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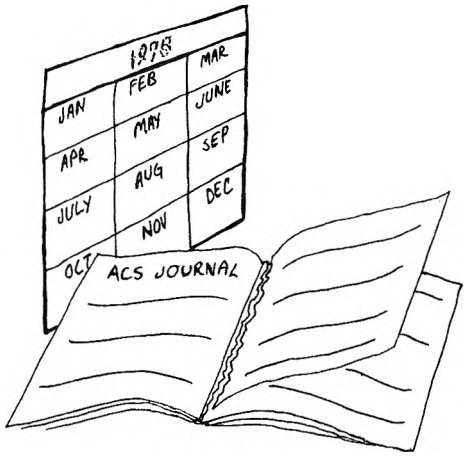

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SEPTEMBER 3, 1976

Synthesis and Chemistry of Some Polychlorinated Oxetanes

Ronald R. Sauers,* Richard Bierenbaum, Robert J. Johnson, John A. Thich, Joseph Potenza, and Harvey J. Schugar

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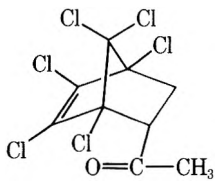
Received April 20, 1976

Three new polychlorooxetanes have been prepared by photocyclizations of the halogenated acylnorbornenes **1**, **2a**, and **2b**. The oxetanes were unusually stable toward acidic reagents, but **4a** was shown to undergo a deep-seated rearrangement on treatment with sulfuric acid. The major product of this reaction was shown by x-ray crystallography to be the nortricyclanone derivative **5** which is believed to have been formed via intramolecular participation of a methoxyl group concurrent with ring opening of the oxetane ring. Some aspects of bond shortening effects in cyclopropyl ketones are discussed, and it is concluded that hybridization effects could be sufficient to explain the data.

Studies of the synthesis and chemistry of polyhalogenated ring systems have generated a wealth of useful synthetic intermediates and numerous mechanistically interesting transformations. For example, many novel ring systems have been synthesized by a general route which involves photocyclization of a polyhalonorbornene followed by a ring contraction reaction of the Favorskii type. Ring systems which have been prepared by this sequence include the following: secocubane,[1] homocubane,[2] cubane,[3] and norcubane.[4] Other ring systems, e.g., bishomocubane[5] and "bird-cage" systems,[6] have been prepared directly by intramolecular photocycloaddition reactions of polyhalogenated ring systems. The chemistry of these molecules is frequently characterized by deep-seated molecular rearrangements as a consequence of strain relief and the electronic influence of the halogen atoms on the reaction intermediates.[1,5,7,8,9] These results and our interest in the chemistry of polycyclic oxetanes[10,11] stimulated an investigation of the photochemistry of the polychloroacylnorbornenes **1**, **2a**, and **2b**.



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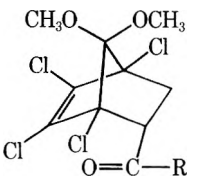
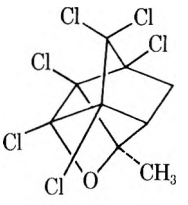


2a, R = CH_3
b, R = H

These molecules are of photochemical interest in that they offer an opportunity to evaluate the steric and electronic effects of chlorine on the efficiency of intramolecular oxetane formation. In simpler acylnorbornenes, steric inhibition does not appear to play a role,[10] but the increased interactions caused by the four proximate chlorine atoms could be deleterious. In addition, the presence of chlorine on the double bond would be expected to raise the ionization potential of the π system[12] and thereby lower the rate of exciplex formation between that function and the excited carbonyl group.[13,14] Consequently, lowered quantum efficiency and/or side reactions might ensue.

Syntheses. The adducts **1** and **2** were prepared by Diels–Alder reactions according to literature procedures,[7,15] and it is believed that the carbonyl functions are largely or exclusively endo oriented on the basis of NMR data and chemical yield data (vide infra). Irradiations of **1**, **2a**, and **2b** in benzene gave isomeric products whose spectral parameters[16] were



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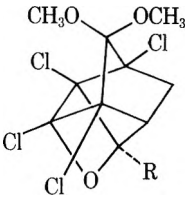


4a, R = CH_3
b, R = H

consistent with oxetane structures **3**, **4a**, and **4b**, respectively. On a qualitative basis it was observed that irradiation times were much longer than those required for the nonhalogenated analogues.

Chemistry of Oxetanes 3 and 4a. Oxetane **3** showed a remarkable stability toward acid-catalyzed rearrangements in contrast to nonchlorinated analogues. The material was recovered unchanged after treatment with perchloric acid in methanol (42 h, reflux), boron trifluoride etherate (72 h, reflux), and concentrated sulfuric acid (0 °C, 1 h). Treatment of **3** with aluminum chloride for 20 h in refluxing benzene resulted in formation of the original ketone **1** in 43% yield. Since the nonchlorinated analogue undergoes acid-catalyzed cleavage at the carbon bearing the methyl substituent,[14] the geminal chlorine atom may actually facilitate the ring opening. The major effect of the chlorine atoms could be to reduce the

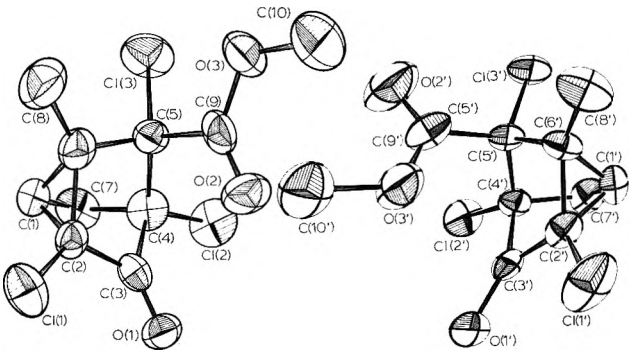


Figure 1. (+)- and (−)-methyl 2,4,5-trichloro-6-methyltricyclo[2.2.1.$0^{2,6}$]heptan-3-one-*syn*-5-carboxylate; 50% probability thermal ellipsoids are shown.

Table I. Selected Bond Lengths[a] of Nortricyclene Derivatives

Bond	Nortricyclene[b]	4-Chloronortricyclene[c]	5[d]
C(1)–C(2)	1.50	1.510	1.52
C(2)–C(6)	1.50	1.510	1.54
C(1)–C(6)	1.50	1.510	1.52
C(1)–C(7)	1.54	1.535	1.50
C(2)–C(3)	1.54	1.535	1.48
C(5)–C(6)	1.54	1.535	1.52
C(3)–C(4)	1.54	1.537	1.55
C(4)–C(5)	1.54	1.537	1.54
C(4)–C(7)	1.54	1.537	1.53

[a] Angstroms. [b] Reference 17. [c] Reference 18, standard deviations range from 0.0078 to 0.0025. [d] Average of the values of the enantiomers.

basicity of the oxygen atom and, hence, the overall reaction rate.

Similarly, oxetane **4a** was shown to be stable toward perchloric acid in methanol (3 days, reflux), $FeCl_3$ (19 h, 80 °C), and sulfuric acid in methanol (3 days, reflux). A rapid reaction was observed upon treatment of **4a** with concentrated sulfuric acid (0 °C, 15 min) from which a crystalline product was isolated in 58% yield. The elemental analysis of this material revealed that it had been formed from **4a** with the loss of the elements of CH_3Cl. The following functionality was identified from an analysis of various spectroscopic data: carbonyl (5.55, 5.65, and 5.75 μ); CH_3O (δ 3.9); and CH_3C (δ 1.6, s). No evidence for unsaturation could be adduced from the spectral data, but the presence of tetrasubstituted double bonds could not be excluded.

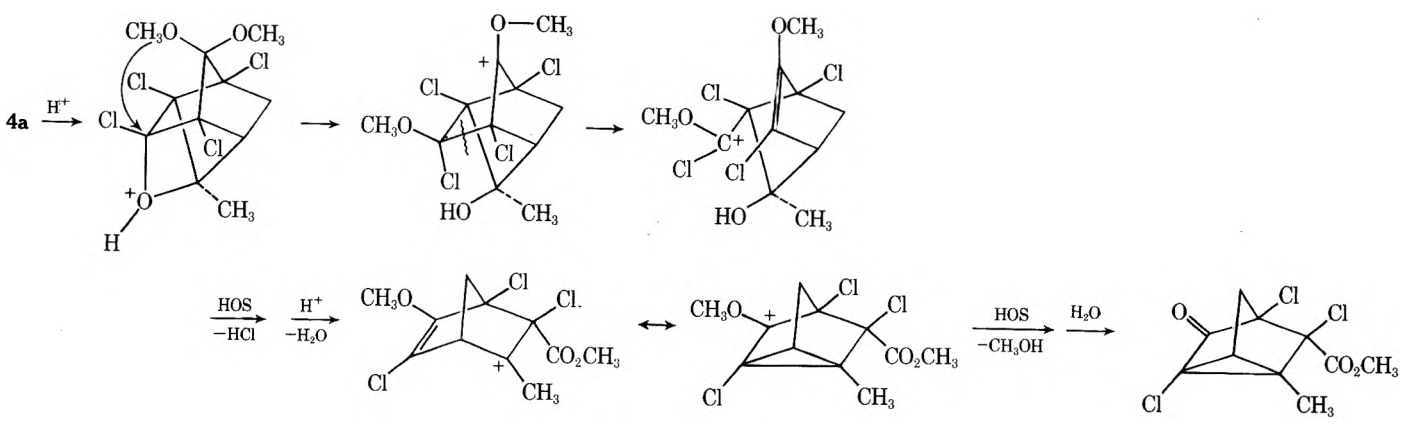
In view of the larger number of possible structures, it was decided to resolve the structure of this product by use of x-ray crystallographic techniques. The results of this determination are shown in the ORTEP plot (Figure 1). The relative orientations of the two enantiomers in the asymmetric unit has been altered slightly from that in the crystal to allow for easier visualization. It is noteworthy that the conformations of the carbomethoxy groupings are nonidentical in the two enantiomers shown. Since the unit cell is centrosymmetric, this asymmetry is balanced by the presence of a mirror image pair elsewhere in the cell.

The structural parameters obtained for this system correspond closely with those obtained for nortricyclene[17] and 4-chloronortricyclene[18] (Table I) with the exception of the C(2)–C(3) bond length. This bond is unusually short, a result which may be a manifestation of conjugation between the orbitals of the cyclopropyl ring and those of the carbonyl π systems.[19] It is generally agreed that this kind of interaction is maximized when the cyclopropyl ring is bisected by the plane which contains the carbonyl group and the adjacent carbon of the ring.[19] This concept is supported by numerous studies on the effect of structure on the absorption spectra of cyclopropyl ketones.[19,20] In addition, other x-ray crystallographic studies on cyclopropyl ketones[21,22] (with one exception[22c]) show a similar bond shortening although a clear correlation between the carbonyl torsion angle and the ultraviolet spectral shift was not found.[22a]

A complete analysis of bond shortening phenomena must also take into account changes attributable to variations in carbon hybridization.[18,23] The effect of the chlorine atoms on carbon hybridization is believed to be negligible (<0.005 Å) by analogy with published results on 1,4-dichloronorbornane.[18] On the other hand, bonds attached to the cyclopropyl ring are known to possess a large fraction of s character in comparison with sp^3 bonds, and a hybridization index of 2 has received theoretical and experimental support.[23-25] Since the C(2)–C(3) bond, an essentially sp^2–sp^2 linkage, could be shortened by as much as 0.05 Å by hybridization effects alone,[26] the importance of "conjugative" bond shortening becomes equivocal. The problem is clearly complex owing to the many interrelated factors, and we conclude that the existing data are not conclusive in this regard.

The formation of **5** from **4a** poses a mechanistic dilemma. The exceptionally mild conditions needed for this transformation are in strong contrast to the much more vigorous conditions needed to hydrolyze similar ketals in polychlorinated systems[1,5,7] and to the inertness of the hexachlorooxetane **3** to more vigorous conditions. Thus, it would appear that synergism is required, and we outline a possible mechanism for this rearrangement in Scheme I which involves participation by the methoxyl group in the ring opening of the pro-

Scheme I



5

tonated oxetane. This kind of assistance by methoxyl groups is well documented in the norbornyl system for which the geometrical relationships are similar.[27]

Since some of the spectroscopic properties of ketone **5** are of more than routine interest, they are discussed briefly here. The ultraviolet spectrum, for example, showed an unusually short wavelength maximum at 265 nm (ϵ 40) which is attributed to the n,π^* transition. The blue shift of this transition relative to that observed for nortricyclanone (**6**) [λ_{max} (EtOH)

6 **7** **8**

285 nm (ϵ 20)][28] is attributable to the effect of the two vicinal carbon–chlorine bonds. This situation is closely analogous to that found in α-chlorocyclohexanones in which equatorially substituted chlorine atoms shift the carbonyl absorption maximum to shorter wavelengths by ~7 nm.[29] The presence of these chlorine atoms is felt in the infrared spectrum also. Whereas nortricyclanone shows maxima for the carbonyl stretching mode at 5.66 and 5.70 μ,[30] ketone **5** shows three maxima at 5.55 (s), 5.65 (m), and 5.75 μ (m). The α-chloro ester grouping accounts for at least one of the longer wavelength bands, and the band at the shortest wavelength is assigned to the ketonic function. The magnitude of the effect of the two chlorine atoms may be estimated from the behavior of compounds **7** (5.64 μ) and **8** (5.51 μ) for which a shift of −0.13 μ is found.[31,32] The calculated values for **5** are 5.53 and 5.57 μ in good agreement with the observed spectrum.

Photochemistry. Since the absorption spectrum of the hexachloro ketone **1** was virtually identical with that of the nonchlorinated analogue *endo*-5-acetylnorbornene (**9**), it is concluded that there are no significant ground state interactions between the chromophores.[10] In addition, it was found that there was no significant fluorescence emission from **1** under conditions which produced easily measurable emission from 2-hexanone (Φ_f = 0.00039).[33,34] From these data, it may be estimated that the lifetime of the singlet state of ketone **1** is no greater than 10^{-11} s.[35] This limit is of the same order of magnitude as that estimated for **9**, and it is presumed that exciplex formation between the carbonyl singlet and the double bond defines the singlet state lifetime in both cases.[10,13] In this context, it is interesting to note that the quantum yield for formation of oxetane **3** (0.026) is ca. six times lower than that measured for the nonchlorinated analogue. This result may be a manifestation of severe steric crowding in the formation of oxetane **3** or a reflection of more efficient decay of the chlorinated exciplex. It should also be noted that the lowered quantum yield observed here is in accord with predictions based on the expected ionization potential of the double bond.[36]

Summary and Conclusions

The generality of the intramolecular oxetane synthesis has been extended by these studies of polychlorinated bicyclic carbonyl systems. The potentially deleterious steric and electronic effects of the chlorine atoms were manifest in a sixfold lowered quantum yield of oxetane formation, but not in the formation of side products. Oxetane **4a** underwent a novel rearrangement under conditions of mild acid catalysis and it was concluded that methoxyl participation with migration was an important aspect of the transformation. The product of this reaction (**5**) is the first example of a nortricyclanone system to be examined by x-ray crystallography. The data revealed that the bond between the carbonyl group and the cyclopropane ring was unusually short (1.48 Å), and it was concluded that hybridization changes could be responsible for this effect.

Experimental Section

Elemental analyses were performed at Robertson Laboratory, Florham Park, N.J. Infrared spectra were determined as Nujol mulls or KBr pellets on a Perkin-Elmer Model 137 spectrometer. Nuclear magnetic resonance data were obtained on Varian Model T-60, CFT-20, and JEOL-100 spectrometers in chloroform with tetramethylsilane as an internal standard. Gas chromatographic data was recorded on an Aerograph Model A-90-P chromatograph. The following columns were employed: 3% SE-30 (5 ft × 0.25 in.) on Chromosorb G and 5% SF-96 (5 ft × 0.25 in.) on Chromosorb P. Mass spectra were determined at 70 eV on a Hitachi RMU 7 mass spectrometer. Melting points were determined on a Mel-Temp apparatus. X-ray diffraction data were collected on a Nonius CAD-3 automated diffractometer. Fluorescence measurements were taken on a Perkin-Elmer MPF-2 spectrometer.

Starting Materials. 1,4,5,6,7,7-Hexachloro-5-norbornen-2-yl methyl ketone (1) was prepared by the procedure of Prill[15] and had mp 70–71 °C (lit. mp 70 °C). The ^{1}H NMR spectrum (100 MHz) showed a single sharp peak at δ 2.40 (CH_3), a quartet centered at 3.76, and complex absorption between 2.50 and 2.80; λ_{max} (C_6H_6) 287 nm (ϵ 27); λ_{max} (CH_3CN) 283 nm (ϵ 16).

1,4,5,6-Tetrachloro-7,7-dimethoxy-5-norbornen-2-yl methyl ketone (2a) was prepared by the procedure of McBee et al.[7] and had mp 85–86 °C (lit. mp 86–87 °C). The ^{1}H NMR spectrum (100 MHz) showed two methoxyl peaks at δ 3.58 and 3.66, and acetyl peaks at 2.34 and 2.38 (rel area ca. 3.5:1); λ_{max} (C_6H_6) 288 nm (ϵ 27).

1,4,5,6-Tetrachloro-7,7-dimethoxy-5-norbornene-2-carboxaldehyde (2b) was prepared according to ref 7, and had bp 148 °C (3 mm) [lit.[7] bp 155–156 °C (5 mm)]. The ^{1}H NMR spectrum showed two methoxyl peaks at δ 3.53 and 3.59, and complex absorptions centered at δ 9.8 indicative of a mixture of epimers.

Photolyses. Preparative scale irradiations were carried out in a 1.1-l. immersion apparatus equipped with a Hanovia 450-W lamp. Nitrogen gas was passed through the solutions throughout the irradiation period. Spectral grade benzene was used as solvent, and the photolyses were run for 7–8 days (polymer was removed from the immersion well as necessary).

1,2,5,6,9,9-Hexachloro-3-methyl-4-oxatetracyclo[4.2.1.$0^{2,5}$.$0^{3,7}$]nonane (3). Irradiation of 10 g of **1** in 1.1 l. of benzene (Vycor filter) in the presence of 1.5 g of piperylene for 200 h sufficed to consume >90% of the ketone (GC, SE-30). The volatiles were removed by evaporation and the residue chromatographed on silica (hexane–benzene eluents) to yield 5.5 g (55%) of oxetane **3**: mp 175–176 °C; ^{1}H NMR δ 1.6 (s, CH_3), 3.3 (m, 2 H), 2.1 (d, J = 12 Hz, 1 H).

Anal. Calcd for $C_9H_6OCl_6$: C, 31.53; H, 1.76; Cl, 62.04. Found: C, 31.82; H, 2.03; Cl, 61.80.

1,2,5,6-Tetrachloro-3-methyl-9,9-dimethoxy-4-oxatetracyclo[4.2.1.$0^{2,5}$.$0^{3,7}$]nonane (4a). Similarly, 10.1 g of **2a** was irradiated for 7 days using a Vycor filter. Evaporation of the benzene gave a solid which was washed with hexane and crystallized from petroleum ether: yield 6.30 g (63%); mp 160–161 °C; ^{1}H NMR δ 3.6, 3.58 (s, CH_3O), 1.50 (s, CH_3), 2.8 (m, 2 H), 1.85 (d, J = 12 Hz).

Anal. Calcd for $C_{11}H_{12}O_3Cl_4$: C, 39.55; H, 3.68; Cl, 42.23. Found: C, 39.59; H, 3.68; Cl, 42.23.

1,2,5,6-Tetrachloro-9,9-dimethoxy-4-oxatetracyclo[4.2.1.-$0^{2,5}$.$0^{3,7}$]nonane (4b). Aldehyde **2b** (5 g) was irradiated for 7 days using a Corex filter. Removal of the benzene and chromatography of the residue on alumina gave 1.22 g (24%) of oxetane **4b**: mp 161–162 °C; ^{1}H NMR δ 4.60 (d, J = 2 Hz, 2 H), 3.50, 3.48 (s, CH_3O, 6 H), 1.8–3.0 (m, 3 H).

Anal. Calcd for $C_{10}H_{10}O_3Cl_4$: C, 37.53; H, 3.15; Cl, 44.31. Found: C, 37.58; H, 3.28; Cl, 44.11.

Methyl 2,4,5-Trichloro-6-methyltricyclo[2.2.1.$0^{2,6}$]heptan-3-one-*syn*-5-carboxylate (5). A mixture of 10 ml of concentrated sulfuric acid and 0.5 g of oxetane **4a** was stirred at 0 °C for 15 min. The solution was poured onto ice and the organic product was extracted into ether. The extracts were washed with saturated sodium bicarbonate solution, brine, and water. The dried extracts were evaporated to give 0.29 g (58%) of a solid which was sublimed at 60 °C (0.5 mm): mp 66°; ^{1}H NMR δ 3.9 (s, OCH_3), 1.55 (s, CH_3), 2.4–3.1 (m, 3 H); ^{13}C NMR (rel intensity) 9.54 (CH_3, 60), 33.87 (94), 39.55 (98), 44.00 (28), 49.31 (12), 54.19 (58), 71.83 (18), 165.94 (CO_2R, 7), 191.58 (C=O, 7); ir 5.55 (s), 5.65, 5.75 μ (m); λ_{max} ($CHCl_3$) 265 nm (ϵ 40).

Anal. Calcd for $C_{10}H_9O_3Cl_3$: C, 42.36; H, 3.20; Cl, 37.51. Found: C, 42.26; H, 3.29; Cl, 37.23.

Treatment of oxetane **3** with concentrated sulfuric acid for 1 h at 0 °C yielded only unreacted starting material.

Treatment of 3 with $AlCl_3$. A mixture of 1.1 g of aluminum chloride and a solution of 1.78 g of **3** in 50 ml of dry benzene was heated at reflux for 20 h. The reaction mixture was poured onto an HCl–ice mixture. The organic phase was washed with water and sodium bicarbonate solution, dried, and evaporated to give 0.78 g (43%) of ketone **1** as shown by comparative infrared spectra.

Quantum Yield Determination. Three sample tubes (Pyrex, 100 × 13 mm) each containing 0.251 M **1** and 0.0098 M tetradecane (internal standard) in 2.0 ml of purified benzene[10] were degassed by the freeze–thaw method and sealed under vacuum (0.05 Torr). Three solutions were irradiated on a merry-go-round apparatus for 31 h with a 450-W Hanovia lamp. The output of the lamp was filtered through 1.9 cm of an aqueous solution of potassium chromate (0.00127 M) and potassium carbonate (0.0543 M). The entire apparatus was immersed in a water bath which was kept at 25 ± 4 °C. The averaged percent conversion of the ketone **1** to the oxetane **3** was 5.5 ± 0.05 as determined by quantitative GC analysis. The corresponding nonchlorinated ketone (0.251 M) served as the actinometer for calculation for the quantum yield. Four separate tubes were sequentially irradiated over the same time period. Using a value of 0.14 for the quantum yield of oxetane formation for this compound, a value of 0.026 ± 0.02 was calculated for oxetane formation from **1**.

Collection and Reduction of X-Ray Data. A crystal approximately 0.34 × 0.43 × 0.69 mm was obtained from an ether–decane solution and mounted in a sealed glass capillary along the a axis. Weissenberg photographs revealed a monoclinic space group with systematic absences of $h0l$, $l = 2n + 1$; and $0k0$, $k = 2n + 1$. The centrosymmetric space group $P2_1/c$ is the only one consistent with these extinctions.

Unit cell constants were determined at 22 ± 1 °C from a least-squares fit of 15 medium intensity reflections centered on an Enraf-Nonius CAD-3 computer controlled diffractometer. The unit cell dimensions were a = 9.066 (4), b = 10.863 (6), c = 24.63 (2) Å, β = 92.35 (4)°, and V = 2424 (2) Å^3. A density of 1.58 (1) g/cm^3 was determined by the density gradient method using a carbon tetrachloride–tetrabromoethane mixture; this compared well with the value of 1.55 g/cm^3 calculated for eight molecules per unit cell.

Data were collected with the Enraf-Nonius diffractometer using graphite monochromated Mo Kα radiation detected with a pulse height analyzer set to admit approximately 95% of the Kα peak. A θ–2θ scan was used to collect a unique data set in the range $2° < \theta < 30°$. Background measurements were made at beginning and end of each scan with the total time for background counting equal to the scan time. Reflections with 2θ less than 4° were shielded by the beam stop and were not recorded. The scan range s was a function of θ chosen according to $s = 1.00 + 0.5 \tan\theta$. Each reflection was scanned before being recorded, and zirconium foil attenuators were automatically inserted if the intensity of the diffracted beam exceeded 6000 counts/s. A circular aperture, 1.3 mm in diameter, was placed 4.4 cm from the crystal. The scan rate was ⅙° per second, and each reflection was scanned repeatedly to a maximum of four scans, or until 5000 total counts were obtained. Intensities were placed on a common scale by dividing by the number of scans and multiplying by the appropriate filter factor. The intensity of a standard reflection, measured at 50 reflection intervals, showed a deviation of ±3%. A total of 3841 reflections was collected and corrected for Lorentz and polarization effects. The data were also scaled using the standard reflection to bring all reflections to a common scale. The linear absorption coefficient for Mo Kα radiation was 7.55 cm^{-1}, while maximum and minimum absorption factors for the data collected were calculated to be 1.37 and 1.28, respectively. Because of this small variation in A^*, absorption corrections were not applied. Standard deviations were assigned to F^2 values according to $\sigma(F^2) = (1/Lp)\,[N_t + (0.02N_n)^2]^{1/2}$, where N_t is the total count (scan plus background), N_n is the net count (scan minus background), and 0.02 is the estimated instrument error. Of the 3841 measured reflections, 1733 with F^2 greater than 3σ were used in the refinement.

Solution and Refinement.[37] The phases of 348 reflections with $|E| \geq 1.50$ were determined by use of the tangent formula. Of the 16 solutions generated by the MULTAN program for four starting reflections (in addition to those defining the origin), one with an absolute figure of merit of 0.97 and a residual of 46.2[38] was used as the basis for a Fourier synthesis. The 6 chlorine atoms and 18 lighter atoms, weighted as carbon, were located from this map. A structure factor calculation based on these 24 atoms gave $R_F = \Sigma||F_o| - |F_c||\Sigma|F_o| = 0.34$. An electron density map prepared using the phases generated by these 24 atoms revealed the remaining eight nonhydrogen atoms and discriminated between oxygen and carbon atoms.

Refinement was based on F. Scattering factors for Cl, O, and C atoms were taken from the compilations of Cromer and Waber,[39] and all atoms were treated as neutral species. Both real and imaginary parts of the anomalous dispersion correction were applied to chlorine.[40] The weighting scheme was chosen by an analysis of variance[41] to make $|\Delta F|/\sigma$ independent of $|F_o|$. A best fit plot led to the following assignments for $\sigma(F_o)$.

$$\sigma(F_o) = 0.33 + 0.12|F_o| \text{ for } |F_o| \leq 15.0$$

$$\sigma(F_o) = 4.59 - 0.16|F_o| \text{ for } 15.01 < |F_o| \leq 22.0$$

$$\sigma(F_o) = -0.20 + 0.05|F_o| \text{ for } |F_o| > 22.0$$

Positional parameters for the six ring hydrogen atoms were calculated using known distances (C–H = 1.08 Å) and tetrahedral angles, and were included for subsequent refinement with the overall temperature factor obtained using Wilson's method. Two cycles of refinement with anisotropic temperature factors for all nonhydrogen atoms gave values of 0.081 for R_F and 0.103 for $R_{wF} = [\Sigma w(F_o - F_c)^2/\Sigma wF_o^2]^{1/2}$.

