Reduction occurs with migration of the double bond.

Experimental Section[11]

Materials. The tosylhydrazones (Table II) were prepared according to the method described by Hutchins et al.[3a]

General Procedure for Reductions. The reduction of 2-octanone is representative. The tosylhydrazone of 2-octanone (52.7 mmol, 15.64 g) was dissolved in 105 ml of chloroform at $-10°$.[12] Catecholborane (58 mmol, 6.31 ml) was added and the hydroboration was allowed to proceed for 20 min. Sodium acetate trihydrate[13] (155 mmol, 21.1 g) was then added and the reaction mixture was brought to a gentle reflux for 1 hr.[14] GLC analysis indicated a 90.8% yield of octane with no evidence for alkene formation. The product was distilled from the reaction mixture, bp 124–127°. The yield of octane was 4.78 g (81%).

Table II
Melting Points of the Tosylhydrazones Utilized

Ketone	Registry no.	Mp, °C
2-Octanone	54798-76-4	96.5–98
Isophorone	21195-62-0	142–144
Cyclohexanone	4545-18-0	155–158
2-Methylcyclohexanone	52826-41-2	112–114
Norbornanone	38397-34-1	194–196

Acknowledgment. We wish to thank the Research Corporation for support of this study.

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(1) See, for example, (a) W. Reusch, "Reduction", R. L. Augustine, Ed., Marcel Dekker, New York, N.Y., 1968, pp 171–211; (b) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 4.
(2) For example the strongly basic conditions required in the Woiff–Kishner reductions preclude the incorporation of functionality such as amide, ester, cyano, halogen, etc. A similar situation holds for the Clemmensen reduction.
(3) See, for example, (a) R. O. Hutchins, C. Milewski, and B. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973); (b) L. Caglioti, *Tetrahedron*, **22**, 487 (1966).
(4) Another useful route involves the reduction of the ketone to the corresponding alcohol, transformation of the alcohol to a suitable leaving group, and displacement of that group with hydride reagents: C. W. Jefford, D. Kirkpatrick, and F. Daley, *J. Am. Chem. Soc.*, **94**, 8905 (1972).
(5) Control experiments indicated that catecholborane did not react with *n*-octyl bromide and acetonitrile after 2 hr under the conditions reported. Even more surprising, 1-octene was not hydroborated after 4 hr by catecholborane at 0° in $CHCl_3$.
(6) Boron hydrides react extremely rapidly with carbonyl groups and their derivatives. See H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972, pp 227–251.
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(10) It should be noted that the reduction of isophorone occurs with migration of the double bond. This phenomenon has been cited as evidence against a mechanism involving carbanion formation. See, for example, ref 3a.
(11) Melting points and boiling points are uncorrected. NMR spectra were obtained using a Varian Associates A-60 instrument.
(12) Methylene chloride gives similar results.
(13) Sodium acetate induces the decomposition of the intermediate 2. The product is obtained in lower yields if no acetate is added.
(14) The product may also be obtained in an identical yield by stirring the mixture at room temperature for 24 hr.

Reaction of o-Chlorotoluene with Alkali Amides. A Study of the Metal Effect in Benzyne Reactions

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Received June 12, 1974

Since the pioneering work by Wittig[1] and Roberts[2] on the chemistry of arynes, extensive research has been done in this area. A monograph which summarizes much of this work has appeared.[3] Roberts[4] and coworkers have observed that *the reaction of o-chlorotoluene with potassium amide yields o- and m-toluidine in approximately equal amounts.* This result is surprising, since one would expect the inductive effect of the methyl group to operate in such a way as to make the amount of the ortho isomer which is formed much greater than that of the meta isomer. For example, treatment of *p*-chlorotoluene with potassium amide in liquid ammonia yields *m*- and *p*-toluidine in a 3:2 ratio,

meta to para, respectively. Roberts suggested that the low yield of the ortho isomer may be due to the operation of a steric factor. It is conceivable that the methyl group offers some steric hindrance to the attacking species, be it ammonia or amide ion. Additionally, Roberts et al.[4] have observed that *the reaction of o-chlorotoluene with sodium amide in liquid ammonia yields o- and m-toluidine in a ratio of 2:1.* If one is to argue that steric hindrance of the methyl group makes it difficult for the carbon atom which is ortho to be attacked by amide ion or ammonia, it is hard to offer a reasonable explanation for the difference in the isomer distribution which is obtained by the action of sodium and potassium amide with o-chlorotoluene in liquid ammonia.

The change in isomer distribution may be linked to the amide's counterion. With this in mind, three experiments were conducted, viz., the reaction of o-chlorotoluene with lithium, sodium, and potassium amide. The results are listed in Table I.

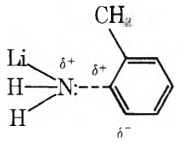
Table I
Reactions of *o*-Chlorotoluene with Alkali Amides, MNH_2

M	% *o*-toluidine	% *m*-toluidine	Ratio, *o*-:*m*-
Li	73	27	~3:1
Na	67	33	2:1
K	54	46	~1:1

In this study the isomer distributions were determined by vapor phase chromatography. Reference to Table I shows that as the metal is varied from lithium to sodium to potassium, the percentage of *o*-toluidine decreases in this order. A possible explanation for this trend follows. It is probable that the metal cation–amide anion bond has some degree of covalency. The extent of covalent bonding should increase as the metal cation is varied from potassium to sodium to lithium since the ionic radii of the metal cations are as follows: Li^+, 0.6 Å; Na^+, 0.95 Å; and K^+, 1.22 Å.[5] Thus lithium ion, having a greater concentration of charge, would have an inherently greater polarizing effect upon the amide ion than would sodium or potassium. This would lead to greater covalent bonding in lithium amide than in sodium or potassium amide.

The differences in the basicities of the alkali amides is also a basis for the contention that there are differences in covalent bonding in alkali amides. Leake[6] found that the reaction of sodium and potassium amide with chlorobenzene gives fair yields of aniline whereas the same reaction with lithium amide gives no aniline and results in a high recovery of chlorobenzene. Since Roberts and coworkers[4] have been able to show that the rate-determining step of the benzyne reaction is the abstraction of a benzenoid hydrogen atom by a strong base, it is possible that Leake's results may be due to differences of basicity of the alkali amides. It is likely that the degree of covalency in the alkali amide series is related to their basicity. The more the electron pair of the basic nitrogen is called on for bond formation, the less it will be available for acid–base reactions. Thus lithium amide would be the least basic, since it probably has the highest degree of covalency.

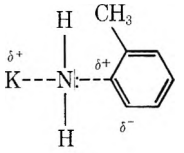
If the assumption is made that the alkali amides have different degrees of covalency in liquid ammonia, then the results become intelligible on the basis of steric repulsion in the transition state. The transition state is pictured as involving the bond formation between the 2-toluyne and the lone pair of electrons on the nitrogen atom of the alkali amide. The geometry of the metal amide is dependent upon the degree of covalency of the metal–nitrogen bond. The more covalent the metal–nitrogen bond is, the more sp^3 character it will have. Conversely, the less covalent character the metal–nitrogen bond has, the more sp character it will have. The proposed transition state of the addition of lithium amide to the toluyne is represented by **1**. It



1

is seen that there is very little steric repulsion between the methyl group of 2-toluyne and the hydrogen atoms of the amide ion because the geometry of the amide ion is probably much closer to a tetrahedron (sp^3 hybridization) than to a linear molecule (sp hybridization) owing to the increased covalency of the lithium amide species. Thus, the ortho isomer can be formed without much difficulty, since there is little interaction between the methyl group and the hydrogen atoms of the amide ion.

However, since potassium amide is not as covalent a compound as lithium amide, it probably has a larger degree of sp character and thus there will be steric repulsion between the methyl group and the amide ion hydrogen atoms. The proposed transition state for the addition of potassium amide to 2-toluyne is shown in **2.**



2

Thus, it appears likely that the metal associated with the alkali amide makes an important contribution to the observed results. The ability of the metal to coordinate with the amide ion in varying degrees probably controls the geometry of the transition state. It should also be pointed out that the nucleophilicity (because of basicity and solvation effects) increases in the order $LiNH_2 < NaNH_2 < KNH_2$. Furthermore, it is known[7] that the species of greatest nucleophilicity (KNH_2 is this case) results in the least selectivity, which in the present experiments would oppose the steric effect and would agree with the results reported in Table I.

Experimental Section

Vapor Phase Chromatography. The isomer distribution analyses were performed with a Kromo-Tog K-2 vapor phase chromatograph. Good resolution of the o- and *m*-toluidine mixture (retention times: o-toluidine, 26.5 min; *m*-toluidine, 30.5 min) was obtained by use of a column containing 10% UCON HB-2000 on Fluropak-80 using helium as the carrier gas at a flow rate of 80 ml/min, a detector voltage of 170 mA, and a temperature of 130°.

Reaction of o-Chlorotoluene with Sodium Amide in Liquid Ammonia. Liquid ammonia (500 ml) and a few crystals of ferric nitrate were added to a 1-l., three-neck, round-bottom flask equipped with a slip-seal stirrer, Dry Ice condenser, and a glass plug. Sodium (4.6 g, 0.2 mol) was added over a 10-min period. After the discharge of the blue color 12.7 g (0.1 mol) of o-chlorotoluene was added dropwise over a 15-min period. The reaction was allowed to continue for 15 min. Then 13.5 g (0.25 mol) of ammonium chloride was added. The Dry Ice condenser was replaced by a West condenser, 150 ml of ether was added, and the ammonia was removed by heating on a water bath. The reaction mixture was poured onto an ice–hydrochloric acid slurry and was extracted with three 100-ml portions of ether. The residual aqueous phase was made basic with sodium carbonate and extracted with three 100-ml portions of ether. The combined ether extracts were dried over sodium sulfate. After evaporation of the solvent, a liquid resi-

due (6.4 g, 60%) containing a mixture of *o*- and *m*-toluidine was obtained. The mixture consisted of 67% *o*-toluidine and 33% *m*-toluidine as determined by vapor phase chromatographic analysis. In addition 4.0 g (31.5%) of *o*-chlorotoluene, bp 157–159° (760 mm), was recovered.

Reaction of o-Chlorotoluene with Lithium Amide in Liquid Ammonia. Using the same procedure as that which was employed with sodium amide and *o*-chlorotoluene, the reaction of lithium amide (0.2 mol) and *o*-chlorotoluene (12.7 g, 0.1 mol) gave upon the removal of the solvent 0.5 g (2%) of a mixture containing 73% *o*-toluidine and 27% *m*-toluidine. In addition, 11.5 g (90.5) of *o*-chlorotoluene, bp 157–159° (760 mm), was recovered.

Reaction of Potassium Amide and o-Chlorotoluene in Liquid Ammonia. The reaction of potassium amide (0.20 mol) and o-chlorotoluene (12.7 g, 0.10 mol) gave upon removal of the solvent 6.7 g (63%) of a mixture containing 54% *o*-toluidine and 46% *m*-toluidine. Also, 3.9 g (30.7%) of o-chlorotoluene, bp 156.5–159° (760 mm), was recovered.

Registry No.—Lithium amide, 7782-89-0; sodium amide, 7782-92-5; potassium amide, 17242-52-3; *o*-toluidine, 95-53-4; *m*-toluidene, 108-44-1; *o*-chlorotoluene, 95-49-8.

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(7) See ref 3, p 149.

The Imidazole–Formaldehyde Reaction. Formation of 1-Imidazolemethanol

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Spectral,[1,2] NMR,[3] and potentiometric[4] studies have shown the formation in solution of 1-imidazolemethanol (**1**) from the reaction of imidazole and formaldehyde, although **1** was not isolated. These studies show that only one nitrogen is involved in methylol formation in basic media.[3,4] In an acid medium,[3,4] both ring nitrogens may be hydroxymethylated. Jones[5] has shown that 1-benzylimidazole forms the 2-hydroxymethyl derivative in nearly quantitative yield in a sealed tube reaction between formaldehyde and 1-benzylimidazole.

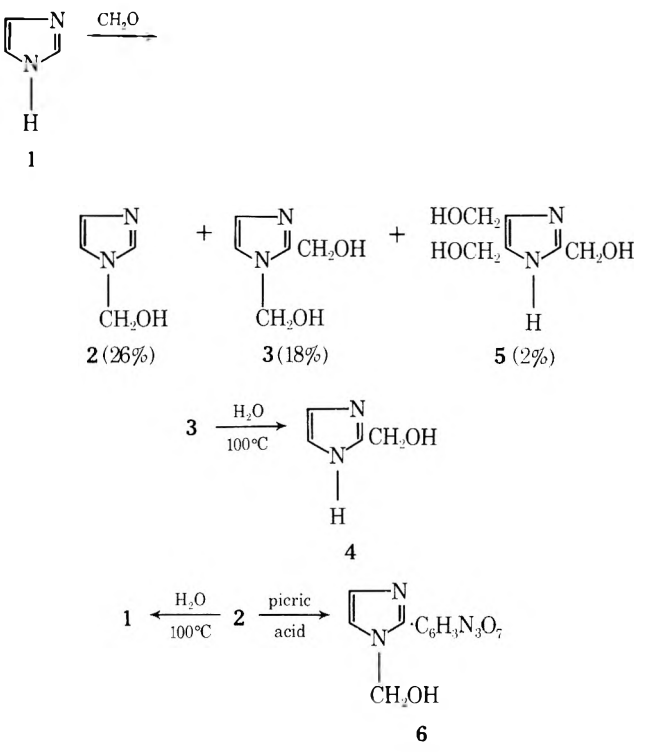
From a sealed tube reaction between imidazole and formaldehyde at 120–130°, a liquid fraction was isolated by chromatography of the crude product. This material gave a picrate derivative (**6**) corresponding to that of a methylolated imidazole. NMR data on the methylolated imidazole indicates the presence of the $-NCH_2O-$ protons by a singlet at δ 5.39 (in D_2O), in agreement with the values reported by Dunlop, Marini, Fales, Sokoloski, and Martin[3] (δ 5.40 in D_2O). Boiling this material in water yields imidazole. These data indicate that the liquid is 1-imidazolemethanol (**2**).

From this same reaction there was obtained a white, crystalline solid (mp 126–127°) which appears to be 1,2-bis(hydroxymethyl)imidazole (**3**). NMR data on this material also show the presence of an NCH_2O- methylene group (NMR peak at δ 5.47 in D_2O) as well as a methylene group (NMR peak at δ 4.75 in D_2O) at the 2 position.

A small amount of a second white, crystalline material (mp 158–159°) was also isolated. Elemental analysis and NMR data indicate that the material is 2,4,5-tris(hydroxymethyl)imidazole (**5**).

Table I summarizes the NMR data on the products of this reaction.[7] Scheme I summarizes the principal reactions.

Scheme I



Experimental Section

Ir spectra were obtained using a Beckman Model 10 grating ir spectrophotometer with potassium bromide cells. Solids were pressed into 1% KBr pellets. NMR spectra, graciously run by Dr.

Table I
Proton Chemical Shifts for Imidazole Derivatives[a-c]

Compd	Proton bands, ppm			
	C_2	C_4, C_5	$-NCH_2O-$	$-CCH_2O$
2-Imidazolemethanol[c]		7.06 (s)		4.64 (s)
1,2-Bis(hydroxymethyl)-imidazole[c]		7.05 (bs)	5.47 (s)	4.75 (s)
1-Imidazolemethanol[c]	7.70 (bs)	7.07 (bs)	5.39 (s)	
2,4,5-Tris(hydroxymethyl)-imidazole[c,d]				4.57 (bs),[c] 4.50, 4.30[d]

[a] Legend to symbols: s, singlet; bs, broad singlet. [b] All chemical shifts are reported in parts per million (δ). [c] D_2O solvent. [d] CH_3OD solvent.

James Woodyard, were recorded with a Varian A-60 spectrophotometer. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. All chromatographic columns were prepared by pouring Merck reagent grade aluminum oxide, previously dried for 2 hr at 100°, onto a column filled with chloroform (reagent grade). The elutant from the column was analyzed by thin layer chromatography using microslides prepared by the method of Peifer[6] from silica gel G (according to Stahl), 1:1 ether–methanol as developing solvent, and iodine vapor for visualization of spots.

Sealed Tube Reaction between Imidazole and Formaldehyde. A solution of 13.6 g (0.20 mol) of imidazole (Sigma Chemical Co.) and 50 g of 37% aqueous formaldehyde solution in sealed Pyrex tubes was heated for 15 hr in an oil bath at 120–130° and was then evaporated in vacuo to give 17.8 g of colorless, viscous syrup. A drop of crude product treated with picric acid gave a resinous picrate derivative. The syrup was extracted with a hot mixture of 140 ml of acetone, 15 ml of methanol, and 15 ml of chloroform. After cooling, the supernatant was decanted from an insoluble syrup. This syrup was dissolved in a small volume of methanol and 35 ml of a 1:1 mixture of chloroform–acetone was added. After cooling overnight at 10° the supernatant was decanted from about 1.5 g of insoluble syrup. The solvents were evaporated from the two extracts, leaving syrupy residues: 10 g of more soluble material; 6 g of less soluble material. These two fractions were separately chromatographed on alumina.

1,2-Dihydroxymethylimidazole. The 10 g of more soluble material was dissolved in an acetone–chloroform mixture, placed on a 15.5 × 4 cm column, and eluted with six 25-ml portions of 3:1 chloroform–acetone, four 24-ml portions of chloroform–acetone mixture plus 1 ml of methanol, and three fractions with increasing amounts of methanol. By digesting the first nine fractions with acetone a total of 3.25 g of white, crystalline solid was obtained. Melting points of the different fractions ranged from 90–115° to 121–125° but all gave identical ir spectra. A sample for analysis recrystallized twice from acetone melted at 126–127°. The NMR spectrum and analysis indicated this material to be 1,2-bis(hydroxymethyl)imidazole.

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 46.79; H, 6.16; N, 22.03.

2-Imidazolemethanol was prepared by the method of Jones;[5] purification by chromatography yielded a white, crystalline solid, mp 112–112.5° (lit.[7] mp 114–115°). The NMR sample of the 1,2-dihydroxymethylimidazole (0.1413 g) was repeatedly digested with water to remove deuterium. The final residue (72 mg after one recrystallization from acetone) melted at 108–109° and gave an ir spectrum identical with that of 2-imidazolemethanol.

The syrupy residues (2.4 g) from recrystallizations of different fractions of 1,2-dihydroxymethylimidazole were combined, boiled with water, and chromatographed, yielding 0.25 g of imidazole, mp 91–92° (identified by ir), and 1.5 g of crude 2-imidazolemethanol (identified by ir).

2,4,5-Trihydroxymethylimidazole. After fractions 10–13 were extracted from the above chromatography with acetone, the combined acetone-insoluble residues were dissolved in methanol. White, crystalline solid slowly separated from solution and after cooling overnight at 10°, 0.2 g of solid, mp 154–155°, was separated by filtration. After one recrystallization from methanol–acetone, a sample for analysis melted at 158–159°.

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.71. Found: C, 46.14, 45.99; H, 6.52, 6.60; N, 18.26, 18.16.

A sample (50 mg) for NMR analysis was dissolved in 0.3 ml of D_2O. Only two adsorptions occurred at δ 4.81 (HOD) and 4.57. The integration data showed a ratio of HOD to $-CH_2$ of 1:1.48. The recovered sample, after boiling with water to remove deuterium, was identical in melting point and mixture melting point with the original sample and gave an identical ir spectrum. This indicates this material to be 2,4,5-trihydroxymethylimidazole.

The remaining materials from this column were divided into 6.5 g of an acetone-soluble residue and a small amount of acetone-insoluble syrup residue.

1-Imidazolemethanol. The above acetone-soluble residue was rechromatographed. The first eight fractions, eluted with 3:1 chloroform–acetone, showed only one component on TLC slides with the major amounts in fractions 2 and 3. The residue from fractions 2–4 (identical ir spectra) weighed 5.2 g and was a colorless liquid. The NMR spectrum of this material in D_2O solution indicates it is 1-imidazolemethanol. No attempt was made to purify this material. Treatment of 0.5 g of this liquid with a saturated alcoholic solution of picric acid yielded 0.49 g of crystalline picrate (**6**), mp 201–202°. A sample recrystallized for analysis from absolute alcohol melted at 202–203°.

Anal. Calcd for $C_{10}H_9N_5O_8$: C, 36.71; H, 2.77; N, 21.40. Found: C, 36.57; H, 2.64; N, 21.47.

Fractions 9 and 10 contained 1.35 g of the proposed 1,2-dihydroxymethylimidazole.

From chromatography of the 6 g of less soluble material from the second extraction of the original reaction mixture only 0.3 g of 1,2-dihydroxymethylimidazole and 0.34 g of 2,4,5-trihydroxymethylimidazole were obtained and the remainder of the material from the column remained unresolved.

Action of Water on 1-Imidazolemethanol. 1-Imidazolemethanol (0.5 g) was digested repeatedly with water. After the final evaporation of water, the residue, a syrup (0.3625 g), was dissolved in acetone and chromatographed, yielding 0.1834 g of imidazole (identified by ir), mp 79–85°.

Acknowledgment. Grateful acknowledgment is made to The American Association of University Women for the Ida M. Green Postdoctoral Fellowship which has supported this research.

Registry No.—**1**, 288-32-4; **2**, 51505-76-1; **3**, 54986-29-7; **4**, 3724-26-3; **5**, 54986-27-5; **6**, 54986-28-6; formaldehyde, 50-00-0.

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A New Synthesis of 3-Substituted 1-Methylnaphthalenes via Ring Expansion of 1-Methylindenes[1]

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Specifically substituted 3-aryl-1-methylnaphthalenes and their derivatives can be synthesized by a convenient and productive reaction sequence,[2] which, however, is suitable for 3-aryl substitution only. A different approach, now reported, was required for the preparation of naphthalenes with other 3 substituents.

Since specifically substituted 1-methylindenes could be prepared easily from 3-arylbutanoic acids, ring expansion to the title compounds offered a convenient route. Parham and his group[3] obtained only 2-chloro-1-methylnaphthalene from attempts to prepare 3-chloro-1-methylnaphthalene by treating 1-methylindene with potassium *tert*-butoxide and chloroform, and they doubted the stability of the indene. Others[4–8] showed that 1-methylindene is stable under neutral or mild acidic conditions at room temperature and that it isomerized rapidly to 3-methylindene in base. We confirmed the stability of 4,6-dichloro-1-methylindene (**6b**) at room temperature under acidic conditions and isomerized it to 5,7-dichloro-3-methylindene (**8b**) by exposure to a small amount of pyridine.[9]

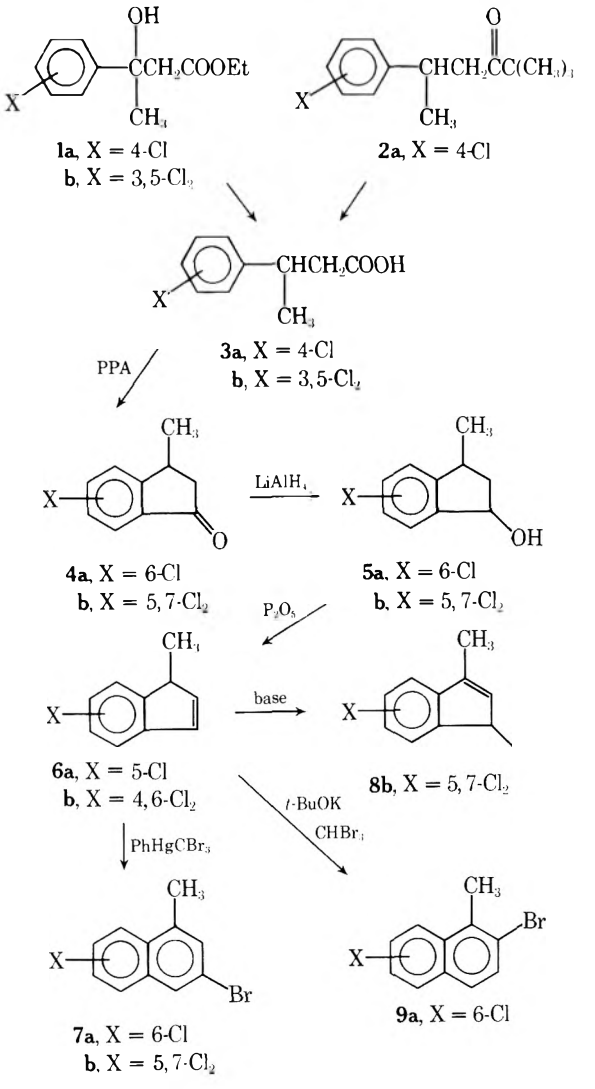
Carried out under neutral conditions, e.g., by carbene generation from phenyl(tribromomethyl)mercury,[10] ring expansion yielded the desired 3-bromo-1-methylnaphthalenes; e.g., 4,6-dichloro-1-methylindene (**6b**) gave 3-bromo-5,7-dichloro-1-methylnaphthalene (**7b**) (Scheme I

Table I
3-Substituted 1-Methylnaphthalenes and Precursors[a]

Compd	Method[b]	Yield, %	Mp or bp, °C (mm)	Solvent of crystn	Molecular formula
1b	*c*	85	105 (0.2)		$C_{12}H_{14}Cl_2O_3$
2a	*d*	97	77 (0.5)		$C_{14}H_{19}ClO$
3a	*d*	88	90–93	MeOH–petroleum ether	$C_{10}H_{11}ClO_2$
	A	87			
3b	A	83	100–103	Petroleum ether	$C_{10}H_{10}Cl_2O_2$
4a	B	74	65 (0.07)		$C_{10}H_9ClO$
4b	B	86	59–61	Petroleum ether	$C_{10}H_8Cl_2O$
5a	*e*	100	78–79	Et_2O–petroleum ether	$C_{10}H_{11}ClO$
6a[f]	C	80	60 (1)		$C_{10}H_9Cl$
6b	C	90	65 (0.02)		$C_{10}H_8Cl_2$
7a	E	40	56–57	MeOH	$C_{11}H_8BrCl$
7b	E	55	169–171	Acetone	$C_{11}H_7BrCl_2$
9a	F	16	53–54	MeOH	$C_{11}H_8BrCl$

[a] Satisfactory analytical data (±0.4% for C, H, Cl, etc.) were reported for all compounds listed in the table. [b] The capital letter refers to the general procedure described in the Experimental Section. [c] Prepared by Reformatsky reaction.[12] [d] Prepared according to ref 2. [e] Prepared by reduction of **4a** with $LiAlH_4$.[13] [f] NMR (CCl_4) δ 7.12 (3 H, broad m, phenyl), 6.58 (1 H, d of d, J_{12} = 2 Hz, =C**H**), 6.40 (1 H, d of d, J_{23} = 6 Hz, =CH), 3.33 (1 H, broad q, J_{1CH3} = 8 Hz, CH_3C**H**), 1.23 (3 H, d, J_{13} = 2 Hz, CH_3).

Scheme I



and Table I), which showed only meta couplings in NMR. Repetition of the method of Parham et al.[2] with 5-chloro-1-methylindene (**6a**) gave the expected product from the rearranged indene, 2-bromo-6-chloro-1-methylnaphthalene (**9a**).

We developed a new method to prepare phenyl(tribromomethyl)mercury by mixing phenylmercuric chloride, sodium hydride, and bromoform in benzene and initiating the reaction with methanol. Although the yields by this method were somewhat lower than those reported by Seyferth,[11] it is a very convenient procedure.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are also uncorrected. NMR spectra were obtained on a Varian A-60 spectrometer. Microanalyses were performed by Microanalysis, Inc., Wilmington, Del.

A. 3-Arylbutanoic Acids (3). A mixture of **1** (0.2 mol), red phosphorus (1 mol), and HI (57%, 240 g) was refluxed for 18 hr and then cooled and diluted with an equal volume of water. The aqueous layer was decanted, and the red gum was extracted with dilute NaOH. The extract was filtered and acidified. The oil that separated was extracted with Et_2O. The ethereal solution was dried (Na_2SO_4), ether was removed, and the product was crystallized. This procedure is based on the work of Spring.[14]

B. 3-Methylindanones (4). **3** (0.01 mol) was added, with good agitation, to hot (115°) polyphosphoric acid (250 g). The reaction mixture was stirred at this temperature for 30 min, cooled, and poured into ice–water. The product was extracted with ether. The ethereal solution was washed with $NaHCO_3$ and dried (Na_2SO_4), and ether was removed.

C. 1-Methylindenes (6). **5** (1 mol) was heated to 100° with stirring. P_2O_5 (5 g) was added quickly in one lot, and the mixture was immediately distilled under vacuum. The receiving flask was cooled with a Dry Ice–acetone bath, so that the product and water were collected together. The distillate was dissolved in ether and dried (Na_2SO_4) and ether was removed.

D. Phenyl(tribromomethyl)mercury. NaH (13 g of 56% dispersion in oil, washed with benzene), phenylmercuric chloride (50 g), bromoform (80 g), and benzene (800 ml) were mixed with rapid stirring and cooled in ice–water. The reaction was initiated with MeOH (0.5 ml), and the rate was maintained if necessary by additional drops of MeOH. After 1 hr the cooling bath was removed. As the reaction progressed, the thick white reaction mixture changed into a thin gray slurry. The mixture was stirred at room temperature overnight. Benzene was removed from the filtered solution using rotary evaporation with a bath temperature of 40° and cooling the trap in a Dry Ice–acetone bath. The heavy white solid residue was washed with petroleum ether and dried in air, yield 50 g. On melting it decomposed at about 120° and was sufficiently pure for use.

E. 3-Bromo-1-methylnaphthalenes (7). A mixture of **6** (0.3 mol), phenyl(tribromomethyl)mercury (0.4 mol), and benzene (600 ml) was refluxed for 4 hr. The solid dissolved at first, and then a precipitate appeared. Benzene was evaporated from the cooled, fil-

tered solution, and the residue was extracted with boiling acetone, from which on cooling the product crystallized.

F. 2-Bromo-6-chloro-1-methylnaphthalene (9a). K (1 g) was dissolved in *t*-BuOH (25 ml), and the solution was cooled in ice–water. **6a** (4 g) was added followed by bromoform (8 g). The solution was stirred in the cold for 2 hr and diluted with water. The precipitated solid was collected, yield 1 g.

Acknowledgments. The authors wish to thank Dr. William J. Welstead, Jr., and Mr. Ashby F. Johnson, A. H. Robins Company, Inc., Richmond, Va., for NMR spectra.

Registry No.—**1a**, 21133-98-2; **1b**, 55058-75-8; **2a**, 55058-76-9; **3a**, 5292-23-9; **3b**, 55058-77-0; **4a**, 54795-05-0; **4b**, 55058-78-1; **5a**, 55058-79-2; **5b**, 55058-80-5; **6a**, 55058-81-6; **6b**, 55058-82-7; **7a**, 55058-83-8; **7b**, 55058-84-9; **8b**, 55058-85-0; **9a**, 55058-86-1.

References and Notes

(1) The work described in this paper was performed under Contract DADA-17-72-C-2078 with the U.S. Army Medical Research and Development Command. This is Contribution No. 1281 from the Army Research Program on Malaria.
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(8) H. Christol, F. Plenat, and C. F. Huebner, *Bull. Soc. Chim. Fr.*, 1640 (1964).
(9) The isomerization was followed by NMR. For 4,6-dichloro-1-methylindene (**6b**) in $CDCl_3$: δ 7.27 (2 H, s, phenyl), 6.88 (1 H, d of d, J_{12} = 2 Hz, =CH), 6.52 (1 H, d of d, J_{23} = 6 Hz, =CH), 3.53 (1 H, broad q, $J_{1\,CH_3}$ = 8 Hz, CH_3CH), 1.28 (3 H, d, J_{13} = 2 Hz, CH_3). For 5,7-dichloro-3-methylindene (**8b**) in $CDCl_3$ with a trace of C_6D_5N: δ 7.17 (2 H, s, phenyl), 6.23 (1 H, m, J_{12} = 2, J_{13} = 2 Hz, =CH), 3.20 (2 H, m, J_{2CH_3} = 2 Hz, CH_2), 2.03 (3 H, m, CH_3).
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Ylidenemalononitriles in Thiophene Ring Annelations

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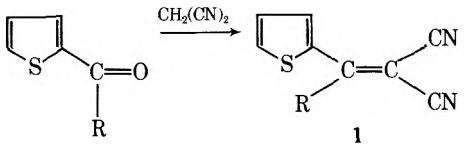
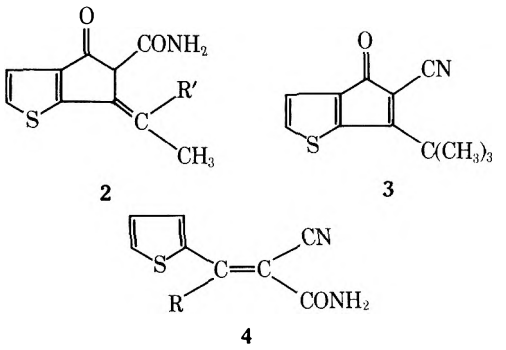
Synthetic methods available for the construction of rings fused to heterocyclic molecules are limited owing to the vulnerability of the heteroatom to the well-established conditions of carbocyclic chemistry. Acid-mediated cyclizations of ylidenemalononitriles[1,2] to form fused keto amides appeared to present a valuable potential for this problem. This has now proven successful in the thiophene series.

The thiophene ylidenemalononitriles (1) were readily obtained by a Knoevenagel reaction between the corresponding precursor[3] and malononitrile.



1

Treatment of **1** (R = C_2H_5) and **1** (R = *i*-C_3H_7) with polyphosphoric acid produced the ring-cyclized products **2**. The structural assignments for **2** were based on spectral data. The ir spectrum (KBr) of **2** (R′ = H) has NH absorption at 3.00 and 3.15 μ, ketone carbonyl at 5.91 μ, and



amide carbonyl at 6.02 μ, while **2** (R′ = CH_3) has similar peaks at 2.98, 3.14, 5.90, and 6.02 μ which is in agreement with similar ring systems in the benzene series.[6] The NMR spectrum (DMSO-d_6) also supports structure **2** by displaying a simple two-proton thiophene absorption with doublets at δ 7.19 (J = 5 Hz) and 7.70 (J = 5 Hz), methine (proton α to amide and ketone carbonyls) absorption at δ 4.32, vinyl quartet absorption (for **2**, R′ = H) at δ 5.75 (J = 7 Hz), and methyl singlets at δ 1.80 and 1.97 for **2** (R′ = CH_3) and a methyl doublet at δ 1.93 (J = 7 Hz) for **2** (R′ = H). The above data is clearly in accord with the bicyclic systems **2** possessing the exocyclic double bond.[7]

On the other hand, when **1** (R = *t*-C_4H_9) was subjected to polyphosphoric acid the anticipated endocyclic fused system (**3**) resulted. The structural assignment for **3** was based on the ir spectrum (KBr) (nitrile absorption at 4.52 μ and a carbonyl band at 5.80 μ) and the NMR spectrum (DMSO-d_6) [two-proton thiophene doublets at δ 7.20 (J = 5 Hz) and 7.62 (J = 5 Hz) and a nine-proton methyl singlet at δ 1.54]. Thus far it has not been possible to hydrolyze the nitrile functionality of **3** to the corresponding carboxamido group.

To complete the series, **1** (R = H and CH_3) was studied under the cyclization conditions and found to yield only (by TLC) **4**. Confirmation of the product formation was obtained when products identical (by melting point and TLC) with **4** were realized from the reactions of thiophenecarboxaldehyde and methyl 2-thienyl ketone with cyanoacetamide.[1,8]

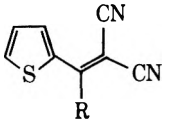
These results suggest that the fusion of a functionalized five-membered ring to a thiophene ring is possible via ylidenemalononitriles which possess at least a secondary γ carbon.[9] If the γ carbon possesses at least one hydrogen the exocyclic products (**2**) are realized as a means of relieving the steric strain which would result with the endocyclic isomer. When the γ carbon is quaternary, the endocyclic isomer (**3**) is the only structure possible and it forms, but in considerably diminished yields compared to **2**.

Experimental Section[10]

Preparation of the Ylidenemalononitriles. A solution of 0.3 mol of the carbonyl agent,[3] 0.5 mol of malononitrile, 12.0 g of ammonium acetate, and 24 ml of glacial acetic acid in 200 ml of toluene was refluxed with the aid of a Dean-Stark trap until the amount of water collected in the trap remained constant (4–24 hr, the sterically hindered ketones requiring the longer reflux time). Following the reflux period, the solution was cooled and decanted from a malononitrile polymer. The polymeric gum was washed with toluene (50 ml) and the combined toluene fractions were washed with water (2 × 50 ml), dried over anhydrous magnesium sulfate, and concentrated to yield the crude product, whose properties are listed in Table I. In the case of **1** (R = *i*-C_3H_7) and **1** (R = *t*-C_4H_9) it was necessary to remove the unreacted ketone (via vacuum distillation) from the crude product mixture to realize the desired ylidenemalononitrile.

Treatment of Ylidenemalononitriles (1) with Polyphosphoric Acid. After 200 g of polyphosphoric acid was warmed to the temperature required for reaction, 2.0 g of **1** was added slowly

Table I
Properties of Thiophene Ylidenemalononitriles



Registry no.	R	Yield, %	Mp, °C	Purification method[a,b]	Anal. calcd (found), %	Ir (ν_{CN}), cm^{-1}	Proton NMR,[c-e] δ ppm
28162-32-5	H[f]	86	95–96	S, C, A	C, 59.98 (60.15) H, 2.52 (2.77)	2220	7.38 (t, 4-H) 7.85 (m, =CH, 3-H and 5-H)
10432-44-7	CH_3	77	85	S, C	C, 62.05 (62.23) H, 3.47 (3.56)	2215	2.74 (s, CH_3) 7.26 (t, 4-H) 7.83 (d of d, 5-H) 8.03 (d of d, 3-H)
54688-90-3	C_2H_5	44	31	A	C, 63.82 (63.77) H, 4.26 (4.30)	2220	1.35 (t, CH_3) 3.04 (q, CH_2) 7.36 (t, 4-H) 7.98 (d of d, 5-H) 8.18 (d of d, 3-H)
54688-91-4	i-C_3H_7	25	56	E	C, 65.32 (65.18) H, 4.98 (5.12)	2220	1.34 (d, 2 CH_3) 3.50 (sp, CH) 7.08 (t, 4-H) 7.70 (d, 3-H and 5-H)
54688-92-5	t-C_4H_9	14	103–104	A	C, 66.63 (66.43) H, 5.59 (5.46)	2230	1.36 (s, 3 CH_3) 7.00 (m, 4-H and 3-H or 5-H) 7.45 (d of d, 3-H or 5-H)

[a] S = sublimation in vacuo; C = chloroform–hexane; A = aqueous ethanol; E = 95% ethanol. [b] All ylidenemalononitriles reported herein are colorless. [c] All spectra were recorded in $CDCl_3$. Chemical shifts are in parts per million from internal Me_4Si. [d] Multiplicity indicated paranthetically by the following abbreviations: s, singlet; d, doublet; t, triplet; sp, septuplet; m, multiplet. [e] Assignments based on spectral integrations. [f] K. Friedrich and W. Ertel [German Patent 1,936,047; *Chem Abstr.*, 74, 76197 (1971)] report this compound but make no mention of its properties.

Table II
Products from Acid Treatment of Thiophene Ylidenemalononitriles

Registry no.	Compd	Yield, %	Mp, °C	Purification method[a]	Anal. calcd (found), %
54738-97-5	**2** (R′ = H)[b]	58	210–211	E	C, 57.95 (58.04) H, 4.38 (4.24)
54688-93-6	**2** (R′ = CH_3)[b]	59	221–223	E	C, 59.73 (59.52) H, 4.98 (5.12)
54688-94-7	**3**[c]	33	142–144	A	C, 66.33 (65.96) H, 5.10 (5.39)
54688-95-8	**4** (R = H)[d,f]	93	166	D	C, 53.92 (53.80) H, 3.39 (3.51)
54688-96-9	**4** (R = CH_3)[e,g]	86	150–151	C	C, 56.23 (55.97) H, 4.19 (4.11)

[a] E = 95% ethanol; A = aqueous ethanol; D = dimethyl sulfoxide–water; C = chloroform–hexane. [b] Colorless crystals. [c] Red crystals. [d] Light gray crystals. [e] Tan crystals. [f] ^1H NMR (dimethyl sulfoxide-d_6) δ 4.50 (br, NH_2), 7.24 (t, 4-H), 7.89 (m, 3-H and 5-H), 8.39 (s, =CH). [g] ^1H NMR (dimethyl sulfoxide-d_6) δ 2.58 (s, CH_3), 7.23 (t, 4-H), 8.00 (m, 3-H and 5-H); no NH_2 could be discerned.

under mechanical stirring. The resulting mixture was heated at 85–95° for 3 hr (R = H), 85° for 2 hr (R = CH_3), 50° for 2 hr (R = C_2H_5), 90° for 3 hr (R = i-C_3H_7), and 90° for 6 hr (R = t-C_4H_9) and then cooled and poured over 500 ml of ice water with vigorous stirring. After standing overnight the aqueous solution was filtered and the isolated product was air dried and purified to yield the products summarized in Table II.

Condensation of Thiophenecarboxaldehyde and Methyl 2-Thienyl Ketone with Cyanoacetamide. A 100-ml absolute ethanolic solution of 0.2 mol of the alkehyde or ketone, 0.2 mol of cyanoacetamide, 0.5 g of ammonium acetate, and 2.0 g of glacial acetic acid was refluxed for 6 hr. Upon cooling the cyanoacetamide (4) precipitated and was purified by recrystallization (R = H, 93% yield; R = CH_3, 86% yield). These products were identical (by mixture melting point and TLC in chloroform) with that obtained from the polyphosphoric acid treatment of 1 (R = H and CH_3) as characterized in Table II.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the

American Chemical Society, for their support of this research.

Registry No.—2-Thiophenecarboxaldehyde, 98-03-3; methyl 2-thienyl ketone, 88-15-3; ethyl 2-thienyl ketone, 13679-75-9; isopropyl 2-thienyl ketone, 36448-60-9; *tert*-butyl 2-thienyl ketone, 20409-48-7; malononitrile, 109-77-3.

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(3) Thiophenecarboxaldehyde, methyl 2-thienyl ketone, and phenyl 2-thienyl ketone were available from Aldrich Chemical Co., whereas ethyl 2-thienyl ketone was obtained from Columbia Organic Chemicals Co. Isopropyl 2-thienyl ketone[4] and *tert*-butyl 2-thienyl ketone[5] were prepared by the method of J. R. Johnson and G. E. May, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 8.
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(6) D. A. Templer, Ph.D. Thesis, Indiana University, Bloomington, Ind., Aug 1968.
(7) Compound **2** (R′ = H) was a single isomer by TLC. However, to date it has not been possible to assign the exact geometrical stereochemistry for **2** (R′ = H) and the representation given here is arbitrary but is believed to be correct based on data accrued in ref 6 for a similar benzene system.
(8) The stereochemistry of **4** (obtained as a single isomer by TLC) was not crucial to this aspect of the problem and has not been established. However, the condensation between thiophenecarboxaldehyde and methyl 2-thienyl ketone and cyanoacetamide is apparently stereospecific, since only the product (by TLC) corresponding to **4** was produced in quantitative yield.
(9) Several less functionalized, and therefore less versatile, derivatives of the cyclopenta[*b*]thiophene ring system have been reported. For example, see (a) O. Meth-Conn and S. Gronowitz, *Acta Chem. Scand.*, **20**, 1577 (1966); (b) K. Aparajithan, A. C. Thompson, and J. Sam, *J. Heterocycl. Chem.*, **3**, 466 (1966); (c) J. Skramstad, *Acta Chem. Scand.*, **25**, 1287 (1971).
(10) Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. The NMR spectra were obtained on a Varian A-60 spectrometer using Me_4Si as an internal standard. Ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. The microanalyses were performed by Het-Chem-Co., Harrisonville, Mo.

Stereochemical Course of Sulfolane Fragmentation

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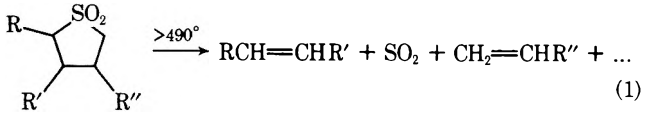
At elevated temperatures, simple sulfolanes (tetrahydrothiophene 1,1-dioxides) are pyrolyzed to sulfur dioxide and olefins (eq 1: R, R′, R″ = H; R = CH_3, R′, R″ = H; R′ =

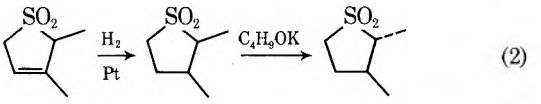


(1)

CH_3, R, R″ = H; R′, R″ = CH_3, R = H; R, R″ = CH_3, R′ = H, etc).[1] We have now examined the stereochemistry of this reaction (R, R′ = CH_3; R″ = H), with a view to detecting possible concertedness.

Results

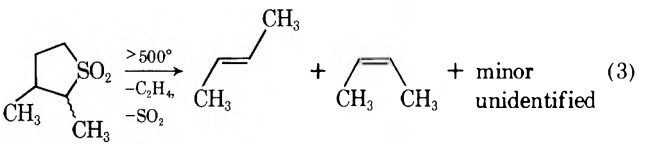
The requisite sulfones were obtained (eq 2) via 2,3-dimethylsulfolene (adduct from 3-methyl-1,3-pentadiene plus SO_2).[2] Catalytic hydrogenation (PtO_2) gave an inseparable mixture of sulfolanes (ca. 95:5) of which the major isomer was assigned the cis configuration (**1**) on the basis of steric considerations and subsequent results. Epimerization of this mixture with potassium *tert*-butylate in *tert*-butyl alcohol (eq 2) gave a new mixture (ca. 10:90), enriched in the trans isomer (**2**). Isomer ratios were estimated by NMR analysis.



(2)

1 **2**

Thermolyses were carried out by injection of the enriched mixtures of **1** and **2** into a hot (>500°) bed of silicon carbide chips. The effluent gases were collected in a cold trap, and the butenes were subsequently analyzed by GLC. The results are summarized in eq 3.



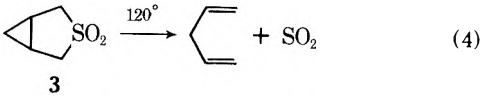
(3)

1 (95% cis)	36 ± 6%	53 ± 3%	9 ± 6%
2 (90% trans)	51 ± 6%	40 ± 3%	9 ± 6%

In the appropriate control experiments, it was found that from a partial pyrolysis **1** could be recovered unchanged (no appreciable epimerization to **2**). Furthermore, authentic *cis*-2-butene when passed through the reactor suffered less than 2% isomerization to *trans*-2-butene. In view of the substantial crossover in the thermolysis of **1** and **2** it was felt that attempts to refine the experiment by further purification of **1** and **2** or by improving the GLC resolution of the products were unwarranted.

Discussion

It has previously been demonstrated that pericyclic [$_\sigma2_s$ + $_\sigma2_s$ + $_\sigma2_s$] fragmentation in the strained system **3** (eq 4)



(4)

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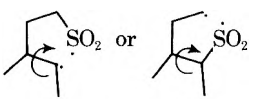
proceeds concertedly by tests of stereospecificity and kinetic facility.[3] Although equivalent thermolysis of simple sulfolanes requires temperatures more than 200° higher than for **3**, it was considered plausible that **1** and **2** might dissociate with retention of methyl group stereochemistry in view of the fully synchronous nature of the *sulfolene* reaction.[4] The experimental results indicate otherwise. From either sulfolane (**1** or **2**) mixtures of 2-butenes were obtained (uncorrected trans/cis ratios 0.7 *E*:1.0 *Z* and 1.0 *E*:0.8 *Z*, respectively). We suggest that the results are best accommodated by a multistep mechanism, in which diradical (or zwitterionic) intermediates exist for appreciable lifetimes. It is sufficient that internal rotation within such an intermediate (**4**) be competitive with bond scission. In



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spite of our control experiments the possibility cannot rigorously be excluded that fragmentation is in fact concerted, but that isomerization occurs subsequently (SO_2 catalysis). However, it is difficult to envision such a latter mechanism which would not in actuality be available to the incipient reaction products in the primary step.

The low residual stereospecificity is reminiscent of other recently reported extrusion reactions.[5] We would only comment that concepts of diradical chemistry should be adjusted to accommodate what appears to be a pattern of partial stereochemical retention.

Experimental Section

Synthesis. 2,3-Dimethylsulfolene was prepared essentially as previously described.[2] The crude product was purified by column chromatography (silicic acid, benzene eluent) rather than distillation, in order to avoid decomposition. Of several hydrogenation catalysts tried, platinum oxide (Adams) in ethyl acetate afforded the greatest stereoselectivity (ca. 95%) for the reduction to **1**. Refluxing a *t*-BuOK–*t*-BuOH solution of **1** for several hours followed by work-up yielded a mixture enriched in **2** (ratio **2**:**1** 9:1). Isomer percentages were estimated from resolved NMR resonances in the methyl region ($CDCl_3$ solution).

Anal. (for enriched **1**). Calcd for $C_6H_{12}O_2S$: C, 48.64; H, 8.16. Found: C, 48.54; H, 8.25.

Thermolysis. As previously indicated, ca. 0.5-g portions of **1** or **2** were injected slowly via syringe into a heated reservoir (SiC chips at >500°) connected to a cold trap. Some refluxing was noted. Subsequently, the butenes were allowed to vaporize and were sampled by GLC [column, 15 ft of 25% $AgNO_3$–propylene glycol (1:2) on Chromosorb W, 25°]. Comparison was made to authentic 2-butenes. A minor, unidentified pyrolysate component was eluted shortly after (and overlapping) *trans*-butene. It has previously been asserted that sulfolane thermolysis affords 9–19% of "saturated hydrocarbon".[1] In the present case a complete analysis of product balance was not undertaken, since our interest only extended to alkene geometry.

Acknowledgment. One of us (I.M.) thanks the Rotary Foundation for a Graduate Fellowship. This work was partially supported by the National Science Foundation.

Registry No.—**1**, 54910-40-6; **2**, 54910-39-3; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; 2,3-dimethylsulfolene, 10033-87-1.

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Complete Resolution of *cis*-1-Benzyl-3-methyl-1-phenylphospholanium Iodide. Use of the Optically Active Salt in Stereochemical Studies

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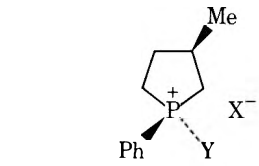
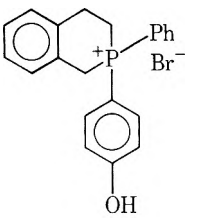
The literature records no total resolutions of heterocyclic phosphonium salts containing an asymmetric phosphorus atom. We report herein the first such instance, the complete resolution of racemic *cis*-1-benzyl-3-methyl-1-phenylphospholanium iodide (**1**) with the aid of silver (+)-10-camphorsulfonate. Compounds **2**,[1] **3**,[2] and **4**[3] have been partially resolved, although the resolution of **2** could not be reproduced and details of the resolution of **4** have not yet been disclosed. The spiro salt (**5**), which has been totally resolved, owes its optical activity to molecular dissymmetry rather than to an asymmetric phosphorus atom of the $R^1R^2R^3R^4P^+X^-$ type.[4]



(and enantiomer)
1, Y = CH_2Ph; X = I
6, Y = O^-; X = nil
7, Y = CH_2Ph; X = (+)-10-camphorsulfonate
8, Y = lone pair; X = nil
9, Y = CH_2Ph; X = Br
12, Y = OMe; X = PF_6



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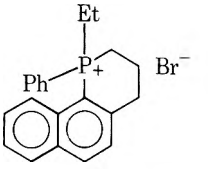

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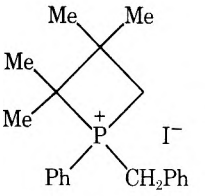

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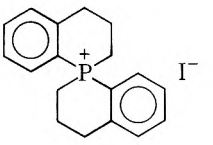

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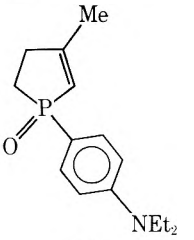

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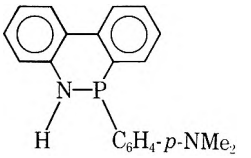

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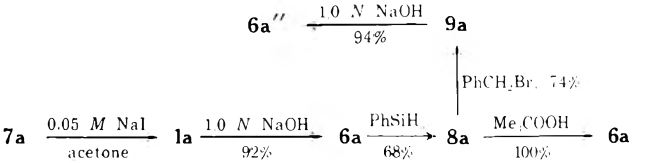
With the optically active phosphonium salts (**1**) available, we wished to verify earlier conclusions[5,6] that hydroxide cleavage of **1** occurs with complete retention of configuration at phosphorus. The NMR analyses leading to these conclusions were possibly subject to considerable error, although predominant retention had been rigorously proved. Within experimental error, the results shown in Scheme I are compatible with complete retention of configuration for base cleavage and phenylsilane reduction as previously reported.[5,6] This is true only if the oxide epimeric at phosphorus, produced by inversion of configuration at phosphorus, does not have a rotation comparable to that for the (+)

Scheme I[a]



Compd	Mp or bp, °C (mm)	$[\alpha]^{22}D$, deg (c)
7a	244–246	+28.09 ± 0.49 (2.980, EtOH)
1a	184.5–185.5	+2.16 ± 0.09 (15.57, $CDCl_3$)
6a	130 (0.5)	+23.52 ± 0.67 (7.590, $CDCl_3$)
8a	90 (0.5)	+22.18 ± 0.42 (6.710, MeOH)
6a'	132 (0.6)	+22.53 ± 0.59 (7.395, $CDCl_3$)
6a''	135 (0.6)	+22.59 ± 0.63 (6.505, $CDCl_3$)

[a] **9a** was not recrystallized prior to cleavage. *tert*-Butyl hydroperoxide oxidations of phosphines occur with retention of configuration: D. B. Denney and J. W. Hanifin, Jr., *Tetrahedron Lett.*, 2177 (1963). Phenylsilane has been found to reduce phosphine oxides with retention of configuration: K. L. Marsi, *J. Org. Chem.*, **39**, 265 (1974). Distillations were accomplished by use of a Kugelrohr.

enantiomer of **6**, since two chiral centers are present. However, the NMR spectra of both enantiomers, **1a** and **1b**, and **6a** gave no indication whatsoever of the presence of diastereomeric material.

Resolution was accomplished by treatment of the racemic bromide salt (**9**)[7] with silver (+)-10-camphorsulfonate and recrystallization of the diastereomeric salts utilizing a triangular scheme of recrystallization.[8] The head fraction was recrystallized to give **7a** of constant rotation and melting point (cf. Scheme I). **7a** was metathesized with sodium iodide in boiling acetone to provide **1a**, which was also recrystallized to constant rotation and melting point (cf. Scheme I). The tail fractions, enriched in **7b**, were combined and similarly converted to the optically impure iodide (**1b**), which was recrystallized from acetone to a constant rotation of $[\alpha]^{22}D$ $-2.14 \pm 0.11°$ (*c* 16.22, $CDCl_3$) and melting point of 184–185°. Because of the greater solubility of the racemic mixture in acetone, it was likewise possible to obtain optically pure **1a** as the less soluble fraction from mixtures of **1a** and **1b**, enriched in **1a**, by simple recrystallization from acetone.