A difference Fourier at this point revealed the positions of at least one hydrogen atom on each methyl group. These positions were used to calculate the remaining methyl hydrogen positions. Methyl hydrogen atoms were assigned the isotropic temperature factor obtained from the Wilson plot plus 1.0. Two final cycles of refinement varying all parameters except hydrogen temperature factors gave final values of 0.062 and 0.077 for R_F and R_{wF}, respectively. A final difference map showed no significant features and a general background of 0.3 electron/Å^3. Final atomic parameters and their estimated standard deviations are shown in Table II. Selected bond distances and angles are given in Tables III and IV, respectively (see paragraph at end of paper regarding supplementary material).

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Registry No.—**1**, 15584-73-3; **2a**, 59473-95-9; **2b**, 59473-96-0; **3**, 59473-97-1; **4a**, 59473-98-2; **4b**, 59473-99-3; **5**, 59474-00-9.

Supplementary Material Available. Tables of final atomic parameters, selected bond distances, and selected bond angles for compound **5** (4 pages). Ordering information is given on any current masthead page.

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Photochemical Cyclization of 4-Methallyl-4-methylcyclopentenone. 220-MHz Nuclear Magnetic Resonance Spectra of Tricyclo[3.3.0.$0^{2,7}$]octanes

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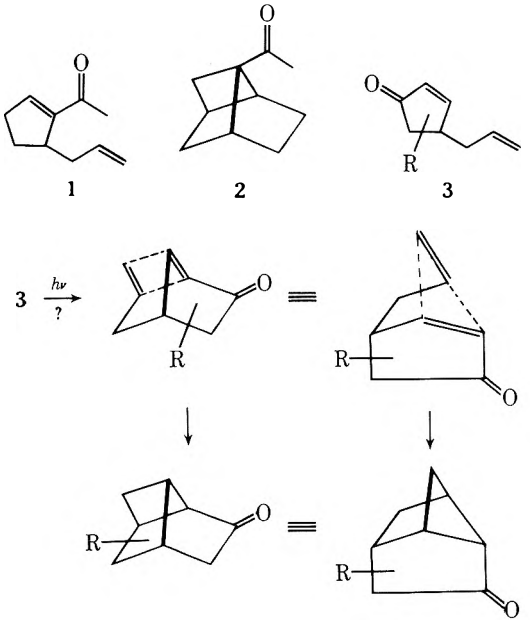
Preparation of 4-methallyl-4-methylcyclopentenone (**4**) from hydroxy ketone **5** is described. Irradiation of **4** leads to [2 + 2] cycloaddition and formation of tricyclic ketone **10** in high yield. NMR spectra (220 MHz) of ketones **10**–**13** are recorded and interpreted in a consistent fashion.

Irradiation of 1-acetyl-5-allylcyclopentene (**1**) leads to [2 + 2] cycloaddition between the two olefinic double bonds with formation of tricyclic ketone **2**.[1] Other representatives of this tricyclo[3.3.0.$0^{2,7}$]octane ring system have been long known through intramolecular photocycloaddition of vinylcyclohexenes.[2–5] However, the cyclization of **1** was the first example of formation of this skeleton from an allylcyclopentene, and this result suggests that similar cyclization might occur photochemically in suitable 4-allylcyclopentenones (**3**),

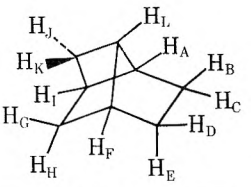


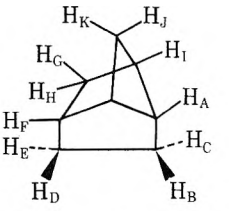
(1)

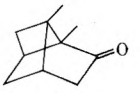
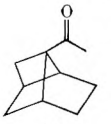
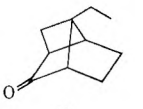
as illustrated in eq 1. The position of the carbonyl group on the ring double bond is reversed on passing from **1** to **3**, but the available evidence indicates that this change should not influence the mode of cyclization.[3,5] As others have noted before,[5] regiospecificity in intramolecular photocycloaddition of 1,5-hexadienes to yield bicyclo[2.1.1]hexanes (and not bicyclo[2.2.0]hexanes) is quite general, and apparently it is insensitive to the nature and position of substituents on the reacting double bonds. The only aberrant example of which we are aware has been described as being "structurally inhibited" from reaction in the usual fashion.[6] In this report we describe the intramolecular cycloaddition of an allylcyclopentenone according to eq 1, along with the 220-MHz ^1H NMR spectra of several tricyclo[3.3.0.$0^{2,7}$]octanes that were determined in the course of securing the structure of the photoproduct.

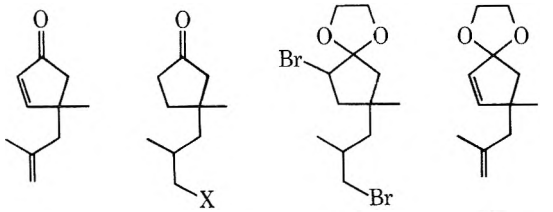
A convenient substrate for this work was 4-methallyl-4-methylcyclopent-2-enone (**4**), since it could be prepared from the related hydroxy ketone **5**, which was already on hand for another investigation.[7] The hydroxyl group of **5** was converted to the corresponding tosylate **6**, which yielded bromide **7** on reaction with sodium bromide in acetone. Treatment of **7** with bromine in ethylene glycol, according to the procedure of Garbisch,[8] then gave the dibromo ketal **8**. A double dehydrohalogenation took place when **8** was exposed to potassium *tert*-butoxide in dimethyl sulfoxide, furnishing the diene ketal **9**. Use of the primary bromide **7** rather than the corresponding tosylate **6** was desirable in this sequence in order to minimize competing ether formation during treatment with alkoxide;[9] for the same reason we employed *tert*-butoxide as base rather than methoxide, which was originally suggested.[8] In the event

Table I. NMR Spectra of Tricyclo[3.3.0.0^{2,7}]octanes 10–13

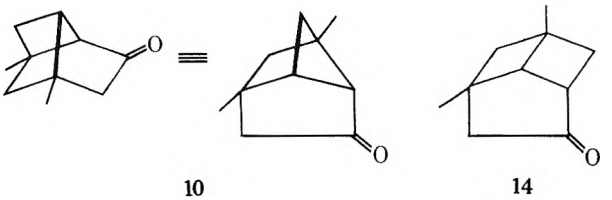




	 10 (59463-13-7)	 11 (39196-52-6)	 12 (52358-84-6)	 13 (52358-99-3)
H_A	2.21 dd $J_{AL} \sim 2$, $J_{AH} \sim 0.5$		2.25–2.35 m	2.46 m $W_{1/2} = 8$
H_D	2.05 dd $J_{DE} = 16.5$, $J_{DG} = 1.5$	2.15 ddd $J_{DE} = 17$, $J_{DF} = J_{DG} = 2$		
H_E	1.96 d $J_{ED} = 16.5$	2.04 d $J_{ED} = 17$		
H_F		2.28 br s $W_{1/2} \geq 6$	2.25–2.35 m	2.25 br s $W_{1/2} = 7$
H_G	1.19 dd $J_{GH} = 11$, $J_{GD} = 1.5$	1.24 ddd $J_{GH} = 11$, $J_{GD} = J_{GF} = 2$	1.26 ddd $J_{GH} = 10$, $J_{GD} = J_{GF} = 2$	
H_H	1.46 dd $J_{HG} = 11$, $J_{HA} = 0.5$	1.90 dd $J_{HG} = 11$, $J_{HI} = 7$		
H_I		2.33 m $W_{1/2} \sim 14$	2.25–2.35 m	2.73 dd $J_{IA} = J_{IJ} = 3$
H_J	1.79 $W_{1/2} \sim 8$	2.05 m $W_{1/2} \leq 14$	1.93 ddd $J_{JK} = 7$, $J_{JF} = J_{JI} = 3$	
H_K	1.52 d $J_{KJ} = 7$	1.41 d $J_{KJ} = 7$	1.58 d $J_{KJ} = 7$	1.67 d $J_{KJ} = 8$
H_L	2.31 dd $J_{LA} = 2$, $J_{LJ} = 1.5$			
Me	1.28 s 1.22 s	1.05 s 1.00 s	2.02 s	0.93 t $J = 7.5$



4 5, X = OH 6, X = OTs 7, X = Br 8 9

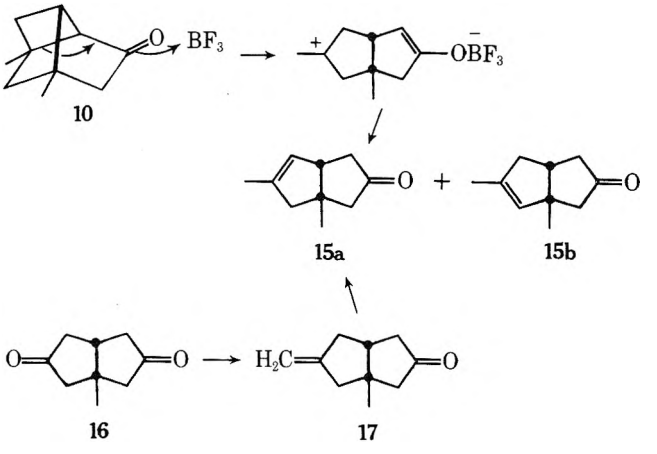


10 14

dehydrohalogenation of 8 was clean, and no *tert*-butyl ether was found. Brief treatment of ketal 9 with 3% aqueous sulfuric acid then gave the desired cyclopentenone 4.

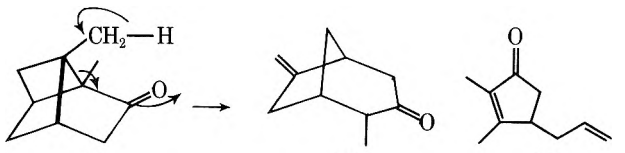
Irradiation of this ketone in benzene solution (~0.0067 M, $\lambda > 3400$ Å) led to rapid isomerization to a single photoproduct in 87% yield. The assignment of structure 10 to this product rests on the NMR data in Table I and on chemical evidence discussed below. In Table I are presented the interpretable portions of spectra of 10 and three tricyclo[3.3.0.0^{2,7}]octane derivatives of known structure.[10] For 12 (≡ 2) and 13 only partial analyses are possible, but 10 and 11 give 220-MHz spectra which can be completely interpreted. The recorded assignments are internally consistent and also agree well with earlier data[11] for bicyclo[2.2.1]heptanes and bicyclo[2.1.1]hexanes. Both of these simpler rigid ring systems are incorporated in the tricyclo[3.3.0.0^{2,7}]octane skeleton. The alternative mode of photocyclization of 4 would lead to structure 14, a tricyclo[4.1.1.0^{3,7}]octan-4-one that incorporates a bicyclo[2.2.0]hexane in its skeleton. No members of the tricyclic series are available for comparison, but it is well known that representative bicyclo[2.2.0]hexanes have NMR spectra quite different from those of bicyclo[2.1.1]hexanes.[12] The data in Table I therefore strongly support 10 as the correct structure for the photoproduct.

Treatment of the photoproduct with boron trifluoride in ether led to rupture of the cyclobutane ring and generation of a mixture of the bicyclo[3.3.0]octenones 15a,b. An authentic sample of these olefins was prepared starting with the readily



10 15a 15b 16 17

available diketone **16**.[13] A Wittig reaction yielded methylene ketone **17**, which was fully characterized, and which on exposure to the acid conditions used with **10** gave the bicyclooctenones **15a,b**. The path depicted for rearrangement of **10** to **15a,b** is straightforward, but such a rearrangement starting with **14** is unlikely; thus, this transformation provides further evidence favoring structure **10**. The ring opening of **10** may be contrasted with the cleavage which occurs on prolonged exposure of carvonecamphor (**11**) to basic alumina. In the latter case, presumably because of the different location of the methyl substituents, it is the alternative cyclobutane bond that breaks with formation of the bicyclo[3.2.1]octanone **18**.[3]



11 18 19

Pyrolysis of carvonecamphor (**11**) results in cleavage of two cyclobutane bonds and formation of the allylcyclopentenone **19**.[3] For this reason we anticipated that pyrolysis of **10** would furnish starting dienone **4**. This proved correct; in the event **4** was accompanied by the mixture of bicyclooctenones **15a,b**, which possibly arises from thermal cleavage of a single cyclobutane bond of **10** and subsequent hydrogen transfer.

These results then provide a new example of regiospecificity in the intramolecular photocyclization of 1,5-hexadienes as well as a route to tricyclo[3.3.0.0^{2,7}]octan-3-ones alternative to the irradiation of vinylcyclohexenes.

Experimental Section

Materials and Equipment. In general these were as previously described.[12] VPC columns used in the present work were A, 25% DEGS, 25 ft × 0.375 in.; B, 10% Carbowax 20M, 5 ft × 0.25 in.; C, 25% DEGS, 15 ft × 0.25 in.; D, 25% DEGS, 25 ft × 0.25 in. All were prepared using 40/60 Chromosorb W and aluminum tubing.

3-Methyl-3-(3-bromo-2-methylpropyl)cyclopentanone (7). The ketol **5**[7] (6.107 g, 35.9 mmol) was treated with *p*-toluenesulfonyl chloride (10.25 g, 53.8 mmol) in pyridine (75 ml) at 0 °C overnight. Standard workup with ether yielded the tosylate as an oil (9.654 g, 83%): ir 3050 (w), 2945 (s), 2860 (m), 1745 (s), 1595 (m), 1462 (m), 1402 (m), 1370 (s), 1185 (s), 1175 (s), 1098 (m), 945 (s), 660 cm^{-1} (m). A mixture of this crude tosylate (9.654 g, 29.8 mmol) and lithium bromide (5.16 g, 59.6 mmol) was heated to reflux in anhydrous acetone (215 ml) for 24 h with protection from atmospheric moisture. The reaction mixture was cooled and some of the acetone was removed in vacuo; water (200 ml) was added and the mixture was extracted twice with ether. The combined ethereal extracts were washed with sodium bisulfite, water, and brine and were dried over $MgSO_4$. Distillation afforded the bromo ketone (6.120 g, 89%, mixture of diastereomers): bp 95–100 °C (0.75 mm); ir 2950 (s), 2925 (m), 2880 (m), 1747 (s), 1458 (m), 1405 (m), 1380 (m), 1227 (m), 1155 cm^{-1} (m); NMR (220 MHz) δ 3.29 (m, 2 H), 2.23–1.60 (m, 8 H), 1.33 (m, 1 H), 1.11 and 1.08 (d, *J* = 6 Hz, 3 H), 1.08 (s, 3 H); mass spectrum *m/e* 232.0461 (M$^+$, calcd for $C_{10}H_{17}BrO$, 232.0462).

4-Methyl-4-(2-methylprop-2-enyl)cyclopentenone (4). The bromo ketone **7** (6.120 g, 26.4 mmol) was brominated in ethylene glycol–tetrahydrofuran (50:2 ml) at 40 °C according to the procedure of Garbisch.[8] The crude dibromo ketal (9.165 g) was taken up in dimethyl sulfoxide (125 ml), and potassium *tert*-butoxide (18 g) was added with external cooling. The mixture was heated at 80 °C for 3.5 h under a nitrogen atmosphere. After cooling and addition of water, the reaction mixture was extracted thrice with pentane. The combined pentane extracts were washed with water and brine and dried over $MgSO_4$. After solvent removal, deketalization was effected with 3% H_2SO_4.[8] Bulb-to-bulb distillation afforded 1.89 g, bp 130–140 °C (8 mm). VPC analysis on column A indicated a multicomponent mixture. The major peak (~35%) was collected and identified as **4**: ir 3060 (w), 2950 (m), 2910 (m), 2855 (w), 1718 (s), 1640 (w), 1585 (w), 1450 (m), 1410 (m), 1370 (m), 1340)w), 1188 (m), 895 cm^{-1} (s); NMR (220 MHz) δ 7.44 (d, *J* = 6 Hz, 1 H), 6.02 (d, *J* = 6 Hz, 1 H), 4.96 (br t, *J* = 0.5 Hz, 1 H), 4.78 (br s, 1 H), 2.34 (d, *J* = 18 Hz, 1 H), 2.22 (d, *J* = 0.5 Hz, 2 H), 2.00 (d, *J* = 18 Hz, 1 H), 1.76 (d, *J* = 0.5 Hz, 3 H), 1.22 (s, 3 H); mass spectrum *m/e* 150.1052 (M$^+$, calcd for $C_{10}H_{14}O$, 150.1044).

5,7-Dimethyltricyclo[3.3.0.0^{2,7}]octan-3-one (10). A benzene solution (70 ml) of dienone **4** (98.5 mg) was irradiated through an uranium glass filter as previously described.[12] The photolysis was terminated when ir spectroscopy indicated no remaining starting material. VPC analysis of the residue remaining after solvent removal indicated one major component. Bulb-to-bulb distillation gave **10** in 87% yield: ir 2950 (s), 2910 (m), 2860 (s), 1742 (s), 1450 (m), 1405 (w), 1375 (m), 1318 (m), 1230 (w), 1185 (w), 1157 (w), 1130 (m), 1090 (w), 1040 (w), 1015 cm^{-1} (w); for NMR see Table I; mass spectrum *m/e* 150.1043 (M$^+$, calcd for $C_{10}H_{14}O$, 150.1044).

1-Methyl-7-methylenebicyclo[3.3.0]octan-3-one (17). Dione **16**[13] (912 mg, 6 mmol) was treated with ethylene glycol (0.34 ml, 6 mmol) and *p*-toluenesulfonic acid (10 mg) in refluxing benzene for 1.5 h with separation of water. The resulting solution was washed with 5% aqueous $NaHCO_3$, then water and dried. The solvent was removed in vacuo to give a yellow oil (988 mg, 84%). Ir and NMR of the crude oil confirmed that ketalization had occurred: ir 1150–1050 cm^{-1} (4 bands, br); NMR (60 MHz) δ 3.80 (–OCH_2CH_2O–). VPC on column B revealed the presence of unreacted dione, some diketal, and the desired monoketal (>50%). A solution of the crude ketal mixture (0.59 g, ~3 mequiv of carbonyl functionality) in dimethyl sulfoxide (0.5 ml, freshly distilled from CaH_2) was added to a solution of methylenetriphenylphosphorane reagent (9 mmol, freshly prepared[14] from 0.45 g of 50% NaH dispersion in oil and 3.24 g of $(C_6H_5)_3PCH_3Br$ in 13.5 ml of dry Me_2SO). The mixture was stirred overnight at room temperature, under nitrogen atmosphere. The resulting mixture was poured over ice (ca. 20 ml), and the water layer was saturated with NaCl and extracted with pentane. The combined pentane layer was dried and the solvent removed in vacuo to give a yellowish oil (0.514 g, 88%). NMR of the crude product confirmed the formation of the desired product **17**: (60 MHz) δ 3.80 (–OCH_2CH_2O–), 4.74 (=CH_2). This crude oil (330 mg, 1.7 mmol) was deketalized using 3.5 ml of 5% HCl for 1 h at room temperature, and the reaction mixture was worked up in the usual fashion to give a yellowish oil (140 mg, 55%). The major component of the mixture was isolated by VPC on column C and identified as enone **17**: ir 3065 (w), 2950 (m), 2920 (w), 2860 (w), 2825 (w), 1745 (s), 1650 (w), 1455 (w), 1432 (w), 1405 (m), 1378 (w), 1265 (w), 1245 (w), 1167 (w), 1130 (w), 880 cm^{-1} (m); NMR (60 MHz) δ 1.18 (s, 3 H), 1.88–2.97 (m, 9 H), 4.83 (m, 2 H); mass spectrum *m/e* 150.1047 (M$^+$, calcd for $C_{10}H_{14}O$, 150.1044).

1,7-Dimethylbicyclo[3.3.0]oct-6- (and 7-) en-3-one (15a,b). A. From 17. A solution of ketone **17** (10 mg) in CH_2Cl_2 (2.5 ml) was treated with boron trifluoride etherate (22 μl of a 1:1 solution in CH_2Cl_2) at 0 °C for 1 h. The mixture was washed with 5% aqueous $NaHCO_3$ and dried over $MgSO_4$. Removal of solvent and VPC on column D gave one peak (>90%). This material was isolated and identified as a mixture of **15a,b** by the characterization data given below.

B. From 10. The procedure described in A above was applied to **10** (20 mg) and yielded >90% of the same mixture of **15a,b**, having ir and NMR spectra and retention time virtually identical with those of the authentic material.

C. From the Ketal of 17. For preparative purposes it was convenient to prepare **15a,b** from the crude ketal of **17** described above. This mixture of olefins was not separable under any conditions tried. In all cases material which was an ~65:35 mixture with the following properties was obtained: ir 3020 (w), 2945 (m), 2905 (m), 2850 (m), 2825 (w), 1740 (s), 1650 (w), 1442 (m), 1400 (m), 1375 (w), 1323 (w), 1245 (m), 1160 (m), 860 cm^{-1} (s); NMR (60 MHz) δ 1.20 and 1.25 (both s, total 3 H, 1.20 major), 1.68 (br s, 3 H), 1.93–2.93 (m, 7 H), 5.13 (m, 1 H).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.07; H, 9.38.

Cyclopentenone 4 from Pyrolysis of 10. Ketone **10** (20 mg, 0.13 mmol) was placed in a glass tube, and the tube sealed under vacuum and held in a Wood's metal bath at 280 °C for 15 min. VPC of the resulting mixture on column D revealed several products and starting material (50%). Two of these were identified as **15a,b** and **4** by ir and NMR spectral comparisons with authentic materials.

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Registry No.—**4**, 59463-14-8; **5**, 59463-15-9; **6**, 59473-88-0; **7** isomer a, 59463-16-0; **7** isomer b, 59463-17-1; **15a**, 59463-18-2; **15b**, 59463-19-3; **16**, 21170-08-1; **16** ethylene acetal, 59463-20-6; **17**, 59463-21-7.

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Photochemistry of 3-Cyano-4,4-dimethyl-2,5-cyclohexadienone. Evidence for Selectivity during the Photorearrangement of Unsymmetric Cyclohexadienones[1]

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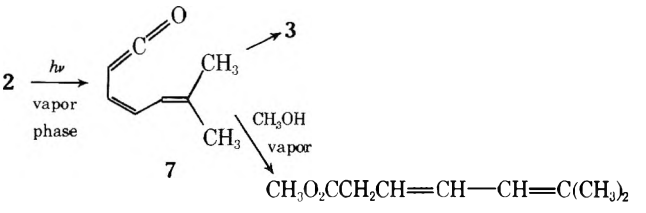
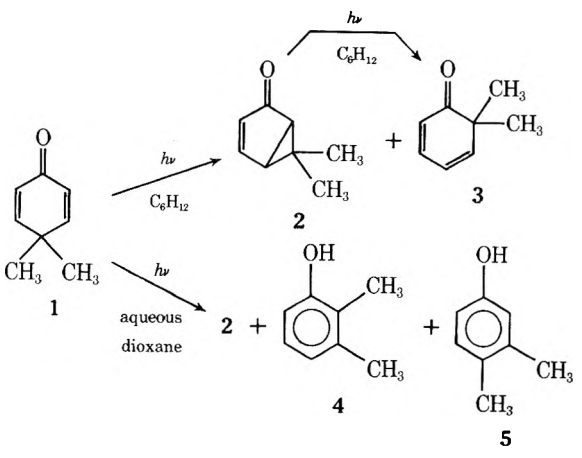
The irradiation of 3-cyano-4,4-dimethyl-2,5-cyclohexadienone (**13**) in *tert*-butyl alcohol gave *tert*-butyl 3-cyano-6-methylhepta-3,5-dienoate (**19**). Irradiation of **13** in moist *tert*-butyl alcohol yielded, in addition to **19**, (3-methyl-2-butenylidene)succinimide (**14**) and 3-carbamoyl-6-methylhepta-3,5-dienoic acid (**16**). Although no isomers resulting from photorearrangement of **13** were observed, the structures of the isolated products indicated that this process had occurred. Consistent with studies of similar systems, the results may be explained in terms of dienone rearrangement to one of two possible bicyclo[3.1.0]hexenones, which affords the observed products via a common ketene intermediate. The exclusive intermediacy of only one bicyclic ketone suggests that the photorearrangement of **13** involves excited-state diradical species.

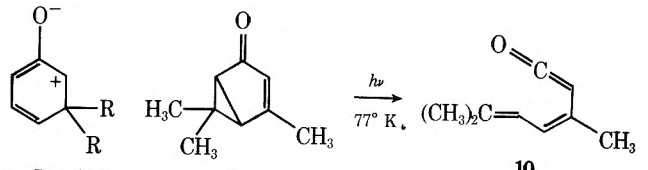
The intramolecular photorearrangements of 2,5-cyclohexadienones in general give rise to three product types: bicyclo[3.1.0]hex-3-en-2-ones, phenols, and 2,4-cyclohexadienones, the latter resulting from recyclization of an intermediate ketene. In nucleophilic media, solvent addition to the ketene affords unsaturated acids or esters. All of these processes are well documented[2] and are typified by the photochemistry of 4,4-dimethyl-2,5-cyclohexadienone (**1**).[3] Irradiation of **1** in cyclohexane yields 6,6-dimethylbicyclo[3.1.0]-hex-3-en-2-one (**2**) and 6,6-dimethyl-2,4-cyclohexadienone (**3**). Irradiation of **2** in cyclohexane affords **3**, while photolysis



of **1** in aqueous dioxane gives **2** plus phenols **4** and **5**. The gas-phase irradiation of **2** likewise affords **3**, whereas addition of methanol vapor effects the formation of ester **6**. The intermediacy of a ketene (**7**) was postulated[3] to account for this behavior.



Extensive investigations of the photorearrangements of 2,5-cyclohexadienones have shown that the bicyclic ketone (e.g., **2**) is the only primary photoproduct.[2c,3] Further transformations of this intermediate are responsible for production of the other species isolated from cyclohexadienone photolysates. To some extent the stepwise nature of these photoconversions has facilitated elucidation of mechanistic details. For example, compelling evidence is available for the intermediacy of a zwitterionic species (e.g., **2a**,[3] **8**[4]) in the photoformation of phenols from bicyclic ketones, and spectroscopic



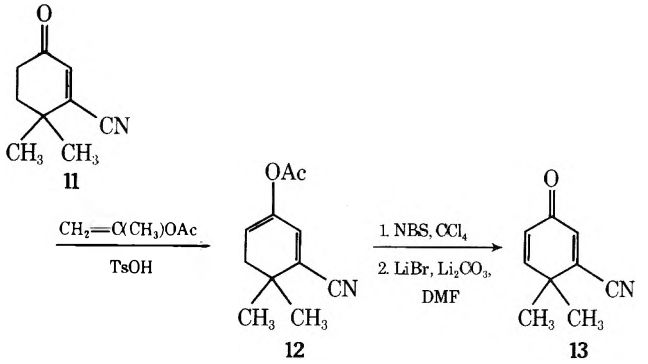
2a, R = CH_3
8, R = C_6H_5 **9** **10**

detection of a ketene intermediate (**10**) during low-temperature irradiation[5] of 4,6,6-trimethylbicyclo[3.1.0]hex-3-en-2-one (**9**) confirms the pathway involved in linear dienone and photoester formation.

Perhaps least well understood are the mechanistic details of the primary photoprocess, 2,5-cyclohexadienone photorearrangement. While the proposed[2c] stepwise mechanism involving 3,5 bonding followed by skeletal rearrangement has been widely applied to explain photorearrangements of this class of compounds, the electron distribution in the molecule at any given point during the transformation remains debatable. Some evidence is available that skeletal rearrangement occurs from a zwitterionic intermediate.[6] In order to probe the electronic character of the carbon skeleton during the rearrangement process, a 2,5-cyclohexadienone was synthesized with a cyano substituent at the C-3 position. This powerful electron-withdrawing group would be expected to destabilize electron-deficient species, thereby retarding rearrangement if it proceeded via a zwitterionic mechanism. On the other hand, electron-rich intermediates should be stabilized and reactivity enhanced.

In designing a suitably substituted 2,5-cyclohexadienone, structural features which might either inhibit 3,5 bonding or induce rearrangement in an atypical fashion (as has been observed for some fused-ring dienones)[2b] were avoided. As anticipated by our previous investigation,[7] 3-cyano-4,4-dimethylcyclohex-2-en-1-one (**11**) was utilized for the synthesis of 3-cyano-4,4-dimethyl-2-cyclohexenone (**13**). A published[8] multiple-step route was utilized, with modifications, as outlined in Scheme I.

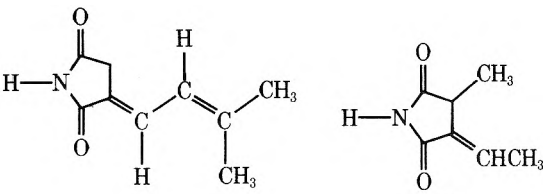
Scheme I



11 **12** **13**

Results

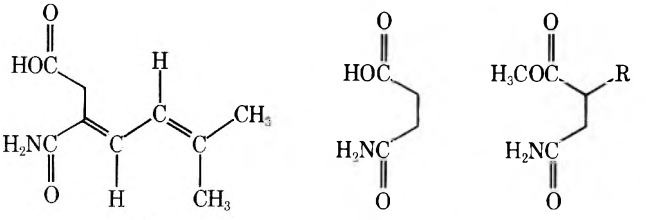
Irradiation of a 10^{-2} M solution of **13** in moist[9] *tert*-butyl alcohol resulted in rapid destruction of the starting material (VPC analysis). Removal of most of the solvent caused precipitation of a tan solid; high-resolution mass spectral analysis of the purified product indicated a molecular formula equivalent to **13** plus the elements of water. The absence of nitrile and ketone functions was determined from ir and qualitative chemical analyses, which also indicated the presence of an imide moiety. A detailed analysis of the NMR and mass spectra permitted identification of the photoproduct as (3-methyl-2-butenylidene)succinimide (**14**). The ir and NMR spectral data reported[10] for methylethylidenesuccinimide (**15**) provide additional support for the correctness of structure **14**.



14 **15**

The structural assignment of compound **14** is also confirmed by its ^{13}C NMR spectrum (Table I). The observed chemical shifts are in good agreement with the predicted values,[11] based on appropriately substituted 1,3-butadienes.[12]

Low-temperature vacuum sublimation of the volatile components of the remaining photolysate afforded a solid residue. The high-resolution mass spectrum of the pure product indicated a molecular formula corresponding to **13** plus the elements of two molecules of water. The ir spectrum showed the presence of OH, C=O, and NH_2 groups, and the absence of a nitrile substituent. On the basis of additional chemical data and the similarity of its proton and ^{13}C NMR spectra (Table I) to those of **14**, this photoproduct was identified as 3-carbamoyl-6-methylhepta-3,5-dienoic acid (**16**).



16 **17** **18**

R = *n*-pentyl, *n*-hexyl, *n*-heptyl

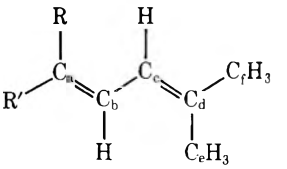
Additional supportive evidence was obtained from the ir spectra of succinamic acid (**17**)[13] and the methyl esters[14] of 2-alkylsuccinamic acids (**18**). An intense peak at *m/e* 124.0762 in the mass spectrum of **16**, corresponding to $(M - C_2H_3O_2)^+$, provided further evidence that the methylene group is situated between the carboxyl group and the olefinic chain, as shown.

The remaining volatile photolysate contained one component in addition to residual solvent and a trace of unreacted **13**. This component was isolated in good yield when **13** was irradiated in anhydrous *tert*-butyl alcohol. Chemical and spectral data suggested that this compound was a nitrile-substituted, unsaturated *tert*-butyl ester. However, the olefinic region of the NMR spectrum, which accounted for two of the 19 protons, exhibited complex coupling which could not be explained on the basis of two adjacent protons in any structure which correlated with the other available data. Spin decoupling experiments revealed that each olefinic proton resonance was in fact a pair of protons in slightly different magnetic environments. The ratio of each of the two proton pairs was approximately 40:60. These data indicated a mixture of two quite similar isomers. Although no method was found which effected complete separation of the isomers without decomposition, partial separation was achieved by column chromatography. Spectral analysis permitted their identification as a mixture of geometric isomers having the general formula **19**. The nonequivalence of the olefinic protons and

$(CH_3)_2C{=}CHCH{=}C(CN)(CH_2)_xCO_2R$
19, R = $(CH_3)_3C$; $x = 1$
20, R = C_2H_5; $x = 0$

previous reports[2b,15] of the isolation of cis and trans photoacids and -esters from cyclohexadienone photolysates suggest structures **19a** and **19b** for the photoesters. Additional support for structure **19** was provided by a detailed analysis of the

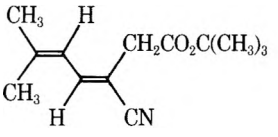
Table I. Carbon-13 Chemical Shifts for Photoproducts of 13[a]



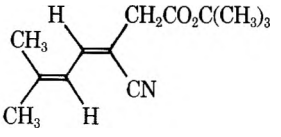
14, R, R′ = $CH_2CONHCO$
16, R = CH_2CO_2H; R′ = $CONH_2$
19a, R = $CH_2CO_2C(CH_3)_3$; R′ = CN
19b, R = CN; R′ = $CH_2CO_2C(CH_3)_3$

Compd (solvent)	C_a	C_b	C_c	C_d	C_e	C_f	C=O	CH_2	*t*-Butyl C–O	*t*-Butyl CH_3	CN
14 ($CDCl_3$)	122.8	130.9	121.1	149.7	19.1	26.9	170.7 174.0	33.5			
16 (Me_2SO-d_6)	126.2	130.7	120.8	143.1	18.5	26.4	170.1 172.1	*b*			
19[c] ($CDCl_3$)	102.8 103.1	141.9 143.3	119.5 122.0	146.5 148.0	19.0	26.5 26.8	167.9 168.4	35.5 40.3	81.6 81.7	27.9	117.5 120.7

[a] The ^{13}C NMR spectra were obtained by the Fourier transform method at 22.63 MHz on a Bruker HFX-90 spectrometer, and chemical shifts are reported in parts per million from Me_4Si internal standard; methine, methylene, and methyl carbons were identified by single frequency off-resonance decoupling for 14 and 19. [b] Chemical shifts of Me_2SO-d_6 solvent appeared in the region where this resonance is expected. [c] The spectrum was obtained only for a mixture of 19a and 19b; chemical shift values were not assigned to the individual isomers.



19a



19b

NMR spectrum of ethyl 2-cyano-5-methylhexa-2,4-dienoate (**20**)[16] (see Experimental Section).

The presence of two structurally similar isomers also follows from the ^{13}C NMR spectrum of **19** (Table I), which exhibits a pair of chemical shifts for each carbon, with the exception of the vinyl and *tert*-butyl methyl carbons which are sufficiently far from the site of geometric isomerism to be equivalent. The chemical shift difference between the two methylene carbons (4.8 ppm) further indicates that in one isomer the methylene group is cis to the isobutenyl moiety, while in the other isomer it is trans. This is also the case for the two nitrile carbons ($\Delta\delta$ 3.2 ppm).[17]

Discussion

The structural similarities in the four products obtained from the photolysis of **13** indicate that they very likely arise from a common intermediate. Ketene **21** is the likely precursor

$(CH_3)_2C{=}CH{-}CH{=}C(CN)CH{=}C{=}O$

21

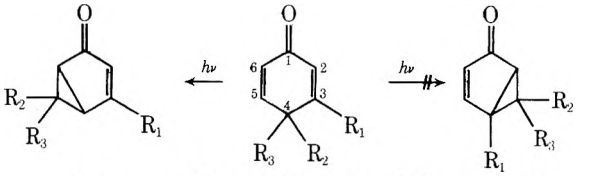
both on the basis of previous studies and structural features of the products. The ketene, in turn, doubtlessly arises either directly or indirectly from a bicyclo[3.1.0]hexenone derived from **13**.

Since it was known[3,5] that bicyclic ketones which readily afford acids or esters in nucleophilic media could be isolated from cyclohexadienone photolyses carried out in cyclohexane, **13** was irradiated in the latter solvent. Although the starting material was rapidly consumed, no low molecular weight products were formed. In another experiment, acetophenone sensitization of the photorearrangement of **13** gave the same products as direct irradiation in *tert*-butyl alcohol. Although this result suggests that the rearrangement occurs via a triplet, the intermediacy of a bicyclic ketone in the phototransformation of **13** has not been demonstrated. However, in light of previous studies and in view of the fact that ketene **21** cannot be formed from **13** by any reasonable bond alteration process not involving at least a transient bicyclic ketone species, 4-cyano-6,6-dimethylbicyclo[3.1.0]hex-3-en-2-one (**22**) is included to explain the formation of the observed products on irradiation of **13** in *tert*-butyl alcohol. Scheme II outlines the overall process.

Irradiation of **13** in *tert*-butyl alcohol results in photoexcitation to **13a**, which, whether diradical or zwitterionic, undergoes 3,5 bonding and rearrangement to give the bicyclic ketone **22**. Cleavage of the 1,2 and 5,6 bonds in **22** affords ketene **21**. Addition of water to **21** gives imide **14** and acid **16**, while *tert*-butyl alcohol addition gives ester **19a** which may partially photoisomerize to **19b**.

The mechanistic details of the formation of **14** and **16** from **21** were not investigated; however, addition of water to the ketene moiety of **21** would give a β-cyano acid. Addition of a second molecule of water would occur spontaneously to give amic acid **16**.[18] Although intramolecular rearrangement of the β-cyano acid could occur to give imide **14**, the sequence of water addition and ring closure to form this product is unresolved, since no precedent could be found in the literature.

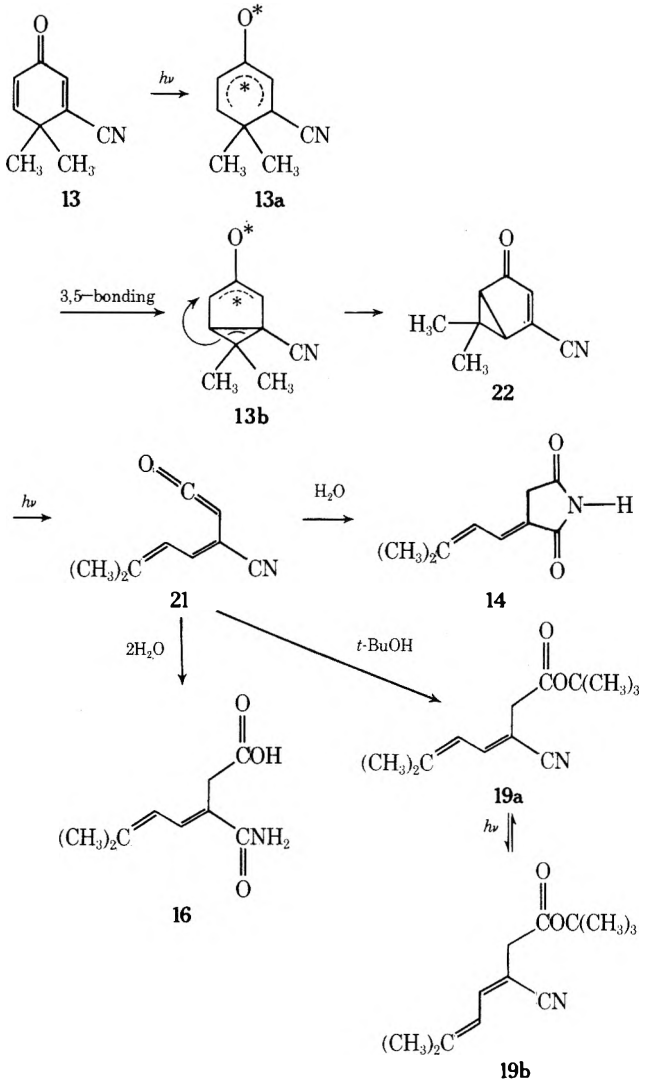
Of particular interest is the indication, based on the structures of the isolated products, that the photorearrangement of **13** gives only one of the two possible bicyclic ketones. This specificity is not unique to **13**; only one bicyclic ketone was reported in each case from the photolyses of the unsymmetrical dienones **23**[5] and **24**.[19] In all of these cases[20] the C-3 substituent completely quenches skeletal rearrangement which would result in bonding between C-2 and C-4 (**26**). The



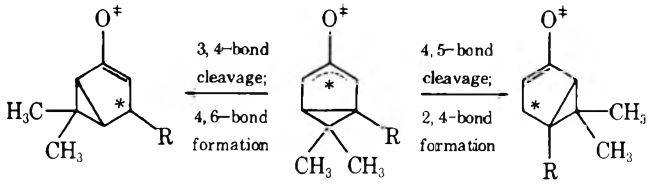
22 **13**, $R_1 = CN$; $R_2 = R_3 = CH_3$ **26**
9 **23**, $R_1 = R_2 = R_3 = CH_3$
25 **24**, $R_1 = R_2 = CH_3$; $R_3 = CCl_3$

preference for rearrangement to the side of the molecule not bearing the C-3 substituent can be explained in terms of a

Scheme II



stepwise mechanism. Following 3,5 bonding, cleavage of the 3,4 bond in **13b** or **23b** results in the formation of a tertiary radical or cation (**13c** or **23c**); on the other hand, formation of **13d** or **23d** via 4,5-bond cleavage would afford a less stable



13c, R = CN
23, R = CH_3

13b, R = CN
23b, R = CH_3

‡ = · or −
* = · or +

13d, R = CN
23d, R = CH_3

secondary radical or cation. Furthermore, although no judgment can be made regarding the electronic nature of the photoexcited species during rearrangement of **23**, since the methyl group at C-3 is capable of stabilizing either cationic or radical character at that position (**23c**), formation of **13c** indicates that the photorearrangement of **13** proceeds via excited-state diradical intermediates, because prior demotion would lead to a zwitterionic species in which the positive charge at C-3 is destabilized by the adjacent cyano group. Indeed, if the 3,5-bonded intermediate **13b** were zwitterionic in nature, the preferred mode of rearrangement in this case would be 4,5-bond cleavage to give **13d** (* = +). This transformation does not occur, however, since no products resulting from a 2,4-bonded bicyclic ketone were present in the photolysate of **13**.[21]

Experimental Section

Instruments and Methods. All melting points are corrected. NMR spectra were measured on Varian A-60, Hitachi Perkin-Elmer RE-20, and Varian HR-220 spectrometers. Ultraviolet spectra were recorded on a Beckman DK-2A spectrophotometer and, unless otherwise noted, were obtained in 95% ethanol. Mass spectra were measured at 70 eV on CEC 21-103C, CEC 21-110B, Hitachi Perkin-Elmer RMU-6, and Finnigan Model 3000 spectrometers. VPC analyses were performed on Varian Model 202b, 1525c, 90P-3, and 1400 instruments. Separations were effected with the following columns: (A) 5 ft × 0.125 in. 3% SE-30 on 100–120 mesh Aeropak 30 (flame ionization); (B) 5 ft × 0.25 in. 20% SE-30 on 60–80 mesh Chromosorb W (thermal conductivity).

1-Cyano-3-acetoxy-6,6-dimethylcyclohexa-1,3-diene (12). A mixture of 30.0 g (0.20 mol) of **11**, 100 g (1.00 mol) of isopropenyl acetate, and 0.50 g (0.0026 mol) of *p*-toluenesulfonic acid monohydrate was heated at 125–130 °C with stirring. The course of the reaction was followed by VPC (column B at 150 °C), and the acetone produced was distilled as formed through a 30-cm zig-zag column maintained at 50–65 °C. After 24 h it was determined that less than 20% of the starting material had been converted; an additional 50 ml of isopropenyl acetate and 0.5 g of *p*-toluenesulfonic acid were added. After 90 h total reaction time VPC analysis showed greater than 95% conversion.

The reaction mixture was cooled and the residual isopropenyl acetate was removed under reduced pressure. The residue was taken up in 1 l. of 1:1 pentane–benzene; this solution was washed with 200 ml of 10% sodium bicarbonate solution. The residue, after solvent removal under reduced pressure, was dissolved in 1 l. of pentane. This solution was concentrated under reduced pressure until a dark polymeric material precipitated. The mixture was filtered and the solid was repeatedly extracted with hot pentane. The filtrate and pentane extracts were combined and concentrated. The residue was dissolved in methylene chloride, dried over sodium sulfate, filtered, and concentrated. Distillation of the residue yielded 33.3 g (0.174 mol, 87.2%) of **12**: bp 88–89 °C (0.4 mm); NMR ($CDCl_3$) δ 6.37 (d, 1, *J* = 1.8 Hz, CH=CCN), 5.67 (d of t, 1, *J* = 5.0 Hz, 1.8 Hz, CH_2 CH=COAc), 2.35 (d, 2, *J* = 5.0 Hz, CH_2), 2.15 (s, 3, $OCOCH_3$), and 1.22 [s, 6, $C(CH_3)_2$].

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.00; H, 7.13; N, 7.19.

3-Cyano-4,4-dimethylcyclohexa-2,5-dienone (13). A mixture of 33.3 g (0.174 mol) of **12**, 32.5 g (0.182 mol, 5% excess) of *N*-bromosuccinimide, and 400 ml of carbon tetrachloride was heated with stirring at the reflux temperature for 7 h. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was taken up in 125 ml of ether and filtered into a separatory funnel; the filtrate was washed with 50 ml of 10% sodium bicarbonate solution and 20 ml of water. The etherate was dried over sodium sulfate, filtered, and concentrated. The residual liquid, which showed a carbonyl peak at 1725 cm^{-1}, was dehydrobrominated without further purification.

To a solution of the above bromination product in 100 ml of *N,N*-dimethylformamide (DMF) were added with stirring 44.7 g (0.513 mol) of lithium bromide and 38.0 g (0.513 mol) of lithium carbonate, followed by an additional 250 ml of DMF. The mixture was stirred at the reflux temperature under nitrogen for 5 h and cooled, and the salts were removed by filtration. The filtrate was poured into 500 ml of water and extracted with four 100-ml portions of methylene chloride. The organic layer was washed with 75 ml of 10% sodium bicarbonate solution followed by 100 ml of water. The resulting mixture was dried over sodium sulfate, filtered, and concentrated. Residual DMF was distilled under aspirator pressure, leaving a black, tarry material which partially solidified upon standing.

The tarry residue was taken up in methylene chloride, and hexane was added until polymeric material precipitated. This mixture was filtered, and the solid was repeatedly extracted with hot hexane. The filtrate and hexane extracts were combined, and the solvents were removed under reduced pressure. The orange-yellow crystalline residue was sublimed twice and finally recrystallized from hexane, yielding 18.2 g (0.124 mol, 61.9%) of greenish-white crystals: mp 62–63.5 °C; ir (CCl_4) 1601 (C=C), 1630 (C=C), 1665 (C=O), 1730, and 2225 cm^{-1} (C≡N); NMR ($CDCl_3$)[22] δ 6.92 [d, 1, *J* = 10.0 Hz, CH=CHC$(CH_3)_2$], 6.72 (d, 1, *J* = 1.6 Hz, CH=CCN), 6.27 [d of d, 1, *J* = 10.0, 1.6 Hz, CH=CHC$(CH_3)_2$], and 1.45 (s, 6, CH_3); uv λ_{max}

(EtOH) 239 nm (ε 16 600) and 334 (39), λ_{max} (*t*-BuOH) 239 nm (ε 17 000) and 334 (38); mass spectrum (70 eV) *m/e* 147 (M^+).

Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.25; H, 6.21; N, 9.63.

The 2,4-dinitrophenylhydrazone was obtained from 95% ethanol as dark orange crystals, mp 190–191.5 °C dec.

Irradiation of 13 in Anhydrous *tert*-Butyl Alcohol. A 500-ml photoreaction vessel equipped with a water-cooled internal Pyrex immersion well was dried at 110 °C for 1 h and was cooled under a nitrogen atmosphere. Into this vessel were placed 3.00 g (0.0204 mol) of **13** and a magnetic stirring bar. *tert*-Butyl alcohol was then distilled from sodium metal directly into the reactor, to a volume of 500 ml. The solution concentration was ca. 0.041 M. A sparging tube was inserted and dry helium was bubbled through the stirred solution for 12 h prior to and during irradiation with a 450-W Hg lamp.

Irradiation was terminated after 180 min. The *tert*-butyl alcohol was removed under reduced pressure at 48 °C. VPC analysis (column B at 155 °C) of the residual oil indicated the presence of one volatile component. This oil was repeatedly extracted with hexane and the combined extracts were concentrated. The residue (3.41 g) was distilled under reduced pressure to yield 2.45 g (0.111 mol, 54.3%) of a light yellow oil; bp 99.5 °C (0.05 mm); NMR ($CDCl_3$)[23] δ 1.43 [s, 9, $C(CH_3)_3$], 1.83 [m, 6, *J* = 1.5, ~0.5 Hz, $(CH_3)_2C{=}C$], 3.12 (m, 40% of 2, *J* = 1, ~0.5 Hz, CH_2CO_2), 3.18 (m, 60% of 2, *J* = 1, ~0.5 Hz, CH_2CO_2), 6.04 [d with secondary splitting, 60% of 1, *J* = 11.5, 1.5 Hz, $(CH_3)_2C{=}CH$], 6.13 [d with secondary splitting, 40% of 1, *J* = 11.5, 1.5 Hz, $(CH_3)_2C{=}CH$], 6.93 [d with secondary splitting, 40% of 1, *J* = 11.5, 1 Hz, $CH{=}C(CN)CH_2$], and 7.06 [d with secondary splitting, 60% of 1, *J* = 11.5, 1 Hz, $CH{=}C(CN)CH_2$]; ir (liquid film) 2215 (C≡N), 1740 (C=O), and 1642 cm^{-1} (C=C); uv λ_{max} 271 nm (ε 27 950); mass spectrum (70 eV) *m/e* (calcd) 221.1426 (221.1415, M^+), 165.0789 (165.0789, M − C_4H_8), 148.0765 (148.0762, M − C_4H_9O), 121.0891 (121.0891, M − $C_5H_8O_2$), 120.0817 (120.0813, M − $C_5H_9O_2$).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.32; H, 8.65; N, 6.41.

This oil gave a negative test with 2,4-dinitrophenylhydrazine reagent.

Double irradiation of the proton resonances in the NMR spectrum indicated the presence of two very similar isomers. No satisfactory method was found for separating these isomers without decomposition; however, partial separation was effected by column chromatography. A 40 × 1 cm column of 100–200 mesh SilicAR CC-7 was prepared and washed with AR hexane. A 0.5-g sample of the above oil was applied; elution was begun with AR hexane. Fractions 1–18 (25 ml each) were combined and concentrated. The residue was analyzed as follows: NMR ($CDCl_3$)[23] δ 1.43 (s, 9), 1.83 (m, 6, *J* = 1.5, ~0.5 Hz), 3.12 (m, 2, *J* = 1, ~0.5 Hz), 6.13 (d with secondary splitting, 1, *J* = 11.5, 1.5 Hz), 6.93 (d with secondary splitting, 1, *J* = 11.5, 1 Hz); ir (liquid film) 2216 (C≡N), 1738 (C=O), and 1642 cm^{-1} (C=C); uv λ_{max} 271 nm.

Elution was continued with 100 ml of hexane–ether (90:10 v/v), followed by 100 ml of 80:20 (v/v) hexane–ether. The combined fractions were concentrated and the residue was analyzed: NMR ($CDCl_3$)[23] δ 1.43 (s, 9), 1.83 (m, 6, *J* = 1.5, ~0.5 Hz), 3.18 (m, 2, *J* = 1, ~0.5 Hz), 6.04 (d with secondary splitting, 1, *J* = 11.5, 1.5 Hz), 7.06 (d with secondary splitting, *J* = 11.5, 1 Hz); ir (liquid film), 2221 (C≡N), 1739 (C=O), and 1641 cm^{-1} (C=C); uv λ_{max} 271 nm.

Each sample of partially purified isomer showed partial decomposition; attempts to further purify these samples resulted in increased decomposition. The NMR and ir spectra of each isomer indicated the presence of minor amounts of the other isomer.

Approximately 50 mg of a light tan solid was isolated from the pot residue of the vacuum distillation of the photolysate. This substance was identified as **14** (vide infra) on the basis of its melting point, solubility properties, and NMR spectrum. No other products were isolated.

Irradiation of 13 in Moist[9] *tert*-Butyl Alcohol. A solution of 3.00 g (0.0204 mol) of **13** in 2.0 l. of moist *tert*-butyl alcohol was placed in a cylindrical irradiation vessel equipped with a water-cooled internal Pyrex immersion well containing a 550-W Hg lamp. UHP nitrogen was bubbled through the solution for 1 h prior to and during irradiation.

Irradiation was terminated after 60 min. The uv spectrum of the photomixture was then obtained by pipetting a 1.0-ml aliquot into a 250-ml volumetric flask and diluting to volume with 95% ethanol. This spectrum showed a λ_{max} 271 nm, *A* − 1.075; no shoulders or other maxima were observed at this concentration (4.1×10^{-5} M) from 220 to 360 nm.

Most of the solvent was removed from the photolysate under reduced pressure. Upon standing, 0.37 g of tan solid separated from the residue. This material was isolated by suction filtration, washed with pentane, and air dried, mp 223–227 °C dec. Recrystallization from ethyl acetate gave white crystals: mp 225–227 °C dec; ir (KBr) 3160 (s), 3060 (s), 2930 (m), 2780 (sh, w), 1755 (m), 1695 (s), and 1618 cm^{-1} (s); NMR (Me_2SO-d_6)[23] δ 11.22 (br s, 1), 7.13 (m, 1, *J* = 12, 2.2, ~1 Hz), 5.95 (m, 1, *J* = 12, ~1 Hz), 3.30 (m, 2, *J* = 2.2, ~1 Hz), and 1.90 (m, 6, *J* = ~1 Hz); uv λ_{max} 289 nm (ε 20 600); mass spectrum (70 eV) *m/e* (calcd) 165.0792 (165.0789, M^+), 150 (150, M − CH_3), 122.0609 (122.0605, M − C_2H_3O), 94.0784 (94.0782, M − CONHCO), 79 [79, M − (CONHCO + CH_3)].