Preparation of only one other simple five-membered ring phosphine oxide in optically active form has been reported previously. **10** was partially resolved with (+)-9-camphorsulfonic acid to afford the levorotatory isomer.[9]

Reduction of (+)-**6a** with phenylsilane yielded optically pure dextrorotatory phosphine **8a**. The optical purity of the phosphine is attested to by its conversion to the (+) oxides **6a'** and **6a''**, both of which showed, within experimental error, the same rotation as the dextrorotatory parent phosphine oxide **6a**. This is the first report of the preparation of an optically active saturated heterocyclic phosphine. It should be noted that two optically unstable isomers of the phosphorus heterocycle **11**[10] have been prepared by lithium aluminum hydride reduction of the corresponding optically active oxides, but that the activity of **11** may be due to molecular dissymmetry.[11] Optically active analogs of the oxides of **11** fail to undergo lithium aluminum hydride reduction to produce optically active phosphines[12] but fragment instead.

We have recently shown that alkoxyphospholanium salts (**12**) experience nucleophilic displacement at phosphorus to yield a mixture of oxides of inverted and retained configuration at phosphorus.[13] This observation leads us to believe that the preparation of optically pure phospholane oxides such as **6** by Mislow's method,[14] so useful for the synthesis of optically active acyclic phosphine oxides, would probably not be successful. Our resolution thus provides ready access to both optically isomeric phospholane oxides and phospholanes useful for stereochemical studies. The optically active phosphines may have additional value in the preparation of chiral phosphine–metal complexes.[15]

Experimental Section

(+)-1-Benzyl-3-methyl-1-phenylphospholanium Camphorsulfonate (7a). To 80.52 g of **9**[6] dissolved in 500 ml of ethanol was added 78.24 g of silver (+)-10-camphorsulfonate. Silver bromide was removed by filtration and the filtrate was further clarified by filtration through diatomaceous earth. The filtrate was evaporated to dryness and the residue was redissolved in a minimum amount of hot ethanol to which ethyl acetate was added dropwise to the cloud point. Triangular recrystallization,[8] carried out in this manner, gave a head fraction of constant melting point and rotation (cf. Scheme I).

Anal. Calcd for $C_{28}H_{37}O_4PS$: C, 67.18; H, 7.45. Found: C, 66.91; H, 7.40.

(+)-1-Benzyl-3-methyl-1-phenylphospholanium Iodide (1a). To 61 ml of 0.05 *M* sodium iodide in acetone was added 1.542 g of optically pure **7** and the mixture was stirred under gentle reflux for 45 min. Precipitated sodium camphorsulfonate was recovered in quantitative yield by filtration of the cooled reaction mixture. Crude **1a**, obtained after evaporation of the filtrate, was recrystallized from acetone to constant rotation and melting point (cf. Scheme I).

Anal. Calcd for $C_{18}H_{22}IP$: C, 54.56; H, 5.60. Found: C, 54.61; H, 5.55; S, 0.00.

It was discovered that head fractions of optically impure camphorsulfonate (**7a**) could be similarly converted to the optically impure iodide (**1a**) and the iodide conveniently recrystallized from acetone to the optically pure dextrorotatory form. Likewise, tail fractions concentrated in the more soluble diastereomeric camphorsulfonate, when treated as described above, produced the optically pure levorotatory isomer of mp 184.0–185.0°, $[\alpha]^{22}D$ $-2.14 \pm 0.11°$ (*c* 16.220, $CDCl_3$).

Anal. Calcd for $C_{18}H_{22}IP$: C, 54.56; H, 5.60. Found: C, 54.44; H, 5.76.

Hydroxide Cleavage of 1a and Recovery of Product. The procedure followed was essentially as described elsewhere for the racemic bromide salt.[6]

Acknowledgment. The authors are indebted to the National Science Foundation for sponsorship under Grant GP-38756.

Registry No.—(±)-**1**, 54964-37-3; **1a**, 54964-38-4; **1b**, 54932-22-8; **6a**, 54932-23-9; **7a**, 54932-25-1; **7b**, 54932-27-3; **8a**, 54932-28-4; **9**, 54932-29-5; silver (+)-10-camphorsulfonate, 20520-61-0.

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Hydrogenation of Unsaturated Carboxylic Acids with Alkanes by Aluminum Chloride Catalysis

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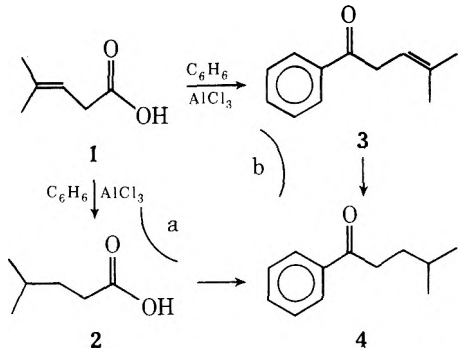
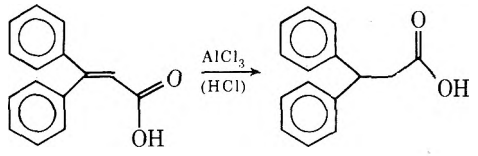
In the course of a previous study[1] of the Friedel–Crafts reactions of some unsaturated carboxylic acids on benzene, we observed the presence of an unexpected saturated ketone **4**, which could possibly arise from the reaction of the saturated counterpart **2** of the starting material **1** (Scheme I, pathway a). An alternative route (Scheme I, pathway b) was of course possible.[2] The finding that even a poor hydride donor like 4,4-dimethyltetralone, one of the reaction products, was able to perform the hydrogenation of **1** in the presence of aluminum chloride led us to investigate better hydrogen donors for the reduction, also in view of the great practical importance of the hydrogenation of fatty acids.

Alkanes were the obvious first choice. It should be mentioned that hydrogen transfer to unsaturated carboxylic acids was reported previously only in the particular case of

Scheme I



a highly hindered double bond during attempted Friedel–Crafts alkylation of benzene with aluminum chloride.[3]



Our preliminary experiments show that hydrogen can be transferred from alkanes to unsaturated fatty acids by means of aluminum chloride. 4-Methyl-3-pentenoic acid (**1**), 4-methyl-2-pentenoic acid (**5**), 3-methyl-2-butenoic acid (**6**), and cinnamic acid (**7**) underwent reduction to different extents to the corresponding saturated compounds **2**, **2**, **9** and **10** with *n*-hexane or ligroin (Table I).

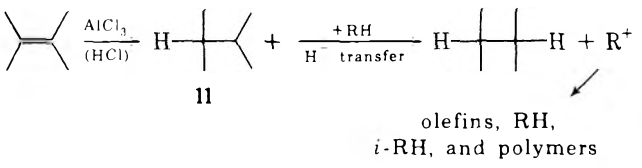
Table I
Reactions of Some Unsaturated Carboxylic Acids with Alkanes and $AlCl_3$[a]

Unsaturated acid	Alkane	Acid product(s)	Yield, %
4-Methyl-3-pentenoic (**1**)	*n*-Hexane	4-Methylpentanoic (**2**)	89
4-Methyl-2-pentenoic (**5**)	Ligroin	4-Methylpentanoic (**2**)	22
3-Methyl-2-butenoic (**6**)	*n*-Hexane	3-Methylbutanoic (**9**)	72
2-Butenoic (**14**)	*n*-Hexane or ligroin	Butanoic (**8**)	Trace
Cinnamic	Ligroin	Hydrocinnamic (**10**)	19
		p-Phenylenedipropanoic (**12**)	11

[a] Experimental details are recorded in the Experimental Section.

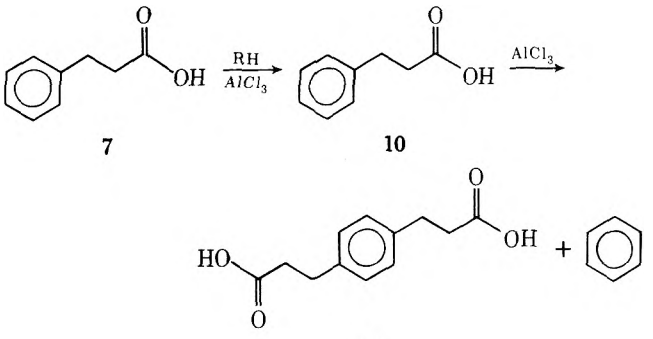
The results show some correlation of the yields with the structural possibilities of producing, directly or by hydride shift, a relatively stable intermediate carbonium ion, say **11**. This observation leads us to offer the mechanistic hypothesis shown in Scheme II.

Scheme II



An analogy to this behavior is presented by the reduction of some alkyl halides by hydrocarbon in the presence of Friedel–Crafts reagents,[4] where the initial carbonium ion interacts with the hydrocarbon, which may eventually transfer a hydride ion.

Cinnamic acid (**7**) underwent hydrogenation to 19% hydrocinnamic acid (**10**) and 11% *p*-phenylenedipropanoic acid (**12**); a third less separated peak in the GLC profile of



the methyl esters of the acidic fraction from the reaction mixture was not identified. Disproportionation in Friedel–Crafts reactions of alkyl-substituted aromatics is very common. It seems quite reasonable that **10** underwent such a reaction to **12** and benzene (**13**).

Experimental Section

Materials. 4-Methyl-3-pentenoic acid (**1**), 4-methyl-2-pentenoic acid (**5**), and their saturated counterpart **2** were prepared as previously described.[1] 2-Butenoic acid (**14**), cinnamic acid (**7**), and their saturated analogs were obtained from Erba (Milan, Italy) and 3-methyl-2-butenoic acid (**6**) from Schuchardt; they were used as such after preliminary purity checks by GLC on the corresponding methyl esters prepared by treatment with ethereal diazomethane of the free acids. *n*-Hexane and ligroin (bp 100–110°) were dried with sodium before use.

Analyses. The reaction mixtures from the interaction of the unsaturated acids with hydrocarbons in the presence of aluminum chloride were poured into crushed ice–hydrochloric acid. The ether extracts were treated with aqueous sodium hydroxide (10%); the acids were recovered by acidification with concentrated hydrochloric acid and ether from the aqueous solution. The ether solution of the acidic material was directly chromatographed (GLC), when suitable, or pretreated with diazomethane and chromatographed (GLC). A suitable column for the free acids was a 2 m × 0.25 mm column packed with 1% FFAP–10% phosphoric acid on Chromosorb W (80–100 mesh). A 2 m × 0.25 mm column packed with GAL (10%) on Chromosorb W washed with acid (60–80 mesh) was used for the quantitative determination of the methyl esters. Yields were evaluated with the internal standard method with preliminary weight–area response calibration. Glc analyses were performed with a Perkin-Elmer 900 gas chromatograph equipped with a flame ionization detector. Identification of the GLC peaks was secured by the enhancement technique, mass spectrometry (gas chromatograph–mass spectrometer, Perkin-Elmer 270), and ir and NMR techniques on separated samples, when deemed necessary.[5]

4-Methyl-3-pentenoic Acid (1), *n*-Hexane, and $AlCl_3$. The acid **1** (20 mmol), *n*-hexane (25 ml), and aluminum chloride (40 mmol) were stirred at room temperature during 8 hr and left standing during 46 days. The obtained acid material did not react with bromine in carbon tetrachloride and showed no olefinic bond absorption in the ir: bp 61° (1 Torr); GLC homogeneous; yield 86%. Its properties (ir, GLC retention time, mass spectrum) were identical with those of an authentic sample of 4-methylpentanoic acid (**2**). A similar yield of **2** (89%) was obtained in a shorter time (4 hr) by refluxing **1** (20 mmol) with *n*-hexane (25 ml) and aluminum chloride.

4-Methyl-2-pentenoic Acid (5), Alkanes, and $AlCl_3$. A. The acid **5** (20 mmol), *n*-hexane (25 ml), and aluminum chloride (40 mmol) were kept at reflux during 4 hr. Usual work-up gave an acid residue (2.12 g); GLC analyses showed the presence of 4-methylpentanoic acid (**2**) and unreacted **5** in a 1:2 ratio.

B. When hexane was substituted by ligroin (bp 100–110°), 24% hydrogenated acid **2** was present with no more starting acid **5** left.

3-Methyl-2-butenoic Acid (6), *n*-Hexane, and $AlCl_3$. The acid **6** (20 mmol), *n*-hexane (25 ml), and aluminum chloride (40 mmol) were refluxed during 4 hr to give 3-methylbutanoic acid (**9**), yield 72%. No starting material was present in the final acidic part of the reaction mixture.

2-Butenoic Acid (14), Alkanes, and $AlCl_3$. The acid **14** (20 mmol), *n*-hexane or ligroin (25 ml), and aluminum chloride (40 mmol) were refluxed during 4 hr to yield only a small transformation into butanoic acid (8). Most of the starting material did not react.

Cinnamic Acid (7), Ligroin, and $AlCl_3$. The acid **7** (20 mmol), ligroin (25 ml), and aluminum chloride (40 mmol) were refluxed during 4 hr to yield 1.99 g of acid material from which crystals of *p*-phenylenedipropanoic acid (**12**) separated on cooling. The recrystallized (water) solid showed mp 230° (lit. mp 230°,[6] 224° [7]); ir (KBr) 3030 m, 2924 m, 2858 m, 2728 w, 2649 w, 1703 s, 1520 w, 1434 s, 1405 m, 1362 w, 1312 m, 1275 m, 1222 s, 1189 m, 1133 w, 945 w, and 830 cm^{-1} m. Its methyl ester **15**, mp 120° (methanol) (lit.[7] mp 117–118°), was obtained by treatment with diazomethane in ether: ir (KBr) 3024 w, 2929 m, 2894 w, 2838 w, 1728 s, 1520 m, 1434 s, 1368 s, 1303 s, 1272 m, 1193 s, 1180 s, 1141 s, 1105 w, 1050 m, 1000 w, 976 m, 900 w, 838 s, and 793 cm^{-1} w; mass spectrum (80 eV) *m/e* (rel abundance) 117 (100), 91 (28), 130 (28), 190 (28), 131 (19), 115 (19), 77 (13), 176 (12), 118 (12), 59 (11), 250 (M^+, 11), and 39 (9); metastable ions *m/e* 144.5, 113.5, and 89; doubly charged ions (at half integer masses) *m/e* 95.5[8] and 88.5; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 2.74 (AA'BB' multiplet, 8 H), 3.67 (singlet, 6 H), and 7.13 ppm (singlet, 4 H). GLC quantitative analysis showed **12** to be present in 11% yield and **10** in 19% yield together with other unidentified materials. None of the starting acid **7** survived the treatment.

Registry No.—**1**, 504-85-8; **5**, 10321-71-8; **6**, 541-47-9; **7**, 621-82-9; **12**, 4251-21-2; **14**, 3724-65-0; **15**, 5312-03-8; $AlCl_3$, 7446-70-0; hexane, 110-54-3.

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(8) The peaks at *m/e* 95 and 96 are about of equal intensity and one-fourth as intense as *m/e* 95.5, after background subtraction.

A Novel Cyclization Catalyzed By Magnesium Methyl Carbonate

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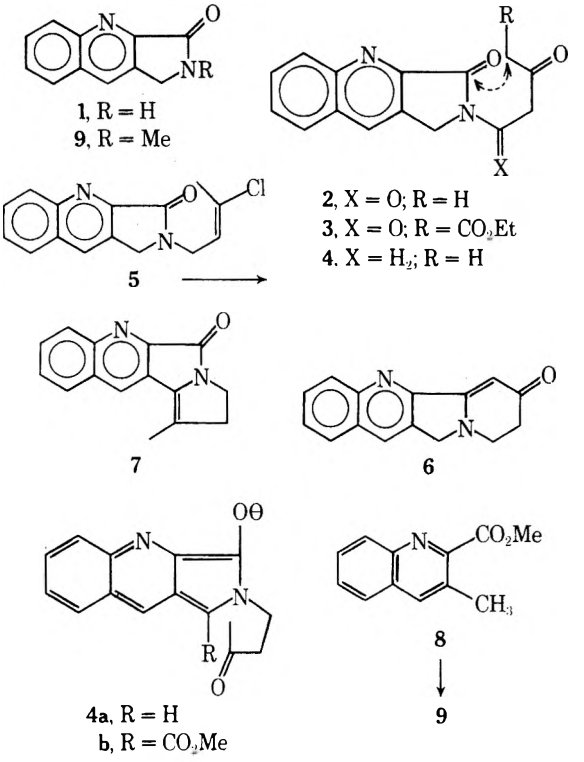
The synthesis of the tricyclic lactam **1** in 75% yield from 2-oxobutyric acid and *o*-aminobenzaldehyde has been described.[2,3] Its ready availability made it an attractive substrate for studying lactam annelation reactions with a view toward the syntheses of camptothecin and analog structures.[4,5] The strategy was based on acylation of the lactam nitrogen, followed by cyclization of a nucleophilic center in the side chain with the lactam carbonyl group.

Our original efforts were addressed to the acetoacetyl derivative **2** (X = O; R = H). This compound, mp 242–245°, was prepared (55%) by the reaction of **1** with *n*-butyllithium followed by diketene. In our hands, compound **2** could not be induced to undergo cyclodehydration in the sense indicated, under a variety of catalytic situations. Under mild conditions (e.g., boron trifluoride etherate or sodium acetate–acetic anhydride), **2** was recovered in high yield. Under more severe conditions (sodium ethoxide or potassium *tert*-butoxide) deacylation, leading to a high recovery of **1**, resulted. Parallel results have been reported by Sugasawa.[6] The eventual solution, which was discovered by the Japanese workers,[6] involved the use of the 3-ketoglutaryl system, **3** (X = O; R = CO_2Et). The added acidity conferred by the β-keto ester linkage allowed for smooth dehydration.



In the light of the serious competing reaction of deacylation in the case of **2**, we investigated the preparation and reactions of the β-acetoethyl derivative **4** (X = H_2; R = H). Lactam **1** was alkylated with 1,3-dichloro-2-butene to give **5**, mp 202–203°, in 57% yield. The chloroolefin linkage was smoothly cleaved (86%) with concentrated H_2SO_4 to give **4**, mp 184–185°.

Treatment of **4** with triethylamine resulted in high recovery of starting material. However, reaction of **4** with pyrrolidine gave (71%) lactam **1**. Presumably this transformation occurs by reversible formation of the trisubstituted enamine which suffers retro-Michael type elimination of **1**. Substantial β-elimination was also observed in the reaction of **4** with potassium *tert*-butoxide.

Treatment of **4** with sodium methoxide–methanol gave, in 2% yield, a yellow, crystalline product, mp 283–284°, whose mass spectrum and combustion analysis define it to be a dehydration product. The NMR spectrum of this compound establishes it to be pyrrolizidinone derivative **7** rather than the desired (and expected) dehydration product, **6**. Clearly, **7** arises by deprotonation of a benzylic carbon followed by internal aldolization. It will be seen that this deprotonation produces an extensively delocalized anion, one resonance form of which is drawn as **4a**.

In an effort to influence the course of cyclodehydration in the direction of compound **6**, lactam **4** was treated with magnesium methyl carbonate (MMC) in methanol.[7-9] The high tendency of MMC to effect specific carboxylation of the methyl group of methyl alkyl ketones is well known.[10] The hope was that such a carboxylation would increase the likelihood of Knoevenagel-type attack toward the carbonyl group of the lactam function.

We were thus surprised to find that reaction of **4** with MMC in methanol turned out to be the best way we have yet devised (65–75%) to effect its transformation to **7**. Initially it was assumed that carboxylation would occur at the

methyl group. In an effort to produce compound **6** the product of the MMC reaction was heated with potassium *tert*-butoxide. Instead compound **7** was obtained in 67% yield. Subsequently it was shown that the base treatment is not necessary, i.e. that compound **7** was produced by the MMC treatment alone.

That this reaction is not due to a special catalytic effect of magnesium methoxide was shown by treatment of **4** with methanolic magnesium methoxide under reflux. These conditions gave largely (75%) recovered **4** and some retro-Michael product, **1**.

The simplest interpretation of the remarkable effect of the MMC is that carboxylation occurs at the benzylic position, thus facilitating formation of deprotonated system **4b**. This is followed by aldolization, decarboxylation, and dehydration.

A crucial element in this formulation is the feasibility of carboxylation at the benzylic center α to the lactam nitrogen. A test of this proposal involved attempted carboxylation of the *N*-methyl lactam, **9**. This compound, mp 260–262°, was obtained by bromination (NBS–CCl_4) of 2-carbomethoxy-3-methylquinoline (**8**)[3] followed by reaction of the intermediate 3-bromomethyl compound with methanolic methylamine.

Compound **9** was subjected to the action of MMC in methanol under reflux for 48 hr. Upon acidification, it was recovered to the extent of 98%. While we cannot rule out the possibility of carboxylation to a very slight extent, or the occurrence of decarboxylation under our conditions of work-up, no positive evidence favoring carboxylation of the pyrrolo system under the influence of MMC could be obtained. Accordingly, the mechanism for the MMC-induced transformation of **2** → **3** is, at this time, not understood. Nevertheless, this work suggests that MMC may be useful in catalyzing a greater variety of processes than has been supposed.

Experimental Section[11]

Acetoacetylation of Lactam 1. Formation of Imide 2. To a suspension of quinoline lactam **1** (1.302 g, 7.1 mmol) in 50 ml of dry monoglyme was added *n*-butyllithium (8 mmol) in hexane under nitrogen. After 30 min, a solution of diketene (0.660 g, 7.9 mmol) in 20 ml of dry monoglyme was added dropwise. The reaction mixture was heated under reflux for 10 hr.[12] The solution was made weakly acidic with dilute HCl and reduced in volume to 10 ml. A solid which separated was filtered and recrystallized from chloroform to give imide **2**, mp 242–245°.

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 66.95; H, 4.55; N, 10.35.

λ_{max} (Nujol) 5.73, 5.82, and 5.90 μ; δ (CF_3CO_2H) 2.57 (s, 3), 4.56 (s, 2), 5.46 (s, 2), 8–9 (m, 4); 9.84 (s, 1); MS *m/e* 268 (parent), 184 (base peak).

Alkylation of Lactam 1 with 1,3-Dichloro-2-butene. Formation of 5. Lactam **1** (2.25 g, 0.012 mol) was suspended in 100 ml of dry DMF. Sodium hydride (0.61 g of 57% oil suspension, or 0.015 mol) was added and the mixture was heated at 35° for 23 hr. After cooling to room temperature, freshly distilled 1,3-dichloro-2-butene (4.10 g, 0.032 mol) was added, dropwise, over a 15-min period. The mixture was heated at 50–60° for 4 hr. Water (50 ml) was added, the solution was extracted with methylene chloride, and the organic phase was dried over $MgSO_4$. The volatiles were evaporated at the water pump and the residue was recrystallized from THF to afford 1.89 g (57%) of **5**, mp 202–203°.

Anal. Calcd for $C_{15}H_{13}N_2OCl$: C, 66.06; H, 4.80; N, 10.27. Found: C, 66.26; H, 4.66; N, 10.35.

λ_{max} (Nujol) 5.93, 6.00 μ; δ ($CDCl_3$) 2.16 (s, 3), 4.3–4.7 (m, 4), 5.6–5.8 (m, 1), 7.3–8.5 (m, 5); MS *m/e* 272 (parent), 184 (base peak).

Hydrolysis of 5. Formation of Acetoethylated Lactam 4. A solution of compound **5** (2.48 g, 9.1 mmol) in 20 ml of concentrated H_2SO_4 was kept at 0° for 3.5 hr. After dilution with 10 ml of water the system was cautiously neutralized with aqueous sodium hydroxide and extracted with methylene chloride. The organic layer was dried over $MgSO_4$ and the volatiles were evaporated at the water pump. The solid residue was recrystallized from THF to give 1.96 g (86%) of **4**, mp 184–185°.

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.02; H, 5.64; N, 10.91.

λ_{max} ($CHCl_3$) 5.88 μ; λ_{max} (EtOH) 305 mμ (ϵ 9600), 317 sh, 328 sh; δ ($CDCl_3$) 2.2–3.0 (m, containing s at 2.17, 5), 3.9 (t, 2), 4.6 (s, 2), 7.3–8.6 (m, 5).

Cyclization of Keto Lactam 4 with Magnesium Methyl Carbonate. Formation of 7. A. With Added Base. A solution of keto lactam **4** (1.18 g, 4.7 mmol) was treated with a 16-fold excess of methanolic MMC[13] (based on 0.75 mol of magnesium). After 65 hr, 12 ml of a solution of potassium *tert*-butoxide–*tert*-butyl alcohol (0.4 *M*) was added. Refluxing was continued for an additional 54 hr. The reaction mixture was poured into 100 ml of 15% HCl and stirred for 30 min. The aqueous solution was made weakly basic with aqueous sodium bicarbonate and extracted with methylene chloride. Evaporation of the volatiles at the water pump left a residue which upon recrystallization from chloroform gave 73.4 mg (71%) of **7**, mp 280–284°.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.11; H, 5.11; N, 11.63.

λ_{max} (Nujol) 5.82, 5.92, and 5.95 μ; δ (CF_3CO_2H) 2.57 (s, 3), 3.5 (s, 2), 4.35 (s, 2), 8–10 (m, 5, containing s at 9.6); MS *m/e* 236 (parent).

B. Without Added Base. The keto lactam (200 mg, 0.78 mmol) was added to 11.2 mmol of MMC[13] in 25 ml of methanol. The solution was heated under reflux for 48 hr. An aliquot[14] of 10 ml was withdrawn and added to 5 ml of saturated methanolic HCl. This was added to 25 ml of water and extracted with 50 ml of methylene chloride. Evaporation of the volatiles left a residue of 71 mg of a yellow solid (crude compound **7**). Another aliquot[15] of 8 ml was withdrawn and added to 5 ml of aqueous HCl. Extraction with methylene chloride and evaporation left 61 mg of a yellow solid (crude compound **7**). Recrystallization of the combined solids gave compound **7**, mp 278–282°, in 71% yield.

Preparation of 2-Methyl-3-oxopyrrolo[3,4-*b*]quinoline. To a solution of 2-carbomethoxy-3-methylquinoline (0.69 g, 3.4 mmol) in 20 ml of CCl_4 was added *N*-bromosuccinimide (0.68 g, 3.8 mmol) and dibenzoyl peroxide (5 mg, 0.02 mmol). The mixture was heated under reflux for 24 hr. The reaction mixture was cooled and filtered. The filtrate was concentrated at the water pump, leaving an oily residue (2-carbomethoxy-3-bromomethylquinoline) which was dissolved in 50 ml of anhydrous methanol. A stream of methylamine was passed through the solution, which was heated under reflux for 2 hr. After the reaction mixture was cooled to room temperature, a white solid compound, **9** (332 mg), was obtained by crystallization. A second crop (200 mg) was obtained by concentration of the filtrate. The combined solid (77%) was recrystallized from methylene chloride–ether to give an analytical sample of **9**, mp 260–262°.

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.72; H, 5.05; N, 14.14. Found: C, 72.54; H, 5.15; N, 13.96.

λ_{max} ($CHCl_3$) 5.87 μ; δ ($CDCl_3$–CF_3CO_2H) 3.47 (s, 3), 5.00 (s, 2), 8.0–8.3 (m, 4), 9.98 (s, 1); MS *m/e* 198 (parent).

Acknowledgments. This research was supported by PHS Grant CA-12107-05-10. NMR spectra were obtained on facilities supported by PHS Grant RR-00292-05.

Registry No.—**1**, 34535-42-7; **2**, 53544-28-6; **4**, 54934-00-8; **5**, 54934-01-9; **7**, 54934-02-0; **8**, 53821-46-8; **9**, 54934-03-1; glyme, 110-71-4; 1,3-dichloro-2-butene, 926-57-8; magnesium methyl carbonate 142-72-3; *N*-bromosuccimide, 128-08-5; 2-carbomethoxy-3-bromomethylquinoline, 54934-04-2.

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on Varian Associates A-60, A-60D, and T-60 spectrometers with tetramethylsilane as internal standard. Data are reported in parts per million (δ) from Me_4Si. Infrared spectra were obtained from Perkin-Elmer 137 or 247 spectrophotometers. Mass spectra were measured on an LKB 9 combined GLC–mass spectrometer by direct insertion. Analyses were conducted by Galbraith Laboratories, Inc., Knoxville, Tenn.

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(14) This was done in an effort to isolate a methyl ester of carboxylated material.
(15) This was done in an effort to isolate intermediate acid.

Isolation of a Cyclopropene from Dehydrochlorination of a *gem*-Dichlorocyclopropane

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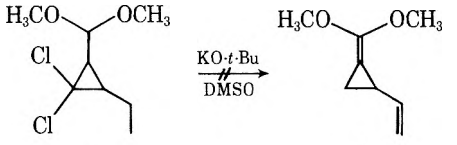
Received June 3, 1974

Although the direct observation of cyclopropenes from dehydrochlorination of chlorocyclopropanes has been reported,[2] usually isomerization products[3] or adducts with nucleophiles[4] are obtained. We report here an unusual example of cyclopropene formation from dehydrochlorination which we observed while attempting to prepare **1**, a potentially interesting receptor of singlet oxygen.[5]

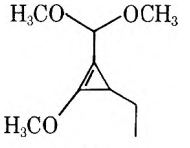
Thus addition of KO-*t*-Bu (2.36 equiv) in dimethyl sulfoxide (DMSO) to a solution of **2** (eq 1) in DMSO did not



(1)

2 **1**

give the expected **1**; however, the reaction was reproducible and gave a single major product (decomposition occurred on GLC columns) whose NMR, ir, and mass spectrum allowed assignment of structure **3**. The mass spectrum re-

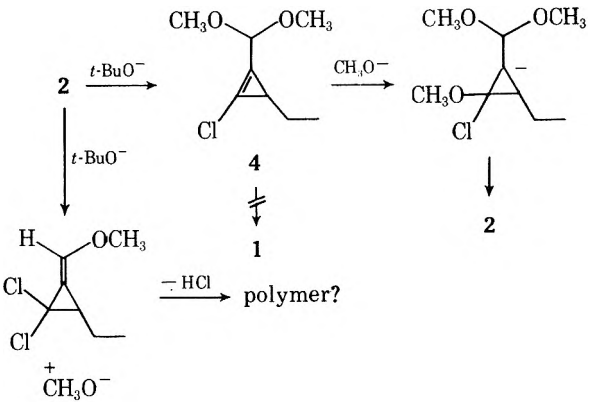


3

vealed the absence of chlorine and showed a parent ion at *m/e* 172. The NMR spectrum showed methoxyl signals at δ 3.27, 3.37, and 3.92. The dimethyl acetal proton appeared as a singlet at δ 5.1, in good agreement with the one at δ 5.0 in *cis*-2-pentenal dimethyl acetal. A triplet at δ 0.9 (3 H) and a multiplet at δ 1.4 (2 H) showed that the ethyl group was undisturbed. A strong, broad ir band at 1880 cm^{-1} was so unusual that it was relatively simple to assign it to the C=C stretch of a disubstituted cyclopropene.[6] These data and the absence of olefinic protons in the NMR spectrum showed that the ethyl, dimethyl acetal, and methoxyl were bound to different cyclopropene carbons. The collapse of the triplet at δ 2.25 upon irradiation of the methylene group identified the methine carbon of the cyclopropene.

A plausible mechanism for the formation of **3** is shown in Scheme I. The failure of product **3** (or **4**) to undergo double-bond isomerization[3] to the exocyclic position is unprecedented; we conclude, on the basis of a study by Davis and Brown,[7] that the cause was steric hindrance of the approach of *t*-BuO^- to the acetal methine proton.

Scheme I



Experimental Section

Infrared spectra were run on a Beckman IR-8 instrument and NMR spectra were recorded on a Varian A-56/60 spectrometer. The mass specta were recorded on a CEC 21-110B instrument. All reactions were conducted in a nitrogen atmosphere.

***cis*-2-Pentenal Dimethyl Acetal (5).** Ethylmagnesium bromide (2 mol) in THF was prepared by the method of Skattebøl, Jones, and Whiting.[8] The flask was then equipped with a Dry Ice–acetone condenser and 1-butyne (Farchan Research Laboratories, 100 g, 1.85 mol) was added dropwise over a 7-hr period at 25° with evolution of ethane. The solution was allowed to stand for 15 hr and trimethyl orthoformate (244 g, 2.3 mol) was added. The resulting brown transparent solution was heated with stirring to about 50° for 5 days and then 1 l. of THF was removed by distillation. CuCl (1%) was then added and the reaction mixture was refluxed for 11 hr. The remaining THF was distilled until the stillhead temperature reached 95°. The black reaction mixture was cooled and diluted with 500 ml of ether and the magnesium salts were filtered and washed with an additional 50 ml of ether. A 38% solution of NH_4Cl was used to destroy any remaining Grignard. The ethereal solution was decanted, dried through a cone of $MgSO_4$, and stored over Na_2SO_4. Distillation provided 122.4 g (50%) of alkyne, bp 77–78° (47 mm).

Reduction to the olefin was carried out as follows. The alkyne (40 g, 0.312 mols), quinoline (800 mg, 2% by wt), 5% Pd/$CaCO_3$ (800 mg, 2% by wt), and 200 ml of pentane were shaken in a Parr apparatus under H_2 (5 lb) until 1 equiv was absorbed. The product was then filtered through Celite and the pentane removed in vacuo. The light-yellow product, containing the quinoline, weighed 40.8 g (99% yield). GLC on a 10 ft × 0.25 in. 10% Apiezon J on 80–100 mesh Chromosorb W (acid washed) column at 100° showed only a single peak. Spectra: NMR δ 9.0 (t, J = 7 Hz, 3 H), 2.15 (quintet, J = 7 Hz, 2 H), 3.2 (s, 6 H), 5.0 (d, J = 5 Hz, 1 H), 5.15–5.9 (m, 2 H); ir 3040, 2830, 1665, 1190, 1112, and 1050 cm^{-1}. Spectral properties match reported values.[9]

***cis*-2,2-Dichloro-3-ethylcyclopropanecarboxaldehyde Dimethyl Acetal (2).** The olefin **5** (40.8 g, 0.314 mol, 1 equiv) and ethanol-free $CHCl_3$ (94 g, 0.785 mol, 0.015 equiv) were stirred rapidly in a 1-l. Morton flask, after which 50% aqueous NaOH was added. The reaction mixture quickly warmed to 60° and turned black. More NaOH was added when the reaction mixture had cooled to 50° until a total of 110 g (1.37 mol, 4.38 equiv) was added. When the reaction mixture had cooled to 45°, about 2 hr, it was poured into a separatory funnel and extracted with ether, and the ethereal solution was washed three times with water. The ethereal solution was then washed with saturated sodium chloride solution and dried over sodium sulfate. After removal of pentane in vacuo, distillation afforded first a reaction weighing 10.5 g, bp 50° (40 mm), followed by **2**, bp 60° (4 mm) (12.9 g, 19.3%). The product gave a single GC peak on the Apiezon J column described above. Spectra: NMR δ 1.09 (t, J = 5 Hz, 3 H), 1.3–1.9 (m, 4 H), 3.27 (s, 3 H), 3.37 (s, 3 H), 4.18 (d, J = 7 Hz, 1 H); ir 2980, 1450, 1195, 1142, 1110, 1065, and 810 cm^{-1}. The mass spectrum had no parent ion but showed peaks at *m/e* 211 (M − 1) and 181 (M − OCH_3); exact *m/e* calcd for $C_7H_{11}OCl_2$ (M − OCH_3), 181.0186; found, 181.0188.

2-Methoxy-3-ethylcycloprop-1-enecarboxaldehyde Dimethyl Acetal (3). The cyclopropane **2** (1 g, 4.96 mmol, 1 equiv) and DMSO (7 ml) were placed in a 50-ml flask equipped with a magnetic stirring bar and pressure-equalizing addition funnel.

KO-*t*-Bu (1.2 g, 10.7 mmol, 2.16 equiv) dissolved in 10 ml of DMSO was then added dropwise over 2.3 hr at 25°. The resulting dark solution was stirred for an additional 1 hr, poured into water, and extracted with pentane. The aqueous layer was saturated with NaCl to break the emulsion. The pentane extracts were washed twice with water and twice with saturated sodium chloride solution. Removal of pentane in vacuo gave nearly pure **3** (330 mg, 38%): mass spectrum parent ion *m/e* 172; exact *m/e* calcd for $C_9H_{16}O_3$, 172.1099; found, 172.1094.

Acknowledgment. We gratefully acknowledge the Robert A. Welch Foundation and Eli Lilly and Co. for support of this work.

Registry No.—**2**, 54276-74-3; **3**, 54276-75-4; **5**, 54276-76-5; ethyl bromide, 74-96-4; 1-butyne, 107-00-6; trimethyl orthoformate, 149-73-5; 2-pentynal dimethyl acetal, 54276-77-6.

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Organometallic Chemistry. VI. Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study of α-Ferrocenylcarbenium Ions[1]

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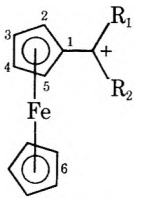
Kinetic studies of the solvolysis of α-ferrocenylcarbinyl derivatives and actual isolation of stable salts demonstrate the remarkable stability of α-ferrocenylcarbenium ions.[2] Although extensive work has been done in the past, the nature of ferrocenyl-stabilized carbocations is still under dispute.[3] Carbon-13 nuclear magnetic resonance spectroscopy provides an understanding of distribution of positive charge in carbocations, in a more quantitative way than does the proton NMR. This is also indicated by several earlier investigations on ferrocenylcarbenium ions.[3,4] Interested in the nature of these ions, we wish to report our further ^{13}C NMR spectroscopic investigation of a series of α-ferrocenylcarbenium ions.

Results and Discussion

Cations **1–4** were prepared in sulfuric acid solution at 0° from their corresponding alcohols.[5] The proton NMR spectra of α-ferrocenylcarbenium ions were in accordance with those previously reported.[6] The carbon-13 NMR spectra of the cations were obtained by the Fourier-transform method. Carbon shifts (δ ^{13}C, in parts per million from external Me_4Si), multiplicities, and coupling constants (J_{CH}, in hertz) are summarized in Table I. The assignments of the carbon resonances were made with the aid of either off-resonance or proton-coupled spectra.



1, $R_1 = R_2 = H$
2, $R_1 = H$; $R_2 = CH_3$
3, $R_1 = R_2 = CH_3$
4, $R_1 = CH_3$; $R_2 = CH_2CH_3$

The present results reveal several interesting features of the carbon-13 NMR spectra of α-ferrocenylcarbenium ions. First of all, the carbocationic centers in these ions are unusually shielded, instead of being deshielded as observed in conventional carbenium ions. Secondly, the replacement of a hydrogen atom in primary ion **1** by a methyl group causes about 30 ppm deshielding of the carbenium center. Further replacement of the second hydrogen by a methyl group causes additional deshielding of about 37 ppm. Ethyl substitution causes about 43 ppm deshielding from **3** to **4**. Thirdly, consecutive methylation at carbenium centers from primary to tertiary ions causes slight shielding at C_1, C_2, and C_3, while C_4 (and C_5) and C_6 (cyclopentadienyl carbons) are almost unaffected. A deshielding of 5 ppm at carbons (C_1) adjacent to the carbenium center is observed for substitution of each methyl going from primary to tertiary ions.

It is also interesting to see that C_3 (and C_4) are more deshielded than the carbenium center (C^+) in the primary

Table I
Carbon-13 NMR Parameters of α-Ferrocenylcarbenium Ions in Sulfuric Acid Solution[a]

Ion	C^+	C_1	C_2	C_3	C_4	C_5	C_6	Δ_1[b]	Δ_2[b]
1	87.8	110.6	84.8	94.5	94.5	84.8	82.4	+22.8	9.7
	(t, 168.9)	(s)	(d, 188.0)	(d, 183.7)	(d, 183.7)	(d, 188.0)	(dt, 184.1, 6.0)		
2[c]	117.9	105.6	81.0[d]	93.9[d]	94.2[d]	81.8[d]	82.3	−12.3	11.9
	(d, 164.9)	(s)	(d, 187.6)	(d, 183.0)	(d, 183.0)	(d, 190.0)	(dt, 182.9, 6.0)		
3[e]	155.1	100.1	78.3	93.6	93.6	78.3	82.2	−55.0	15.3
	(s)	(s)	(dd, 187.5, 5.0)	(d, 185.0)	(d, 185.0)	(as C_2)	(dt, 180.0, 6.0)		
4[f]	160.6	100.3	78.9[d]	93.8[d]	94.0[d]	78.4[d]	82.2	−60.3	15.1
	(s)	(s)	(d, 178.2)	(d, 183.3)	(d, 183.3)	(d, 180.9)	(dt, 182.5, 6.0)		

[a] Carbon shifts (δ ^{13}C) are in parts per million from external Me_4Si (capillary). Multiplicities and coupling constants (J_{CH}, in hertz) are given in parentheses: d, doublet; dt, doublet of triplets; t, triplet; dd, doublet of doublets; s, singlet; and q, quartet. [b] $\Delta_1 = \delta\ ^{13}C_1 - \delta\ ^{13}C^+$, $\Delta_2 = \delta\ ^{13}C_3 - \delta\ ^{13}C_2$. [c] $\delta_{CH_3} = 19.8$ (q, 129.8). [d] Interchangeable values. [e] $\delta_{CH_3} = 26.6$ (q, 127.5). [f] $\delta_{CH_3} = 25.7$ (q, 129.5), $\delta_{CH_3} = 16.6$ (q, 129.1), and $\delta_{CH_2} = 35.9$ (t, 131.0).

cation **1**, and less so or even shielded in the secondary and tertiary ions. Despite the change in carbon shifts at carbocationic centers going from primary to tertiary ions (about 80 ppm), C_3 and C_4 show almost no change. The lack of variation of deshielded cyclopentadienyl carbons, C_3 and C_4, not only indicates positive charge delocalization into the ferrocenyl moiety at these positions, but also shows that the interaction between the iron atom and the carbocationic center is reduced going from primary to tertiary ions. One also finds that carbon–hydrogen coupling constants (J_{CH}, in hertz) at the carbenium centers are smaller than those in the cyclopentadienyl moiety, presumably caused by some interaction between iron and the carbenium center. The magnitude of J_{CH} is significantly different from those in, for example, dimethyl- and diphenylcarbenium ions (J_{CH} = 169 and 164 Hz, respectively).

The observed diastereotropism of the carbon pairs (C_2 and C_5, and C_3 and C_4) in the unsymmetrically substituted α-ferrocenylcarbenium ions (**2** and **4**) undoubtedly indicates slow rotation about the exocyclic C^+–C_1 bond, which could arise from either the double bond character between C^+ and C_1 or the direct interaction between iron and the carbocationic center.

The present ^{13}C NMR studies demonstrate that α-ferrocenylcarbenium ions indeed have the positive charge substantially delocalized into the metallocenyl moiety. Although the detailed mechanism for the interaction between the iron nucleus and the neighboring carbenium center is not yet clear, such interaction seems to be weaker in tertiary than in primary or secondary species.

Experimental Section

Materials. All α-ferrocenylcarbinols were prepared according to literature procedures.[5]

Carbon-13 NMR Spectra. A Varian Associates Model XL-100 NMR spectrometer equipped with a Fourier transform accessory, a spin decoupler, and a variable-temperature probe was used to obtain the carbon-13 NMR spectra. Carbon shifts were referred to external Me_4Si (capillary).

Preparation of the Ions. α-Ferrocenylcarbenium ions were prepared from corresponding alcohols in cold sulfuric acid solution at −10° and carefully transferred to NMR tubes for study.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No.—**1**, 12129-36-1; **2**, 12129-73-6; **3**, 12295-38-4; **4**, 12295-58-8.

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An Improved Procedure for the N-Demethylation of 6,7-Benzomorphans, Morphine, and Codeine

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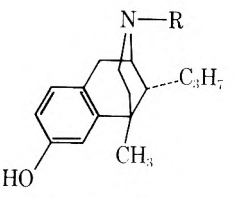
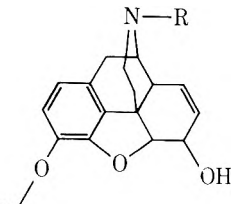
The N-demethylation of tertiary methylamines has been accomplished in several ways. The classic von Braun reaction,[1] using cyanogen bromide, was improved upon for many amines by the use of benzyl or ethyl chloroformate.[2] Further improvement involved the use of phenyl chloroformate;[2,3] the intermediate carbamate formed with this reagent proved easier to hydrolyze. Ethyl azodicarboxylate has been used[4] to demethylate thebaine and various 6-ester derivatives of morphine and codeine in reasonable yield. However, this procedure gave only ca. 40% yields of an *N*-nor-6,7-benzomorphan.[5] Recently, 2,2,2-trichloroethyl chloroformate[6] has been found to give a carbamate intermediate which could be cleaved by zinc in acetic acid or methanol. These reagents N-demethylated morphine in 75% yield. However, in our hands, the trichloroethyl chloroformate procedure gave poor yields (<40%) of the *N*-nor product from 2′-hydroxy-2,5-dimethyl-9α-propyl-6,7-benzomorphan (**1b**).



1a, R = H
b, R = CH_3



2a, R = R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = CH_3
d, R = R′ = CH_3

We utilized a modified phenyl chloroformate procedure to produce an intermediate carbamate, and have found that the carbamate can be easily cleaved with a 1:1 mixture of 64 and 95% hydrazine. The method has been applied to morphine (**2b**), codeine (**2d**), and 6,7-benzomorphans to give the *N*-nor compounds in excellent yield. Hydrazine has, of course, been used in the past to cleave amides in peptides and other compounds.[7]

The procedure of Abdel-Monem and Portoghese[3] for the preparation of *N*-normorphine involved the hydrolysis of *N*,3,6-tricarbophenoxynormorphine to *N*-carbophenoxynormorphine, its chromatography and crystallization, followed by cleavage with ethanolic KOH, in an overall yield of ca. 40%. We found it unnecessary in our procedure to isolate and purify the intermediate carbamate and, with the benzomorphan, the *N*-nor product precipitated from the hydrazine reaction mixture; washing and drying gave analytically pure product in 95% overall yield. *N*-Normorphine

and *N*-norcodeine were obtained in overall yields of 84 and 89%, respectively.

Care should be exercised in the preparation of the carbamate to ensure continuous, efficient stirring, especially in larger scale preparations. Inefficient mixing could be responsible for localized acid formation which might promote the formation of acid-catalyzed by-products from the *N*-normorphine and codeine carbamates to give, possibly, the epimeric 6-hydroxyl (6-iso) or 8-hydroxyl (from allylic rearrangement) *N*-normorphine (or codeine). Efficient stirring and an increased (over the former procedure[3]) amount of base tended to eliminate by-products.

A further precaution involved the use of 64% hydrazine in the hydrazine mixture which ensured the presence of hydrazine hydrate in the vapor of the refluxed mixture, rather than the air-sensitive (explosive) anhydrous hydrazine; safety shields should also be employed.

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are corrected. Microanalyses were performed by the Laboratory's Section on Microanalytical Services and Instrumentation. Ir (Perkin-Elmer 21), NMR (Varian A-60 or HR-220), and mass (Hitachi Perkin-Elmer RMU 6E) spectra were consistent with the assigned structures.

(±)-5-Methyl-2'-hydroxy-9α-propyl-6,7-benzomorphan (1a). In a modification of the usual procedure,[3] phenyl chloroformate (26.0 g, 166 mmol) was added to a slurry of (±)-2,5-dimethyl-2'-hydroxy-9α-propyl-6,7-benzomorphan (**1b**, 5.0 g, 19.3 mmol) in $CHCl_3$ (500 ml). After stirring for several minutes the reaction mixture became homogenous and $KHCO_3$ (34.0 g, 340 mmol) was added. The mixture was refluxed for 48 hr and cooled and water (200 ml) was added. When the inorganic material had dissolved, the $CHCl_3$ was separated and washed with 1 *N* HCl (50 ml) and water (100 ml). The $CHCl_3$ was evaporated in vacuo and to the residue was added MeOH (310 ml) and a solution of KOH (14.5 g, 220 mmol) and $KHCO_3$ (22 g, 220 mmol) in H_2O (220 ml). After stirring at 25° overnight, the solution was acidified with 37% HCl and concentrated in vacuo until KCl separated. The aqueous suspension was washed with Et_2O and the combined extracts were dried ($MgSO_4$) and solvent was removed. The major portion of the residual phenol by-product was removed by distillation under high vacuum (bath 100–120°), to give a gum which was dissolved in Et_2O and filtered through a layer of silica gel (70–230 mesh). The silica gel was washed with Et_2O and the combined filtrate and washings were evaporated to yield the crude *N*-carbophenoxy derivative of **1a** (9.6 g) as a yellow foam that resisted crystallization from a variety of solvents and which still contained some phenol. To this material was added 64% hydrazine (35 ml) and 95% hydrazine (35 ml). The mixture was stirred (under N_2), and refluxed (behind a safety shield) for 1.5 hr. Crystalline **1a** separated from the reaction mixture. After an additional 18 hr of refluxing, the reaction mixture was cooled. The white solid was filtered and washed well with H_2O and then Et_2O (20 ml). The resulting white solid was dried in vacuo at 65° to yield 4.52 g (95.5%) of analytically pure **1a** directly, as small, irregular prisms, mp 248.5–250.5°.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.07; H, 9.25; N, 5.73.

Normorphine (2a). To a suspension of anhydrous morphine (**2b**, 2.50 g, 8.76 mmol) and finely divided $KHCO_3$ (15.0 g, 150 mmol) in $CHCl_3$ (250 ml) was added phenyl chloroformate (11.5 g, 73.4 mmol). The reaction mixture was vigorously stirred, refluxed for 60 hr, and cooled, most of the $CHCl_3$ was decanted, and the remaining inorganic material was dissolved in H_2O (100 ml). This solution was added to the decanted $CHCl_3$ and after shaking well the $CHCl_3$ was separated and washed with H_2O (50 ml) and then with 1 *N* HCl (50 ml). The $CHCl_3$ was dried ($MgSO_4$) and evaporated in vacuo, and most of the phenol was evaporated from the residue under high vacuum (bath 100–110°). To the residue was added 64% hydrazine (20 ml) and 95% hydrazine (20 ml) and the solution was refluxed (safety shield) under N_2 for 60 hr. The mixture was cooled, H_2O (100 ml) was added, and the solvent was removed in vacuo. The phenol remaining was evaporated under high vacuum (bath 100–120°), H_2O (20 ml) was added, and 37% HCl was added to pH 2.0 (Hydrion paper). The solutions was filtered, and the filtrate was made alkaline with NH_4OH. When crystallization (at 5°) was complete, the solid was filtered, washed with cold H_2O, and dried to give **2a**·$2H_2O$ (2.24 g, 84%), mp 275–277° dec (lit.[8] mp 276–277°).

Anal. Calcd for $C_{16}H_{17}NO_3 \cdot 2H_2O$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.45; H, 6.77; N, 4.60.

Norcodeine (2c). To a solution of codeine (**2d**, 2.99 g, 10 mmol) in $CHCl_3$ (250 ml) was added $NaHCO_3$ (21.0 g, 250 mmol) and phenyl chloroformate (11.5 g, 73.4 mmol). The reaction mixture was refluxed with efficient stirring for 18 hr, cooled, filtered, and evaporated. To the resulting syrup (14.1 g) was slowly added 95% hydrazine (5 ml). When the strongly exothermic reaction was over, additional 95% hydrazine (10 ml) and 64% hydrazine (10 ml) were added. The solution, under N_2, was refluxed (safety shield) for 24 hr and cooled, and H_2O was added and then removed (twice, 100 ml each) in vacuo. Most of the remaining phenol was removed (high vacuum, bath 100–120°) to give a semisolid which was dissolved in a mixture of $CHCl_3$ (150 ml) and H_2O (75 ml). The aqueous phase was made alkaline with NH_4OH, and the $CHCl_3$ was separated and extracted with sufficient 10% KOH to remove the remaining phenol. The $CHCl_3$ solution was washed with H_2O (50 ml), dried (Na_2SO_4), and evaporated to give 2.54 g (89%) of norcodeine (**2c**), mp 183.5–185° (lit.[9] mp 185°).

Registry No.—**1a**, *55058-87-2*; **1b**, *55058-88-3*; **2a**, *466-97-7*; **2b**, 57-27-2; **2c**, 467-15-2; **2d**, 76-57-3; phenyl chloroformate, 1885-14-9.

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Formation of *gem*-Dinitrates from Acetaldehyde and Trifluoroacetaldehyde[1]

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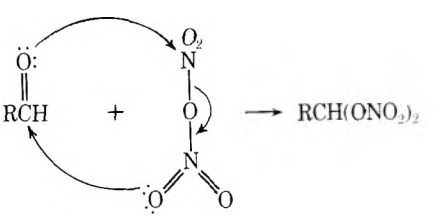
The new *gem*-dinitrates 1,1-dinitratoethane, $CH_3CH(ONO_2)_2$, and 1,1,1-trifluoro-2,2-dinitratoethane, $CF_3CH(ONO_2)_2$, have been synthesized by the reaction between dinitrogen pentoxide and acetaldehyde and trifluoroacetaldehyde. The combination of the aldehydes and N_2O_5 in a 1:1 mole ratio can be explained by the heterolytic cleavage of the latter involving a nucleophilic oxygen atom attack, i.e.



R = CH_3, CF_3

although the reaction need not be concerted.[2] This route is also similar to that for perchlorate formation reported by

Table I
Vibrational Spectra of $CF_3CH(ONO_2)_2$

Raman		Infrared		
Frequency, cm^{-1}	Intensity	Frequency, cm^{-1}	Intensity	Tentative assignments
		2996	wm	ν_{C-H} and
		2975	sh	combination 1280 + 1718
		1786	w	
1712 dp	2	1718 doublet		ν_{NO_2} (antisym)
1700 dp	2	1705 doublet	vs	
1458	1			
1375 dp	3	1365	m	ν_{C-F}
1350 dp	3	1348	sh	
1312	26	1302	m	ν_{NO_2} (sym)
1281	2	1280	vs	
		1210	vs	
1181	2	1178	vs	ν_{C-F} region
1086	3	1081	m	
1026	1	1029	ms	
912	17	906	m	ν_{C-O}
837	29	829	vs	ν_{N-O}
781	4	780	s	π_{NO_2}
762	5			
743	2	730	w	
700	6	690	wm	δ_{NO_2} (sym)
650 dp	9			
612 sh				combination 262 + 343
594	19	595	ms	δ_{NO_2} (antisym)
536 dp	13	566		CF_3 group bending
525 dp	14			
381 sh	17			and rocking
356	32			deformations
343 sh				
262	100			δ_{CON}

Baum[3] and to that for acylal formation by reaction of an aldehyde with an acid anhydride.[4]

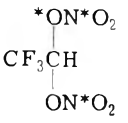
The chemical and physical properties, as well as the synthetic stoichiometry, match the proposed structure for both compounds and appear to favor it over other possibilities. On standing at room temperature or above, $CF_3CH(ONO_2)_2$ appears to decompose to the initial reactants, dinitrogen pentoxide or the elements thereof and trifluoroacetaldehyde. The former is inferred via its decomposition product, NO_2. Nitrogen dioxide is also a thermal decomposition product of alkyl nitrates.[5] The mass spectrum, too, substantiates this result because, upon excitation from electron impact, the compound shows many fragmentation ions common to nitrogen oxides and trifluoroacetaldehyde. The compound hydrolyzes in alkali by a similar path, i.e., by loss of N_2O_5, present in the form of nitrate ion, to give trifluoroacetaldehyde, witnessed by its hydrolysis product, fluoroform.[6] A small amount of nitrite is formed and its

$$CF_3CH(ONO_2)_2 + 2OH^- \longrightarrow CF_3C(O)H \cdot aq + 2NO_3^- + H_2O$$

$CF_3C(O)H \cdot aq \longrightarrow$ fluoroform

presence is puzzling; however, it is known that covalent nitrates can produce both nitrate and nitrite ions upon hydrolysis, although nitrate ion is commonly the major product.[5] The thermal disintegration of $CH_3CH(ONO_2)_2$ is strikingly different than that of the trifluoro derivative not only because it disappears at a much faster rate but also because acetaldehyde is not a main product while both HNO_3 and NO_2 are major products. The small amount of CH_3COOH monomer is present owing to oxidation of CH_3CHO by HNO_3. This reaction also explains the presence of N_2O. Analogous to $CF_3CH(ONO_2)_2$, however, 1,1-dinitratoethane yields acetaldehyde and nitrate from base hydrolysis. Refer to the Experimental Section.