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.31; H, 6.86; N, 8.44.

This compound was found to be insoluble in cold 5% HCl and cold 10% $NaHCO_3$, very slightly soluble in acetone, ether, benzene, CCl_4, CH_2Cl_2, and CH_3CN, slightly soluble in cold water and cold 95% ethanol, and soluble in cold 5% NaOH and cold dimethyl sulfoxide. Negative test results were obtained with 2,4-dinitrophenylhydrazine reagent, $FeCl_3$ (in H_2O or $CHCl_3$), and benzenesulfonyl chloride, while a brown precipitate formed on addition of aqueous potassium permanganate. Based on these data, structure **14** was assigned to this compound.

Low-temperature vacuum sublimation of the filtrate effected separation of volatile and nonvolatile components. The solid residue weighed 0.47 g, mp 153.5–154.5 °C dec. Recrystallization from ethyl acetate gave white crystals: mp 155.0–155.5 ° dec; ir (KBr) 3395 (s), 3205 (s), complex series of bands 3000–2300 (m-w), 1722 (s), 1656 (s), 1638 (m), 1605 (m), and 1570 cm^{-1} (m); NMR (Me_2SO-d_6)[23] δ 12 (br s, 1), 7.17 (br s, 2), 7.16 (d, 1, *J* = 11.5 Hz), 6.07 (m, 1, *J* = 11.5, 1.0 Hz), 3.31 (br s, 2), and 1.86 (d, 6, *J* = 1.0 Hz); uv λ_{max} 278 nm (ε 8700); mass spectrum (70 eV) *m/e* (calcd) 183.0905 (183.0895, M^+), 168 (168, M − CH_3), 166 (166, M − OH), 139.0994 (139.0996, M − CO_2), 124.0762 (124.0762, M − $C_2H_3O_2$).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.56; H, 7.23; N, 7.64.

This compound was very slightly soluble in acetone, ether, benzene, CCl_4, CH_2Cl_2, and CH_3CN, slightly soluble in cold water, moderately soluble in cold 5% HCl and cold 95% ethanol, and soluble in cold 5% NaOH, cold 10% $NaHCO_3$, and cold dimethyl sulfoxide. Functional group tests gave negative results with 2,4-dinitrophenylhydrazine, $FeCl_3$ (in H_2O or $CHCl_3$), and benzenesulfonyl chloride, while addition of aqueous $KMnO_4$ gave a brown precipitate. On the basis of these data, this compound was assigned structure **16.**

VPC analysis (column B at 155 °C) of the volatile portion of the photolysate indicated the presence of a single component (in addition to a trace of **13**). This material was identified by its uv, ir, and NMR spectra as a mixture of **19a** and **19b.**

Irradiation of 13 in Cyclohexane. A solution of 2.00 g (0.0136 mol) of **13** in 750 ml of spectroquality cyclohexane was placed in a 750-ml photolysis vessel equipped with a water-cooled lamp well, magnetic stirring bar, and gas inlet and exit tubes. Deoxygenation was accomplished by bubbling UHP nitrogen through the stirred solution for 1 h prior to and during irradiation with the 550-W Hg arc lamp. Aliquots removed from the reaction mixture at 15-min intervals were analyzed by VPC (column A at 100 °C). The following data were obtained (Table II).

Table II

Irradiation time, min	Relative peak area of **13**	mmol of **13**
0	101	13.6
15	66	8.89
30	35	4.71
45	28	3.77
60	24	3.23
75	23	3.10
90	19	2.56

Irradiation was terminated after 1.5 h. VPC analysis (column A at 100 °C) indicated the absence of an appreciable amount of volatile components other than **13** and solvent. A film of ivory-yellow solid material coated the lamp well. This was dissolved in ether and added to the photolysate. Solvents were removed under reduced pressure, leaving 2.0 g of light yellow gummy residue. An attempt was made to partially separate the components of the mixture by precipitation of high molecular weight solids with hexane. This procedure resulted in isolation of 0.1 g of a yellow solid which, on heating, decomposed at 185–200 °C. NMR analysis (acetone-d_6) showed no olefinic absorption and suggested the presence of many types of methylene and

methyl groups. Elemental analysis did not permit calculation of an empirical formula.

The remainder of the mixture was subjected to steam distillation to isolate volatile components. The steam distillate was extracted with methylene chloride and the combined extracts were dried over sodium sulfate. Filtration and concentration gave a light yellow oil which by VPC and NMR analyses was identified as unchanged **13**. No other volatile components could be isolated from the photolysate.

Ethyl 2-Cyano-5-methylhexa-2,4-dienoate (20). This compound was prepared in 15.1% yield according to a published procedure.[16] The NMR spectrum ($CDCl_3$) was interpreted in greater detail[23] than was reported in the literature:[16] δ 1.31 (t, 3, J = 7 Hz, CH_2CH_3), 2.04 [d, 6, J = 1.5 Hz, $(CH_3)_2C{=}C$], 4.28 (q, 2, J = 7 Hz, CH_2CH_3), 6.43 [d with secondary splitting, 1, J = 12, 1.5 Hz, $(CH_3)_2C{=}CH$], 8.10 [br d, J = 12 Hz, $(CH_3)_2C{=}CHCH{=}C$]. Sharpening of the doublet at δ 8.10 was observed on irradiating the peak at δ 2.04.

Irradiation of 13 in the Presence of Acetophenone. A solution of 0.524 g (0.0036 mol) of **13** and 52.8 g (0.44 mol) of acetophenone in 350 ml of *tert*-butyl alcohol was deoxygenated with UHP nitrogen for 30 min prior to irradiation through a Pyrex filter with 350-nm light. The relative concentrations were adjusted so that at this wavelength acetophenone absorbed 97% of the incident radiation.

After 1 h the irradiation was terminated and the solvents were removed under reduced pressure to give 0.48 g of an amber oil. Spectral analysis of the photolysate indicated the presence of **14** and **19**, in addition to unreacted **13**. No **22** was detected.

Registry No.—**11**, 54303-58-1; **12**, 59463-22-8; **13**, 55341-17-8; **13**, 2,4-DNPH, 59463-23-9; **14**, 59463-24-0; **16**, 59463-25-1; **19a**, 59463-26-2; **19b**, 59463-27-3; **20**, 28525-73-7; isopropenyl acetate, 108-22-5.

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(20) The same selectivity has been reported for two 3-methylspirodienones.[2b]
(21) Alternative mechanistic interpretations,[4b,4c] in which skeletal rearrangement and electron redistribution occur simultaneously, fail to account for the striking selectivity exhibited by 2,5-cyclohexadienones bearing C-3 substituents.
(22) Coupling constants were determined at 220 MHz.
(23) Coupling constants were determined from double irradiation experiments at 60 MHz.

Alicyclic Ring Closure. 1. Preferential Formation of Five-Membered over Seven-Membered Rings in Aldol Ring Closure Reactions

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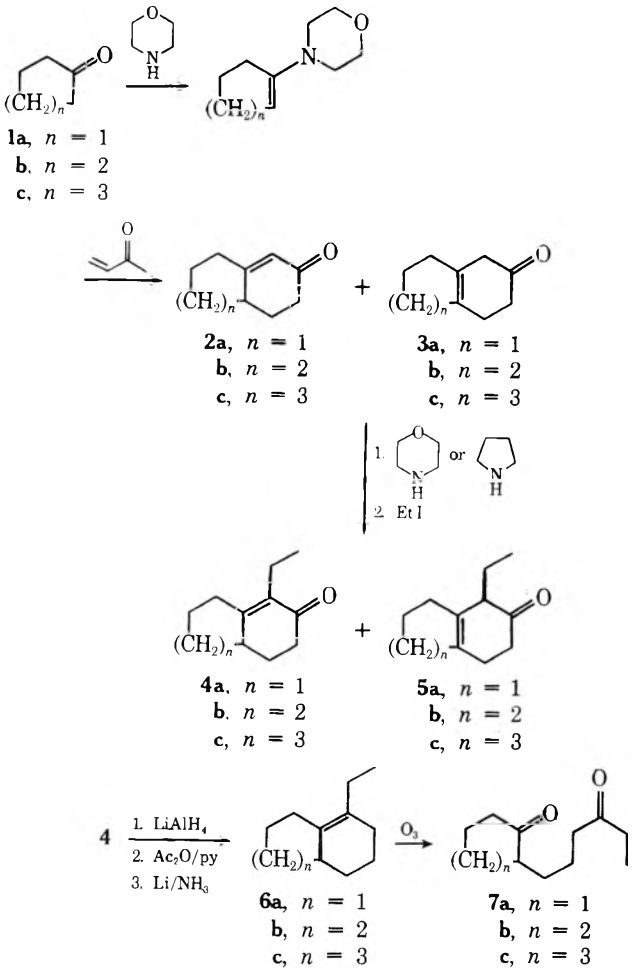
Diones **7a**, **7b**, and **7c**, synthesized from cyclopentanone, cyclohexanone, and cycloheptanone, respectively, were subjected to base-catalyzed aldol cyclization yielding principally an α,β-unsaturated ketone **8**, along with lesser amounts of the β,γ-unsaturated isomer **9**. No seven-membered ring unsaturated ketone **10** could be detected.

The closure of six-membered alicyclic rings has long been recognized as a facile process, particularly by enolate addition to a carbonyl group as in the ring closure step of the Robinson ring annelation procedure.[1] When a five- or seven-membered ring has to be closed, the same methods which work well in closing six-membered rings are usually employed. In the case of the five-membered rings, these are often successful, although sometimes they fail. When they do fail, that fact usually rates only passing mention, making systematic search of the literature for them all but impossible. Any attempt at explanation is usually confined to an inference of adverse steric interaction and/or strain. When the enolate addition methods are used in attempts to close a seven-membered ring, they often fail, although there are successful examples in the literature. Nevertheless, a large percentage of syntheses of compounds containing seven-membered rings, e.g., the hydroazulenic sesquiterpenoids, are actually achieved by ring expansion procedures, either chemical or, more often, photochemical. Nature herself appears to make the hydroazulenic compounds by cyclization of a ten-membered ring.[2] We, therefore, were interested to examine the products obtained from molecules able to close to give a five- or a seven-membered ring, but not a six-membered one. We have examined several such cyclizations where the reaction involved was an aldol reaction performed under conditions where both enolate ion formation and the first step of the aldol were reversible.

Results and Discussion

Diones **7a**, **7b**, and **7c** were synthesized by the route indicated in Scheme I. Robinson annelation reactions of methyl

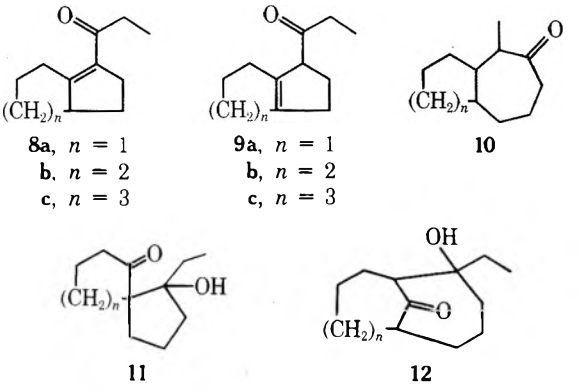
Scheme I



vinyl ketone on the morpholine enamine of the appropriate cycloalkanone **1** gave[3,4] the α,β-unsaturated ketones **2** together with some β,γ-unsaturated[5] isomers **3**. The morpholine or pyrrolidine enamines of **2** were monoalkylated[6] in the α position with 1 equiv of ethyl iodide to give the α,β-unsaturated ketones **4**, again accompanied by the β,γ-unsaturated[5] isomer **5**. No alkylated product could be obtained using ethyl bromide in place of the ethyl iodide. Each ketone mixture **4** and **5** was reduced with lithium aluminum hydride and acetylated, and the allylic acetate was reductively cleaved with lithium in liquid ammonia[7] to yield the alkene **6** together with traces of other isomers. The desired diones **7** were then obtained by ozonolysis, and purified by preparative GLC.

These diones, as relatively dilute solutions, were each refluxed in methanol with ca. 2 equiv of sodium methoxide for 24 h. In each case, the only products detected were the α,β-unsaturated ketone **8** and the β,γ-unsaturated[5] isomer **9**. In the case of diones **7a** and **7b**, a number of different bases were tried, in protic and aprotic solvents, but the products were in each case the same as those obtained using sodium methoxide.

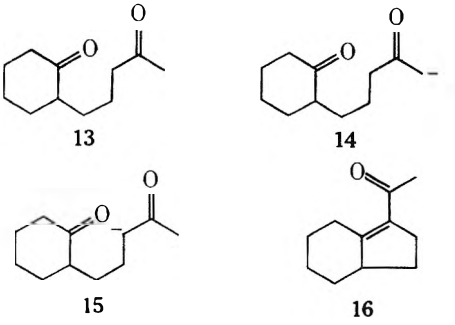
Diones **7** were chosen for this study as being the simplest diones in which opportunities for five- and seven-membered ring closure onto an existing ring are structurally and mechanistically equal, each of the possible enolate ions being C-alkylated. It is usual for the formation of aldols to be reversible.[8] Indeed, were it not for the intramolecular nature of the reaction, it would be expected that the equilibrium would favor the uncyclized diones. Even in these cases, it is not certain that the aldols would be predominant at equilibrium, but the essentially irreversible dehydration which follows serves to drive the reaction to completion. The keto alcohols **11** and **12**, if formed, cannot dehydrate into conjugation, and therefore only the conjugated ketones **8** and **9** are to be expected.



The use of ca. 2 equiv of base was determined to be the best compromise between the formation of by-products and the necessity of excessively long reaction times. The presence of large excesses of base, commonly used in aldol reactions to force the reaction quickly to completion, presumably promotes further (intermolecular) reactions of the various enolates possible.

We could detect no significant difference in the time or conditions required to effect cyclization of the three diones **7a**, **7b**, and **7c**. It is therefore concluded that the size of the ring (five, six or seven membered) *onto* which the new five-membered ring is fused has little influence on the ease of cyclization.

While we recognized at the outset that the bulk of the available evidence pointed to five-membered rings being easier to form than seven-membered ones, we were surprised to find none of the seven-membered ring product. Examination of models does not reveal any steric interaction which can be used to convincingly explain this complete lack of any seven-membered ring product. Interactions involving the terminal methyl groups (of the ethyl groups) in **7** would appear to be relatively unfavorable for formation of the seven-membered ring keto alcohol, yet Meyer and Wolfe[9] found the analogous exclusive formation of the five-membered ring unsaturated ketone **16** from dione **13**, even using a large excess



of base, which would favor the reaction of the kinetically formed[10] enolate **14**. The reaction was, however, slow, and doubtless the thermodynamically favored enolate **15** predominated. No significant unfavorable interaction can be seen to be created upon dehydration of the seven-membered ring keto alcohols, although reluctance of a seven-membered ring to adopt a conformation allowing a planar α,β-unsaturated carbonyl system has been observed[11,12] in monocyclic systems.

We also suppose that C-3 of the side chain comes into proximity of the ring carbonyl much more frequently than

C-5. There is no evidence that seven-membered rings once formed are any less thermodynamically stable than five-membered ones. The heats of combustion of the five-, six-, and seven-membered rings cycloalkanones and cycloalkenones do not, however, appear to have been determined.

Experimental Section[13]

Morpholine Enamines of Cycloalkanones.[14] A solution of 98 g (1.0 mol) of cyclohexanone in ca. 300 ml of benzene was refluxed for 30 h with 95 g (1.5 mol) of morpholine with continuous separation of water. Ca. 20 ml (theory 18 ml) of water was collected. The benzene and excess morpholine were removed under reduced pressure, and the residue distilled, yielding 134 g (80%) of 1-(1-morpholino)cyclohexene as a colorless liquid, bp 93–96 °C (6.0 mm).

Using a similar procedure, 84 g (1.0 mol) of cyclopentanone when refluxed for 18 h with 126 g (2.0 mol) of morpholine gave 103.4 g (80%) of 1-(1- morpholino)cyclopentene, bp 60–64 °C (1.0 mm). Cycloheptanone (112 g, 1.0 mol) refluxed for 48 h with 95 g (1.5 mol) of morpholine and 0.5 g of *p*-toluenesulfonic acid gave 137 g (87%) of 1-(1-morpholino)cycloheptene, bp 125–130 °C (14 mm).

Addition of Methyl Vinyl Ketone to Cycloalkanone Enamines. Cyclohexanone Enamine. A solution of 67 g (0.40 mol) of 1-(1-morpholino)cyclohexene in 400 ml of freshly distilled dioxane was placed in a 3-l. three-necked flask equipped with a mechanical stirrer, condenser, and dropping funnel. A solution of 30 g (0.42 mol) of freshly distilled methyl vinyl ketone was added to the stirred enamine solution over 1 h. The mixture was refluxed for 4 h. Ca. 500 ml of water was added and the reflux continued for 15 h. After the solution cooled to room temperature, it was poured into 650 ml of water and extracted four times with ether (total 300 ml). The ethereal solution was washed with 3 N HCl, saturated sodium bicarbonate solution, and water, and dried over $MgSO_4$. The ether was removed under reduced pressure and the residue distilled, yielding 52 g (56%) of a mixture of ca. 80% $\Delta^{1(2)}$-bicyclo[4.4.0]decenone-3 (**2b**) and ca. 20% $\Delta^{1(6)}$-bicyclo[4.4.0]decenone-3 (**3b**): bp 120–125 °C (12 mm) [lit.[4] 55–60 °C (0.3 mm)]; uv max (EtOH) 239 nm (lit.[3] 238) due to **2b**; ir for **2b** 1680 cm^{-1}; ir for **3b** 1720 cm^{-1}; NMR of **2b** 5.68 ppm (s, vinyl hydrogen); MS *m/e* 150 29, M^+), 121 (100, M − 29).

Cyclopentanone Enamine. A solution of 54 g (0.77 mol) of methyl vinyl ketone was added over 1 h to 100 g (0.65 mol) of 1-(1-morpholino)cyclopentene in 150 ml of benzene. The mixture was refluxed for 6 h and the benzene removed by distillation. Ca. 200 ml of aqueous methanol was added and the solution refluxed overnight. Most of the methanol was distilled off, ca. 400 ml of water was added, and the mixture was extracted with ether. The ethereal solution was dried over $MgSO_4$, the ether removed under reduced pressure, and the residue distilled to yield 67.6 g (65%) of a mixture of $\Delta^{1(2)}$-bicyclo[4.3.0]nonenone-3 (**2a**) and $\Delta^{1(6)}$-bicyclo[4.4.0]nonenone-3 (**3a**), bp 112–116 °C (1.0 mm) [lit.[15] 80–81 °C (0.4 mm)]. The ratio of products varied, apparently depending largely on the length of the reflux with aqueous methanol, from 67% **2a**, 33% **3a** in the above preparation to virtually 100% **2a** when the reflux was extended to 48 h. Spectral details: uv max (EtOH) 237 nm (lit.[16] 237 nm) due to **2a**; ir 1655 cm^{-1} (**2a**), 1710 cm^{-1} (**3a**); NMR 5.73 ppm (s, or perhaps unresolved quartet, J = 2 Hz, vinyl H in **2a**); MS *m/e* 136 (19, M^+), 108 (100, M − 28), 107 (28, M − 29).

Cycloheptanone Enamine. The procedure described for the cyclohexanone enamine was employed. 1-(1-Morpholino)cycloheptene (95 g, 0.52 mol) yielded 67 g of a compound, bp 95–98 °C (0.1 mm), which spectral data, especially the singlet at 2.09 ppm in the NMR, indicated was 2-(oxobutyl)cycloheptanone, the product of the initial Michael step of the Robinson annelation. This dione (65 g) in anhydrous methanol was refluxed overnight under dry nitrogen with ca. 5 g of sodium methoxide. Ether and water were added and the ether separated, washed with 5% HCl, water, and dried over $MgSO_4$. The ether was removed under reduced pressure and the residue distilled, yielding 60 g (70%) of a mixture of $\Delta^{1(11)}$-bicyclo[5.4.0]undecenone-10 (**2c**) and $\Delta^{1(7)}$-bicyclo[5.4.0]undecenone-10 (**3c**): bp 96–98 °C (0.5 mm); uv max (EtOH) 240 nm **2c** [lit.[17] 240 nm (EtOH)]; ir 1660 (**2c**), 1720 cm^{-1} (**3c**); NMR 5.73 ppm (s, vinyl H in **2c**); MS *m/e* 164 (56, M^+), 136 (100, M − 28), 122 (64, M − 42), 108 (66, M − 58).

Alkylation of Unsaturated Ketones 2. Ketone 2b. A solution of 52 g (0.35 mol) of ketone **2b** in 500 ml of toluene was refluxed with 64 g (1.05 mol) of morpholine for 40 h with continuous separation of water. Slightly more than the theoretical quantity of water was obtained. The toluene and excess morpholine were distilled off and the residue distilled yielding 60 g (78%) of the morpholine enamine of **2b**, bp 130–135 °C (0.28 mol). A mixture of 59 g (0.27 mol) of the enamine, 42 g (0.27 mol) of iodoethane, and ca. 250 ml of dry dioxane was refluxed for ca. 50 h. Dilute HCl was added and the solution refluxed overnight. the product was extracted with ether; the ethereal solution was washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated under reduced pressure and the residue was distilled to yield 14.4 g (30%) of a mixture of ca. 70% 2-ethyl-$\Delta^{1(2)}$-bicyclo[4.4.0]decenone-3 (**4b**) and its β,γ isomer 2-ethyl-$\Delta^{1(5)}$-bicyclo[4.4.0]decenone-3 (**5b**) and ca. 30% starting ketone **2b** and its β,γ isomer **3b**. Fractions of almost exclusively alkylated ketones **4b** and **5b** were obtained by distillation on a spinning column, bp 86–92 °C (0.8 mm). **4b** showed uv max (EtOH) 242 nm; ir 1670 cm^{-1}; NMR 0.88 ppm (t, J = 7 Hz, methyl H); MS *m/e* 178 (56, M^+), 163 (6, M − 15), 150 (100, M − 28), 149 (98, M − 29). **5b** showed uv end absorption; ir 1710 cm^{-1}; NMR 0.88 ppm (t, J = 7 Hz, methyl H); MS *m/e* 178 (M^+).

Ketone 2a. A solution of 330 g (2.42 mol) of ketone **2a** in ca. 3 l. of toluene was refluxed with 320 g (4.5 mol) of pyrrolidine for ca. 48 h with continuous separation of water. A total of 50 ml (theory 43 ml) was obtained. The toluene and excess pyrrolidine were distilled off and the enamine distilled, yielding 357 g (78%), bp 120–130 °C (0.50 mm). A mixture of 357 g (1.89 mol) of the enamine and 296 g (1.90 mol) of iodoethane was refluxed in 1 l. of dioxane for 72 h. The mixture was acidified with dilute HCl and refluxed overnight. The mixture was distilled until much of the dioxane had been removed. Water was added, and the mixture extracted with ether. The ethereal extract was washed with water, dried over magnesium sulfate, and distilled to yield a mixture of 2-ethyl-$\Delta^{1(2)}$-bicyclo[4.3.0]nonenone-3 (**4a**), 2-ethyl-$\Delta^{1(5)}$-bicyclo[4.3.0]nonenone-3 (**5a**), and starting ketone **2a**. Fractions of almost exclusively alkylated ketones **4a** and **5a** were obtained by spinning band distillation, bp 78–84 °C (0.07 mm). **4a** showed uv max (EtOH) 227 nm, with shoulder 283 nm; ir 1655 cm^{-1}; NMR 0.91 ppm (t, J = 7 Hz, methyl H); MS *m/e* 164 (47, M^+), 149 (6, M − 15), 136 (100, M − 28), 135 (52, M − 29).

Ketone 2c. A solution of 64 g (0.39 mol) of ketone **2c** in 200 ml of toluene was refluxed with 42 g (0.59 mol) of pyrrolidine for 24 h with continuous separation of water. The toluene and excess pyrrolidine were distilled off and the enamine distilled, yielding 64.2 g (76%), bp 130–135 °C (0.18 mm). A mixture of 64 g (0.39 mol) of the enamine and 96 g (0.615 mol) of iodoethane was refluxed in 500 ml of dioxane for 24 h. Two layers formed, the lower of which contained the enamines. The mixture was acidified with dilute HCl and refluxed overnight. The mixture was extracted with chloroform, and the chloroform extracts washed with saturated $NaHCO_3$ and water and dried over $MgSO_4$. The chloroform was removed under reduced pressure and the residue distilled yielding a mixture of 11-ethyl-$\Delta^{1(11)}$-bicyclo[5.4.0]undecenone-10 (**4c**), 11-ethyl-$\Delta^{1(6)}$-bicyclo[5.4.0]undecenone-10 (**5c**), and starting ketone **2c**. Fractions rich in the alkylated ketone **4c** were obtained by spinning band distillation, bp 115–125 °C (0.28 mm). **4c** showed uv max (EtOH) 243 nm; ir 1670 cm^{-1}; NMR 0.89 ppm (t, J = 7 Hz, methyl H); MS *m/e* 192 (3, M^+), 175 (34, M − 17), 148 (26, M − 54), 77 (100, M − 115).

Partially purified samples of all alkylated ketones were obtained by preparative GLC on a 12 ft Carbowax 20M column at 150 °C. Satisfactory analyses could not be obtained, apparently because the ketones were not particularly stable compounds.

Conversion of Ketones 4 into Alkenes 6. Ketone 4b. A solution of 1.05 g (0.0059 mol) of ketone **4b** in 30 ml of anhydrous ether was added dropwise, under nitrogen, to a cooled (0 °C) suspension of 0.123 g (0.00324 mol) of lithium aluminum hydride in 20 ml of ether. The mixture was allowed to warm to room temperature and stirred for 1.5 h. Water (0.12 ml) was carefully added, followed by 0.12 ml of 15% NaOH and 0.36 ml of water. The salts which precipitated were removed by filtration. The ether solution was separated, dried over $MgSO_4$, and evaporated under reduced pressure to yield 0.60 g (56%) of 2-ethyl-$\Delta^{1(2)}$-bicyclo[4.4.0]decenol-3: ir 3320, 1660 cm^{-1}; NMR 0.97 (t, J = 7, methyl H), 5.4 ppm (broad, CHOH); MS *m/e* 180 (10, M^+), 163 (27, M − 17), 90 (100, M − 90). The crude alcohol, which rapidly oxidized in air, was immediately dissolved in 10 ml of dry pyridine and 2 ml of freshly distilled acetic anhydride added. The mixture was allowed to stand at room temperature overnight. Water was added and the product extracted with chloroform. The chloroform extract was dried over $MgSO_4$, and evaporated under reduced pressure to yield 0.43 g (58%) of 2-ethyl-3-acetoxy-$\Delta^{1(2)}$-bicyclo[4.4.0]decene: ir 1740 cm^{-1}; NMR 0.92 (t, J = 7 Hz, methyl H), 1.99 (s, CH_3CO–), 5.28 ppm (d?, CHOAc); MS *m/e* 222 (0.5, M^+), 162 (65, M − 60), 133 (100, M − 89). The acetate (0.42 g), without further purification, was dissolved in ca. 15 ml of liquid ammonia, and 1.0 g of lithium added. After 2 min, the mixture turned blue. Ether (25 ml) was added, and the ammonia allowed to evaporate. Water was carefully added, followed by dilute HCl. The ether layer was separated, dried over $MgSO_4$, and evaporated to yield 0.32 g (ca. 100%) of crude 2-ethyl-$\Delta^{1(2)}$-bicyclo[4.4.0]decene (**6b**). Pure samples were obtained by preparative GLC

on a 12 ft Carbowax 20M column at 150 °C. In **6b**, ir does not show the double bond stretch; NMR 0.92 (t, J = 7 Hz, methyl H), 1.88 ppm (q, J = 7 Hz, CH_2CH_3), no vinyl signal; MS m/e 164 (27, M^+), 122 (100, M − 42).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.94; H, 12.10.

Ketone 4a. Lithium aluminum hydride (0.07 mol) reduction of 11.4 g of ketone **4a**, using the above procedure, gave 11.87 g (ca. 100%) of 2-ethyl-$\Delta^{1(2)}$-bicyclo[4.3.0]nonenol-3: ir 3300 cm^{-1}; NMR 0.96 (t, J = 8 Hz, methyl H), 5.4 ppm (d?, J = 7 Hz, CHOH); MS m/e 166 (15, M^+), 165 (16, M − 1), 148 (38, M − 18), 147 (47, M − 19), 137 (47, M − 29), 119 (100, M − 47). This crude alcohol was acetylated in 83% yield to give 2-ethyl-3-acetoxy-$\Delta^{1(2)}$-bicyclo[4.3.0]nonene: ir 1735 cm^{-1}; NMR 0.94 ppm (t, J = 7 Hz, methyl H); MS m/e 208 (0.5, M^+), 176 (10, M − 32), 148 (35, M − 60), 147 (35, M − 61), 133 (9, M − 75), 119 (100, M − 89). The crude acetate was reduced with Li/NH_3 to give, *after distillation*, a 50% yield of 2-ethyl-$\Delta^{1(2)}$-bicyclo[4.3.0]nonene (**6a**): bp 51–55 °C (0.25 mm); ir does not show the double bond stretch; NMR 0.95 ppm (t, J = 7 Hz, methyl H); MS m/e 150 (53, M^+), 121 (100, M − 29), 107 (17, M − 43), 93 (50, M − 57).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93, H, 12.07. Found: C, 87.99; H, 12.02.

Ketone 4c. Lithium aluminum hydride reduction of 44 g of ketone **4c** gave 39 g (85%) of 11-ethyl-$\Delta^{1(11)}$-bicyclo[5.4.0]undecenol-10: ir 3350 cm^{-1}; NMR 1.00 (t?, J = 7 Hz, methyl H), signals at 6.23 (s) and 6.82 ppm (d) are assigned to the –CHOH protons in the two epimeric alcohols possible; MS m/e 194, (4, M^+), 193 (10, M − 1), 176 (46, M − 18), 175 (100, M − 19), 150 (84, M − 44), 135 (71, M − 59). Acetylation of the alcohol gave 11-ethyl-10-acetoxy-$\Delta^{1(11)}$-bicyclo-[5.4.0]undecene; ir 1735 cm^{-1}; NMR the methyl triplet appears to be at 0.93 ppm, but is obscured by other signals; the CH_3CO signal at 1.93 ppm is split, presumably due to the two epimers present, signals at 6.22 (s) and 6.83 ppm (d) are assigned to the CHOAc protons in the two epimers; MS parent ion is not seen convincingly, m/e 174 (61, M − 62), 149 (100, M − 85). The crude acetate (10 g) was reduced with Li/NH_3 to yield 12 g (ca. 100%) of 2-ethyl-$\Delta^{1(11)}$-bicyclo[5.4.0]undecene (**6c**): ir double bond stretch does not show; NMR 0.96 ppm (t, J = 7 Hz, methyl H); MS 178 (46, M^+), 163 (8, M − 15), 149 (100, M − 29), 135 (46, M − 43), 122 (24, M − 56).

Anal. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.39; H, 12.38.

Diones 7a, 7b, 7c. Dione 7b. Batches of 6 g of alkene **6b** (total 44 g, 0.27 mol) in 35 ml of methylene chloride containing 1 ml of freshly distilled pyridine[18] was ozonized at −78 °C for 3 h. The mixture was allowed to come to room temperature, and the successive batches were added dropwise to a stirred mixture of 750 ml of water, 6.6 g of zinc dust, and 23 ml of glacial acetic acid. The stirring was continued for 1 h after the last addition. The solution was filtered, extracted with chloroform, the chloroform extracts washed with $NaHCO_3$ and water, and dried over anhydrous $MgSO_4$. The residue was distilled to yield 48 g (91%) of 2-(4-oxohexyl)cyclohexanone (**7b**), bp 107–110 °C (0.05 mm). A small sample was purified by preparative GLC on a 15 ft Carbowax column at 185 °C: ir 1700 cm^{-1}; NMR 1.00 (t, J = 7 Hz, methyl H), 2.32 ppm (complex signal due of protons on C's α to carbonyls); MS m/e 196 (16, M^+), 149 (63, M − 57), 121 (62, M − 75), 98 (100, M − 98).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.22; H, 10.10.

Dione 7a. Alkene **6a** was ozonized as above to give 2-(4-oxohexyl)-cyclopentanone (**7a**): ir 1745 and 1720 cm^{-1}; NMR 1.00 (t, J = 7 Hz, methyl H), 2.2–2.5 ppm (complex signal due to protons on C's α to carbonyls); MS m/e 182 (30, M^+), 153 (10, M − 29), 138 (47, M − 44), 135 (43, M −47), 110 (100, M − 72), 107 (67, M − 75).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.35; H, 9.96.

Dione 7c. Alkene **6c** was ozonized as above to give ca. 50% yield of 2-(4-oxohexyl)cycloheptanone (**7c**), which was purified by filtration through a silica column in CCl_4/ether. Spectral and analytical samples were again purified by preparative GLC: ir 1710 cm^{-1}, with some evidence of splitting; NMR 1.00 (t, J = 8 Hz, methyl H), 2.2–2.6 ppm (complex signal due to protons on C's α to carbonyls); MS m/e 210 (6, M^+), 167 (16, M − 43), 163 (20, M − 47), 135 (26, M − 75), 126 (32, M − 84), 112 (100, M − 98).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.32: H, 10.68.

All diones slowly turned yellow in light, and were stored under N_2, in the dark at 0 °C or below.

After samples of the pure diones and intermediates were available, losses in the syntheses, resulting mainly from purification problems, were greatly reduced by carrying all steps from the ketones **2** to the diones **7** without intermediate purification. The major impurities were compounds with molecular weight (by MS) 28 amu higher than those of the desired compounds. These doubtless arise from dialkylation of the starting ketones, a not unexpected side reaction.[6]

Cyclization of Diones. Dione 7b. Dione **7b** (0.20 g, 1.02 mmol) in 15 ml of anhydrous methanol was refluxed overnight under nitrogen with 0.11 g (2.04 mmol) of sodium methoxide. Water was added, and the mixture extracted with ether. The ether extract was washed three times with water, dried over $MgSO_4$, and evaporated to give 0.19 g of a crude mixture of two products. Samples of the products were obtained by preparative GLC on a 15 ft Carbowax column at 160 °C. The major component was 8-propionyl-$\Delta^{1(9)}$-bicyclo[4.3.0]nonane (**8b**): uv max (EtOH) 255 nm (ϵ 4356);[19] ir 1675, 1610 cm^{-1}; NMR 1.00 ppm (t, J = 7 Hz methyl H), no vinyl signals; MS m/e 178 (73, M^+), 149 (100, M − 29), 121 (33, M − 57).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.62; H, 10.08.

The minor component was 8-propionyl-$\Delta^{1(6)}$-bicyclo[4.3.0]nonane (**9b**): uv (EtOH) end absorption 207 nm (ϵ 3570); ir 1705 cm^{-1}; NMR 0.98 (t, J = 7 Hz, methyl H), 2.37 (q, J = 7 Hz, CH_2CH_3), 2.1 ppm (signal due to allylic H); MS m/e 178 (15, M^+), 149 (13, M − 29), 121 (100, M − 57).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.94; H, 9.98.

Dione 7a. Treatment of dione **7a** in the same manner yielded, as major component, 2-propionyl-$\Delta^{1(2)}$-bicyclo[3.3.0]octene (**8a**): uv max (EtOH) 253 nm (ϵ 4230); ir 165 cm^{-1}, with shoulder at 1640 cm^{-1}; NMR 1.09 (t, J = 7 Hz, methyl H), 2.60 ppm (q, J = 7 Hz, $COCH_2CH_3$), no vinyl signals; MS m/e 164 (55, M^+), 135 (100, M − 29), 107 (38, M − 57).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.23; H, 9.82.

The minor component was 2-propionyl-$\Delta^{1(5)}$-bicyclo[3.3.0]octene (**9a**): uv end absorption; ir 1705 cm^{-1}; NMR 1.03 ppm (t, J = 7 Hz, methyl H). no vinyl signal; MS m/e 164 (18, M^+), 135 (12, M − 29), 107 (100, M − 57).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 81.56; H, 9.96.

Dione 7c. Treatment of dione **7c** in the same manner yielded, as major component, 10-propionyl-$\Delta^{1(10)}$-bicyclo[5.3.0]decene (**8c**): uv max (EtOH) 257 nm (ϵ 4163); ir 1660, 1600 cm^{-1}; NMR 1.00 ppm (t, J = 7 Hz, methyl H), no vinyl signal; MS m/e 192 (26, M^+), 163 (100, M − 29), 135 (16, M − 57).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.89; H, 10.66.

The minor component was 10-propionyl-$\Delta^{1(7)}$-bicyclo[5.3.0]decene (**9c**): uv (EtOH) end absorption 209 nm (ϵ 3676); ir 1705 cm^{-1}; NMR 1.08 ppm (t, J = 7 Hz, methyl H), no vinyl signal; MS m/e 192 (10, M^+), 163 (10, M − 29), 135 (100, M − 57).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.37; H, 10.25.

Other Cyclization Conditions. Dione **5a** was cyclized to the same product mixture as above under each of the following conditions: potassium *tert*-butoxide in *tert*-butyl alcohol, reflux 24 h; potassium *tert*-butoxide in Me_2SO, reflux 24 h; KOH in EtOH/water, reflux 48 h; K_2CO_3 in EtOH/water, reflux 48 h.

Dione **5b** was also cyclized to the same mixture as above using potassium *tert*-butoxide in *tert*-butyl alcohol.

Acknowledgments. We acknowledge the generous financial support of the Robert A. Welch Foundation. We thank Robert S. Brown, Purvis Harper, and Mary B. Neal for assistance with the syntheses.

Registry No.—**2a,** 1489-28-7; **2b,** 1196-55-0; **2c,** 19198-29-9; **3a,** 14661-63-3; **3b,** 13837-12-2; **3c,** 59562-88-8; **4a,** 59562-89-9; **4b,** 59562-90-2; **4c,** 59562-91-3; **5a,** 59562-92-4; **5b,** 59562-93-5; **6a,** 59563-01-8; **6b,** 59563-02-9; **6c,** 59563-03-0; **7a,** 59574-51-5; **7b,** 59574-52-6; **7c,** 59574-53-7; **8a,** 59562-95-7; **8b,** 59562-96-8; **8c,** 59562-97-9; **9a,** 59562-98-0; **9b,** 59562-99-1; **9c,** 59563-00-7; 1-(1-morpholino)cyclohexene, 670-80-4; methyl vinyl ketone, 78-94-4; 1-(1-morpholino)cyclopentene, 936-52-7; 1-(1-morpholino)cycloheptene, 7182-08-3; 2-ethyl-$\Delta^{1(2)}$-bicyclo[4.4.0]decenol-3, 59574-54-8; 2-ethyl-3-acetoxy-$\Delta^{1(2)}$-bicyclo[4.4.0]decene, 59574-55-9; 2-ethyl-$\Delta^{1(2)}$-bicyclo[4.3.0]nonenol-3, 59574-56-0; 2-ethyl-3-acetoxy-$\Delta^{1(2)}$-bicyclo[4.3.0]nonene, 59574-57-1; *cis*-11-ethyl-$\Delta^{1(11)}$-bicyclo-[5.4.0]undecenol-10, 59574-58-2; *trans*-11-ethyl-$\Delta^{1(10)}$-bicyclo[5.4.0]undecenol-10, 59574-59-3; *cis*-11-ethyl-10-acetoxy-$\Delta^{1(10)}$-bicyclo[5.4.0]undecene, 59574-60-6; *trans*-11-ethyl-10-acetoxy-$\Delta^{1(10)}$-bicyclo[5.4.0]undecene, 59574-61-7; 2-(oxobutyl)cycloheptanone, 26871-79-4.

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Equilibria between α,β- and β,γ-Unsaturated Ketones in Six-Membered Rings Fused β,γ to Five-, Six-, and Seven-Membered Rings

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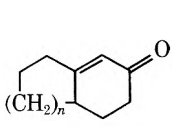
The equilibria between α,β- and β,γ-unsaturated ketones have been determined for a series of bicyclic ketones **2**, **4**, and **8** and **3**, **5**, and **9**. Alkylation on the α position increases the percentage of β,γ-unsaturated isomer at equilibrium. Steric and hyperconjugation effects in these and other acyclic and cyclic unsaturated ketones, esters, carboxylic acid salts, and nitriles are discussed.

In the course of the synthetic work described in the preceeding paper,[1] we encountered several α,β-unsaturated ketones in which the percentage of β,γ-unsaturated isomer present, even after equilibration, seemed significantly high. Accordingly, we undertook a systematic study of the available unsaturated ketones.

It has long been recognized that α,β-unsaturated carbonyl compounds, when treated with acid or base, tautomerize to a mixture of α,β- and β,γ-unsaturated isomers. The earliest work was that of Kon and Linstead, who investigated alkali catalyzed equilibria in series of acyclic unsaturated carboxylic acids[2-8] **17a/18a**, cyanides[9-10] **17b/18b**, and ethyl esters[5,11] **17c/18c**. This work has been summarized with the assistance of Linstead.[12] Unsubstituted carboxylic acid salts and esters equilibrate to give almost exclusively the α,β isomer. One γ-alkyl substituent will shift the equilibrium toward the β,γ isomer, while two γ substituents will suffice to make the β,γ isomer predominate. Substitution on the β carbon seems, from limited evidence in the acid series, to favor the β,γ isomer, but not to the same degree as a γ substituent. α-Substitution in the carboxylic acid series moderately favors the α,β isomer.



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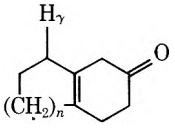
b, $n = 2$
c, $n = 3$



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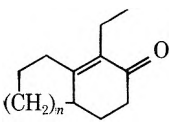

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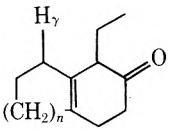

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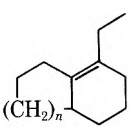

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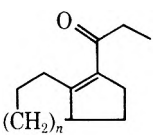

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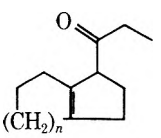
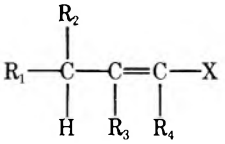
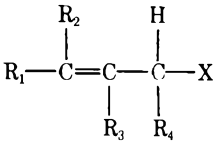


9a, $n = 1$
b, $n = 2$
c, $n = 3$



17a, X = CO_2^-
b, X = CN
c, X = CO_2Et
d, $R_1 = R_3 = R_4 = H$; $R_2 = Et$; X = $COCH_3$
e, $R_1 = Et$; $R_3 = H$; $R_4 = Me$; X = CO_2Et



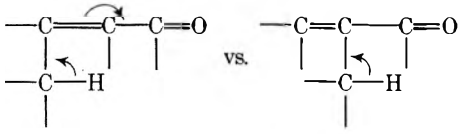
18a, X = CO_2^-
b, X = CN
c, X = CO_2Et
d, $R_1 = R_3 = R_4 = H$; $R_2 = Et$; X = $COCH_3$
e, $R_1 = Et$; $R_3 = H$; $R_4 = Me$; X = CO_2Et

In an acyclic ketone experiment, Eccott and Linstead[13] reported an equilibrium composition of 25% β,γ isomer, 75% α,β isomer for the heptenones **17d/18d**, and it has been stated[12] that β- and γ-substitution affect the equilibrium in ketones much as in the acid and ester series, but that α-substitution also shifts the equilibrium toward the α,β isomer, in contrast to the carboxylic acid series. The basis of this statement is not clear.

That a γ-alkyl substituent should stabilize the β,γ isomer is not surprising, and Rinehart and Dolby[14] have shown that for the ethyl esters **17e/18e**, the percentage of α,β isomer is 45% for R_2 = Me, 68% for R_2 = Et, 78% for R_2 = *i*-Pr, and 86% for R_2 = *t*-Bu, the order to be expected if hyperconjugation is the major factor stabilizing the β,γ double bond. There must, of course, also be some steric factors involved in the above series. Dolby and Riddle[15] have very carefully examined the equilibria for a series of unsaturated esters **19/20**, where the hyperconjugative effects are transmitted through the phenyl ring, and where steric effects are essentially the same in all members of the series. Again, the order predicted on the basis of hyperconjugation is found; the percentage of α,β-unsaturated isomer at equilibrium, using sodium ethoxide in ethanol at 77 °C, was 59% where R = H, 40% where R = Me, 46% where R = Et, 50% where R = *i*-Pr, and 52% where R = *t*-Bu. Bateman and Cuneen[16] used stabilization factors derived from equilibrations of γ-alkylphenylpropenes to quantitatively evaluate the equilibria studied by Kon and Linstead, with some success.

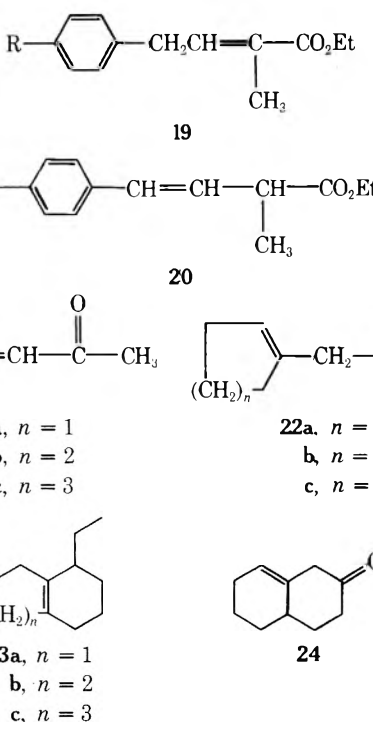
A β-alkyl substituent will stabilize the double bond in both the α,β- and β,γ-unsaturated isomers. Bateman and Cuneen used the same stabilization factor for hyperconjugation between an alkyl group and a nonconjugated double bond and between an alkyl group and either carbon of the C–C double bond of a conjugated system. Hence, their analysis predicts that a β substituent will not change the equilibrium. The fact that such a substituent does change the equilibrium in favor of the β,γ isomer (at least in cases where there is also a γ substituent) suggests that hyperconjugative stabilization of the nonconjugated double bond is greater.

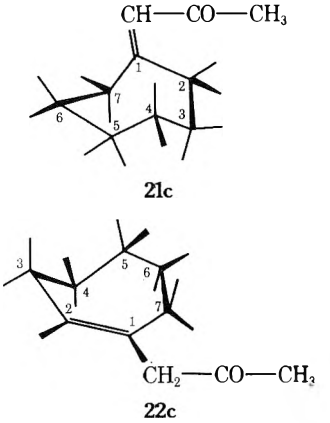
Hyperconjugation due to an α-alkyl substituent on an α,β-unsaturated carbonyl (or similar) system may well not be as powerful a stabilizing force as hyperconjugation at a terminal (β) position. In the latter case, the hyperconjugation is



supplying electrons to a carbon which is clearly becoming electron deficient. Unfortunately, insufficient experimental evidence is available on this point.

In cyclic systems, steric effects can be much more important than in acyclic systems. Kon and co-workers examined the equilibria between the cycloalkylidene methyl ketones **21** (α,β unsaturated) and the cycloalkenyl methyl ketones **22** (β,γ unsaturated). The five-membered ring compounds **21a/22a** equilibrated to 77% α,β isomer,[17,18] the six-membered ring ketones **21b/22b** to 23% α,β isomer,[19] and the seven-membered ring ketones **21c/22c** to 60% α,β isomer.[18,20] These equilibria were obtained first in alkaline conditions, but later the same results were obtained under acid conditions.[21] Clearly, conformational effects are the controlling influence in these ketones. Presumably the added angle strain of a second sp^2 carbon mitigates against the β,γ isomer in the five-membered ring. In comparing the exocyclic (α,β isomer) and endocyclic (β,γ isomer) double bonds in the six-membered ring, the cyclohexane ring in the α,β isomer **21b** adopts approximately a chair conformation,[22] with 1,3-diaxial interactions between C-2 and C-4, C-2 and C-6, C-4 and C-6, and C-3 and C-5. The β,γ isomer **22b** adopts the flattened cyclohexene conformation,[23] with only two 1,3-diaxial interactions (C-4, C-6 and C-3, C-5). This difference is apparently enough to shift the equilibrium so that it favors the β,γ isomer. The seven-membered ring with the exocyclic double bond (α,β isomer **21c**) shows a conformation (see diagram) with 1,3-diaxial interactions between C-3 and C-5, C-4 and C-6, and C-5 and C-7, with the C-3, C-5 interaction being increased by the hydrogens being pointed toward each other. There is also a C-3 and C-7 1,4-diaxial interaction. The β,γ isomer **22c** (see diagram) has normal 1,3-diaxial interactions between C-3 and C-5, C-4 and C-6, and C-5 and C-7. It also has a C-3 and C-7 1,4-diaxial interaction. Thus, the β,γ isomer is favored only because of the abnormally severe C-3 and C-5 interaction in the α,β isomer. It does appear then that Kon's results can be explained using conformational factors.





The acid-catalyzed equilibria between α,β- and β,γ-unsaturated ketones in a series of 4-alkylcyclohexenones has been investigated by Lewis and Williams.[24] With no 4-alkyl substituent, essentially no β,γ isomer is present at equilibrium. The percentage of β,γ isomer varies from 30% for methyl and ethyl, 40% for isopropyl, to 50% for *tert*-butyl. This is, of course, opposite to the order expected from hyperconjugation effects, and was explained in terms of the absence of any significant steric interaction between the alkyl group and ring hydrogens in the β,γ isomer in its nonflexible flattened boat

Table I. Equilibria under Acidic Conditions[a]

α,β		β,γ		ΔG°
2a	>99%	**3a**	<1%	
2b	>99%	**3b**	<1%	
2c	>99%	**3c**	<1%	
4a	92%	**5a**	8%	+1.5
4b	96%	**5b**	4%	+1.9
4c	96%	**5c**	4%	+1.9
8b	44%	**9b**	50%	−0.14

[a] ΔG° values in kcal/mol. All experiments carried out in light.

conformation, and the presence of such an interaction in the α,β isomer.

Results

The unsaturated ketones **2a**, **2b**, **2c**, **4a**, **4b**, **4c**, and **8a**, **8b**, **8c** were prepared as previously described[1] by cyclization of the appropriate dione. As obtained from the syntheses, all ketones contained varying but significant (usually 20% or more) amounts of the corresponding β,γ-unsaturated ketones **3**, **5**, and **9**.

It has been found[25] that α,β- and β,γ-unsaturated ketones have a tendency to reequilibrate on attempted distillation, possibly due to the glass having sufficient basic or acidic properties (depending on its previous treatment) to catalyze the equilibration. Gas chromatography on a Carbowax column was chosen as the most convenient analytical technique. It was, however, essential to show that equilibration did not occur in the injection port or on the column. Details of the GLC procedures and precautions are given in the Experimental Section.

For equilibration studies, the procedure adopted for each pair of compounds was as follows. Small quantities of pure α,β-unsaturated and pure β,γ-unsaturated isomers were obtained by preparative GLC. These were separately dissolved in methanol and stirred with HCl at room temperature until no further changes in isomer ratios could be observed on the GLC. A maximum of about 18 h was required. The isomer ratios obtained by measurement of the area under each peak proved to be identical in each equilibration within the limits of measurement error. These results are shown in Table I.

We also attempted to study the isomer mixtures arising from kinetic protonation of the enolate ion, formed using potassium *tert*-butoxide in *tert*-butyl alcohol, with dilute acetic acid after the method of House et al.[26,27] As can be seen from Table II, we obtained results identical within experimental error with those obtained by equilibration with HCl, leading us to believe that the conditions we were using did not prevent isomerism subsequent to protonation, or were achieving protonation on oxygen to give the enol, which was tautomerizing to the equilibrium mixture. In the case of **2b**, for which House[26] reported a mixture of 15% **2b**, 30% **3b**, and 55% **24** by NMR analysis, we repeated the experiment several times (increasing the concentration of base, using more dilute acetic acid, etc.), but could not detect any of the isomer **24**. We have not yet pursued these experiments further. It should be noted that we did not distill our products and that our experiments were on a much smaller scale.

In order to gain some insight into the relative stability of the double bond in ketones **4** and **5**, we subjected the alkenes **6** and **23** equilibration with *p*-toluenesulfonic acid in benzene, under reflux initially to hasten the attainment of the equilibrium. The alkenes **23** required to approach the equilibrium from that side were obtained by preparative GLC from the mixtures produced by acid treatment of the alkenes **6**. The results are shown in Table III.

Table II. Product Mixtures Observed on Protonation of Enolate Ions[a]

α,β		Registry no.	β,γ		Registry no.	ΔG°
2a	>99%	1489-28-7	**3a**	<1%	14661-63-3	
2b	>99%	1196-55-0	**3b**	<1%	13837-12-2	
2c	>99%	19198-29-9	**3c**	<1%	59562-88-8	
4a	93%	59562-89-9	**5a**	7%	59562-92-4	+1.5
4b	96%	59562-90-2	**5b**	4%	59562-93-5	+1.9
4c	96%	59562-91-3	**5c**	4%	59562-94-6	+1.9
8a	67%	59562-95-7	**9a**	33%	59562-98-0	+0.42
8b	44%	59562-96-8	**9b**	56%	59562-99-1	−0.14
8c	41%	59562-97-0	**9c**	59%	59563-00-7	−0.22

[a] ΔG° values in kcal/mol. All experiments carried out in light.

Table III. Equilibration of Alkenes[a]

Compd with exocyclic double bond		Compd without exocyclic double bond		ΔG°	Registry no. 6	Registry no. 23
6a	54%	**23a**	46%	+0.1	59563-01-8	59563-04-1
6b	17%	**23b**	83%	−0.9	59563-02-9	59563-05-2
6c	42%	**23c**	58%	−0.2	59563-03-0	59563-06-3

[a] ΔG° values in kcal/mol.

Discussion

It can be seen from Table I that, although the α,β-unsaturated isomer remains favored by a substantial energy difference, alkylation in the α position *decreases* the percentage of α,β-unsaturated isomer at equilibrium. However, the percentage of α,β-unsaturated isomers **2** and **4** is, in each case, higher than most of the examples discussed in the introduction. Ketones **2/3** can be considered as β,γ dialkylated and ketones **4/5** as α,β,γ trialkylated. It must be remembered, however, that is is the differences between the α,β and β,γ isomers rather than the actual substitution pattern which is important unless the hyperconjugative factors override the steric interactions. In the light of the data presented in the introductory discussion, this appears unlikely. An examination of models reveals that in the β,γ isomer, there is an eclipsed 1,3 interaction between the quasi-equatorial hydrogen or methyl group on the α carbon and the quasi-equatorial hydrogen on the nearest allylic carbon (H_γ in **3** and **5**). This interaction is much less—it is staggered—in the α,β isomer, and may be the major difference. The interaction is more severe in the alkylated ketones **5**, so that the greater percentage of β,γ isomer in those cases may reflect the hyperconjugative effect of the alkyl group, only partly counteracted by the added steric interaction.