The infrared spectrum of $CF_3CH(ONO_2)_2$ is interpreted in terms of the tentative assignments in Table I that are the best choices for the more diagnostic absorption bands.[5,7,8] Also, to further substantiate the nitrogen–oxygen and carbon–oxygen vibrational assignments, tagged ^{17}O dinitrogen pentoxide was prepared by the glow discharge of nitrogen and isotopically enriched oxygen. If the mechanism is correctly described above, then the tagging should appear in the following way.



That is, only one oxygen, from the original carbonyl group, should not be labeled. Consequently, all the $X-^{16}O$ frequencies should become diminished in intensity and bands due to the heavier oxygen atom should appear at lower frequencies. This indeed has been found to be the case. The frequencies ascribed to the NO_2 group stretching and bending motions as well as the N–O and C–O stretching frequencies all show the predicted changes.[9] Furthermore, the splitting of the C–O stretching band at 912 cm^{-1} agrees with the labeled structure and justifies the assignment. Also, all six of the $-ONO_2$ group fundamental frequencies have been assigned.

The infrared spectrum of $CH_3CH(ONO_2)_2$ in the 2.7–15-μ region shows nitrate absorptions at 1722, 1300, 859, 810, and 680 cm^{-1}. The intensities and frequencies are close to those measured for the $CF_3CH(ONO_2)_2$ congener. A band at 910 cm^{-1} near the 906-cm^{-1} absorption in $CF_3CH(ONO_2)_2$, assigned to the C–O stretching vibration, is also present. Bands in the C–H stretching[10] and bending[11] regions are also present.

The NMR spectra of these compounds are also consistent with their formulation (Table II). For $CF_3CH(ONO_2)_2$,

Table II
NMR Spectra

Compd	$^{19}F^a$	$^{17}O^b$	$^1H^c$	Area ratios
$CH_3CH(ONO_2)_2$	81.3	340, 430	6.2	1:4.0 (^{17}O)
$CF_3CH(ONO_2)_2$			0.37, 6.0[d]	2.99:1.0 (^1H)

[a] ϕ^* relative to CCl_3F. [b] Relative to $H_2{}^{17}O$. [c] Relative to Me_4Si. [d] The resonance at 0.37 is a doublet and the one at 6.0 is a quartet, J = 6 Hz.

the ^{17}O spectrum is of particular interest. It shows two absorptions, at 340 and 430 ppm in a 1:4 area ratio and assigned to the $\mathbf{O}NO_2$ and ONO_2 oxygen nuclei, respectively. These chemical shifts compare favorably with those obtained from our measurements on other nitrates, e.g., $CH_3C(O)ONO_2$ at 360 ($\mathbf{O}NO_2$) and 485 ppm (ONO_2) and N_2O_5 at 331 (**N**ON) and 469 ppm (ONO_2). Furthermore, the area ratio is expected from the structural formula, above, that shows the positions of the tagged oxygen atoms. The ^1H spectrum of the hydrocarbon derivative shows the predicted two resonances, one for the methyl and the other for the CH group, having proper area ratio and coupling constant.

The mass spectra of the dinitratoethanes are similar to a large degree since there are many analogous fragment ions predicted from their assumed structure. In both cases the most abundant ions are NO_2^+, CHO^+ and NO^+. Also, both show the molecule ion less a NO_3 group. Only $CF_3CH(ONO_2)_2$ exhibits a molecule ion.

Experimental Section

General Procedures. Trifluoroacetaldehyde was prepared by the slow addition of trifluoroacetaldehyde ethyl hemiacetal to a large excess of a 50% by weight mixture of 85% orthophosphoric acid and phosphorus pentoxide, polyphosphoric acid, at 170°. The volatile products were passed through traps set at −80 and −126°. The latter contained the trifluoroacetaldehyde and the former unreacted hemiacetal. The dinitrogen pentoxide was made by combining excess ozone with dinitrogen tetroxide within the reactor for the dinitrate synthesis. Enriched ^{17}O (14%) oxygen was purchased from Yeda R & D Co., Ltd., Divison of Miles Laboratories, Inc.

A standard Pyrex-glass vacuum apparatus with an attached preparative gas chromatograph was used to manipulate and purify volatile chemicals. The ozone was generally prepared using a Welsbach Corp. ozonator and collected in a flow-through Pyrex bulb and then separated from the unconverted oxygen by passage through a trap maintained at −196°. Vapor pressures were determined using a diaphragm pointer gauge described by Foord.[12] A cathetometer was employed to observe the null on the pointer, and pressures were monitored with a Wallace and Tiernan Series 1500 gauge. A water bath with an immersion heater was used for temperature control.

Infrared spectra were recorded with a Perkin-Elmer 21 infrared spectrometer. Gas samples were placed in 10-cm path length cells, either Pyrex or Monel, with sodium chloride or silver chloride windows. The spectrum of $CH_3CH(ONO_2)_2$ was recorded at pressures up to 15 Torr and that of $CH_3CH(ONO_2)_2$ at about 2–3 Torr. Raman spectra of liquid samples were obtained with a Spectra-Physics Model 125 helium–neon laser and a Spex Model 1401 double monochrometer. Samples were sealed in Pyrex tubes and excited by the 6328-Å laser line. Table I shows the infrared and Raman spectra of $CF_3CH(ONO_2)_2$. The ^1H NMR spectra were taken with a Varian Model A-60D NMR spectrometer at 56.4 and 8.13 MHz, respectively. Samples were placed in 5-mm o.d. tubes and all spectra were measured between 0 and −30°. External standards were used. See Table II. A Hitachi Perkin-Elmer RMU-6D mass spectrometer operating at 10–70 eV was used to obtain the mass spectra, and the inlet system was at room temperature.

Synthesis and Properties of $CF_3CH(ONO_2)_2$. Dinitrogen tetroxide (1.2 mmol, corrected for monomer) and an excess of ozone, but added in increments, were distilled at −196° into a 100-ml Pyrex reactor. The reactor was allowed to warm very slowly to about −80° and then recooled to −196°. This process was repeated several times until the blue color of liquid ozone no longer appeared on recooling. More ozone was added and the procedure was repeated until the blue color permanently remained. The N_2O_4 was thus completely converted to N_2O_5. The excess ozone was pumped out and then CF_3CHO (1.2 mmol) was distilled into the reactor at −196°. The reactor was brought to −80° and then allowed to warm slowly to −30° over a 4-hr period. The reaction had terminated within this period and the products were slowly distilled through cold traps at −64 and −196°.

The $CF_3CH(ONO_2)_2$ (1.1 mmol, 92% recovery) was retained at −64°, and a trace of the dinitrate as well as small quantities of NO_2 and HNO_3 were collected in the latter. The contents of the −64° trap were then passed through the preparative GC consisting of a 5-ft Pyrex column containing KEL-F grease on Fluoropak 80 at a 60 ml/min helium flow rate; retention time of $CF_3CH(ONO_2)_2$ 9.5 min; gas density molecular weight 208 g/GMV (theory 206); glasses, flow point at −116°; vapor pressures, reported as $P_{(Torr)}$ (temp, °C) 18.2 (0.0), 25.7 (6.2), 32.0 (11.2), 41.5 (15.9), 52.4 (20.9), 80.7 (30.4), 100.7 (33.4), 113.2 (35.4), 145.4 (42.1), 153.3 (44.1), 187.0 (49.9). Decomposition at higher temperatures was too rapid for meaningful measurements. The boiling point (extrapolated) was 85.7°; latent heat and entropy of vaporization 8.392 kcal/mol and 23.3 eu, respectively; vapor pressure equation in the above indicated temperature range $\log P_{(torr)} = -1834/T + 7.966$; mass spectrum NO_2^+, CHO^+, NO^+, CF_3^+, CO_2^+, CO^+, O_2^+, CHF_2^+, CF_2^+, CF_3CHO^+, CF^+, CF_3CH^+, CF_2CH^+, $CF_3CH(ONO_2)^+$, CF_3CO^+, and molecular ion (very low intensity) in the order of decreasing intensity.

Anal. Calcd for $C_2HF_3N_2O_6$: C, 11.65; H, 0.485; N, 13.59. Found: C, 11.66; H, 0.57; N, 13.50.

Synthesis and Properties of $CH_3CH(ONO_2)_2$. A similar procedure (vide ante) was used to prepare this compound. Dinitrogen tetroxide (1.18 mmol) was introduced into the same reactor and was converted to N_2O_5. Acetaldehyde (0.75 mmol) in a 1:10 mole ratio with dry nitrogen was added into the reactor at −45° in very small aliquots over a several-hour period. When all the aldehyde was placed into the reactor, it was cooled to −196° and the nitrogen was pumped out, and then the mixture was allowed to warm very slowly to approximately 0°. The product was purified by distillation through traps kept at −18 and −196°.

The $CH_3CH(ONO_2)_2$ (0.62 mmol, 83% recovery) remained in the former while the excess N_2O_5, along with traces of NO_2 and HNO_3 (0.45 mmol total), was held in the latter. The $CH_3CH(ONO_2)_2$ is a colorless liquid, mp −45.7 ± 0.7°, and has several Torr vapor pressure at 24°: ir spectrum 3040 (w), 2990 (w), 1722 (vs), 1455 (w), 1395 (w), 1350 (w), 1300 (ms), 1098 (m, br), 1076 (sh), 928 (sh), 910 (m), 859 (ms), 810 (s), 743 (w) (possibly due to N_2O_5 trace impurity) and 680 cm^{-1} (m, br); mass spectrum, given in the order of decreasing ion intensity, NO_2^+, NO^+, CHO^+, CO_2^+ and CH_3CHO^+, CH_3CO^+, CH_3^+, CO^+ and CH_3CH^+, CH_2^+ and N^+, $CH_3CH(ONO_2)^+$, CH_2CO^+, $C_2H_2^+$, CH^+, $CHCO^+$, C^+, $C_2H_3^+$, O_2^+, and HNO_3^+.

Anal. Calcd for $C_2H_4N_2O_6$: C, 15.79; N, 18.42; H, 2.63. Found: C, 16.32; N, 18.32; H, 2.82.

Caution: The direct combination of CH_3CHO and N_2O_5 (neat) at −196° leads to a violent explosion. In one elementary analysis trial a sample exploded upon being placed in the hot zone of the C, H, N analyzer.

Synthesis of ^{17}O-Enriched N_2O_5. Oxygen-17 enriched N_2O_5 in each oxygen position was prepared in a Pyrex-glass glow-discharge apparatus in the following way. Equal amounts of nitrogen and labeled oxygen were placed in the discharge at −80° to form $N^{17}O$, which was then allowed to react with excess enriched oxygen to form $N_2{}^{17}O_4$. Ozone was prepared by subjecting $^{17}O_2$ to a discharge

at −196°. The $N_2{}^{17}O_5$ was finally obtained from the reaction of $N_2{}^{17}O_4$ with ozone in the manner illustrated previously.

Aging and Hydrolysis. The ir cell described above was loaded with $CF_3CH(ONO_2)_2$ to 10 Torr pressure and allowed to stand at ambient temperature while the ir spectrum was recorded periodically. After 1.5 hr a small amount of decomposition took place and CF_3CHO and NO_2 were the observed products. Upon more prolonged standing, much smaller amounts of CF_3COOH and HNO_3 were found. The decomposition was only partial after 24 hr. A sample of $CF_3CH(ONO_2)_2$ (0.75 mmol) was dissolved in 10% NaOH solution and after standing for several hours at ambient temperature an ir spectrum of the volatile substances over the aqueous solution revealed that fluoroform was produced. Spectrophotometric analysis[13] for nitrate and nitrite, mutually present, indicated NO_3^- (0.93 mmol) and NO_2^- (0.33 mmol).

The $CH_3CH(ONO_2)_2$ is less thermally stable. At ambient temperature the liquid immediately evolved HNO_3 and NO_2 and a viscous liquid residue remained. The decomposition of a gaseous sample of this compound at room temperature produced NO_2, HNO_3, N_2O, CH_3CHO, and probably CH_3COOH monomer, a minor product, according to ir analysis. Initially, NO_2 and HNO_3 were apparent, and CH_3CHO grew in slowly but reached a maximum after a few hours. The HNO_3 also attained its maximum concentration within this period but decreased as time progressed and a new species believed to be CH_3COOH was observed, and N_2O also appeared. Acetaldehyde was a minor product, and within 18 hr no $CH_3CH(ONO_2)_2$ remained. Hydrolysis was accomplished by adding excess base, described above, to a 0.23-mmol sample. An emulsion formed which slowly dissipated within 1 hr of gentle warming and stirring. The odor of acetaldehyde was apparent and the solution turned yellow. Because of the acetaldehyde carbonyl group absorption, λ_{max} 283 nm, that interferes with the spectrophotometric measurements of NO_3^- and NO_2^-, an alternate procedure[14] was used: NO_3^- (0.38 mmol), NO_2^- (ca. 0.05 mmol).

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Registry No.—$CF_3CH(ONO_2)_2$, 55044-05-8; $CH_3CH(ONO_2)_2$, 55044-04-7; trifluoroacetaldehyde, 75-90-1; trifluoroacetaldehyde ethyl hemiacetal, 433-27-2; dinitrogen tetroxide, 10544-72-6; dinitrogen pentoxide, 10102-03-1; acetaldehyde, 75-07-0.

References and Notes

(1) This study was prompted because of the relevance of nitrogen oxides (NO_x) and hydrocarbons to atmospheric chemistry in the urban environment. Unusual nitrate structures have been reported to be formed, acylperoxy nitrates, and it was intented to isolate and more completely characterize some of these substances which have short lifetimes. Our results were unexpected since *gem*-dinitrates were formed. A synthesis involving a fluorinated aldehyde was selected because it would yield a product of greater stability which would lead to a more thorough structural characterization that could be used to compare with $CH_3CH(ONO_2)_2$.
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Thermolysis of *N,N'*-Dimethyldiazenedicarboxamide

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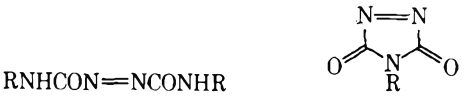
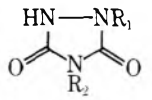
Investigation of the thermal decomposition of carbamoyl-substituted azo compounds has been limited to *N,N'*-diphenyldiazenedicarboxamide,[2] 2-cyano-2-propylazoformamide,[3] and, most recently, diazenedicarboxamide (**1a**) and *N,N'*-diethyldiazenedicarboxamide (**1b**).[4] In the latter study, Fantazier and Herweh convincingly demonstrated that the thermal decomposition of **1a** involves two competitive processes: cyclization of *cis*-**1a** to the unstable triazoline (**2a**) and thermal decomposition of **1a** to produce nitrogen and formamoyl radicals. These authors reported that the thermolysis of **1b** in dimethyl sulfoxide (DMSO) affords 4-ethylurazole (**3a**) and a product that was tentatively identified as tris(*N*-ethylcarbamoyl)hydrazine (**4a**).



RNHCON=NCONHR

1a, R = H
b, R = Et
c, R = Me

2a, R = H
b, R = Me
c, R = Ph



3a, R_1 = H; R_2 = Et
b, R_1 = H; R_2 = Me
c, R_1 = CONHMe; R_2 = Me

This note reports the results of our study of the thermolysis of *N,N'*-dimethyldiazenedicarboxamide (**1c**). Neat thermolysis of **1c** at 176° resulted in rapid, exothermic decomposition yielding 1,3-dimethylurea (47%), 4-methylurazole (**3b**, 37%), and small amounts of 1-methylcarbamoyl-4-methylurazole (**3c**). The volatile components of the reaction were identified as nitrogen (28%), carbon monoxide (8%), and an undetermined quantity of methyl isocyanate. Thermolysis of **1c** in DMSO (120°) gave 36% of 4-methylurazole and unidentified dark oils.

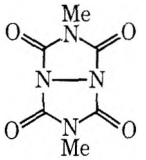
When the thermolysis of **1c** was conducted in refluxing o-dichlorobenzene, a very small quantity of 1,3-dimethylurea was formed and no 4-methylurazole could be isolated. Under these conditions, the major product is *N,N'*-dimethyl-1,2-hydrazinedicarboxamide (**5a**, 41%). Small quantities (6% each) of **3c** and 3,7-dimethyl-2,4,6,8-tetraoxo-1,3,5,7-tetraazabicyclo[3.3.0]octane (**6**) were isolated.

$(RNHCO)_2NNHCONHR$

4a, R = Et
b, R = Me

RNHCONHNHCONHR

5a, R = Me
b, R = Et



6

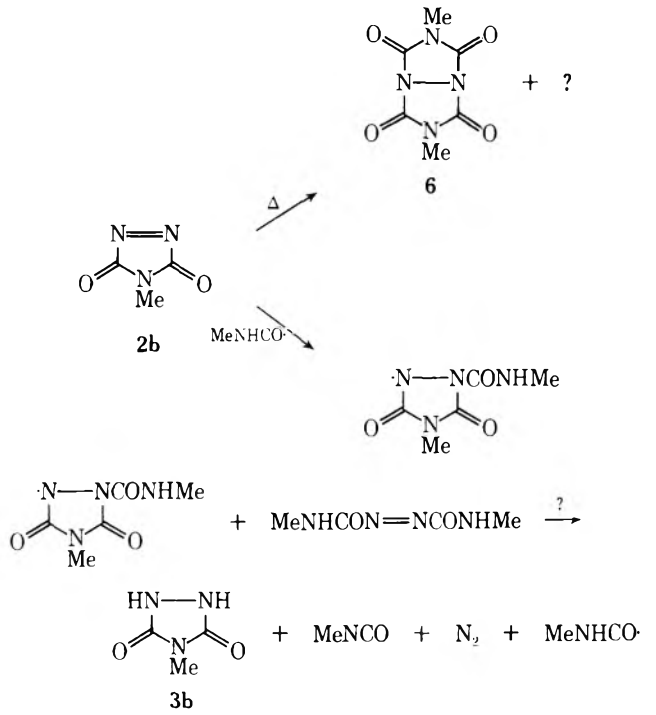
Under these conditions, 31% of water-insoluble gases (assumed to be nitrogen and carbon monoxide) were obtained.

Thermolysis of *N,N'*-diethyldiazenedicarboxamide (**1b**)

in refluxing *o*-dichlorobenzene gave *N,N'*-diethyl-1,2-hydrazinedicarboxamide (**5b**) in 53% yield.

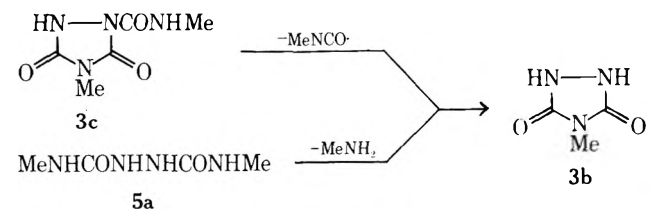
The products obtained from the thermal decomposition of **1c** may be accounted for by assuming that the azo compound initially decomposes by pathways analogous to those proposed for diazenedicarboxamide (**1a**),[4] i.e., trans → cis isomerization followed by cyclization to 4-methyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (**2b**) and, competitively, thermal decomposition of **1c** to produce nitrogen and methylcarbamoyl radicals. We have conducted control experiments that implicate the triazoline **2b** as an intermediate leading to the formation of both **3c** and **6.**

The reaction of equimolar quantities of **1c** and **2b**[5] in refluxing *o*-dichlorobenzene gave **3c** in 54% yield. This experiment supports the formation of **3c** via addition of methylcarbamoyl radicals to the N=N bond of **2b.** We have designated **1c** as a probable hydrogen donor in the addition reaction. The bicyclic product **6** is apparently formed by thermal decomposition of **2b,** since thermolysis of **2b** in refluxing *o*-dichlorobenzene afforded a tarry reaction mixture from which it was possible to isolate **6.** The latter reaction finds precedence in the previously reported conversion of **2c** to the diphenyl analog of **6.**[6]



The formation of *N,N'*-dimethyl-1,2-hydrazinedicarboxamide (**5a**) may be accounted for by addition of methylcarbamoyl radicals to **1c** to give thermally unstable tris(*N*-methylcarbamoyl)hydrazine (**4b**), which is converted to **5a** by elimination of methyl isocyanate. The latter pathway is analogous to that proposed to account for the formation of biurea from thermal decomposition of **1a.**[4]

When **1c** is thermally decomposed in the absence of solvent by heating at 173°, the temperature of the reaction mixture was observed to rise to 259°. Under these conditions, 4-methylurazole may be formed by either cyclization of *N,N'*-dimethylhydrazinedicarboxamide (**5a**)[7] or by elimination of methyl isocyanate from 1-methylcarbamoyl-4-methylurazole (**3c**), since both **5a** and **3c** are quantitatively converted to 4-methylurazole when heated at 245 and 230°, respectively.



However, control experiments indicate that neither **3c** nor **5b** are reasonable precursors of 4-methylurazole and 4-ethylurazole, respectively, when the thermolysis reactions are conducted in DMSO. DMSO solutions of **3c** and **5b** gave unchanged starting material when heated at 115–120° for 24 hr. Reduction of the triazoline **2b** by methylamine[8] may serve as the source of 4-methylurazole under these conditions.

The formation of 1,3-dimethylurea is most reasonably explained by reaction of methyl isocyanate with either methylamine or moisture.

The formation of 8% carbon monoxide from the neat thermolysis of **1c** suggests an additional pathway for the decomposition of the intermediate triazoline **2b,** i.e., thermal decomposition to methyl isocyanate, carbon monoxide, and nitrogen.[9]

$$\mathbf{2b} \longrightarrow CO + N_2 + MeNCO$$

Methyl isocyanate was detected by odor and mass spectrometry and was chemically identified among the volatile products by conversion to 1-methyl-3-phenylurea and trimethyl isocyanurate. Methylamine could not be chemically detected among the volatile thermolysis products. However, the complex mass spectrum of the thermolysis products (200°) displayed a low-intensity methylamine molecular ion (*m/e* 31) and an M − 1 peak of approximately twice the intensity of the molecular ion, which is characteristic of the reported methylamine spectrum.[10]

Experimental Section

Melting points are uncorrected and were determined with a Mel-Temp apparatus. NMR spectra were determined on a Perkin-Elmer R-20 spectrometer utilizing hexamethyldisiloxane as the internal standard. Thin layer chromatography (TLC) was carried out on microscope slides coated with silica gel. Iodine vapor was employed as a visualizing agent. Unless otherwise indicated, chromatograms were developed with ethyl acetate–methanol (5:1).

Neat Thermolysis of *N,N'*-Dimethyldiazenedicarboxamide (1c). The azo compound[11] (12.0 g) was placed in a 100-ml flask fitted with an air condenser and heated at 176° for 5 min. A vigorous, exothermic reaction was observed. In a separate experiment, the temperature of the reaction mixture was observed to rise to 259°. The pungent odor of methyl isocyanate was apparent in the gases evolved. The semisolid residue (9.1 g) was digested with 80 ml of boiling chloroform. Filtration of the cooled suspension afforded 3.6 g (37%) of crude 4-methylurazole (**3b**), mp 215–235°. Recrystallization from water gave white needles, mp 233–235°. Identity was established by elemental analysis and by comparison of the ir spectrum and R_f value (TLC) with data from an authentic sample, mp 235–237° (lit.[7] mp 233°).

Evaporation of the chloroform solution afforded a hygroscopic yellow oil. NMR and TLC revealed a complex mixture with 1,3-dimethylurea as the major component. The 1,3-dimethylurea component of the mixture could be visualized on the TLC plate only after prolonged exposure to iodine vapor.

The oil obtained above was partitioned between 30 ml of chloroform and 30 ml of water. Evaporation of the aqueous solution in vacuo gave an oil which on trituration with 10 ml of ethanol gave 0.29 g of a white solid, mp 150–162° (two components by TLC). Similar treatment of the chloroform residue gave 0.15 g of white solid, mp 195–205°, which was not further investigated. Recrystallization of the material obtained from the aqueous residue from ethanol afforded 1-methylcarbamoyl-4-methylurazole (**3c**) as white crystals: mp 203–206°; ir (KBr) 1700 (s), 1780 cm^{-1} (m); mass spectrum *m/e* 172 (molecular ion); NMR (DMSO-d_6) δ 2.68 (d, ca. 3, J = 5 Hz, slowly converted to a singlet on addition of D_2O), 2.80 (s, ca. 3), 7.2–7.8 (broad NH, slow exchange, ca. 2). A low-intensity singlet was observed at δ 2.91 which was also present after D_2O exchange was complete. It is felt that this signal may be due to an additional CH_3NHCO signal caused by restricted rota-

tion about the C–N bond. The other component of the expected doublet could be obscured by the δ 2.80 singlet. Identical results were observed with highly purified **3c** obtained from the reaction of **1c** with **2b**.

Anal. Calcd for $C_5H_8N_4O_3$: C, 34.9; H, 4.7; N, 32.6. Found: C, 35.1; H, 4.8; N, 32.7.

In a separate experiment, 10 g of the azo compound afforded 6.1 g of chloroform-soluble oil and 2.2 g of crude 4-methylurazole, mp 210–220°. A 0.50-g portion of the oil was distilled at 140° (0.1 mm) in a Kügelrohr distillation apparatus to give 0.23 g of colorless distillate which partially crystallized on standing. NMR and TLC established the material to be 1,3-dimethylurea: NMR δ 2.50 (d, J = 4 Hz), 5.8 (broad, NH). Several minor impurity peaks (<10%) were noted between δ 2.9 and 3.4. The extrapolated yield of distilled 1,3-dimethylurea from this experiment is 47%.

Decomposition of 0.25 g (1.7 mmol) of the azo compound at 180° in a flask connected to a gas buret gave 0.61 mmol (36%) of a mixture of CO and N_2. The mixture was determined to consist of 80% N_2 and 20% CO by comparison of peak heights in the high-resolution mass spectrum.

The presence of methyl isocyanate was detected in the gaseous products by carrying out the thermolysis of 1.0 g of **1c** in small portions and leading the effluent gases into a solution of 1.5 g of aniline in benzene. The benzene was evaporated and the residue was treated with 10 ml of 6 N HCl. The acid solution was extracted with chloroform. Evaporation of the chloroform gave a gummy residue that separated into two components with TLC. These components had the same R_f values as 1-methyl-3-phenylurea and trimethyl isocyanurate.

The complex mass spectrum of the thermolysis products (70 eV, 200°) included the following significant peaks: m/e (rel intensity, assignment) 198 (5, $7^{\cdot+}$), 115 (14, $4^{\cdot+}$), 88 (5, $CH_3NHCONH\text{-}CH_3^{\cdot+}$), 57 (50, $CH_3NCO^{\cdot+}$), 31 (5, $CH_3NH_2^{\cdot+}$), 30 (10), 28 (100).

Thermolysis of *N,N'*-Dimethyldiazenedicarboxamide (1c) in *o*-Dichlorobenzene. The azo compound (15 g) was suspended in 300 ml of *o*-dichlorobenzene and the suspension was stirred and heated under reflux for 1.5 hr. Filtration of the hot suspension afforded 6.1 g (41%) of crude *N,N'*-dimethyl-1,2-hydrazinedicarboxamide (**5a**), mp 227–232°. Identity was established by comparison of the ir spectrum and R_f values (TLC) with data from an authentic sample, mp 256° (lit.[7] mp 260°).

The cooled dichlorobenzene filtrate afforded a solid that was suspended in 30 ml of boiling ethanol. Filtration of the hot suspension gave 0.63 g (6%) of 3,7-dimethyl-2,4,6,8-tetraoxo-1,3,5,7-tetraazabicyclo[3.3.0]octane (**6**), mp 300–303°. Recrystallization from aqueous *N,N*-dimethylformamide gave white crystals: mp 303–304°; ir (KBr) 1760 cm^{-1}; mass spectrum m/e 198 (molecular ion); NMR (DMSO-d_6) δ 2.88 (s).

Anal. Calcd for $C_6H_6N_4O_4$: C, 36.4; H, 3.1; N, 28.3. Found: C, 36.5; H, 3.0; N, 28.5.

The cooled ethanol filtrate deposited 0.51 g (6%) of crude 1-methylcarbamoyl-4-methylurazole (**3c**), mp 176–182°. After recrystallization from ethanol, white crystals, mp 196–198°, were obtained. Identity was established by comparison of the ir spectrum with that of an authentic sample.

In a separate experiment, 3.0 g of the azo compound was decomposed as described above, giving 1.43 g of solid material which was insoluble in *o*-dichlorobenzene. The filtrate was evaporated in vacuo to give 0.42 g of an oil which partially crystallized on standing. The NMR spectrum of this material revealed it to be a complex mixture with 1,3-dimethylurea as the major component.

Decomposition of 0.50 g (35 mmol) as described above resulted in the evolution of 11 mmol (31%) of water-insoluble gases.

Preparation of 1-Methylcarbamoyl-4-methylurazole (3c). A solution containing 2.15 g (0.019 mol) of **2b**[5] and 2.74 g (0.019 mol) of **1c** in 100 ml of *o*-dichlorobenzene was heated and stirred under reflux for 2 hr. After decantation of the hot solution from a small amount of tarry material the cooled solution deposited 1.78 g (54%) of crude product (mp 164–185°) which on recrystallization from ethanol afforded 0.82 g of white crystals, mp 200–203°. An additional recrystallization raised the melting point to 204–206°. The NMR spectrum of the product was identical with that of the material isolated from the thermolysis of **1c**.

When heated at 230° for 12 hr, **3c** evolved methyl isocyanate and was quantitatively converted to 4-methylurazole, mp 225–228°.

Thermal Decomposition of 4-Methyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (2b). The triazoline[5] (0.5 g) was suspended in 5 ml of *o*-dichlorobenzene and heated under reflux with stirring for 2 hr. The solution was decanted from tarry material and allowed to evaporate. A yellow powder (0.2 g), mp 240–260°, was obtained which was identified as **6** from its NMR and ir spectra (no impurity peaks were noted in the NMR spectrum).

Thermolysis of *N,N'*-Dimethyldiazenedicarboxamide (1c) in Dimethyl Sulfoxide. A solution of 2.0 g of **1c** in 30 ml of dimethyl sulfoxide was heated at 120° for 22 hr. The solvent was removed in vacuo and the dark residue was treated with 10 ml of chloroform. Filtration yielded 0.55 g (36%) of crude 4-methylurazole (identified by ir and TLC), mp 195–203°. The filtrate deposited 60 mg of unidentified material, mp 225–228°. Evaporation of the chloroform gave a dark oil.

Thermolysis of *N,N'*-Diethyldiazenedicarboxamide (1b) in *o*-Dichlorobenzene. The azo compound[12] (1.5 g) was suspended in 30 ml of *o*-dichlorobenzene and heated under reflux with stirring for 1 hr. Stirring was continued at room temperature overnight. Filtration afforded 0.8 g of crude *N,N'*-diethylhydrazinedicarboxamide (**5b**), mp 230–235°. Identity was established by comparison of the ir spectrum with that obtained from an authentic sample,[13] mp 247–249°. Evaporation of the filtrate gave an uncharacterized oil.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Foundation of State University of New York for support of this project. We are indebted to Professors Martin S. Gibson and Albert Padwa for providing the mass spectra. We also wish to acknowledge the cordial cooperation of Drs. J. E. Herweh and R. M. Fantazier in providing preprints of their diazenedicarboxamide results and valuable discussions.

Registry No.—**1b**, 18880-19-8; **1c**, 18880-14-3; **2b**, 13274-43-6; **3b**, 16050-65-0; **3c**, 55029-97-5; **5a**, 2937-76-0; **5b**, 2937-75-9; **6**, 55029-98-6; 1,3-dimethylurea, 96-31-1; 1-methyl-3-phenylurea, 1007-36-9; trimethyl isocyanurate, 827-16-7.

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(9) Triazoline **2a** is extremely labile and decomposes to nitrogen, carbon monoxide, and isocyanic acid.[4] Thermal decomposition of **2c** to phenyl isocyanate, nitrogen, and carbon monoxide has been proposed[2b] to account for the products resulting from the thermolysis of *N,N'*-diphenyldiazenedicarboxamide.
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Nucleosides. XVII. Benzylation–Debenzylation Studies on Nucleosides

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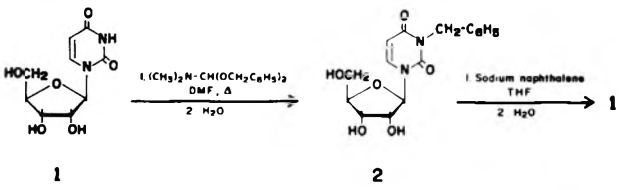
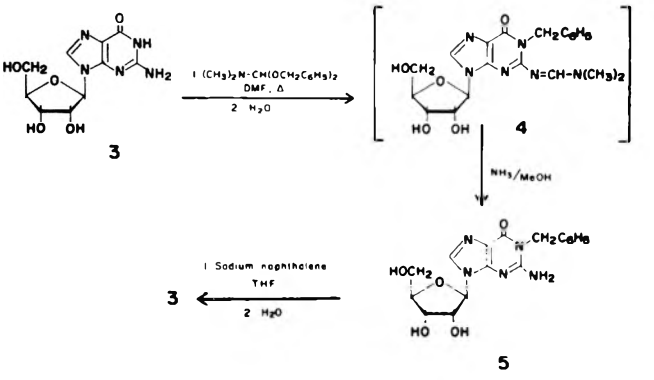
The present study was prompted by an internal need to develop a facile blocking–deblocking sequence of the –CONH– moiety in uridine (**1**) and guanosine (**3**) so that the corresponding (blocked) intermediates would be amenable to purification via anion exchange chromatography.

Scheme I



Scheme II



To this end, benzylation–debenzylation procedures were reexamined.

The benzylation of **1** with benzyl bromide and sodium hydride in either DMSO or DMF leads in low yield to a mixture of N^3-benzyluridine (**2**) and N^3-2′-*O*-dibenzyluridine,[1] although the latter can be hydrogenolyzed to **2**. By contrast, **2** itself is resistant to hydrogenolysis in the presence of either Pd/C or $Pd/BaSO_4$.[1]

In the purine series, the monobenzylation of inosine can be accomplished with benzyl chloride in DMF containing sodium bicarbonate to give N^1-benzylinosine in 50% yield.[2] Only partial catalytic hydrogenolysis has been effected.[2]

The use of *N,N*-dimethylformamide acetals as alkylating agents of the acidic amide group of heterocyclic bases[3-6] and as esterifying agents for carboxylic acids[7,8] has been well documented. In cases of the neopentyl acetal, which is too hindered sterically to serve as an alkylating agent, intramolecular cyclization[9] and decarboxylative elimination of uronic acids[8,10] are observed.

It was found that uridine (**1**) is quantitatively converted into **2** by heating with *N,N*-dimethylformamide dibenzyl acetal in DMF for 3 hr at 80°, as indicated by TLC and paper chromatography; crystallization from THF gave an 85% yield of **2** (Scheme I).

Guanosine (**3**), treated under nearly identical conditions, gave the *N*-dimethylaminomethylene derivative **4** [uv λ_{max} (water) 315 nm] which was readily converted into N^1-benzylguanosine (**5**) by action of methanolic ammonia. The deblocked derivative **5** was chromatographically homogeneous, and crystallization from water gave N^1-benzylguanosine (**5**) in 76% yield (Scheme II). This product was assigned structure **5** on the basis of a comparison of its uv data at several pH values with the uv data of other alkyl (N^1-, N^7-, and O^6-) guanosine derivatives[11] together with the known alkylating properties of *N,N*-dimethylformamide acetals.

It is of interest to note that while uridine and inosine are readily N-methylated with *N,N*-dimethylformamide dimethyl acetal in DMF, guanosine (**3**) is not.[12] The fact that guanosine, by contrast, is readily benzylated can be explained by the increased reactivity of the dibenzyl acetal relative to that of the dimethyl derivative.

Sodium naphthalene has been used for the reductive cleavage of toluenesulfonates to regenerate the corresponding alcohols,[13] and more recently for the reduction of syn and anti oxime benzoates while maintaining the stereochemistry of the oxime.[14] We have found that sodium naphthalene in THF readily reduces both N^3-benzyluridine and N^1-benzylguanosine in good yield to give the parent compounds **1** and **3**. Debenzylation of **2** was accomplished by treatment with an excess of sodium naphthalene in THF for 3 hr to give **1** in 84% yield after crystallization from water–methanol (Scheme II), and N^1-benzylguanosine (**5**) was similarly converted to guanosine in 76% yield (Scheme II).

N^3-Benzyluridine (**2**) and N^1-benzylguanosine (**5**) could readily be eluted from a Dekker column (Dowex-1, OH^-) by 50% methanol–water and 70% methanol–water, respectively, contrary to the behavior of uridine and guanosine,[15] indicating the absence of acidic protons (–CONH–) on the base and thus supporting the structural assignments of **2** and **5**. Uridine and guanosine derivatives that are modified in the sugar moiety should readily be separable via this high-yielding benzylation–debenzylation procedure.

Experimental Section

General Methods. Evaporations were carried out in a Buchi rotary evaporator in vacuo. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich. Thin layer chromatography (TLC) in chloroform–methanol (9:1) was performed on 6 × 2 cm, precoated, silica gel F-254 aluminum foils (Merck, Darmstadt, Germany). Paper chromatograms were run by the descending method in isopropyl alcohol–ammonium hydroxide–water (7:1:2). Paper electrophoresis was conducted on a Savant electrophoresis flat plate using 0.02 *M* disodium hydrogen phosphate (pH 7.5) as a buffer on Whatman No. 1 paper at 40 V/cm for 1 hr. Uv-absorbing compounds were detected using a Mineralight lamp. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Uv spectra were measured on a Cary Model 11 spectrophotometer. *N,N*-Dimethylformamide was dried with Linde molecular sieves, 4A. *N,N*-Dimethylformamide dibenzyl acetal was a product of Fluka, Switzerland.

Sodium Naphthalene. Sodium chips (0.9 g, 40 mmol) and naphthalene (5.24 g, 41 mmol) were placed in a flask under a nitrogen atmosphere, and dry THF (100 ml) was added with a syringe. The mixture, which began to turn green immediately indicating the presence of the radical anion, was magnetically stirred (glass-covered stir bar) for 12 hr to ensure complete dissolution of the sodium. The solution was stored under a nitrogen atmosphere and was assumed to have a concentration of 0.35 *M*. Aliquots were removed under nitrogen by syringe and added to the reaction mixtures under nitrogen.

N^3-Benzyluridine (2). Uridine (**1**, 1.0 g, 4.1 mmol) was coevaporated with DMF (2 × 10 ml) to remove traces of water, and DMF (30 ml) and *N,N*-dimethylformamide dibenzyl acetal (5.2 ml, 20 mmol) were added. The reaction mixture was heated at 80° for 3 hr and evaporated, and the resulting syrup was kept in water (20 ml) for 1 hr at room temperature to destroy any 2′,3′-orthoamide formed. The aqueous solution was evaporated and the semisolid was crystallized from THF: yield 1.2 g (85%); mp 172–173° (lit.[1] mp 175.5–176.5); $[\alpha]^{25}D$ +20° (c 0.5, water); λ_{max} (pH 1) 263 nm (ε 8300), λ_{min} 235 nm (ε 2700); λ_{max} (pH 11) 263 nm (ε 7300), λ_{min} 234 nm (ε 2400); NMR (DMSO-d_6 + D_2O) δ 3.47 (m), 3.83 (m, 2, H-3′,4′), 4.98 (s, 2, $CH_2C_6H_5$), 5.72 (m, 2, H-1′ + H-5), 7.14 (broad s, 5, $CH_2C_6H_5$), 7.78 (d, 1, H-6, $J_{5,6}$ = 8 Hz). The compound was homogeneous by TLC, paper chromatography, and paper electrophoresis.

N^1-Benzylguanosine (5). Guanosine (**3**, 1.0 g, 3.5 mmol) was evaporated with DMF (2 × 10 ml) to remove traces of water, and DMF (25 ml) and *N,N*-dimethylformamide dibenzyl acetal (4.7 ml, 18 mmol) were added. The reaction mixture was heated for 5 hr at 80° and then evaporated to a pale yellow syrup. This syrup was taken up in water (50 ml) and kept for 1 hr at room temperature to destroy any 2′,3′-orthoamide formed; the aqueous solution was evaporated to give a yellow syrup whose uv spectrum showed a strong absorption at 315 nm, indicating that the *N*-dimethylaminomethylene derivative **4** had been formed. The syrup was kept in MeOH–NH_3 (saturated at 0°) for 24 hr at ambient temperature, after which time the peak at 315 nm disappeared completely. The

solution was evaporated to dryness and crystallized from water to give 0.99 g (76%) of **5**: mp 149–150°; $[\alpha]^{25}D$ −36° (c 0.5, water); λ_{max} (pH 1) 258 nm (ε 12,000); λ_{min} 231 nm (ε 3700), 280 s (7100); λ_{max} (pH 11) 256 nm (ε 14,000), λ_{min} 229 nm (ε 4200), 280 s (7900); NMR (DMSO-d_6 + D_2O) δ 3.5–4.4 (broad m), 5.18 (s, 2, $CH_2C_6H_5$), 5.68 (d, 1, H-1′, $J_{1',2'}$ = 6.0 Hz), 7.18 (broad s, 5, $CH_2C_6H_5$), 7.89 (s, 1, H-8). The compound was homogeneous by TLC, paper chromatography, and paper electrophoresis.

Anal. Calcd for $C_{17}H_{19}N_5O_5$: C, 54.68; H, 5.13; N, 18.76. Found: C, 54.37; H, 5.34; N, 18.34.

Debenzylation of N^3-Benzyluridine (2). Sodium naphthalene in dioxane (7.7 ml, 2.7 mmol) was added to **2** (100 mg, 0.30 mmol) in dioxane (20 ml) under nitrogen, and the mixture was stirred for 3 hr, after which time TLC indicated complete disappearance of **2**. The solution was left open to the atmosphere until the green color disappeared and then evaporated to dryness. The solid was washed with diethyl ether (3 × 10 ml) to remove the naphthalene and then taken up in water and treated with Amberlite IR 120 (H^+) to remove the sodium ions. The resin was removed by filtration and washed with water (10 ml), and the combined filtrates were evaporated to a solid that was recrystallized from water–methanol to give **2** (78 mg, 84%) which was identical in all respects with uridine.

Debenzylation of N^1-Benzylguanosine (5). The debenzylation of **5** (50 mg, 0.13 mmol) in THF (20 ml) with sodium naphthalene in THF (3.3 ml, 1.2 mmol) was carried out as described for N^3-benzyluridine (**2**) except that sodium ions were removed with Dowex 50 (pyridinium), yield 28 mg (76%).

Ion-Exchange Chromatography. Samples of N^3-benzyluridine (**2**, 5 mg) and N^1-benzylguanosine (**5**, 5 mg) were applied to analytical ion-exchange (Dowex 1, OH^-) columns as described by Dekker.[15] N^3-Benzyluridine was readily eluted in 50% methanol–water and N^1-benzylguanosine in 70% methanol–water.

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Registry No.—**1**, 58-96-8; **2**, 14985-34-3; **3**, 118-00-3; **4**, 55043-74-8; **5**, 55043-75-9; *N,N*-dimethylformamide dibenzyl acetal, 2016-04-8.

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Photochemical Reaction of α,β-Epoxy Esters in Protic Solvent

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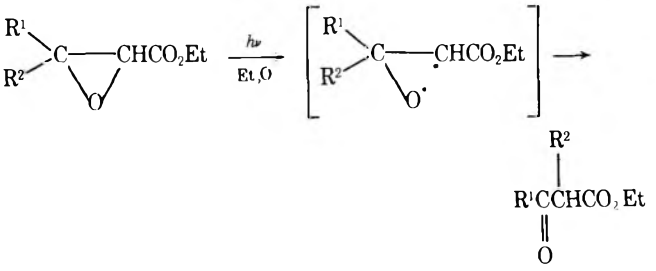
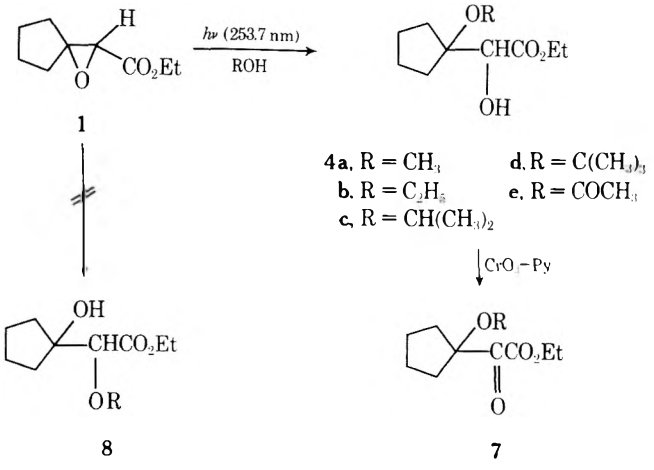
It was previously reported that α,β-epoxy esters with simple alkyl substituents were rearranged to the corresponding β-keto esters when they were irradiated in an aprotic solvent such as diethyl ether and carbon tetrachloride.[1] These transformations have been also reported in various types of α,β-epoxy ketones, and the mechanism involved may well be a homolytic fission of α carbon–oxygen bond followed by a transfer of β-alkyl substituent.[2] The present investigation was undertaken to determine whether homolytic fission of the epoxy ring would preferentially occur even when irradiated in a protic solvent.



Irradiation of ethyl 1-oxaspiro[2,4]heptane-2-carboxylate (**1**) in methanol with 253.7-nm light produced α-hydroxy ester **4a** in a 67% yield. The structure of **4a** was determined by NMR spectroscopy and an oxidation reaction. The NMR spectrum of **4a** in DMSO-d_6 exhibits a doublet at δ 5.47 (J = 5.8 Hz) attributable to the hydroxyl proton, which indicates the presence of a secondary hydroxyl group.[3] Oxidation with chromium trioxide–pyridine complex yielded α-keto ester **7a**. Acid-catalyzed thermal reaction of **1** in methanol produced **4a** and ethyl 2-hydroxy-2-(1-cyclopentenyl)acetate. From these results it is concluded that the alternative product (**8**) is not produced in this reaction. Dark reaction of **1** in methanol for 15 days was confirmed not to provide a detectable amount of **4a**. Irradiation of **1** with a high-pressure mercury vapor lamp produced only a small amount of **4a** because of the secondary photolytic decomposition of the product.



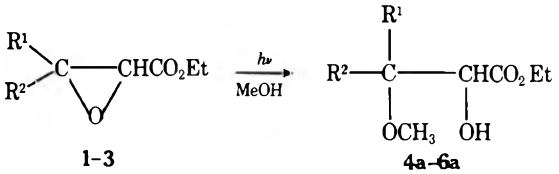
Irradiation of **1** in several protic solvents produced the corresponding α-hydroxy esters (**4a–e**). These results are summarized in Table I. Dark reaction in acetic acid under the same conditions produced a 75% yield of **4e** in a 31% conversion. The lower yield of **4e** in the photochemical reaction is due to the fast photolytic decomposition of the product. On the other hand, the lower yields of **4c** and **4d**[4] are probably due to the weak nucleophilicities of 2-propanol and 2-methyl-2-propanol, because the acid-catalyzed thermal reactions in both solvents produced low yields of **4c** and **4d**.

Ethyl 1-oxaspiro[2,5]octane-2-carboxylate (**2**) and ethyl 3-methyl-3-ethyl glycidate (**3**) also produced the corresponding α-hydroxy-β-methoxy esters **5a** (26%) and **6a** (34%) in 66 and 96% conversions, respectively, when irra-

Table I
Photochemical Reaction of Ethyl 1-Oxaspiro[2,4]heptane-2-carboxylate in Various Solvents[a]

Solvent	Product	Conversion, %	Yield, %[b]
Methanol	4a	72	67
Ethanol	4b	30	57
2-Propanol	4c	10	Trace
2-Methyl-2-propanol	4d	18	Trace
Acetic acid	4e	47	30

[a] Irradiated for 74 hr. [b] Based upon epoxy ester consumed.



1-3 4a-6a

1, 4a, $R^1 = R^2 = -(CH_2)_4-$
2, 5a, $R^1 = R^2 = -(CH_2)_5-$
3, 6a, $R^1 = C_2H_5$; $R^2 = CH_3$

diated in methanol with 253.7-nm light. The product 6a involved nearly equal amounts of diastereomers.

Although some reports concerning a photochemical ionic reaction of an oxirane ring are available,[5-7] the exact natures of these reactions are unknown. Photolysis of methanol in the presence of oxygen was reported to yield an acidic substrate, which initiated the ionic reaction.[7] However, irradiation of 1 in methanol under nitrogen, oxygen atmosphere, or vacuum (1×10^{-4} mm) produced almost the same yields of **4a** with similar conversions. Rather than the effect of oxygen, some acidic substrate produced photochemically probably plays an important role in these reactions. Irradiation of 1 in the presence of sodium carbonate in methanol was confirmed not to yield **4a.** Consequently, although it is unknown as to what the nature of the acidic substrate is, heterolytic cleavage of the β carbon–oxygen bond to give **4–6** with no detectable formation of the alternative product such as 8 indicates that these reactions probably proceed via a photochemical protonation and not via an excitation of ester carbonyl followed by homolytic fission of the α carbon–oxygen bond.

Although the photochemical transformation of α,β-epoxy ester to β-keto ester was quenched by a triplet quencher,[1] the photochemical ionic reaction of 1 to give 4 was not affected by an addition of piperylene, benzene, and naphthalene in concentrations ranging from 0.02 to 0.2 *M*.

Experimental Section

Gas–liquid chromatographic analyses were carried out with a Hitachi K-53 and preparative works were done with a Varian Autoprep 700. Infrared spectra were obtained with a Hitachi EPI-G22, and nuclear magnetic resonance spectra were measured with a Jeol 3H-60 using tetramethylsilane as an internal standard. Mass spectra were obtained with a Hitachi RM-50 GC. Quantitative GLC analyses were carried out by an internal standard method. All melting points and boiling points are uncorrected.

The starting α,β-epoxy esters 1, bp 106.0–106.5° (12 mm) [lit.[8b] bp 90–95° (3–4 mm)], 2, bp 124.5° (15 mm) [lit.[8a] bp 134–137° (21 mm)], and 3, bp 84–86° (12 mm) [lit.[8c] bp 91–95° (17 mm)], were prepared using the procedure of Johnson et al.[8a] and distilled before use. Methanol, ethanol, 2-propanol, and 2-methyl-2-propanol were dried over calcium oxide.

Photochemical Reactions. A mixture of α,β-epoxy ester (1–3) and protic solvent (0.08 *M*) in a quartz tube was cooled in water and externally irradiated with a 15-W low-pressure mercury vapor lamp. Nitrogen gas was allowed to pass through the mixture during the irradiation. The products were separated by distillation and preparative GLC, and identified from ir, NMR, and mass spectral data.

Ethyl 2-hydroxy-2-(1-methoxycyclopentyl)acetate (4a) had n^{26}D 1.4576; ir (CCl_4) 3510, 1725, 1100 cm^{-1}; NMR (CCl_4) δ 1.28 (t, 3), 1.68 (m), 3.15 (s, 3), 4.17 (q, 2), 2.76 (s, 1, OH), 3.95 (s, 1); NMR (DMSO-d_6) δ 1.18 (t, 3), 1.60 (m, 8), 3.10 (s, 3), 4.06 (q, 2), 5.47 (d, 1, OH, J = 5.8 Hz), 4.16 (d, 1, J = 5.8 Hz); mass spectrum *m/e* (rel intensity) 129 (21), 99 (100), 67 (72). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.33; H, 9.12.

Oxidation of **4a** with the mixture of chromium trioxide and pyridine[9] produced **ethyl (1-methoxycyclopentyl)glyoxalate (7a)**: bp 110–111° (11.5 mm); ir (CCl_4) 1745, 1725 cm^{-1}; NMR (CCl_4) δ 1.36 (t, 3), 1.75 (m, 4), 1.92 (m, 4), 3.18 (s, 3), 4.29 (q, 2); mass spectrum *m/e* 200 (M^+), 99, 67, 55, 45, 41. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.76; H, 7.94.

Ethyl 2-hydroxy-2-(1-ethoxycyclopentyl)acetate (4b) had n^{25}D 1.4530; ir (CCl_4) 3500, 1722, 1112 cm^{-1}; NMR (CCl_4) δ 1.07 (t, 3), 1.32 (t, 3), 1.71 (s, 8), 3.46 (q, 2), 4.23 (q, 2), 2.93 (s, 1, OH), 4.01 (s, 1); mass spectrum *m/e* (rel intensity) 143 (17), 113 (100), 85 (95), 67 (76). Anal. Calcd for $C_{11}H_{20}O_4$; C, 61.09; H, 9.32. Found: C, 61.07; H, 9.29.

Ethyl 2-hydroxy-2-(1-acetoxycyclopentyl)acetate (4e) had n^{20}D 1.4530; ir (CCl_4) 3580, 3500, 1720, 1745, 1230 cm^{-1}; NMR (CCl_4) δ 1.30 (t, 3), 2.12 (s, 3), 1.70 (s, 8), 4.21 (q, 2), 2.80 (s, 1, OH), 4.82 (s, 1); mass spectrum *m/e* (rel intensity) 188 (11), 170 (5), 104 (100), 97 (53), 85 (36), 76 (36). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.29; H, 7.90.

Ethyl 2-hydroxy-2-(1-methoxycyclohexyl)acetate (5a) had n^{20}D 1.4664; ir (CCl_4) 3520, 1725, 1087 cm^{-1}; NMR (CCl_4) δ 1.32 (t, 3), 3.20 (s, 3), 1.50 (s, 10), 4.23 (q, 2), 2.90 (s, 1, OH), 3.93 (s, 1); mass spectrum *m/e* (rel intensity) 113 (100), 81 (83). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.82; H, 9.24.