The six-membered ring can be expected to adopt at least approximately the same conformation in all the α,β-unsaturated isomers, because of the planar nature of the conjugated system. The β,γ isomers appear, from models, to each have a similar flattened boat conformation.[23] Thus, the differences between the equilibria in **4a/5a**, **4b/5b**, and **4c/5c** should reflect the conformational effects of the other ring. It is seen that the observed results do not parallel those of Kon in the cycloalkylidene methyl ketones **21**. Our results with the alkenes **6** and **23** (Table III) indicate that there are significant differences in the relative stabilities of the double bonds as the ring size varies. Interestingly, these results do closely parallel those in the cycloalkylidene methyl ketone series.

It seems clear that the equilibria between α,β- and β,γ-unsaturated ketones, particularly in cyclic compounds, are

subject to conformational and hyperconjugation effects, as well as the more commonly appreciated resonance stabilization of the α,β isomer. It clearly is wrong to always assume that the α,β isomer will predominate.

The difference between the reported[26] 97% α,β- and 3% β,γ-unsaturated isomer for equilibration of **2b/3b** using 5% aqueous HCl in ethanol and our results (>99 and <1%, respectively) in almost anhydrous methanol probably reflects the greater polarity of the alcohol/water solvent. The conjugation present in the α,β-unsaturated isomer presumably serves to disperse the charge on the carbon of the carbonyl, marking that isomer more preferred in a less polar solvent.

The equilibrium between ketones **8** and **9** (Table II) showed much higher percentages of β,γ-unsaturated isomer at equilibrium. It appears that the two isomers were of comparable thermodynamic stabilities. However, the equilibration of **8b** appeared to involve a photochemical effect,[28] for, after several hours in the dark, the mixture contained less than 5% of the β,γ-unsaturated isomer **9b**. The quantities of ketones **8a**, **8b**, and **8c** available were not sufficient for a thorough investigation. We are pursuing this aspect with more readily accessible compounds containing the appropriate structural elements.

Experimental Section[29]

Typical Equilibration Procedure. Samples of pure α,β- and β,γ-unsaturated isomers were collected by preparative GLC. This was often done in conjunction with the collection of these isomers for spectral determinations and analyses.[1] In the course of these collections, other components were present and collected.[30] The pure α,β- and β,γ-unsaturated isomers (ca. 100 mg) were separately dissolved in ethanol, and a few drops of concentrated HCl added. The mixtures were stirred at 25 °C and the equilibrations allowed to continue until no further change was observed in either reaction, at which time the mixtures were carefully analyzed by measurement of the areas of GLC peaks. If necessary, the reaction was continued until the ratio of components was the same in both reactions. The equilibrations generally took less than 18 h.

Typical Enolate Ion Formation and Protonation.[26] Samples of α,β- and β,γ-unsaturated isomers were collected as above. Samples, ca. 100 mg, were added to a solution of 10 equiv of potassium *tert*-butoxide in ca. 10 ml of *tert*-butyl alcohol and the mixture stirred for at least 2 h. The mixture was poured into ca. 50 ml of cold 10% aqueous acetic acid. The solution was extracted with ether, and the ethereal extract washed with sodium bicarbonate, dried over $MgSO_4$, and evaporated to small bulk. The product was then examined by GLC.

Since this enolate protonation did not give the results reported[26] by House for ketones **2b**, the experiment was repeated several times, increasing and decreasing the concentration of both the base and the quenching acetic acid, but no difference in the ratio of products was observed.

Alkene Equilibration Procedure. For each series, samples of the alkenes **6** and **23** were obtained pure by preparative GLC on a Carbowax column. Samples (ca. 100 mg) of each were separately dissolved in benzene (ca. 10 ml) with a tenfold excess of *p*-toluenesulfonic acid. The mixtures were refluxed overnight or until no further change was observed in the isomer ratios, determined by GLC. The mixtures were then allowed to stand at room temperatures for 2–3 h before the final GLC analyses were performed. In each case, the ratio of isomers was the same in both experiments.

GLC Precautions. In every case, the pure α,β- and β,γ-unsaturated isomers were separately collected as they emerged from the GLC detector. Reinjection of each collected isomer gave only one peak at the same retention time as before, verifying that no detectable isomerization was occurring in the GLC system.

In order to make use of the method of internal normalization[31] for analysis, it was then necessary to ascertain that no selective irreversible retention was occurring. This was done by taking a mixture of the α,β- and β,γ-unsaturated isomers **2b** and **3b**, and determining the ratio of the areas under the peaks. The GLC conditions were then altered by increasing the temperature and carrier gas flow rates so that the isomers were no longer separated. The mixture was collected as it came off the chromatograph, the former GLC conditions were restored, and a sample reinjected. The ratio of the areas under the peaks was determined to be the same within normal measurement error. Furthermore, a 1-μl sample of pure isomers gave peak areas within 10% of that given by 1 μl of an α-decalone, a structurally similar ketone (but not an unsaturated ketone).

The possibility that one of the supposed pure isomers contained some other double bond isomer of identical retention time was ruled out by the spectra of the isomers as collected from the GLC. Any such other isomer would contain a vinyl hydrogen. Ketones **3**, **4**, and **5** showed[1] no vinyl hydrogen signal in the NMR. Ketones **2** showed[1] only one vinyl proton in the NMR and showed[1] no nonconjugated ketone in the ir.

The alkenes **6** and **23** were also purified in similar manner. Although small amounts of other double bond isomers were clearly formed in the preparation of these alkenes **6**, only **6** and **23** were observed on equilibrating pure samples of each with acid. The absence[1] of any vinyl signals in the NMR confirmed that this was so. The absence of any selective irreversible retention was verified as above.

In view of the extreme similarity of the compounds—identical molecular formula, virtually identical functional groups—differences in response to the thermal conductivity detector were assumed negligible. The reproducibility of the GLC analyses was ±1%, although the overall uncertainty in the results may be somewhat higher.

Acknowledgment. We thank the Robert A. Welch Foundation for generous financial support.

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(30) Diethylated compounds were specifically identified by the presence of a molecular ion at 28 amu higher than the corresponding monoethylated compound. Small quantities of the dialkylated products were detected in the product mixtures from which the following ketones were isolated for equilibrium studies: **8a/9a**, **8b/9b**, **8c/9c**. Product mixtures used for isolation of ketones **4** and **5** had been freed of dialkylated impurities by spinning band distillation.
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N-(p-Bromophenyl)[2.2](2,5)pyrrolophane. Synthesis and Self-Condensation

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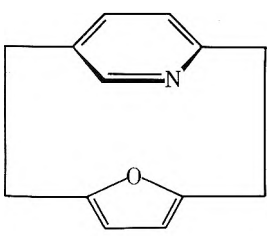
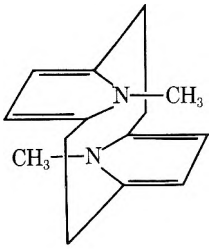
The N-(p-bromophenyl)[2.2](2,5)pyrrolophane was prepared and shown to exist in the anti structure. This compound readily rearranges to 13-(p-bromophenyl)-13,14-diazatetracyclo[8.2.1.1^{4,7}.0^{1,14}]tetradeca-4,6,11-triene. The structure of the latter was established by x-ray crystallographic analysis.

We have recently described the synthesis and structure of [2.2](2,5)furano(2,5)pyridinophane (1).[1,2] Contrary to expectations, the two rings are not parallel to each other in this molecule but the furan ring is inclined toward the pyridine at an angle of 23°. Interestingly, of the two heterocyclic rings in this system, only the pyridine ring is significantly nonplanar. These results prompted us to expand our investigations of heterocyclophanes in order to further examine their chemical, spectral, and stereochemical behavior.



1

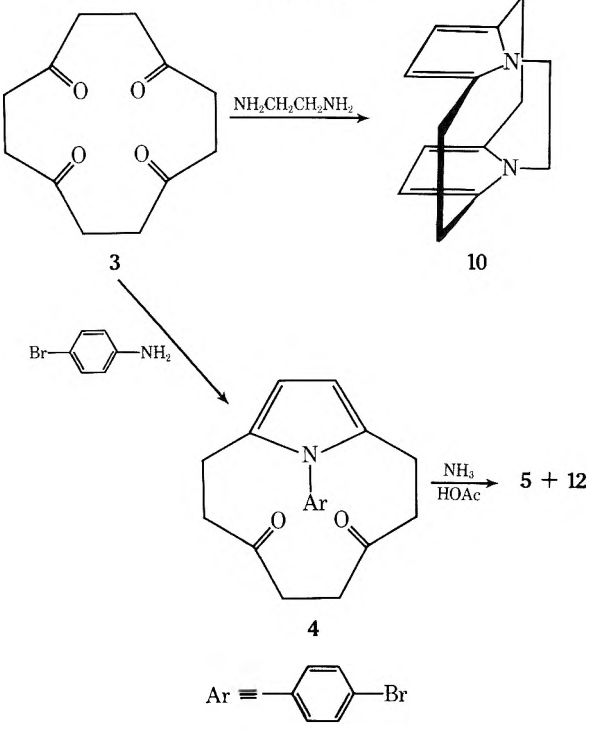


2

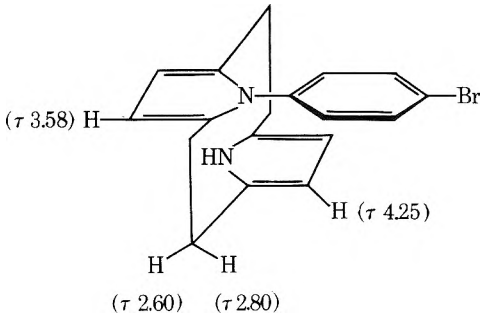
Wasserman and Bailey[3] originally described the synthesis of N,N'-dimethyl[2.2](2,5)pyrrolophane (2) and suggested that the compound exists in the indicated anti structure. Keehn and co-workers later continued these studies to include some other pyrrolophanes.[4]

In order to examine the stereochemical consequences of changing R in the pyrrolophanes such as 2, we prepared a series of these derivatives. This report describes the synthesis and structure determination of the products obtained from the reaction of compound 4 (see Scheme I) with ammonia. This reaction afforded two isomeric compounds, separable by HPLC, of molecular formula $C_{18}H_{17}N_2Br$. A priori, one might suggest that, because of the mode of formation, we are dealing with compounds 5 and 6, respectively. The temperature-insensitive ^1H NMR spectrum of the lower melting isomer was consistent with structure 5 or 6. The spectrum shows the presence of an aromatic A_2B_2 (τ 3.00, 2.66), an A_2 (τ 3.58) as well as the A_2 portion (τ 4.25) of an apparent A_2X system. The latter pattern, upon addition of D_2O to a solution of the compound, degenerates over time[5] to a two-proton singlet (τ 4.25). This change is in accord with a H → D exchange of the proton on the unsubstituted pyrrole ring. The question as to whether this product is 5 or 6 must now be answered.

Scheme I



3 10 4



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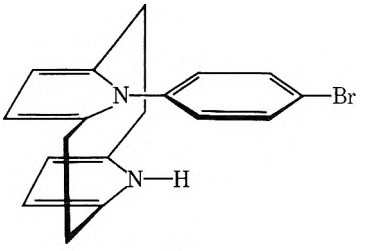
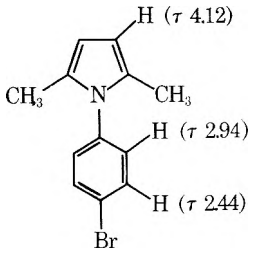
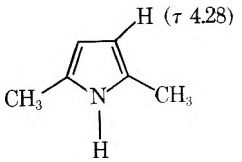


6

A comparison of the proton chemical shifts of the pyrroles 8 and 9 with those of the corresponding protons in the pyrrolophane isomer indicates that the substituted pyrrole protons in the latter are more deshielded ($\Delta\tau$ 0.54) than in the "monomer" 8, while the protons on the unsubstituted pyrrole are not significantly changed in going from the "monomer"



8



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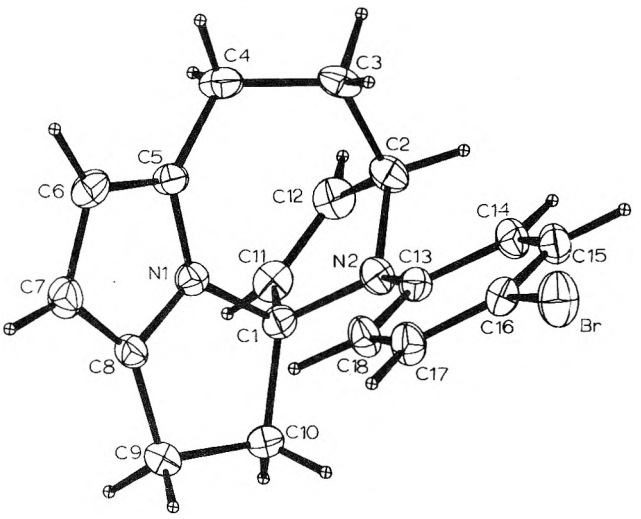
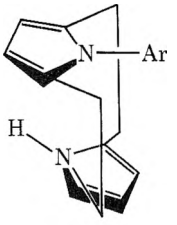


Figure 1. Molecular structure and atom numbering scheme for 13-(*p*-bromophenyl)-13,14-diazatetracyclo[8.2.1.1^{4,7}.0^{1,14}]tetradeca-4,6,11-triene. The atoms are represented as their 50% probability ellipsoids for thermal motion.

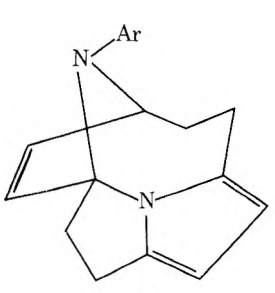
9 to the "dimer". Thus, the substituted pyrrole in the pyrrolophane is within the deshielding region of the unsubstituted pyrrole, while the substituted pyrrole has no significant effect ($\Delta\tau$ 0.03) upon the protons in the unsubstituted pyrrole ring. The only structure that is consistent with these data is the anti isomer **5** with nonparallel rings.



5

A more accurate assessment of the ring to ring angles in these systems will be published elsewhere. The fact that we are dealing with a modified anti structure is further confirmed by the ^{1}H NMR spectrum of compound **10**, prepared as indicated in Scheme I. A comparison of the pyrrole chemical shifts (τ 4.49) of this unique cage-type *syn*-pyrrolophane with those of 1,2,5-trimethylpyrrole (τ 4.26) clearly shows that the pyrrole protons in this pyrrolophane are within the *shielding* region of the opposite pyrrole ring, in contrast to the location of the pyrrole protons in the anti isomer **5**.

The ^{1}H NMR spectrum of the higher melting isomer must now be examined. None of the protons in this spectrum are subject to H → D exchange. Thus, we are not dealing with a structure which has an unsubstituted pyrrole ring. Detailed analysis of the deshielded region shows the presence of an aromatic A_2B_2 (τ 2.79, 3.86) system as well as an ABX (τ_{H_A,H_B} 2.65, 4.24) and AB (τ 4.18, 4.35) pattern. These data could be accommodated by either structure **12** or **13**.



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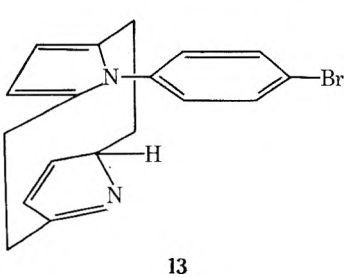
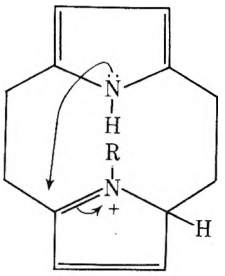


13

The observation that the olefinic protons of the ABX system are so greatly deshielded (τ 2.65, 2.88) seems to preclude structure **13**, especially in view of the fact that the pyrrole protons in the locked syn isomer are all more shielded than in the "monomeric" reference compound. Nevertheless, this analysis does not allow one to assign structure **12** to the compound with complete certainty.

Consequently, recourse was taken to a x-ray crystallographic analysis which proved that we are dealing with compound **12** rather than **13**. A computer-generated structure representation is given in Figure 1. Interestingly, when the anti isomer (**5**) is treated with acetic acid it is converted to compound **12**.

The acid-catalyzed transformation of compound **5** to compound **12** can be envisioned to occur via the C-protonated



14

species **14** (typical for pyrroles) followed by bond formation and deprotonation as indicated.

Experimental Section[7]

Compound 4. 1,4,7,10-Cyclododecatetraone[6] (1.00 g, 4.5 mmol) and 3.87 g (22.5 mmol) of *p*-bromoaniline were dissolved in 50 ml of glacial HOAc and heated at 90 °C under a N_2 atmosphere for 40 min. The mixture was cooled, poured into cold NH_4OH, and extracted with $CHCl_3$. The extracts were washed successively with 5% HCl and water and dried over anhydrous K_2CO_3. Evaporation of the solvent gave a dark residue which was chromatographed on Brockman grade III neutral alumina using C_6H_6 as the eluent to yield 0.70 g (43.3%) of a yellow oil that gradually solidified. Further purification was accomplished by sublimation or recrystallization from acetone–water to give a yellow solid: mp 137–139 °C; ^{1}H NMR τ 2.42, 3.04 (A_2B_2, 4 H), 3.77 (s, 2 H), 8.5–7.0 (m, 12 H); ir 1705 cm^{-1} (C=O); mass spectrum mol wt 359, 361. Anal. Calcd for $C_{18}H_{18}NO_2Br$: C, 60.01; H, 5.04; N, 3.89. Found: C, 60.11; H, 5.07; N, 3.93.

Compounds 5 and 12. Compound **4** (250 mg, 0.70 mmol) was dissolved in 20 ml of glacial HOAc and added to 5 ml of liquid NH_3 cooled to −78 °C for 2 h. After cooling NH_4OH was added and the product was extracted with $CHCl_3$. The extracts were washed with H_2O and dried over anhydrous K_2CO_3. Evaporation of the $CHCl_3$ yielded a dark residue which was chromatographed on Brockman grade II silica gel using 1:1 benzene–cyclohexane as the eluent. This afforded 24 mg of compound **12**, mp 137–140 °C dec, and 100 mg of compound **5**, mp 151.5–153 °C. These compounds can also be separated by HPLC using a 1-m Porasil A column, 4 ml/min flow rate, 20% $CHCl_3$–80% isooctane eluent. Compound **5**: ^{1}H NMR τ 2.76, 3.00 (A_2B_2, 4 H), 3.58 (s, 2 H), 4.25 (d, 2 H), 2.60, 2.80 (A_2B_2, 8 H) (the chemical shift of the hydrogen atom on nitrogen could not be immediately determined; however, integration indicates that it falls within this chemical shift range of the aromatic protons); mass spectrum mol wt 340, 342. Compound **12**: ^{1}H NMR τ 2.79, 3.86 (A_2B_2, 4 H), 2.88, 2.65, 4.24 (ABX, 3 H), 4.18, 4.35 (AB, 2 H), 6.7–8.6 (m, 8 H); mass spectrum mol wt 340, 342. Anal. Calcd for $C_{18}H_{17}N_2Br$: C, 63.36; H, 5.02; N, 8.21. Found for compound **5**: C, 63.25; H, 5.03; N, 8.14. Found for compound **12**: C, 63.62; H, 5.16; N, 8.03.

Compound 10. 1,4,7,10-Cyclododecatetraone (500 mg, 2.25 mmol) was dissolved in 6 ml of glacial HOAc and heated at 80 °C under a N_2 atmosphere. Ethylenediamine (1.3 g, 22.5 mmol, 1.5 ml) was added dropwise and the mixture was heated for 5 min. The reaction mixture was cooled, poured into cold NH_4OH, and extracted with $CHCl_3$. The organic layer was washed successively with 5% HCl, water, and saturated Na_2CO_3 solution and dried over anhydrous K_2CO_3. The $CHCl_3$ extract was evaporated and the residue obtained was chromatographed on Brockman grade III neutral alumina using benzene as the

eluent to give 190 mg (38%) of a white solid: mp 198–202 °C dec; ^{1}H NMR τ 4.49 (s, 4 H), 5.99 (s, 4 H), 7.15 (A_2B_2, 8 H); mass spectrum mol wt 212. Anal. Calcd for $C_{14}H_{16}N_2$: C, 72.83; H, 4.83; N, 22.35. Found: C, 72.83; H, 4.90; N, 22.42.

Conversion of Compound 5 to 12. Compound **5** (50 mg, 0.15 mmol) was dissolved in 5 ml of glacial HOAc and heated at 120 °C for 1 h. The mixture was cooled and added to cold NH_4OH. The aqueous solution was extracted with chloroform (3 × 50 ml) and the combined extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to dryness. The residue was examined using high-pressure liquid chromatography (HPLC) (column 0.5 m Dorasil A, 20% $CHCl_3$, 80% isooctane, Waters ALC 202 instrument) which revealed the presence of compound **12**. Isolation by preparative HPLC afforded 40 mg (80%) of compound **12**.

X-Ray Data Collection. The detailed data are available in the microfilm edition of this journal.[8]

Registry No.—**3**, 25887-95-0; **4**, 59547-39-6; **5**, 59547-40-9; **10**, 59547-41-0; **12**, 59547-42-1; *p*-bromoaniline, 106-40-1; ethylenediamine, 107-15-3.

Supplementary Material Available. A listing of all of the crystallographic data (8 pages). Ordering information is given on any current masthead page.

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(5) The results of a study of these slow exchange rates and of the stereochemistry of these compounds will be published elsewhere.
(6) J. L. Atwood, D. C. Hrnclr, C. Wong, and W. W. Paudler, *J. Am. Chem. Soc.*, **96**, 6132 (1974).
(7) ^{1}H NMR spectra were obtained with either a Varian HA-100 or a Hitachi Perkin-Elmer R20B NMR spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector. The ionizing voltage employed was 70 eV. Elemental analyses were determined by the Analytical Services Laboratory of The University of Alabama Chemistry Department, and Atlantic Microlab, Inc., Atlanta, Ga. Melting points were uncorrected.
(8) See paragraph at end of paper regarding supplementary material.

Bishomoaromatic Interaction in the Disrotatory Ring Opening of Cyclopropyl Carbenoids

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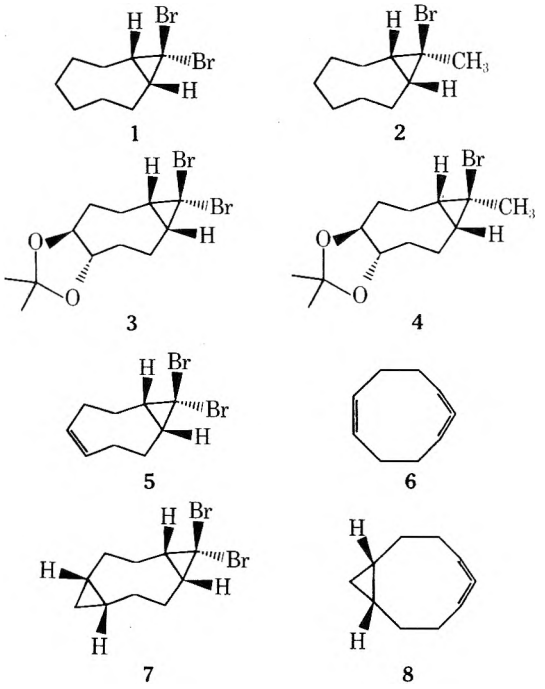
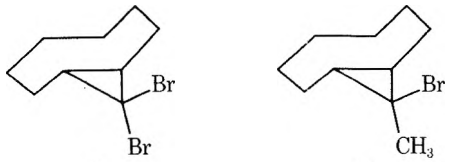
Treatment of 9,9-dibromo-*cis*-bicyclo[6.1.0]nonanes **1**, **3**, and **15** with butyllithium at −95 °C leads to corresponding *endo*-lithio-*exo*-bromo derivatives which upon addition of methyl iodide can be alkylated, leading to the *endo*-methyl-*exo*-bromo derivatives **2**, **4**, and **16** respectively. Even the strained 9,9-dibromo-*trans*-bicyclo[6.1.0]nonane (**9**) is converted in this way to 9-bromo-9-methyl-*trans*-bicyclo[6.1.0]nonane (**10**). However, in the presence of a double bond (**5**) or a cyclopropyl ring (**7**) at $C_{4,5}$ the carbenoids generated with butyllithium at −95 °C undergo a very rapid ring opening to the corresponding allenes. This result may be explained by assuming a bishomoaromatic interaction which favors a facile disrotatory ring opening of the carbenoids.

Geminal dihalo compounds have been shown to produce carbenoid species on reaction with organolithiums.[1] In the specific instance of 1,1-dibromocyclopropanes, the transient carbenes generally prove to undergo either ring opening to allenes[2a–h] or specific insertion in C–H bonds.[3a–i] At very low temperatures (−70 to −105 °C) the geminal dibromocyclopropanes can be easily lithiated to 1-bromo-1-lithiocyclopropanes. The latter behave like anions and are able to undergo alkylation reactions.[4a–c]

Our present research, directed toward the synthesis of nine-membered-ring systems via ring expansions, required the synthesis of 9-*exo*-bromo-9-*endo*-methyl-*cis*-bicyclo[6.1.0]nonane derivatives. To this end a recently described method of Hiyama et al.[4a] was employed, which permits the stereoselective endo methylation of cyclopropylidenes derived from geminal dibromocyclopropanes. Upon reaction of 9,9-dibromo-*cis*-bicyclo[6.1.0]nonane (**1**) with butyllithium at −95 °C and subsequent treatment with excess of methyl iodide in THF, the desired 9-*exo*-bromo-9-*endo*-methyl-*cis*-bicyclo[6.1.0]nonane (**2**) was isolated in essentially quantitative yield. In a similar way, the acetonide of 4,5-*trans*-dihydroxy-9,9-dibromo-*cis*-bicyclo[6.1.0]nonane (**3**) was converted to the corresponding *endo*-methyl derivative (**4**) in 92% yield. However, on treatment of 9,9-dibromo-*cis*-bicyclo[6.1.0]-non-4-ene (**5**) with butyllithium and methyl iodide under identical conditions, 1,2,6-cyclononatriene (**6**) was formed, as evidenced readily by its NMR and ir spectral data.[5a–c] Similar anomalous behavior was observed when a cyclopropane was annelated at $C_{4,5}$.[6] Upon treatment of 10,10-dibromo-*cis*,*cis*-tricyclo[7.1.0.0^{4,6}]decane (**7**) with butyllithium–methyl iodide at −95 °C only *cis*-bicyclo[7.1.0]deca-



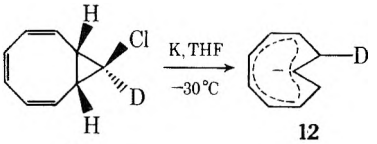


9 10

4,5-diene (8) was obtained. The strained 9,9-dibromo-*trans*-bicyclo[6.1.0]nonane (**9**) proved to be stable under the conditions described above and could be converted smoothly to 9-methyl-9-bromo-*trans*-bicyclo[6.1.0]nonane (**10**). Whereas the formation of allenes is a common reaction at elevated temperatures (>−30 °C), its formation from **5** and **7** at such very low temperatures is rather surprising.

Relying on the ability of cyclopropylidenes to undergo alkylation reactions, they can be regarded as anions at such low temperatures. The prefered mode of ring opening of such species, leading to allenes, will be conrotatory based on orbital symmetry considerations.[7a,b] This has been confirmed by extended Hückel,[8] ab initio,[9] and MINDO/2[10] calculations.

A representative example would be the stereospecific ring opening of 9-*endo*-deuterio-9-*exo*-chloro-*cis*-bicyclo-[6.1.0]nona-2,4,6-triene (**11**) with potassium in THF, leading to the *trans,cis,cis,cis*-cyclononatetraenyl anion (**12**).[11a,b]



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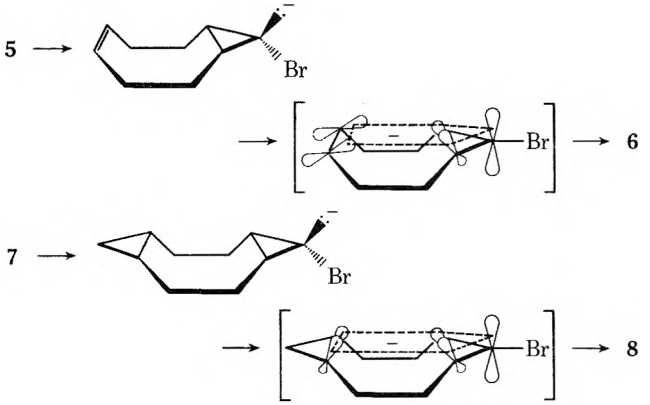
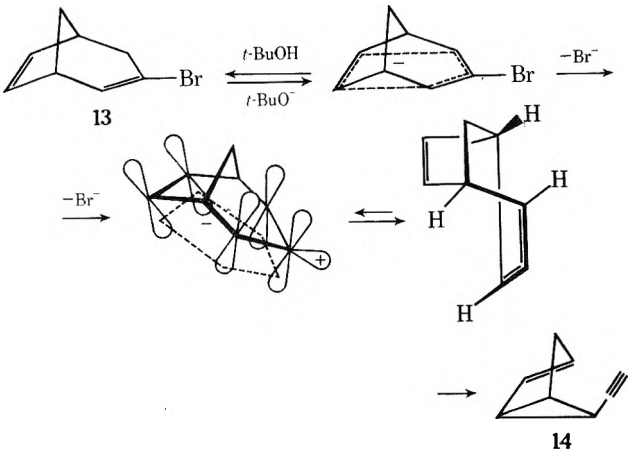
Based on steric considerations the conrotatory mode of ring opening seems to be an unfavorable process at very low temperatures for the carbenoids derived from **1, 3, 5,** and **7,** even for **9,** in which the cyclopropane unit is annelated in a "favorable" trans configuration. This conrotatory mode of ring opening is restricted for **9** because the system has to pass through an initially strained *trans,trans* allylic geometry. The alternative way, viz., a disrotatory movement, seems to be more attractive for systems **1, 3, 5,** and **7,** but in fact it is a forbidden process. Therefore it is most likely that the rapid mode of ring opening of **5** and of **7** is due to a bishomoaromatic



interaction[12] between the cyclopropylidene moiety and the double bond or the Walsh-type orbitals of the cyclopropane unit at $C_{4,5}$, respectively. Extension of the electronic system of the cyclopropylidene by two electrons in this way leads to an aromatic transition state, favoring a disrotatory ring opening. Further evidence for this explanation can be quoted from recent literature on bicyclo[3.2.1]octa-2,6-diene systems.[13a-d] A particular example which is worth recording and which, by its nature, has close similarity to our cases is the base-catalyzed rearrangement of 3-bromobicyclo[3.2.1]octa-



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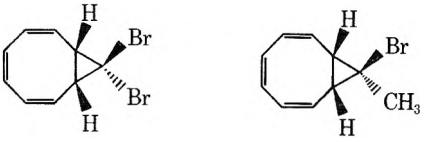
2,6-diene (**13**) to *endo*-6-ethynylbicyclo[3.1.0]hex-2-ene (**14**).[14] In this reaction, the intermediacy of a homoconjugated carbene has been suggested. The model for the rapid ring opening of the cyclopropylidenes derived from **5** and **7** suggests an interaction through space over a relatively large distance. Therefore it became obvious to us that a further requirement might be some flexibility in the bicyclo[6.1.0]nonane skeleton which allows bending of the double bond (in **5**) and of the cyclopropane (in **7**) toward the cyclopropylidene system. An example in this series which does not meet this requirement is 9,9-dibromo-*cis*-bicyclo[6.1.0]nona-2,4,6-triene (**15**), in which the double bond at $C_{4,5}$ is tightly fixed. Indeed, upon treatment of **15** with butyllithium and methyl iodide at −95 °C only 9-*endo*-methyl-9-*exo*-bromo-*cis*-bicyclo[6.1.0]-nona-2,4,6-triene (**16**) was formed. Some experiments carried



15 16

out at higher temperatures showed that the lithiate derived from **15** was stable even up to −45 °C. Above this temperature decomposition to an indefinable mixture of products took place. The lithiate derived from **1** proved to undergo ring opening at an appreciable rate at −40 °C, leading to the corresponding allene.

Experimental Section

General. The starting materials **1** and **5** were prepared by reaction of dibromocarbene with the appropriate olefins according to a known procedure.[15] 9,9-Dibromo-*trans*-bicyclo[6.1.0]nonane (**9**) was obtained from *trans*-cyclooctene[16] by reaction with bromoform and potassium *tert*-butoxide in pentane.[2c] 9,9-Dibromo-*cis*-bicyclo-[6.1.0]nona-2,4,6-triene (**15**) was prepared as indicated by Vogel.[17] Melting points were determined on a Mettler apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as an internal standard.

9-*exo*-Bromo-9-*endo*-methyl-*cis*-bicyclo[6.1.0]nonane (2). To a solution of 2.80 g (0.01 mol) of **1** in 15 ml of dry THF (distilled from $LiAlH_4$) was added dropwise 4 ml of a 20% solution of butyllithium in hexane at −95 °C (toluene–liquid nitrogen bath). After stirring for 10 min 1.5 ml of methyl iodide was added in one portion and after 1 h the mixture was gradually warmed to 0 °C. Then 100 ml of water was added and the product was extracted with ether. Workup and subsequent distillation gave 1.5 g (70%) of **2**:[21] bp 118–121 °C (14 mm); NMR ($CDCl_3$) δ 1.63 (s, 3, CH_3), 1.60–2.20 (aliphatic and cyclopropane H). Anal. Calcd for $C_{10}H_{17}Br$: C, 55.30; H, 7.83. Found: C, 55.31; H, 7.89.

4,5-*trans*-Dihydroxy-9,9-dibromo-*cis*-bicyclo[6.1.0]nonane Acetonide (3). *cis,cis*-Cycloocta-1,5-diene was converted to 1,2-*trans*-dihydroxycyclooct-5-ene by reaction with performic acid and subsequent hydrolysis.[18] Reaction with acetone and anhydrous copper sulfate gave the acetonide.[19] To a solution of 21 g (0.12 mol) of the acetonide and 51 g (0.46 mol) of potassium *tert*-butoxide in 900 ml

of hexane was added dropwise with stirring at −15 °C a solution of 87.3 g (0.35 mol) of bromoform in 200 ml of hexane. Stirring was prolonged for an additional 2 h at ambient temperature, then 1 l. of water was added and the organic layer was separated. After washing, drying, and evaporation, the remaining dark oil was treated with cold 96% ethanol. The precipitated solid was recrystallized from a small volume of diisopropyl ether. This afforded 17 g (42%) of **3**: mp 84–86 °C; NMR ($CDCl_3$) δ 1.38 (5, 6, CH_3), 3.40–4.20 [m, 2, -CH(O)-CH(O)-]. Anal. Calcd for $C_{12}H_{18}Br_2O_2$: C, 40.67; H, 5.08. Found: C, 40.55; H, 5.01.

4,5-*trans*-Dihydroxy-9-*exo*-bromo-9-*endo*-methyl-*cis*-bicyclo[6.1.0]nonane Acetonide (4). To a solution of 1.7 g (0.005 mol) of **3** in 10 ml of dry THF was added 2.2 ml of butyllithium solution and 0.7 ml of methyl iodide in a similar way as described for **2**. Workup afforded 1.22 g (92%) of **4** as a white solid; mp [(*i*-Pr)$_2$O] 70–71 °C; NMR ($CDCl_3$) δ 1.39 (s, 6, CH_3), 1.63 (s, 3, endo CH_3), 3.40–4.35 [m, 2, CH(O)-CH(O)-]. Anal. Calcd for $C_{13}H_{21}BrO_2$: C, 53.98; H, 7.27. Found: C, 54.04; H, 7.10.

Cyclonona-1,2,6-triene (6). To a solution of 2.80 g (0.01 mol) of **5** were added 0.011 mol of butyllithium and excess of methyl iodide at −95 °C as described for the synthesis of . Workup gave an oil which, upon examination by TLC, proved to consist of one component besides some TLC immobile material (silica gel; pentane as eluent). Chromatography gave 0.98 g (81%) of **6**, identical with the compound prepared by other routes:[5a,b] NMR ($CDCl_3$) δ 5.20 (m, 2, allenic H), 5.55 (m, 2, olefinic H), 1.25–2.60 (m, 8, other H); ir (neat) ν 1958 cm^{-1} (allene).

10,10-Dibromo-*cis,cis*-tricyclo[7.1.0.0^{4,6}]decane (7). This compound was prepared by treatment of bicyclo[6.1.0]non-4-ene[20] [NMR ($CDCl_3$) δ 5.58 (m, 2, olefinic H), 0.50–2.60 (m, 12, aliphatic and cyclopropyl H)] with bromoform and potassium *tert*-butoxide as described for **3**: yield 58%; bp 83–85 °C (0.01 mm). Anal. Calcd for $C_{10}H_{14}Br_2$: C, 40.81; H, 4.67. Found: C, 40.53; H, 4.70.

***cis*-Bicyclo[7.1.0]deca-4,5-diene (8).** This compound was prepared in an identical way as described for **6** from 2.94 g (0.01 mol) of **7**. Workup and chromatography over a short column (silica gel; pentane as eluent) provided 0.89 g (67%) of the allene **8**: NMR ($CDCl_3$) δ 5.27 (m, 2, allenic H), 0.40–2.60 (m, 12, aliphatic ring H and cyclopropyl H); ir (neat) ν 1960 cm^{-1} (allene). This compound proved to be thermolabile.

9-Methyl-9-bromo-*trans*-bicyclo[6.1.0]nonane (10). A solution of 2.82 g (0.01 mol) of **9** in 20 ml of THF was treated at −95 °C with butyllithium and methyl iodide as described for **2**. Workup afforded 1.93 g (89%) of **10**: bp 55–60 °C (0.1 mm); NMR ($CDCl_3$) δ 1.65 (s, 3, CH_3), 1.65–2.40 (other H's). Anal. Calcd for $C_{10}H_{17}Br$: C, 55.30; H, 7.83. Found: C, 55.20; H, 7.81.

9-*endo*-Methyl-9-*exo*-bromo-*cis*-bicyclo[6.1.0]nona-2,4,6-triene (16). A solution of 1.38 g (0.005 mol) of **15**[17] in 10 ml of THF was treated with butyllithium and methyl iodide as described for **2**. Workup in the usual way afforded an oil which upon separation of the compounds which had no TLC mobility (silica gel; petroleum ether as eluent), gave 0.89 g (84%) of **16**: NMR ($CDCl_3$) δ 1.61 (s, 3, endo CH_3), 2.09 (s, 2, cyclopropane CH), 5.62–6.05 (m, 6, olefinic H). The compound proved to decompose upon distillation.[22]

9-*exo*-Bromo-*cis*-bicyclo[6.1.0]nonane (17)[6]. To 20 ml of a 1 M solution of dimsyl anion in Me_2SO was added with stirring 2.8 g (0.01 mol) of **1** at such a rate as to maintain the temperature at 25–30 °C. After stirring for an additional 2 h, 150 ml of water was added and the product was extracted with ether. After washing, drying, and evaporation of the organic solvent the residue was distilled and afforded 1.1 g (55%) of **17**, bp 105–110 °C (18 mm).

4,5-*trans*-Dihydroxy-9-*exo*-bromo-*cis*-bicyclo[6.1.0]nonane Acetonide (18). A solution of dimsyl anion was prepared by dissolving 15 g (ca. 0.5 mol) of sodium hydride (80% dispersion in mineral oil) in 500 ml of Me_2SO (CaH_2 dried). In 0.5 h was added dropwise with stirring at 20 °C a solution of 60 g (0.17 mol) of **3** in 100 ml of THF. The mixture was stirred for about 2 h and poured into 4 l. of water. The product was extracted with ether. The oil which remained after washing, drying, and evaporation of the solvent was treated with 95% ethanol and afforded 21 g (45%) of **18**: mp (95% ethanol) 66–67 °C; NMR ($CDCl_3$) δ 1.40 (s, 6, CH_3), 0.60–2.55 (aliphatic and cyclopropyl H), 3.42–4.40 [m, 2, -CH(O)-CH(O)-]. Anal. Calcd for $C_{12}H_{19}BrO_2$: C, 53.36; H, 6.91. Found: C, 52.44; H, 7.06.

Registry No.—**1**, 32644-18-1; **2**, 59474-03-2; **3**, 59474-04-3; **4**, 59474-05-4; **5**, 54809-08-4; **6**, 1502-42-7; **7**, 59474-06-5; **8**, 59493-11-7; **9**, 59531-26-9; **10**, 59531-27-0; **15**, 59474-07-6; **16**, 59474-08-7; **17**, 1551-94-6; **18**, 59474-09-8; butyllithium, 109-72-8; methyl iodide, 74-88-4; *cis,cis*-cycloocta-1,5-diene, 1552-12-1; bicyclo[6.1.0]non-4-ene, 4729-13-9.

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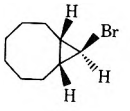
(6) Anomalous behavior of **5** has also been observed in the reduction with sodium hydride in Me_2SO. Whereas **1** and **3** are converted to their corresponding 9-*exo*-bromo derivatives (**17** and **18**, respectively), compound



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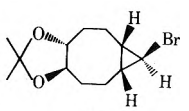

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5 only affords the allene **6** in this reaction. This reaction has been assumed to proceed via carbenoid species as intermediates. See C. L. Osborn, T. C. Shields, B. A. Shoulders, C. G. Cardenas, and P. D. Gardner, *Chem. Ind. (London)*, 766 (1965).

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Interactions of Some Aromatic Salts with Hexadecyltrimethylammonium Bromide Micelles. Viscosity, Counterion Binding, and Calorimetric Observations[1]

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The effect of disodium phenyl phosphate (PP), sodium benzenesulfonate (BS), sodium tosylate (TOS), sodium benzoate (BZ), and sodium *p*-toluate (Tol) on the viscosity of hexadecyltrimethylammonium bromide (CTAB) solutions was studied at low CTAB concentrations. A sharp viscosity increase was observed once a certain salt concentration of TOS or TOL was reached. In the absence of the *p*-methyl group, no effect was observed. Plots of bound bromide vs. [added salt] showed similar behavior for all salts. Apparently, introduction of a *p*-methyl group has a large effect on the size and/or shape of CTAB molecules while not affecting the counterion binding. The transfer of all salts except PP from water to the micelle is exothermic and for TOS depends on the micelle concentration.

In recent years the study of micelle catalyzed reactions has become an active area.[2,3] A chief factor preventing a clear understanding of these reactions is our ignorance of the mutual interactions between micelle and solubilizate. Many have studied the location of the solute in micelles.[4-16] Location of the solute is dependent on its chemical character as well as that of the micelle. A good example of this is the difference in location of pyrene, pyrenebutyric acid, and pyrenesulfonic acid in hexadecyltrimethylammonium bromide (CTAB) micelles.[4] Using a variety of techniques, progress is being made in locating solutes in micelles.

However, we have almost no understanding of the highly specific effects of various solutes on micelle structure. These effects are sometimes characterized by a large increase in the viscosity of a micellar solution caused by some solutes but not by others. The most thorough study of this effect was carried out by Wan, who investigated the effects of a variety of substituted benzoic acids on the viscosity of some cationic micellar solutions.[17] While salicylic acid and its salts increased the viscosity of dodecyl-, tetradecyl-, and cetyltrimethylammonium bromide solutions, *m*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, as well as *o*-, *m*-, and *p*-amino-, chloro-, and nitrobenzoic acids caused no viscosity change.[17a] Larsen and co-workers reported a large viscosity increase for CTAB micellar solutions which was specific for both the organic solute and the inorganic anion present in the solution.[18] Bunton has observed a large viscosity for a CTAB solution containing sodium tosylate but not for one with sodium benzenesulfonate.[19] Stainsby and Alexander observed some time ago that chlorobenzene had pronounced effects on the viscosity of cetylpyridinium chloride in the presence of sodium chloride.[20] The effect of solubilized phenol on the viscosity of CTAB solutions was reported by Good and Milloy.[21] In these last three cases, there is a sharp increase in viscosity followed by a sharp decrease as the concentration of solute increases. This effect is absent with micelles formed from alkylsodium carboxylates.[17a,22] The high substrate specificity of these effects is fascinating. Much needs to be done to characterize the solute structural changes capable of inducing such effects and to determine to what extent all micellar properties are affected, so that plausible models for the structural change may be constructed. We report here a study of the highly specific effect of *p*-methyl substitution of sodium benzoate and sodium benzenesulfonate on the viscosity of CTAB solutions together with calorimetric and counterion binding studies of these systems.

Results

In Figure 1, plots of the viscosity of 0.01 M CTAB solutions as a function of the concentration of sodium benzenesulfonate and sodium benzoate and their *p*-methyl derivatives are shown. A similar plot for disodium phenyl phosphate also is shown. The effect of the *p*-methyl substitution is startling. Without the methyl group, the solution viscosity is not dependent on the concentration of added salt. With the methyl group, there is a sharp increase in viscosity once a certain salt concentration has been reached.

The effect of the same salts on counterion binding is shown in Figures 2–4. The extent of counterion binding was measured using bromide ion selective electrodes as before.[23] A plot of bound bromide vs. salt concentration for all the salts shows two intersecting lines. The changes in slope in the counterion binding plots for the *p*-methyl derivatives occur close to, but at a higher concentration than, those concentrations at which the rapid increase in the viscosity plots begins. In both cases, the methyl group has only a small effect on the binding of bromide to the micelle.

The partial molar heats of transfer of these salts from water to 0.01 M CTAB solution were measured and are reported in Table I. Independent data are available showing that at the soap and salt concentrations used, essentially all of the anionic salts are bound to the micelle.[24] Thus, the heats of transfer reported are heats of transfer from water to the micelle. Additionally, the dependence of the heat of transfer of sodium tosylate on the concentration of CTAB was measured. The effect of varying the soap concentration is significant as shown by the data in Table II.

Discussion

Viscosity. A comparison of Figure 1 with Figures 2–4 leads to the conclusion that the effect of the solutes on the micelle structure and on the counterion binding to the micelle are independent. In all cases, counterion binding shows similar behavior; there is nothing to suggest that *p*-methyl benzoate is behaving any differently than benzoate or tosylate any differently than benzenesulfonate. Obviously the introduction of the methyl group has a profound effect on the structure of the micelle as evidenced from the plots of viscosity vs. solute concentration.

The viscosities of systems such as these are functions of the volume fraction and shape of the micelles in the solution.[25,26] It seems rather unlikely that a sudden change in the total volume of micellar material can be induced by a small change in salt concentration or by the introduction of a methyl group, so we are left with the other alternative. The methyl substituted salts are inducing a sudden change in the shape of the micelle. Solubilization near the micelle surface should result in a decrease in charge density leading to the formation of larger micelles and a change in the shape of the micelle.[27,28] Ellipsoids or rods are expected, both of which would lead to

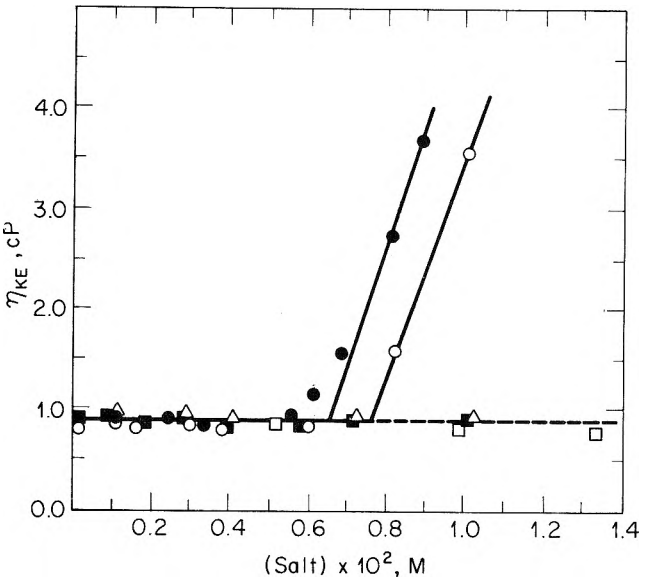

Figure 1. Viscosity of a 0.01 M CTAB solution containing sodium *p*-toluenesulfonate (●), sodium benzenesulfonate (■), sodium *p*-toluate (○), sodium benzoate (□), or disodium phenyl phosphate (△).

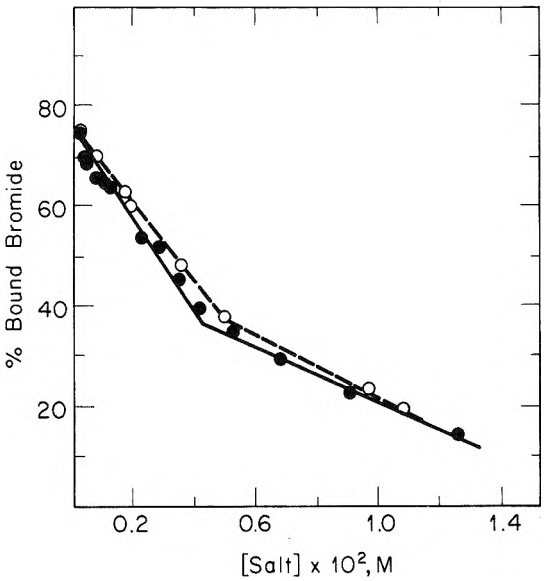

Figure 2. Bromide ion bound to the micelle in the presence of added sodium tosylate (●), or sodium benzenesulfonate (○).

Table I. Heat of Transfer (ΔH_T) of a Series of Salts from Water to Aqueous CTAB (0.01 M) at 25 °C

Salt	$\Delta H_{s(CTAB)}$, kcal/mol	$\Delta H_{s(H_2O)}$, kcal/mol	ΔH_{trans}, kcal/mol
PP	−0.550 ± 0.131	−3.82 ± 0.21	3.27 ± 0.25
TOL	−1.64 ± 0.14	−1.17 ± 0.11	−0.47 ± 0.18
BS	0.445 ± 0.173	1.70 ± 0.18	−1.25 ± 0.25
TOS	1.17 ± 0.23	2.54 ± 0.60	−1.37 ± 0.64

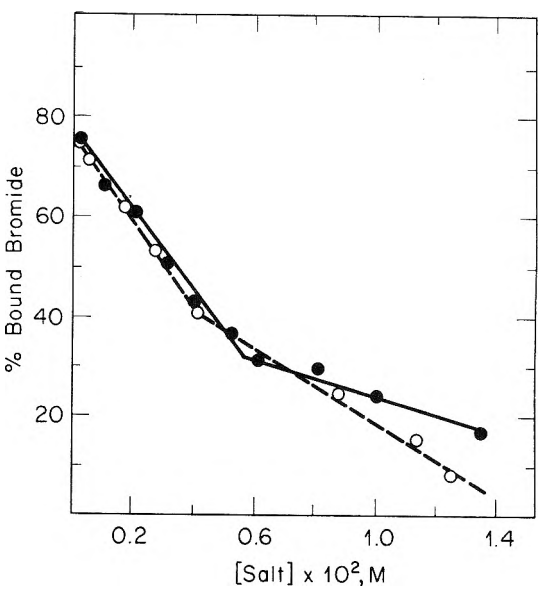

Figure 3. Bromide ion bound to the micelle in the presence of added sodium *p*-toluate (○), or sodium benzoate (●).

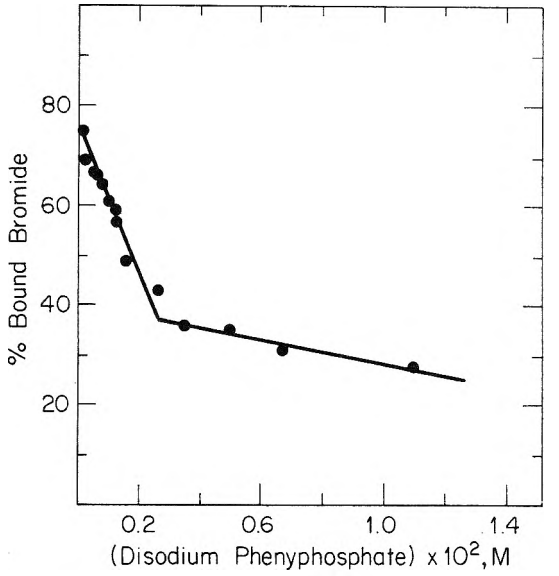

Figure 4. Bromide ion bound to the micelle in the presence of added disodium phenyl phosphate.

Table II. Heat of Transfer (ΔH_T) of Sodium Tosylate to CTAB Solutions at 25 °C

[CTAB], M	$\Delta H_{s(CTAB)}$, kcal/mol	ΔH_{trans},[a] kcal/mol
0.100	0.564 ± 0.232	−1.98 ± 0.64
0.060	0.316 ± 0.380	−2.22 ± 0.71
0.030	0.654 ± 0.133	−1.89 ± 0.61
0.010	1.17 ± 0.23	−1.37 ± 0.63

[a] $\Delta H_{s(H_2O)}$ = 2.54 ± 0.60 kcal/mol.

higher viscosity. However, any change in charge density at the micelle surface is expected to result in a change in counterion binding—and we have pointed out that the viscosity and bromide binding seem to be independent. It is possible that the size and shape changes are caused by changes in charge density too small to be detected by our selective ion electrode measurements. Or possibly the changes are due to alterations of the internal structure of the micelle caused by the methyl group, alterations which have little effect on the surface charge density. It seems of little use to speculate on the origin of the effect until more systems have been studied and data on the size and shape of the micelle together with information on the location of the solute ions in the micelle are available. At this point it is obvious that small solute structural changes can cause pronounced alterations in micelles, a factor which may be of some importance to groups studying micellar catalysis.

There is one other possible explanation. As pointed out by

Tanford,[28] the surface area/volume ratio is larger for a prolate ellipsoid than for an oblate ellipsoid. Thus, it is possible to increase the volume of a micelle at constant surface charge density by moving from a prolate to an oblate ellipsoid. Unfortunately, Tanford also predicts that for a given charge density, oblate ellipsoids will be smaller (lower aggregation number). This is in conflict with the observed viscosity increase. Finally, at large aggregation numbers, especially for prolate ellipsoids, the dependence of charge density on micelle volume is quite shallow, and significant changes in micelle size may occur without large changes in the charge density.