Ethyl 2-hydroxy-3-methoxy-3-methyl valerate (6a) had n^{20}D 1.4383; ir (CCl_4) 3515, 1720, 1095 cm^{-1}; NMR (CCl_4) δ 0.88 (t, 3), 1.30 (t, 3), 1.15 and 1.09 (s, 3, diastereomer), 3.17 (s, 3), 4.22 (q, 2), 1.60 (m, 2), 2.90 (s, 1, OH), 3.91 (s, 1); mass spectrum *m/e* (rel intensity) 161 (4), 87 (100), 55 (58). Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.60; H, 9.66.

Thermal Reaction of 1 in Methanol. A solution of 0.63 g of 1 in 40 ml of methanol was refluxed with 25 μl of concentrated HCl for 1 hr. The resulting mixture was treated in the usual way. GLC analysis of the ethereal solution (Carbowax 20M, 190°) indicated the presence of **1, 4a,** and ethyl 2-hydroxy-2-(1-cyclopentenyl)acetate in a ratio of 10:81:9. Preparative GLC gave ethyl 2-hydroxy-2-(1-cyclopentenyl)acetate: ir (CCl_4) 3515, 3045, 1733 cm^{-1}; NMR (CCl_4) δ 1.28 (t, 3), 1.93 (m, 2), 2.27 (m, 4), 4.22 (q, 2), 5.70 (s, 1), 3.15 (s, 1), 4.60 (s, 1); mass spectrum *m/e* (rel intensity) 170 (M^+, 65), 124 (55), 97 (100), 79 (66), 67 (69). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.20; H, 8.50.

Spectral data of **4a** isolated from a thermal reaction were completely identical with those of the photochemical one.

Registry No.—**1,** 6975-15-1; **2,** 6975-17-3; **3,** 3647-33-4; **4a,** 55043-44-2; **4b,** 55043-45-3; **4e,** 55043-46-4; **5a,** 55043-47-5; **6a** diastereomer a, 55043-18-0; **6b** diastereomer b, 55043-19-1; **7a,** 55043-48-6; ethyl 2-hydroxy-2-(1-cyclopentenyl)acetate, 33487-18-2.

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Nitroxide-Catalyzed Oxidation of Alcohols Using *m*-Chloroperbenzoic Acid. A New Method

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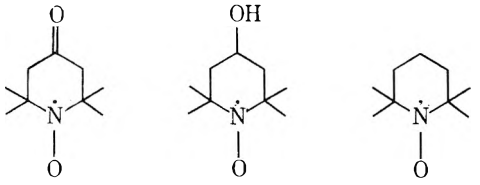
Organic peracids are versatile reagents capable of oxidizing a variety of functional groups under generally mild conditions.[1] Peracids react with olefins,[2] amines,[3] ketones,[4] sulfides,[5] and a number of other functional groups.[1,6] In addition, their solubility in organic solvents, ease of handling, and commercial availability make these reagents particularly attractive for the oxidation of organic compounds.

While an alcohol functionality can influence the stereochemistry of peracid epoxidations, alcohols themselves are generally inert to these reagents.[7] The observation that keto nitroxide **1** is produced in the peracid oxidation of amino alcohol **2**[8] suggests a nitroxide-induced oxidation of alcohols by peracids. Indeed, addition of *m*-chloroperbenzoic acid to a solution of phenyl-2-propanol and a catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl (**3**) in



1 **2** **3**

methylene chloride at room temperature results in nearly quantitative conversion of the alcohol to phenyl-2-propanone after 1 hr. The reaction requires 1 equiv of peracid, though, in practice, a slight excess is employed to offset the simultaneous nitroxide-catalyzed decomposition of the peracid (vide infra). The reaction is also catalyzed by mineral acids;[9] hence the overall oxidation is described by eq 1.

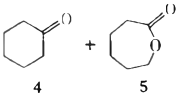
$$R_1R_2CHOH + m\text{-}ClPhCO_3H \xrightarrow{3,H^+} R_1R_2CO + m\text{-}ClPhCO_2H - H_2O \quad (1)$$

The nitroxide catalyst can be conveniently generated in situ by reaction of the corresponding amine, 2,2,6,6-tetramethylpiperidine (TMP), or its hydrochloride (TMP·HCl) with *m*-chloroperbenzoic acid.[3c] (Use of TMP·HCl also satisfies the requirement for acid catalysis.[11]) The reaction can be conducted in methylene chloride, chloroform, or ether. Results of oxidation of a number of representative alcohols by this procedure are presented in Table I. These results clearly demonstrate the efficiency of this method for the conversion of secondary alcohols to ketones. Primary alcohols generally yield carboxylic acids, although in some cases the reaction stops at the aldehyde stage (see Table I).[12]

It is noteworthy that except for the case of cyclohexanol, little or no Baeyer–Villiger reaction of the ketonic products is encountered under the reaction conditions. This is not surprising, since the Baeyer–Villiger reaction generally requires longer reaction times or higher temperatures and employs stronger peracids than are necessary for the alcohol oxidation.[4c] Cyclohexanol (a notable exception) is considerably more reactive than its cyclic congeners in the Baeyer–Villiger reaction.[4e,13] With reactive ketones, such as cyclohexanone, it is possible to suppress or enhance the Baeyer–Villiger reaction by proper choice of reaction conditions. In general, Baeyer–Villiger reaction of the ketonic products can be avoided by conducting the reaction under mild conditions (see Table II).

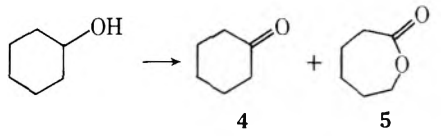
Although no detailed mechanistic studies of this reaction have been undertaken, a number of observations pertinent to a possible mechanism are noteworthy. First, stable radicals other than the piperidine nitroxides, such as galvinoxyl or the pyrrolidine nitroxides,[14] neither catalyze nor retard the oxidation. Inhibitors, such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) or ethyl crotonate, likewise have no effect on the reaction. Second, addition of nitroxide **3** to an acidified solution of *m*-chloroperbenzoic acid in methylene chloride produces an intense yellow color which persists for several hours and then slowly fades if no alcohol is present. In the absence of mineral acid, the yellow color appears gradually. (Alcohols are oxidized more slowly in the latter solutions.) Finally, nitroxide **3** catalyzes the decomposition of *m*-chloroperbenzoic acid in methylene chloride and this decomposition is accelerated by alcohols.[15] Figure 1 com-

Table I
Nitroxide-Catalyzed Oxidation of Alcohols with *m*-Chloroperbenzoic Acid[a]

Alcohol	Registry no.	Product(s)	Registry no.	Yield, %[b]
Cyclopentanol	96-41-3	Cyclopentanone	120-92-3	77
Cyclohexanol	108-93-0	 **4** **5**	108-94-1 (**4**) 502-44-3 (**5**)	See Table II
Cycloheptanol	502-41-0	Cycloheptanone	502-42-1	81
Phenyl-2-propanol	698-87-3	Phenyl-2-propanone	103-79-7	87
2-Octanol	123-96-6	2-Octanone	111-13-7	94
Borneol	507-70-0	Camphor	76-22-2	94
Norborneol	1632-68-4	Norcamphor	497-38-1	95
Cyclopropylmethylcarbinol	765-42-4	Cyclopropyl methyl ketone	765-43-5	81
Benzyl alcohol	100-51-6	Benzaldehyde	100-52-7	76
1-pentanol	71-41-0	Pentanoic acid	109-52-4	90[c]
Isopentyl alcohol	123-51-3	3-Methylbutyric acid	503-74-2	85[c]
1-Heptanol	111-70-6	Heptanal	111-71-7	40[c,d]
3,5-Dimethoxybenzyl alcohol	705-76-0	3,5-Dimethoxybenzoic acid	65-85-0	60[c]

[a] Representative procedure is given in the Experimental Section. [b] Yields are those of pure, distilled products unless otherwise indicated. [c] Yield determined by gas chromatography. [d] Heptanoic acid was also produced in ca. 40% yield.

Table II
Nitroxide-Catalyzed Oxidation of Cyclohexanol[a]



4 5

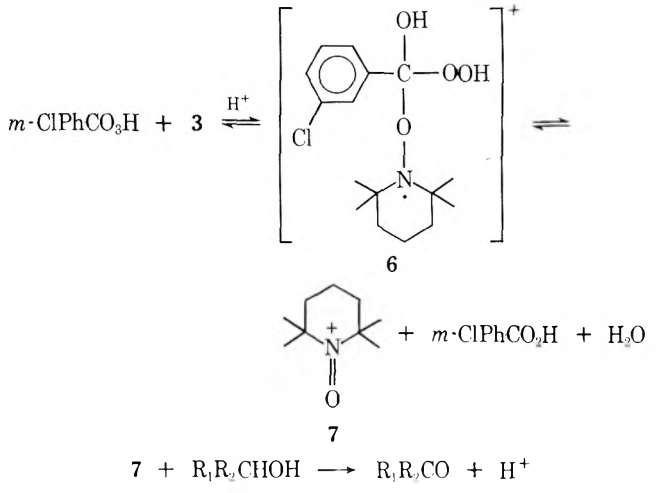
Run	Equiv of peracid (per mol cyclohexanol)	Concn of peracid, *M*	% 4[a]	% 5[a]
1	1.0	0.25	97	3
2	1.5	0.25	94	6
3[b]	2.0	0.13	91	9
4	2.0	0.13	81	19
5	2.0	0.25	76	24
6	3.0	0.25	44	56
7[c]	2.0	0.25	29	71

[a] Product ratios were determined by gas chromatography. Reactions were allowed to proceed for 2 hr prior to work-up. Except for run 1, less than 10% of the starting material remained at the time of analysis. The concentration of nitroxide was ca. 0.002 *M*. [b] Peracid was added over a 1-hr period. [c] Reaction was buffered with solid sodium bicarbonate.

pares the rate of decomposition of *m*-chloroperbenzoic acid by **3** in the presence and absence of mineral acid and in the presence of alcohol.

These observations suggest a reversible, acid-catalyzed complex formation between peracid and nitroxide. This complex could decompose reversibly to starting materials or irreversibly by reaction with solvent or alcohol (Scheme I). A likely structure for this complex is radical cation **6**,

Scheme I



6

7

$$7 + R_1R_2CHOH \longrightarrow R_1R_2CO + H^+$$

the formal result of a carbonyl addition to the protonated peracid by the nitroxide. Complex **6** could dissociate reversibly via electron transfer to produce cation **7**, *m*-chlorobenzoic acid, and water. Cationic species like **7** have been postulated as intermediates in a number of reactions of nitroxides.[16] Indeed, stable oxoammonium salts related to **7** have been isolated and on treatment with alcohols yielded the corresponding ketones.[17] In the absence of further information, the exact nature of the reactive intermediate in this reaction can only be speculative; however, it is clear, since we are dealing with a free-radical species, that a one-electron transfer must be involved at some stage of the reaction.

While this method is limited to those alcohols which do not bear functional groups reactive toward peracids, the

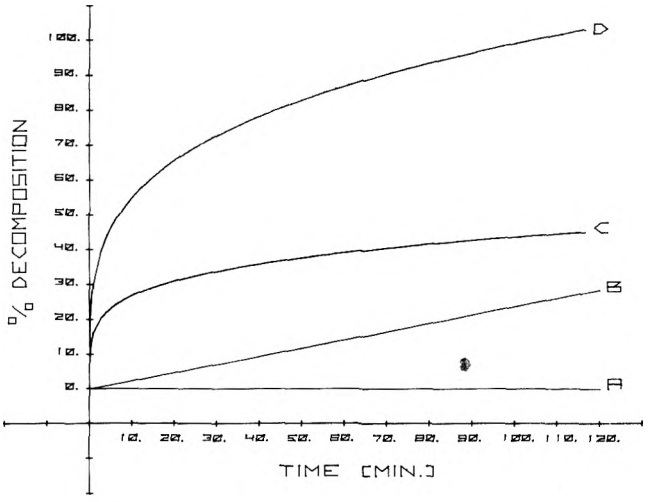
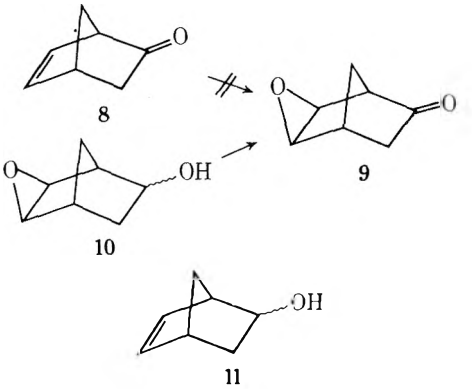


Figure 1. Nitroxide-catalyzed decomposition of *m*-chloroperbenzoic acid in methylene chloride. Plot of percent decomposition of 0.2 *M* *m*-chloroperbenzoic acid vs. time in minutes for peracid solutions containing: A, no additives; B, TMP (0.002 *M*); C, TMP·HCl (0.002 *M*); D, TMP·HCl (0.002 *M*) plus cycloheptanol (0.2 *M*). See Experimental Section for details.

possibility of effecting multistage oxidations by this method is attractive. For example, the epoxidation–oxidation of an olefinic alcohol can avoid the complex product mixtures resulting from epoxidations of olefinic ketones.[18] Attempted preparation of epoxy ketone **9**, by epoxidation of keto olefin **8**, yielded only a rearranged Baeyer–Villiger product.[19] The desired compound was finally prepared in a three-step sequence, the last step (chromium trioxide–pyridine oxidation of epoxy alcohol **10**) of which occurred in only 31% yield.[20] We have achieved a one-pot preparation of **9** in 86% yield by epoxidation of olefinic alcohol **11** with 1



8 9 10 11

equiv of *m*-chloroperbenzoic acid in methylene chloride followed by addition of a second 1 equiv of peracid and a catalytic amount of TMP·HCl to effect oxidation of the alcohol. Clearly, this one-pot sequence is the method of choice for this type of transformation. Combined with the versatile oxidizing properties of peracids, this unique method for alcohol oxidation can provide many novel approaches to multiple oxidations of polyfunctional molecules.

Experimental Section[21]

The alcohols used in this study were obtained from commercial sources. 2,2,6,6-Tetramethylpiperidine hydrochloride was prepared by passing dry hydrogen chloride into an ethereal solution of TMP (Aldrich). The resulting hygroscopic solid was stored in a desiccator or in methylene chloride solutions (approximately 0.2 *M*) containing 1–2% ethanol.

Representative Procedure for Oxidation of Alcohols. To a stirred solution of 2.28 g (20 mmol) of cycloheptanol and 1 ml (0.2 mmol) of a 0.2 *M* solution of TMP·HCl in methylene chloride was added, over 15 min, a solution of 6.0 g (30 mmol) of 85% *m*-chloroperbenzoic acid (Aldrich) in 50 ml of methylene chloride. The re-

sulting mixture was stirred at ambient temperature for 1.5 hr and then transferred to a separatory funnel. The usual work-up[21] afforded a pale yellow residue which was distilled at reduced pressure to yield 1.85 g (81%) of cycloheptanone.

***exo*-5,6-Epoxy-2-norbornanone (9).** To a stirred, ice-chilled solution of 2.20 g (20 mmol) of 5-norbornen-2-ol (11) in 5 ml of methylene chloride was added a solution of 4.3 g (21 mmol) of 85% *m*-chloroperbenzoic acid in 50 ml of methylene chloride. Analysis of the reaction mixture after 2 hr revealed that all of the starting material had reacted. To the resultant mixture was added 1 ml (0.2 mmol) of a 0.2 *M* solution of TMP·HCl in methylene chloride followed by an additional 5.1 g (25 mmol) of *m*-chloroperbenzoic acid in 50 ml of methylene chloride. After 1.5 hr, the mixture was transferred to a separatory funnel and worked up as usual. The residue, a mixture of epoxy ketone **9** and nitroxide **3**, was sublimed to afford 2.1 g (86%) of pure **9** whose melting point and infrared spectrum correlate with those reported:[20] mass spectrum *m/e* (rel intensity) 124 (M^+, 24.4), 106 (2.6), 96 (24.0), 95 (43.0), 82 (77.6), 81 (100), 68 (52.8), 67 (57.1), 41 (38.9), 39 (56.4).

Nitroxide-Catalyzed Decomposition of *m*-Chloroperbenzoic Acid. A stock solution of 0.2 *M* *m*-chloroperbenzoic acid in methylene chloride was divided into four equal portions designated A–D. Solution A was a control. To solutions B–D were added respectively TMP (final concentration 0.002 *M*), TMP·HCl (final concentration 0.002 *M*), and TMP·HCl (0.002 *M*) plus cycloheptanol (final concentration 0.2 *M*). Aliquots were withdrawn at timed intervals and the concentration of peracid was determined iodometrically using the standard procedure.[22] The decomposition was followed for a 2-hr period (approximate time required for completion of the alcohol oxidation). The results are plotted as percent decomposition of peracid vs. time in Figure 1.

Registry No.—**3**, 2564-83-2; **9**, 55044-07-0; **11**, 13080-90-5; TMP·HCl, 935-22-8.

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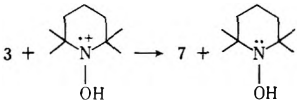

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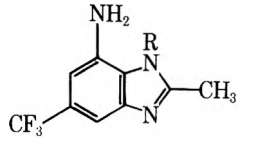
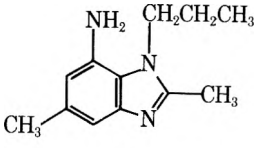
Benzimidazole Chemistry. II. Alkyl Migration of *N*-Alkyl-4-trifluoromethyl-2,6-dinitroanilines on Reduction with Tin

Summary: In reductions of certain *N*-alkyl-4-trifluoromethyl-2,6-dinitroanilines, migration of the alkyl group occurs simultaneously with formation of the triamines, probably by formation of a radical from the *N*-alkyl group followed by rearrangement.

Sir: A study of the syntheses of benzimidazoles[1] was initiated to provide compounds for comparison with the products of bacterial and atmospheric changes of the 2,6-dinitroaniline, agricultural chemicals.[2] The preparation of 1-propyl-7-amino-2-methyl-5-trifluoromethylbenzimidazole (**1c**) was required. The synthetic route that was chosen followed the method of preparation of the 5-methyl analog (**2**);[1] however, the intermediate triamine formed by the reduction of the 2,6-dinitroaniline (**3c**) with tin and hydrochloric acid was obviously not the expected symmetrical compound (**5c**), but the unsymmetrical triamine (**4c**). The unsymmetrical structure was evident from the nonidentity of the aromatic hydrogens in the NMR spectrum.



1a, R = *s*-C_4H_9
b, R = *n*-C_4H_9
c, R = *n*-C_3H_7



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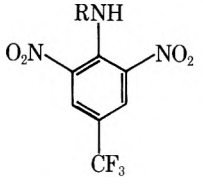
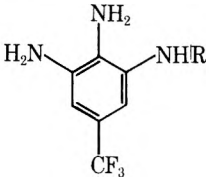
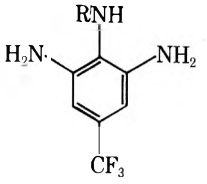


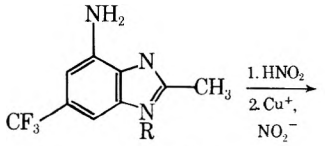
3a, R = *s*-C_4H_9
b, R = *n*-C_4H_9
c, R = *n*-C_3H_7
d, R = *t*-Bu
e, R = $PhCHCH_3$ (|)
f, R = C_6H_5
g, R = H

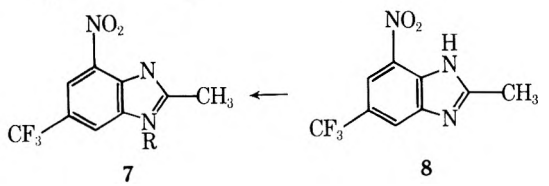


4a, R = *s*-C_4H_9
b, R = *n*-C_4H_9
c, R = *n*-C_3H_7



5a, R = *s*-C_4H_9
c, R = *n*-C_3H_7
g, R = H
f, R = C_6H_5





7 **8**

The structure of the triamine, **4c**, was confirmed by conversion via diazotization and the Sandmeyer reaction to the same alkyl nitrobenzimidazole (**7c**) formed by the alkylation of 2-methyl-7-nitro-5-trifluorobenzimidazole (**8**). The alkylation of such benzimidazoles as **8** has been shown to give the 1-alkyl-4-nitrobenzimidazole.[1] Thus **7** must have the structure 1-alkyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole. The symmetrical triamines (**5**) could be prepared by catalytic hydrogenation. Cyclization gave the 1-alkyl-7-amino-2-methyl-5-trifluoromethylbenzimidazoles (**1**) which were isomeric with the products of cyclization of the amines formed by the rearrangement.

Table I
Results of Tin and Acid Reduction of *N*-Alkyl-4-trifluoromethyl-2,6-dinitroanilines

	%			
3	5[a]	4[a]	5g[a]	Total yield
a	33	67		50
b	5	95		Quant
c		100		Quant
d			100	74
e			100	73
f	100			71

[a] The yields were determined by NMR analysis of the total product mixture.

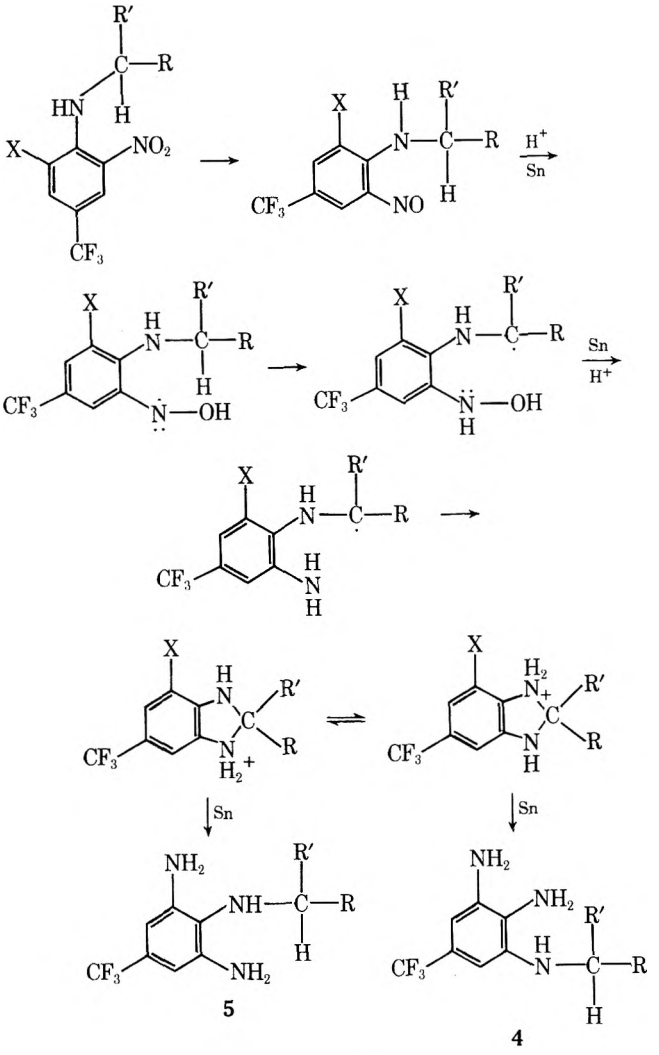
The same rearrangement was observed during the reduction of the dinitroanilines **3a** (R = *s*-butyl), **3b** (R = *n*-butyl), and **3c**, (R = *n*-propyl) to give the corresponding triamine **4**. With the *N*-alkyl groups which are easily eliminated such as *tert*-butyl (**3d**) or α-phenethyl (**3e**), reduction with tin gave the unsubstituted triamine, **5g** (R = H). When the substituent was phenyl no rearrangement or elimination was observed, and the product was 2,6-diamine-1-anilino-4-trifluoromethylbenzene (**5f**). See Table I for a summary of these data.

To determine whether the migration occurred by an internal nucleophile displacement or some intermediate, **3a** ($[\alpha]^{20}D$ +22.0°) was prepared with *S*-*sec*-butylamine. The reduction, however, gave N-*sec*-butyl-2,3-diamino-5-trifluoromethylaniline (**4a**) with no optical activity. For comparison the reduction of **3a** was accomplished with catalytic hydrogenation over platinum to give **5a** ($[\alpha]^{19}D$ −25.3°). These data suggested that the chiral carbon was converted to a carbonium ion[2d] or a radical[2a,c] during the reduction.

There are reported rearrangement of groups from one ortho nitrogen to another. In all previous cases, however, the group is unsaturated and an obvious intermediate heterocycle can be envisioned.[3] No previous migration of a saturated group, such as an alkyl group, between adjacent nitrogens has been reported, and for identification this reaction was called the UNH[4] rearrangement.

A consideration of the experimental data suggests that the reduction of the nitro function with tin produces a radical[5] which abstracts a hydrogen from the *N*-alkyl group and cyclization then occurs. Carbonium ions have also been proposed for these reductions[2d] and cannot be eliminated by this study. Radicals formed from the nitro group by photochemical reactions give benzimidazoles;[2] however, if the nitro group is reduced to the nitroso function prior to alkyl radical formation (Scheme I), the dihydro benzimidazole should be formed. Reduction of this intermediate occurs with C–N bond cleavage to form the symmetrical triamine or with formation of the unsymmetrically substituted triamine **4** giving the UNH[4] rearrangement (see Table I

Scheme I



for relative importance of these two pathways). Similar mechanisms have been proposed for the formation of benzimidazoles by the reductive photolysis of dinitroanilines; however, no rearrangement of the alkyl group has been reported. It is probable, however, that such rearrangement products may be formed but not previously detected.

Acknowledgment. The authors wish to express appreciation to CIBA-GEIGY Corporation for assistance during the study of this problem. Appreciation is also expressed to the University of Virginia, Department of Chemistry, and Dr. Bruce Martin of that Department for assistance with some of the NMR determinations.

References and Notes

(1) R. E. Lyle and J. L. LaMattina, *J. Org. Chem.*, **40**, 438 (1975).
(2) (a) E. Leitis and D. Crosby, *J. Agr. Food Chem.*, **22**, 842 (1974); (b) P. C. Kearney, J. Plimmer, and U. Klingebiel, the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug. 27–31, 1973, PEST-3; (c) C. P. Nilles and M. J. Zabik, *J. Agr. Food Chem.*, **22**, 684 (1974); (d) O-Meth-Cohn and H. Suschitzky, *Adv. Heterocycl. Chem.*, **14**, 211 (1972).
(3) For example see (a) A. J. Boulton and P. B. Ghosh, *Adv. Heterocycl. Chem.*, **10**, 1 (1969); (b) F. Galbraith and S. Smiles, *J. Chem. Soc. (London)*, 1234 (1935).
(4) Since the rearrangement led from a symmetrical to an unsymmetrical product, the reaction is called the "Unsymmetrical Nitrogen Hop" to summarize this process.
(5) H. O. House, "Modern Synthetic Reactions", Second ed, W. A. Benjamin, Inc., Menlo Park, Calif., 1972, pp 148, 211.

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9-Borabicyclo[3.3.1]nonane as A Highly Selective Reducing Agent for the Facile Conversion of α,β-Unsaturated Aldehydes and Ketones to the Corresponding Allylic Alcohols in the Presence of Other Functional Groups[1]

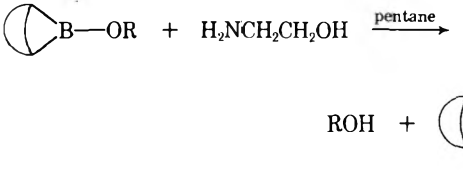
Summary: Reduction of α,β-unsaturated aldehydes and ketones with 9-borabicyclo[3.3.1]nonane proceeds selectively and cleanly to the corresponding allylic alcohols in excellent yield in the presence of many other functional groups.

Sir: 9-Borabicyclo[3.3.1]nonane (9-BBN) is an exceptionally stable bicyclic dialkylborane[2] and hydroborates olefins with very high regio- and stereoselectivity, far greater than those observed with borane and other dialkylboranes.[3] These remarkable characteristics and its commercial availability[4] prompted us to examine the behavior of 9-BBN as a reducing agent toward representative organic functional groups in tetrahydrofuran[5] (THF).

In the course of this investigation we found that 9-BBN reduces aldehydes and ketones rapidly and cleanly (to alcohols) even faster than it hydroborates olefins. For example, $k_{\text{cyclohexanone}}/k_{\text{cyclopentene}}$ was found to be 37 in competition experiments. Thus, the reaction of 2-cyclohexenone with 4 molar equiv of 9-BBN at 25° proceeds rapidly, using 1 equiv of 9-BBN in 10 min, while the uptake of the second equivalent requires 3 days. GLC analysis of the reaction mixture, following hydrolysis at the end of 10 min, indicated the presence of 2-cyclohexenol in 100% yield. Consequently, the reaction involves a rapid initial reduction of the carbonyl group followed by very sluggish subsequent hydroboration. The clean reduction of α,β-unsaturated aldehydes and ketones by hydride reagents has offered considerable difficulty.[6,7] Accordingly, it appeared desirable to examine this reaction in detail.

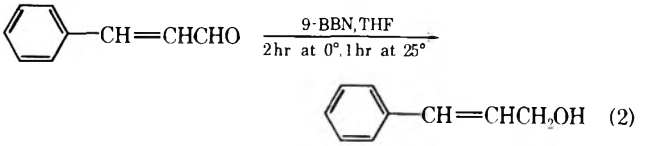
The reductions were carried out by the dropwise addition of an essentially stoichiometric quantity of 9-BBN solution in THF (3–5% excess) to the ketone in THF solution at 0°. The reaction mixtures were stirred for 2–4 hr at 0° and 1 hr at 25°.

Two procedures can be used to isolate the product. The reaction mixture can be treated with alkaline hydrogen peroxide to oxidize the 9-BBN moiety and the allylic alcohol separated by distillation from the 1,5-cyclooctanediol. More conveniently, the THF can be removed under vacuum from the reaction mixture and then pentane added. Addition of 1 mol of ethanolamine then precipitates 9-BBN as the adduct. Distillation of the pentane solution then provides the products[8] (eq 1). This serves as an excellent neutral work-up procedure for compounds containing acid- and base-sensitive groups.



(1)

Simple conjugated aldehydes, such as crotonaldehyde and cinnamaldehyde, are converted into crotyl alcohol and cinnamyl alcohol in yields of 98 and 99%, respectively (eq 2).



(2)

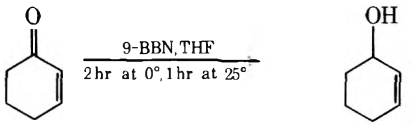
99%

Table I
Reduction of 2-Cyclopentenone with Various Reducing Agents

Reagent	Product composition,[a] % O	OH	O	OH
$LiAlH_4$, THF, 0°[b]	0.0	14.0	2.5	83.5
$LiAlH(O\text{-}tert\text{-}Bu)_3$, THF, 0°[b]	0.0	0.0	11.2	88.8
$NaBH_4$, EtOH, 78°[b]	0.0	0.0	0.0	100.0
AlH_3, THF, 0°[b]	0.0	90.0	6.1	3.9
$i\text{-}Bu_2AlH$, C_6H_6, 0°[c]	0.5	99.0	0.0	0.5
9-BBN, THF, 0°[d]	0.0	100.0	0.0	0.0

[a] Analysis by GLC. [b] Reference 7. [c] Reference 9a. [d] Present work.

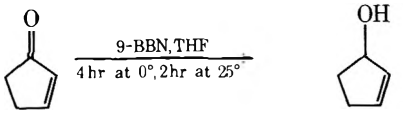
2-Cyclohexenone is converted to 2-cyclohexenol in quantitative yield (eq 3).



(3)

100% (84% isolated)

Even 2-cyclopentenone, known for it's susceptibility to undergo conjugate addition with hydride reducing agents,[7] is cleanly converted to the desired 2-cyclopentenol in essentially quantitative yield (eq 4).

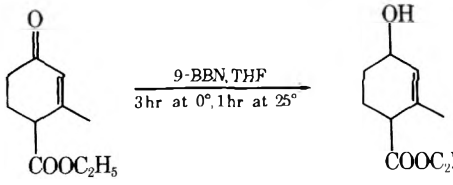


(4)

100% (85% isolated)

Results summarized in Table I clearly reveals the superiority of 9-BBN over previously available reagents, such as lithium aluminum hydride, lithium tri-*tert*-butoxyaluminohydride, sodium borohydride, and aluminum hydride.

Further, the results of the competition experiments involving 2-cyclohexenone and organic compounds containing representative functional groups toward 9-BBN and of other research underway[5] indicate that the present reaction can tolerate the presence of a large variety of functional groups, such as nitro, halogen, epoxide, carboxylic acid, ester, amide, nitrile, sulfide, disulfide, sulfoxide, sulfone, tosylate, azo, etc. This is a major advantage of 9-BBN over other reagents such as diisobutylaluminum hydride.[9] The remarkable utility of 9-BBN for such selective reductions involving polyfunctional substrates is confirmed by the selective conversion of 4-carbethoxy-3-methyl-2-cyclohexenone to 4-carbethoxy-3-methyl-2-cyclohexenol and *o*-nitrocinnamaldehyde to *o*-nitrocinnamyl alcohol in yields of 95 and 76%, respectively (eq 5).



(5)

95% (86% isolated)

The following preparative procedure for the reduction of 2-cyclopentenone to 2-cyclopentenol is representative. An oven-dried 500-ml three-necked flask, equipped with a side arm fitted with a silicone rubber stopple, egg-shaped stirring bar, and pressure equalizing dropping funnel connected to a mercury bubbler through a connecting tube, was flame dried and cooled to room temperature under a dry stream of nitrogen. The flask was charged with 25 ml of dry THF and 8.35 ml (8.21 g, 100 mmol) of 2-cyclopentenone (n^{20}D 1.4814) and cooled to 0° with an ice bath. Then, 171.7 ml (103 mmol) of a 0.6 *M* 9-BBN solution in THF was added dropwise over a period of 2 hr with vigorous stirring. After 4 hr at 0°, the solution was stirred for 2 hr at 25°. Then 0.5 ml of methanol was added to destroy excess 9-BBN. THF was removed under reduced pressure and dry *n*-pentane (100 ml) added, followed by 6.4 ml (6.3 g, 103 mmol) of 2-aminoethanol. Immediately the ethanolamine derivative of 9-BBN precipitated. The mixture was centrifuged and the clean pentane layer decanted. The precipitate was washed with three 30-ml portions of *n*-pentane and centrifuged, and the decantates were added to the main fraction. Pentane was distilled off and the residue on vacuum distillation gave 7.12 g (85%) of 2-cyclopentenol as a colorless liquid, bp 78° (59 mm), n^{20}D 1.4716 [lit.[10] bp 52° (12 mm), n^{20}D 1.4717], >99% pure by GLC.

In conclusion, it should be pointed out that 9-BBN possesses certain major advantages over other reagents for this transformation. It reduces 2-enones, normally highly susceptible to conjugate reduction, cleanly to the allylic alcohols. Yet it is a very mild reducing agent, similar to sodium borohydride and lithium tri-*tert*-butoxyaluminohydride in its selectivity.

References and Notes

(1) Presented at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975.
(2) E. F. Knights and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 5280, 5281 (1968).
(3) C. G. Scouten and H. C. Brown, *J. Org. Chem.*, **38**, 4092 (1973); H. C. Brown, E. F. Knights, and C. G. Scouten, *J. Amer. Chem. Soc.*, **96**, 7765 (1974).
(4) 9-BBN is now available commercially from the Aldrich Chemical Co., Milwaukee, Wis., both as the solid and the solution in tetrahydrofuran.
(5) An extensive study by Drs. S. Krishnamurthy and N. M. Yoon is underway.
(6) For a recent detailed and critical discussion, see M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).
(7) H. C. Brown and H. M. Hess, *J. Org. Chem.*, **34**, 2206 (1969).
(8) This convenient precipitation of the 9-BBN–ethanolamine adduct was developed by Gary W. Kramer of our laboratory for a related application.
(9) (a) K. E. Wilson, R. T. Seidner, and S. Masamune, *J. Chem. Soc., Chem. Commun.*, 213 (1970); (b) "The Use of Aluminum Alkyls in Organic Synthesis", Ethyl Corporation, 1970 and 1973; (c) "Specialty Reducing Agents", Texas Alkyls Inc.
(10) K. Alder and F. H. Flock, *Chem. Ber.*, **89**, 1732 (1956).
(11) Postdoctoral Research Associate on Grant No. DA-ARO-D-31-124-73G148, supported by the U.S. Army Research Office (Durham).

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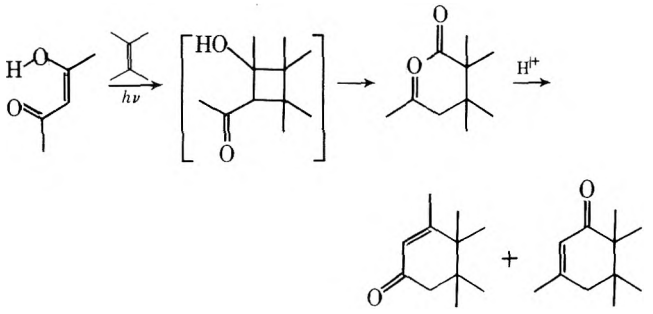
Photoannelations with α-Formyl Ketones. Enol Specificity in the Reaction of Acyclic α-Formyl Ketones with Alkenes[1]

Summary: The irradiation of several acyclic α-formyl ketones in the presence of alkenes gives rise to photoproducts derived exclusively from that tautomer enolized toward the aldehyde carbonyl, which can then be cyclized to provide a new cyclohexenone annelation sequence.

Sir: The photochemical cycloaddition of β diketones to alkenes[2a,b] is well documented and has been adequately reviewed.[3a-e] In general this reaction can be viewed as pro-

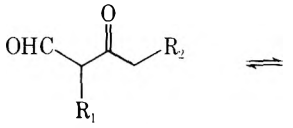
ceeding through one of two possible enols to give a substituted 2-acylcyclobutanol which then suffers ring fragmentation yielding a 1,5 diketone. Subsequent aldol cyclization of the photoproduct affords various cyclohexenones. Al-



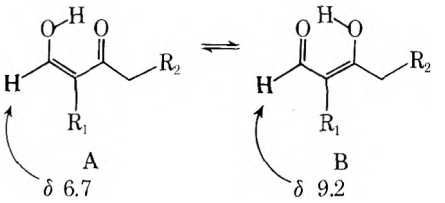
though the material yields are generally good, the considerable synthetic potential of this two-step sequence has not been totally realized. In significant measure this is due to the large number of products which often results. For example, the reaction between an *unsymmetrical* β diketone and an *unsymmetrical* alkene followed by aldolization can give eight structurally different cyclohexenones, neglecting stereoisomers. This multiplicity arises because there are (a) *two* reactive enol tautomers per diketone, (b) *two* alkene orientations per enol, and (c) *two* aldol products per photoproduct. Such mixtures have often restricted the preparative value of the process.[3f]

We now wish to report that the analogous reaction with α-formyl ketones leads to a significant reduction in product complexity and renders the process generally useful.

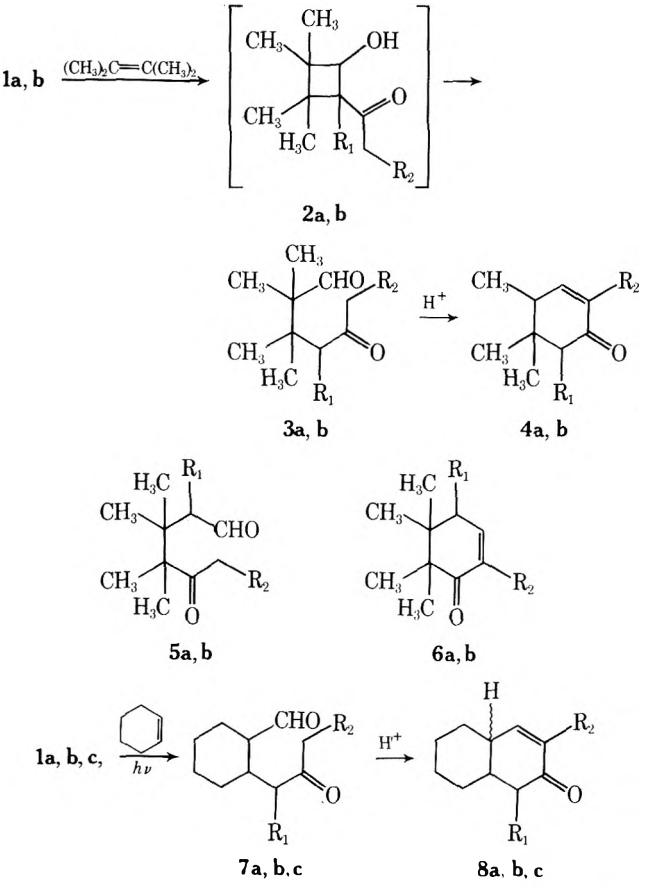
It occurred to us some time ago that acyclic α-formyl ketones might be attractive partners in photochemical annelations. We reasoned that their use could result in significant simplification of the photochemical annelation sequence, as compared to β diketones. For instance, a twofold simplification arises directly because the ketoaldehyde photoproduct can only undergo a single aldol cyclization. We hoped that additional simplification would result if the two enol tautomers were sufficiently different, either in reactivity or concentration, to permit preferential reaction of one tautomer in the photochemical cycloaddition step. It is the purpose of this paper to report that our preliminary findings are in complete accord with these expectations and that a potentially general and useful annelation process has emerged. To date there have been no reports of such reactions with α-formyl ketones, although two groups have employed a dialdehyde in ingenious syntheses of loganin.[4]



1a, $R_1 = R_2 = H$[5a,b]
b, $R_1 = H$, $R_2 = i\text{-}C_3H_7$[5c]
c, $R_1 = R_2 = CH_3$[5d]



The NMR spectra of various acyclic α-formyl ketones clearly indicate that they are totally enolized and that there is an appreciable concentration of both enols in all cases.[6,7] In fact the relative amounts of the two enols are rather insensitive to substitution patterns, in contrast to the formyl derivatives of cyclic ketones.[6a] It was thus somewhat surprising when irradiation of various symmetrical alkenes with α-formyl ketones provided products which were exclusively derived from tautomer A. For instance formylacetone and tetramethylethylene afforded keto aldehyde **3a** in quantitative yield. Particularly diagnostic was the aldehyde singlet at 9.64. There was no trace of an additional aldehyde proton absorption (triplet) for the alternative photoproduct **5a**, ruling out the intervention of tautomer B in the photocycloaddition. Acid-catalyzed cyclization of **3a** then yielded cyclohexenone **4a** (69%)[8] as a single homogeneous substance.[9] Similar results were obtained with 4-isopropylformylacetone (**1b**) which was smoothly converted to keto aldehyde **3b**.[8] In no instance were we able to detect even trace quantities of **5b** which would arise from the alternate enol tautomer B.



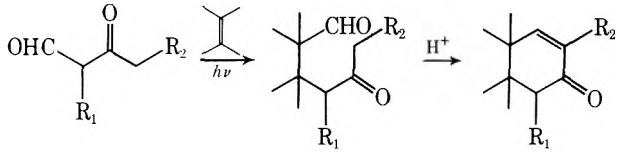
1a-8a, $R_1 = R_2 = H$; **1b-8b**, $R_1 = H$, $R_2 = i\text{-}C_3H_7$; **1c-8c**, $R_1 = R_2 = CH_3$

We have also caused formyl ketones **1a–c** to react with cyclohexene and again the results indicate a specific reaction with tautomer A. For example, formylacetone (**1a**) reacted with cyclohexene at −20° to −30° to give ketoaldehyde **7a** which was then directly cyclized to octalone **8a** (mixture of stereoisomers).[8,10] In a similar fashion, formyl ketones **1b** and **1c** were specifically converted to the substituted octalones **8b** and **8c**.[8,11]

An explanation for the selective enol reactivity observed in this study is difficult to advance at this time. We have made the *qualitative* observation that formyl ketone **1b** affords more product than does acetylacetone in a competitive reaction for excess cyclohexene. However, the reversible formation of intermediates in this reaction[12] does not permit us to determine the relative rates of reaction.

Taken together, the experiments that we have reported here indicate that alkenes can be expected to react preferentially, if not exclusively, with that tautomer of a simple

acyclic α-formyl ketone which is enolized toward the aldehyde carbonyl. Because the photoproducts can only undergo aldolization in a single sense, a fourfold simplification in the overall annelation sequence has resulted, compared with the analogous reactions with β diketones. In terms of net structural change, the reaction can be summarized by the following equation.



The single remaining point of ambiguity, orientation of the photoaddition with unsymmetrical alkenes, is currently under investigation. Based on preliminary findings we expect our studies to result in a general cyclohexenone synthesis which complements existing methods.[13]

References and Notes

(1) (a) We wish to thank the U.S. Public Health Service for financial support (Grant No. 1 R01 GM20780-01). (b) A portion of this work was presented at the 168th National Meeting of the American Chemical Society, Sept 8–13, 1974, Atlantic City, N.J., Orgn 100. (c) We are indebted to Dr. David Rosenthal and Mr. Fred Williams of the Research Triangle Institute for Mass Spectrometry (supported by NIH Grant RR 00330) for mass spectral determinations.

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(7) NMR spectra were determined in CCl_4 solution at ambient temperature; only slight deviations were noted relative to solvolysis conditions (pentane solutions at −20°). The NMR absorption for the "aldehyde" hydrogen (δ 7.6–7.9) was used to calculate the position of the rapid equilibrium (A ⇌ B) assuming extreme values of δ 6.7 and 9.2 for tautomers A and B, respectively.[6a] The ratio concentrations of the tautomers A:B for **1a**, **1b**, and **1c** are 52:48, 52:48, and 64:36, respectively.

(8) New compounds gave satisfactory elemental and spectral analyses. Although the yields of the reactions reported here have not been optimized, they are generally in the range of 60–100% for the photolysis and 60–90% for the aldol cyclization.

(9) Careful analysis of the aldehyde region of the NMR spectra of the crude photoproducts permitted the assignment of structure **3** vs. **5**. These results are in accord with a similar analysis of the cyclized material, **4** vs. **6**. For instance, **3b** exhibited a singlet at δ 9.64 while **4b** showed a singlet at δ 6.05. Compounds **5b** and **6b** would be expected to show a triplet and double doublet, respectively, for the same two protons. Because we could detect no trace of the alternate absorptions, we feel justified in assigning a conservative value of >95% for the enol specificity in the photochemical cycloadditions.

(10) The location of the carbonyl group at C-2 of **8a**, and thus the specificity of this photoaddition, was verified by mass spectral determination of the extent of deuterium exchange in the dihydro derivative of **8a**.

(11) The identity of **8c** was verified by independent synthesis.

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(13) The photolyses reported here were performed with an excess of alkene using a Hanovia 450-W medium-pressure lamp through Corex or Pyrex. The reactor was cooled to −20 to −30° during irradiation, a condition which afforded increased efficiency in product formation as well as cleaner reaction mixtures. Reaction times were generally between 1 and 2 hr for the complete conversion of 2–4 g of formyl ketone.

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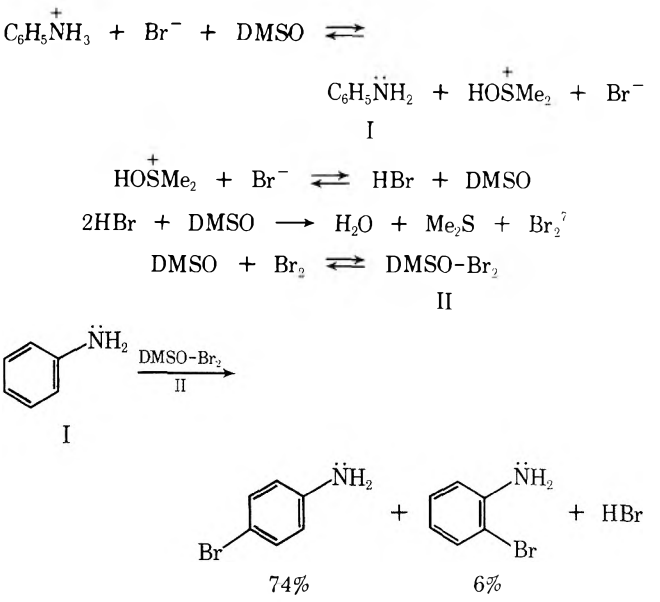
Indirect Bromination by Reaction of Aniline Hydrobromide with Dimethyl Sulfoxide

Summary: Indirect bromination of aniline can be achieved by reaction of the aniline hydrobromide salt with dimethyl sulfoxide to afford *p*-bromoaniline and *o*-bromoaniline in a 12:1 ratio. This simple indirect bromination proceeds with a high degree of regiospecificity to afford predominantly *p*-bromoaniline.

Sir: Fletcher and coworkers[1] have reported that 2-amino-3-bromofluorenone is obtained from the reaction of *tert*-butyl bromide and 2-aminofluorenone in dimethyl sulfoxide and from the reaction of 2-aminofluorenone with 48% HBr in dimethyl sulfoxide. We wish to report that the reaction of aniline hydrobromide with dimethyl sulfoxide at an elevated temperature (refluxed for 45 min) afforded predominantly the *p*-bromoaniline in 74% yield and only 6% *o*-bromoaniline. This indirect bromination process is summarized in Scheme I which depicts the DMSO–Br_2 adduct[2] II as the active brominating species.

Scheme I



The process depicted in Scheme I illustrates the selective indirect bromination of aniline by way of its hydrobromide salt to yield almost exclusively *p*-bromoaniline.[3] This result is somewhat surprising since direct bromination[3b] of aniline in most instances yields di- and trisubstituted derivatives.

Although the DMSO–Br_2 adduct has been depicted in Scheme I as the brominating species we have no direct evidence of its constitution. A second possible brominating agent is the Me_2S–Br_2 adduct;[4] dimethyl sulfide formed in the oxidation of hydrogen bromide could complex with free bromine. However the formation of both of the bromine adducts would be expected to be reversible processes, and it would be anticipated that the reaction conditions would favor the formation of the DMSO–Br_2 adduct (provided that the thermodynamic stabilities of the two adducts are not vastly different), since the reaction is normally carried out in the presence of a large excess of DMSO.

***p*- and *o*-Bromoaniline.** Aniline hydrobromide (13.05 g, 0.075 mol) was added to 100 ml of dimethyl sulfoxide[5] and the resulting mixture was refluxed for 45 min. The reaction was allowed to cool to room temperature and poured into a dilute solution of sodium

hydroxide (3.0 g in 750 ml of H_2O). The resulting mixture was extracted with two 150-ml portions of a 5:1 Skelly B:ethyl ether solution. The extracts were combined, washed with 100 ml of H_2O, dried over anhydrous sodium sulfate, and filtered. Concentration of the organic phase and distillation of the resulting oil afforded 10.1 g (80%) of a semisolid, bp 76–80° (0.5 mm); GLC analysis showed that the mixture consisted of ~74% *p*-bromoaniline and 6% *o*-bromoaniline. Recrystallization of the semisolid from aqueous ethanol afforded 8.7 g (67%) of pure *p*-bromoaniline, mp 62.4–64° (lit.[3a,6] mp 66–66.5°).

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Organolithium Reagents

- Extremely strong bases
- Powerful nucleophiles

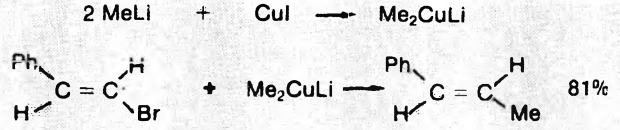
Alkyl and aryllithium reagents have assumed an extremely important place in organic synthesis mainly because of their high nucleophilicity and powerful basicity. The structures and numerous synthetic applications of organolithium compounds have been reviewed recently.[1,2] Other reviews describe their use in metallation[3] and ketone synthesis from carboxylic acid salts.[4] The preparation and use of lithium organocopper compounds have also been reviewed.[5] A few of the many applications of organolithium reagents are highlighted below.

Addition Reactions

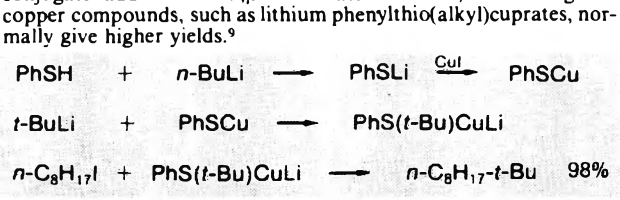
The reactions of organolithium reagents with aldehydes and ketones have been investigated from a synthetic viewpoint.[6,7]

Alkylation of Halides

Halides can be alkylated using organocopper compounds which are readily prepared from organolithium reagents.[8]

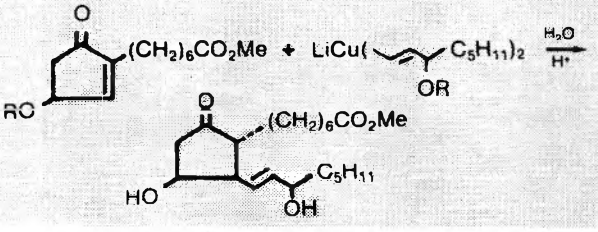


The reaction of lithium dialkylcopper compounds (as in the example above) utilizes only one of the alkyl groups and frequently requires a large excess of the reagent. In the alkylation of halides and conjugate addition to α,β-unsaturated ketones, mixed organocopper compounds, such as lithium phenylthio(alkyl)cuprates, normally give higher yields.[9]



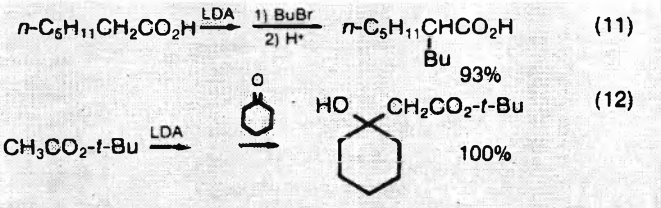
Alkylation of α,β-Unsaturated Ketones

Lithium organocopper compounds undergo conjugate addition with α,β-unsaturated ketones with high regiospecificity. This important reaction has been used successfully in the synthesis of natural products including prostaglandins.[10]



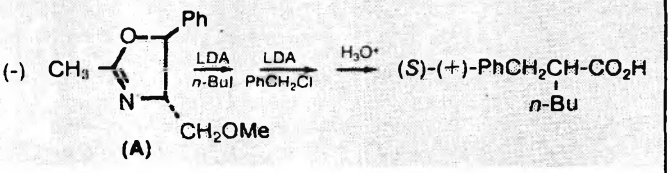
Alkylation *via* Dialkylamides

Lithium dialkylamides are powerful bases yet are weak nucleophiles. As a result, they are used in the formation of carbanions of acids[11] and esters.[12] The α-carbanions, are stable with respect to self-condensation and react with alkyl halides, acid chlorides and ketones. One widely used reagent is lithium diisopropylamide (LDA) which can be prepared from diisopropylamine and *n*-butyllithium.[11]



Alkylation *via* Masked Carbonyl Systems

Organolithium compounds may be used in the formation of anions of masked carbonyl systems.[13] For example, LDA is used in the synthesis of chiral acids by the stepwise alkylation of (4*S*,5*S*)(-)-4-methoxymethyl-2-methyl-5-phenyl-2-oxazoline (**A**) followed by hydrolysis[14] to give the (+) acid of 70% optical purity.



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