The last topic to be discussed is the heats of transfer from water to the micelle. From Sepulveda's data for all the salts except sodium benzoate, we know that at the concentrations used, all of the salts are essentially completely bound to the micelle.[24] Sepulveda calculated an equilibrium constant for binding to the micelle using a model based on a finite number of binding sites per micelle. Such a model should be consistent with a Langmuir isotherm[29] and his data do not appear to be consistent with one. At low soap concentrations, as the salt concentration increases, the moles of salt bound first increase, then decrease. This contradiction raises doubts about Sepulveda's analysis of his binding data and we do not choose to make quantitative use of them.

The heat of transfer of disodium phenyl phosphate is endothermic while the transfer of the other three salts is exothermic. There is not enough data to ascribe these results to any particular effect. The small enthalpic driving force for the transfer of the aromatic carboxylates and sulfonates might have an electrostatic origin or might be due to the known favorable interactions between aromatics and tetralkylammonium salts.[30]

The heats of transfer of sodium tosylate are dependent on the concentration of CTAB as shown by the data in Table II. It seems most reasonable to associate this with changes in micelle size and structure which occur with changes in the CTAB concentration, although there is no compelling evidence for this interpretation.

Experimental Section

The calorimetric techniques[31] and the methods for measuring bound counterions[23] have been described. Hexadecyltrimethylammonium bromide purchased from City Chemical Corp. was recrystallized from carbon tetrachloride and dried in vacuo at 55 °C. It showed no minimum in a plot of surface tension vs. concentration and titration with $AgNO_3$ gave a molecular weight of 364.7 ± 1.3 (actual 364.5). Doubly distilled water was used for all experiments.

Viscometry. The viscosity of the soap solutions was measured using Ostwald capillary viscometers which had been rinsed several times with distilled water and dried in an oven. To each viscometer was added 5.5 ml of the solution to be run, and the solutions were allowed to equilibrate in a constant temperature bath for at least 30 min. In measuring flow times, the solution was drawn up into the bulb of the viscometer using a rubber squeeze bulb attached to a piece of Tygon tubing into which a small wad of cotton had been inserted. Flow times were obtained using a Haydon electronic stop clock and recorded to the nearest tenth of a second. At least five determinations were made on each solution and the average calculated.

Equation 1, which takes kinetic energy into account, was used to calculate the viscosities (η_{KE}). A and B are constants, ρ is the solution density, and t is the flow time in seconds. A and B were determined by measuring the flow times and densities of carbon tetrachloride, distilled water, benzene, and methanol and using their viscosities at 25 °C obtained from the Handbook of Chemistry.[32] The constants for each viscometer were calculated from the resulting four simultaneous equations. A was the same in all cases while B varied. Only the standard deviation in the flow time was used in the final calculations since those associated with A and B were relatively insignificant. Densities were determined using a 25-ml jacketed pycnometer after equilibration of the solution for 30 min in the constant temperature bath.

$$\eta_{KE} = A\rho t - B\rho/t \quad (1)$$

Acknowledgment. The very helpful comments and criticisms of Professors Linda Magid and Luis Sepulveda are gratefully acknowledged.

Registry No.—CTAB, 57-09-0; sodium *p*-toluenesulfonate, 657-84-1; sodium benzenesulfonate, 515-42-4; sodium *p*-toluate, 17264-54-9; sodium benzoate, 532-32-1; disodium phenyl phosphate, 3279-54-7.

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Action of Oxygen on Thiobenzophenone in the Dark

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Thiobenzophenone (**1**) reacts with oxygen in the dark forming benzophenone (**2**), thiobenzophenone *S*-oxide (**3**), sulfur, and sulfur dioxide. The reaction rate was observed to be highly solvent dependent although the product ratio of **3** to **2** was found to be nearly constant (ca. 0.8). Sulfur and sulfur dioxide were found in 47 and 2.9% yields, respectively. The reaction of **1** in the presence of oxygen with other thioketones to give the *S*-oxides corresponding to the latter provides support for an intermediate "$(C_6H_5)_2CSO_2$" (**4**). The possible mechanisms are discussed.

The stability of several thioketones toward oxygen with or without irradiation has been investigated by Schönberg and Mostafa.[1] Thiobenzophenone (**1**) differs from other thioketones in that it is autoxidizable in the dark as well in the solid state.[2] Products from **1** were found to be benzophenone (**2**), sulfur, and sulfur dioxide; yields and mechanistic information, however, were not reported.[1] The solid state reaction yielded in addition a cyclic trisulfide.[2]

In an attempt to study the mechanism of the oxidative conversion of thioketones to ketones, we report here a reinvestigation of the reaction between **1** and oxygen in the dark in different solvents.[3]

Passage of oxygen through a solution of **1** caused the intense blue color to fade in most of the cases studied (cf. Table I). The final reaction mixtures were observed to be slightly green.

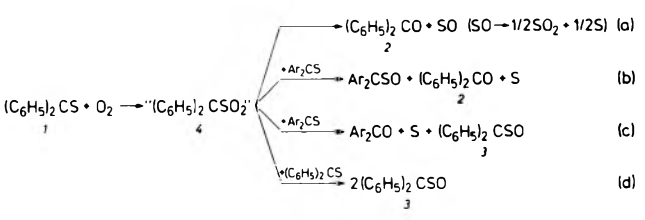
In none of the reactions investigated was there evidence for a cyclic trisulfide, which, if formed, is present to the extent of ≤4% (cf. Table I). However, besides **2** and elemental sulfur, sulfur dioxide was formed in low yields, while thiobenzophenone *S*-oxide (**3**)[4] was obtained in high yield. Although the

$$\underset{1}{(C_6H_5)_2CS} + O_2 \longrightarrow \underset{2}{(C_6H_5)_2CO} + \underset{3}{(C_6H_5)_2CSO} + S + SO_2$$

solubility of oxygen in the different solvents employed is nearly constant,[5] the reaction goes to completion rapidly in most solvents, but is surprisingly slow in acetonitrile and THF. The rather unusual solvent effect has not yet been rationalized. On the other hand, only a small variation in the ratio between the yields of **3** and **2** was observed (Table I). The yield of sulfur dioxide (average for several experiments) was determined to be ca. 3% in the reactions in methanol and benzene. Sulfur yields were determined to be 47%.

Passing oxygen through a solution of sulfine **3** under conditions where a similar solution of **1** had reacted completely caused no change in its concentration. This excludes a mechanism where primary formation of **3** is followed by reaction with oxygen leading to benzophenone. The reaction between thiobenzophenone (**1**) and oxygen consequently appears to involve an intermediate ["$(C_6H_5)_2CSO_2$" (**4**)], which in principle can decompose unimolecularly to give **2** and sulfur monoxide on one hand (Scheme I, path a) or **3** on the

Scheme I

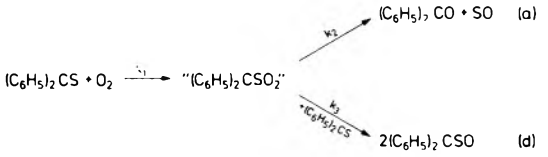


other. Alternatively **3** could be formed in a reaction between **1** and intermediate **4**. The latter is supported by the oxidation of a mixture of **1** and a second aromatic thioketone. Thus oxygen purging of a solution of thioketone **1** containing ca. 10% 4,4′-dichlorothiobenzophenone (**5**) leads to total conversion of the latter to the corresponding 4,4′-dichlorothiobenzophenone *S*-oxide (**6**). Under these conditions a sample of pure **5** is unaffected by oxygen.[6]

For the reaction between intermediate **4** and thioketone, several pathways are possible. Intermediate **4** can oxidize the thioketone to the corresponding sulfine leading to **2** and sulfur (path b), or the thioketone may be directly oxidized to the corresponding ketone and sulfur to yield **3** (path c). The third possibility is the formation of 2 mol of **3** from the reaction between **1** and **4** (path d, Scheme I). In an attempt to distinguish between the above-mentioned sulfine-forming reaction pathways, the reaction was studied at different concentrations of **1** in benzene and methanol. The **3**:**2** ratios are given in Table II. The fact that this ratio was never found to be greater than about 0.9 may rule out path d, since **3**:**2** > 1.0 would be expected at higher concentrations, via selective conversion of the products to **3**. Furthermore, the low yield of sulfur dioxide is in disagreement with path d.

A steady-state treatment of a reaction mechanism involving

Scheme II



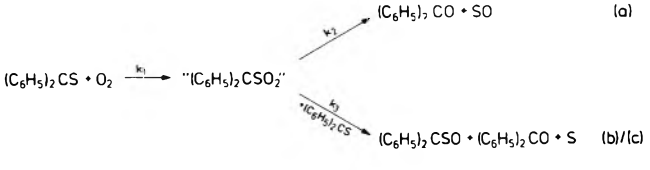
path a and path d (Scheme II) gives the following expression (eq 1).

$$\frac{[(C_6H_5)_2CSO]}{[(C_6H_5)_2CO]} = \frac{2k_3}{k_2}[(C_6H_5)_2CS] \qquad (1)$$

A plot of $[(C_6H_5)_2CSO]/[(C_6H_5)_2CO]$ vs. $[(C_6H_5)_2CS]$ does not give a straight line. Thus path d is effectively ruled out.

However, a mechanism based on simultaneous operation of path a and b or c cannot be distinguished in this way. A steady-state treatment of this mechanism (Scheme III) gives

Scheme III



rise to the following expression (eq 2), which can be transformed into eq 3.

$$\frac{[(C_6H_5)_2CSO]}{[(C_6H_5)_2CO]} = \frac{k_3[(C_6H_5)_2CS]}{k_2 + k_3[(C_6H_5)_2CS]} \qquad (2)$$

Table I. Yields of Thiobenzophenone *S*-Oxide and Benzophenone from the Reaction between Thiobenzophenone and Oxygen as a Function of Solvent

Solvent	% 1 recovered	% 3	% 2	3:2
MeOH	<1	46	52	0.88
2-PrOH	9	40	47	0.85
Benzene	9	38	51	0.75
Acetonitrile	95	~1	~2	
DMF	2	21	77	0.27
THF	>99		<1	

Table II. Ratio between the Yields of Thiobenzophenone *S*-Oxide and Benzophenone by Treatment of Different Concentrations of Thiobenzophenone with Oxygen

Solvent	Concn of 1	3:2
Benzene	0.025	0.61
	0.045	0.75
	0.140	0.80
MeOH	0.024	0.60
	0.034	0.70
	0.040	0.68
	0.123	0.86
	0.157	0.89
	0.179	0.90

$$\frac{k_3}{k_2}[(C_6H_5)_2CS] = \frac{[(C_6H_5)_2CSO]}{[(C_6H_5)_2CO]}\left(1 - \frac{[(C_6H_5)_2CSO]}{[(C_6H_5)_2CO]}\right)^{-1} \quad (3)$$

Figure 1 is a plot based on the data in Table II (methanol), which are well fitted by this expression with $k_3/k_2 = 48.3$. To distinguish between path b and c we attempted to oxidize other thioketones [**5**, 4,4′-dimethylthiobenzophenone (**7**), and 4,4′-dimethoxythiobenzophenone (**8**)], which are not affected by oxygen under the above mentioned conditions with intermediate **4**. Formation of the corresponding thioketone *S*-oxides would indicate path b, while ketone formation would favor path c. Oxygen was passed through solutions of **1** containing ca. 10% of **5**, **7**, or **8**, respectively.

As described above **5** was completely transformed to 4,4′-dichlorothiobenzophenone *S*-oxide (**6**). Compound **7** was partly converted to 4,4′-dimethylthiobenzophenone *S*-oxide (**9**), and in the last case only the products from the reaction between **1** and oxygen were found together with unreacted **8**. The formation of ketone from the substituted thiobenzophenones was not observed during the reactions.

Dondoni and co-workers in 1971 reported kinetics for the reaction between thiobenzophenones and peroxybenzoic acid which yield the corresponding *S*-oxides.[7] They found the Hammett constant for the reaction to be −0.88, indicating that electron-donating groups increase the reaction rate. It is interesting to note that the reverse trend is observed here. The latter could be a result of simple oxygen exchange[8] between initially formed **3** and the added thioketone to form the thermodynamically more stable sulfine (Cl > H ≳ CH_3 > CH_3O). Were this the case, it would not be necessary to postulate the existence of **4**. However, when a solution of **3** containing ca. 15% of the thioketone **5** was treated with oxygen gas as above, the blue color of the thioketones was observed to fade. An analysis of the final reaction mixture showed that 4,4′-dichlorobenzophenone (and not the sulfine **6**) was formed together with benzophenone **2**. This rules out the oxygen exchange mechanism. The data consequently support path b.

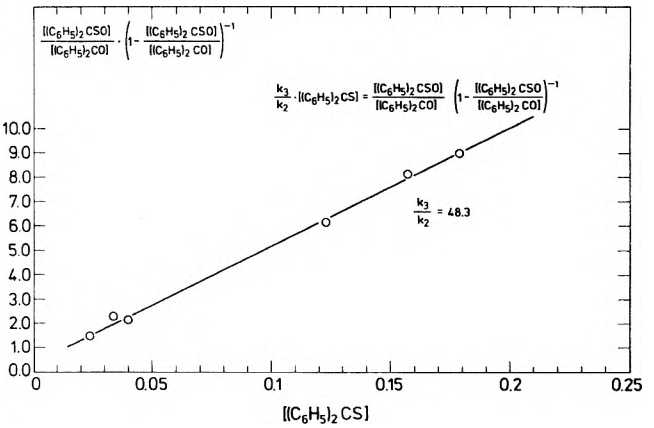
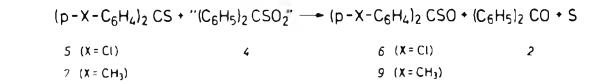
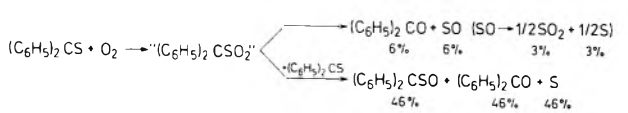


Figure 1. Reaction between thiobenzophenone and oxygen in the dark (0.05 M, methanol).



On this basis the total reaction scheme may now be rationalized (methanol, 0.05 M, cf. Table I) as follows.



Experimental Section

All reactions were carried out in the absence of light.

Reaction between Thiobenzophenone (1) and Oxygen in Different Solvents. Oxygen gas was passed through 0.05 M solutions of freshly prepared **1** for 1.5 h (rate 4.5–5 l./h). The reaction mixtures were submitted to GLC analysis [Pye Unicam 104 chromatograph, dual FID, connected to a Varian Aerograph 477 electronic integrator, on a 2 m × 0.25 in. column with 3% OV-1 (J.J.'s Chromatography Ltd.) on Gas Chrom Q 100/120 mesh (Applied Science Laboratories Inc.) with nitrogen as a carrier gas]. From the chromatograms the amounts of unreacted **1**, benzophenone (**2**), and thiobenzophenone *S*-oxide (**3**) were calculated by comparison with calibration curves. For yields, cf. Table I. By means of $I_2/S_2O_3^{2-}$ titration[9] the yields of sulfur dioxide (average for several experiments) were determined to be 2.9 and 2.5% for the reactions in methanol and benzene, respectively.

Sulfur was isolated by filtration of the final reaction mixtures, washed with ether, and dried in vacuo. Sulfur yields were determined to be 47%. The efficiency of the sulfur isolation was verified by control experiments to be ±3%.

Reaction between Intermediate 4 and Diaryl Thioketones. Oxygen was passed through 0.05 M solutions of **1** methanol containing ca. 10% of the substituted diaryl thioketone for 1.5 h (rate 4.5–5 l./h). The reaction mixtures were analyzed by means of TLC (petroleum ether–benzene, 1:4) and GLC (as described above).

Concentration Dependence in the Reaction between Thiobenzophenone and Oxygen. The solutions of **1** in methanol (or benzene) (concentrations, cf. Table II) were treated with oxygen gas (4.5–5 l./h) for 1 h. The reaction mixtures were analyzed by means of GLC as described above. For yields of **2** and **3**, cf. Table II.

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Registry No.—**1**, 1450-31-3; oxygen, 17778-80-2.

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Mass Spectra of Some Isomeric Monosubstituted Pyridines. Participation of the Ring Nitrogen in the Fragmentation of the 2 Isomers

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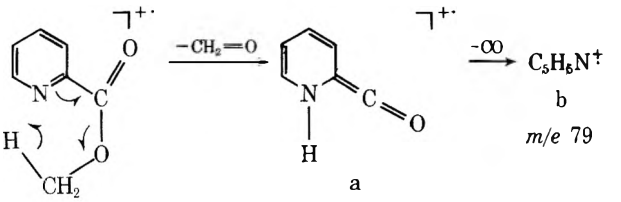
The mass spectra of several isomeric monosubstituted pyridines were investigated. The compounds studied include methyl and ethyl esters of isomeric pyridinecarboxylic acids, pyridinecarboxamides, pyridylacetic acids, and pyridylacrylic acids. The mass spectra of 2-substituted pyridine compounds reported in this study are different from those of their corresponding 3 or 4 isomers. The differences are attributable to the interaction of the side chain in the 2 isomers with the ring nitrogen. This interaction generally results in a hydrogen transfer to the ring nitrogen and elimination of a neutral molecule. The hydrogen transfer can be a six-membered as well as five- or seven-membered transition state.

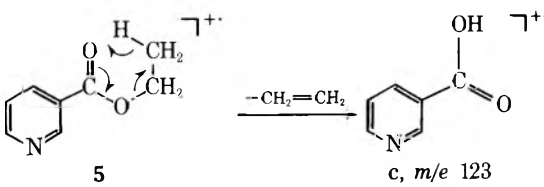
It is often difficult to differentiate between isomers from their mass spectra. In a number of benzenoid aromatic isomers, however, the differentiation can be made as a result of ortho effects[1] or peri effects.[2] In the case of isomeric monosubstituted pyridine derivatives, distinction is sometimes possible due to the interaction of the 2-substituted side chain with the pyridine ring nitrogen.[3-5] In the present study the mass spectra of several sets of isomeric pyridine compounds were investigated to determine if the ring nitrogen is involved in the electron impact induced fragmentation. The participation of the ring nitrogen may be useful for identification purposes in differentiating the 2 isomer from the 3 and 4 isomers.

Methyl Esters of Pyridinecarboxylic Acids. The mass spectra of methyl picolinate (**1**), methyl nicotinate (**2**), and methyl isonicotinate (**3**) are shown in Figure 1. While mass spectra of **2** and **3** are very similar, large differences are observed between the mass spectrum of **1** and those of **2** and **3**. The 3- and 4-substituted pyridines exhibit strong molecular ion peaks and strong fragment ion peaks due to simple bond cleavage α to the carbonyl. In contrast, the mass spectrum of the 2 isomer shows that the molecular ion and an ion due to α-cleavage (m/e 106) are weak. Cooks and co-workers[3] also reported very low molecular ion abundances for the 2-substituted pyridines.

The formation of a relatively strong ion at m/e 107 in the spectrum of the 2 isomer is likely initiated by the interaction of the ring nitrogen with the substituent at the 2 position. The similar reaction product ion is absent or insignificant in the spectra of the 3 and 4 isomers. The relatively weak m/e 107 ion in the spectra of these two isomers is essentially attributed to the natural isotope abundance of the strong m/e 106 ion. The formation of the m/e 107 ion from the ionized 2 isomer **1** can be explained by a transfer of a methyl hydrogen to the ring nitrogen and elimination of formaldehyde to give an ion a in a McLafferty rearrangement. Similar elimination of formaldehyde has been shown in the spectrum of 2-methoxycarbonylimidazole.[6] Ion a further loses a CO to yield a very strong ion b (m/e 79) which is very weak in the spectra of the 3 and 4 isomers. The elemental compositions of ions a and b have been substantiated by high-resolution mass measurements. The fragmentations from m/e 137 to m/e 107 and m/e 107 to m/e 79 as well as other major fragmentation pathways shown in Figure 1 were confirmed by the presence of an appropriate metastable peak (denoted by an asterisk) determined by scanning in the metastable mode (see the Experimental Section).



Ethyl Esters of Pyridinecarboxylic Acids. The mass spectra of ethyl picolinate (**4**), ethyl nicotinate (**5**), and ethyl isonicotinate (**6**) are shown in Figure 2. As in their methyl ester homologues, the mass spectra of the 3- and 4-pyridine isomers are very similar, whereas striking differences are observed between the spectrum of the 2-pyridine compound and those of the 3 and 4 isomers. High-resolution mass measurements show that the strong m/e 123 peak in the spectra of the 3 and 4 isomers is due to the McLafferty rearrangement ion c by elimination of an ethylene molecule from the molecular ion **5**. Similar elimination of ethylene from the molecular ion is not in operation in the spectrum of the 2-pyridine compound. Instead, a McLafferty rearrangement involving a hydrogen



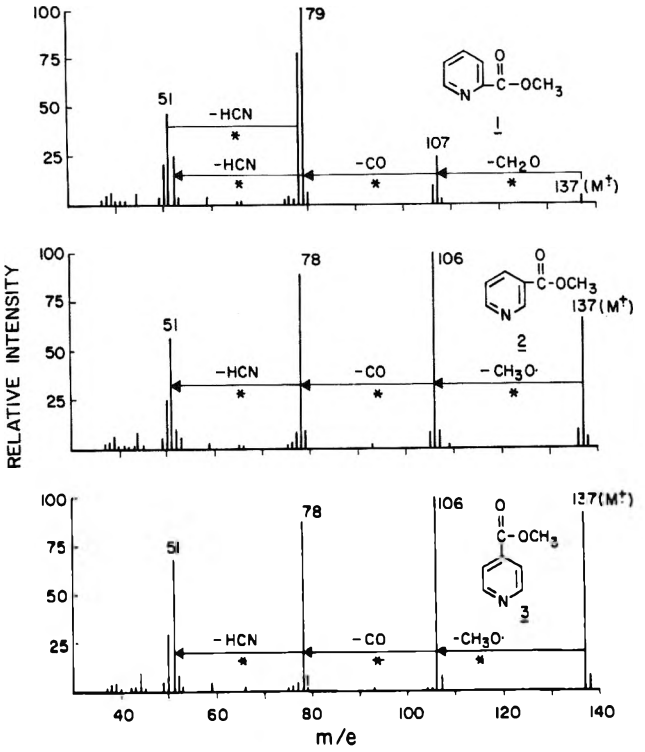


Figure 1. Mass spectra (70 eV) of methyl picolinate (1), methyl nicotinate (2), and methyl isonicotinate (3).

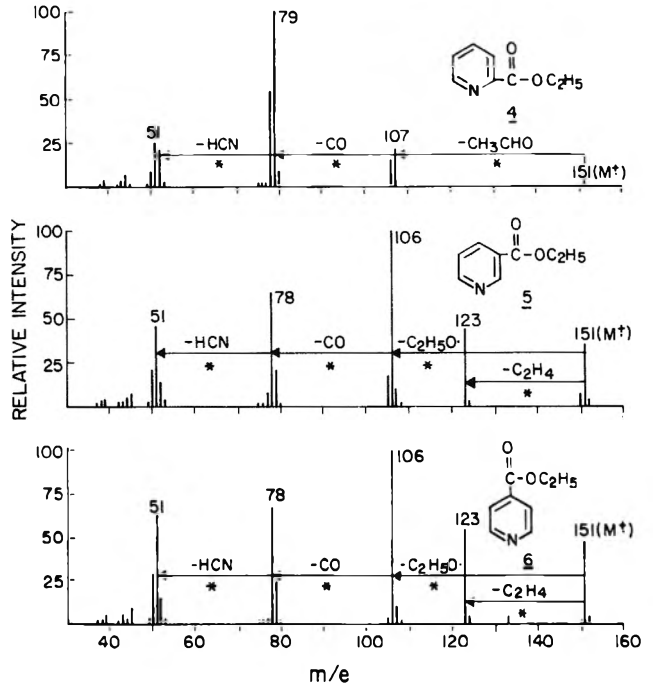
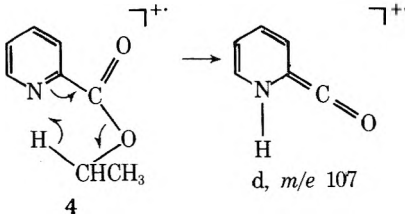


Figure 2. Mass spectra (70 eV) of ethyl picolinate (4), ethyl nicotinate (5), and ethyl isonicotinate (6).

transfer to the ring nitrogen yielding ion d (*m/e* 107) is observed in the spectrum of the 2-pyridine compound **4**. Similar McLafferty rearrangements with a hydrogen transfer from



4 d, *m/e* 107

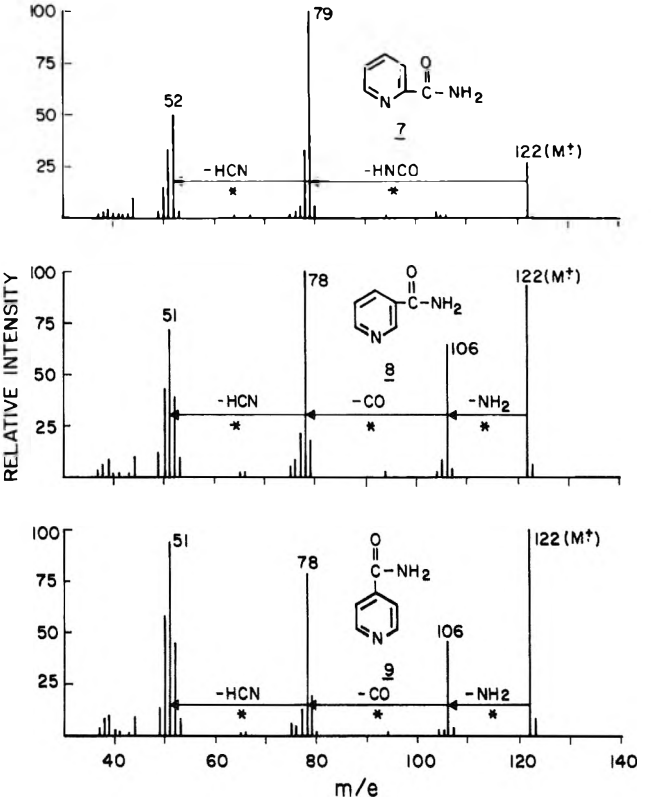
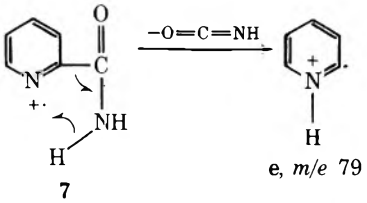


Figure 3. Mass spectra (70 eV) of picolinamide (7), nicotinamide (8), and isonicotinamide (9).

the 2-substituted side chain to the pyridine ring nitrogen have been reported by Cooks et al.,[3] Tomer and Djerassi,[4] Moser and Brown,[7a] and Lightner et al.[8] Deuterium labeling of the methylene hydrogens of compound **4** confirmed that the hydrogen which transfers to the ring nitrogen originates from the α hydrogens of the ethoxy group. The transfer of this hydrogen is facilitated by a six-membered transition state in addition to being a secondary hydrogen.

The mass spectrum of the 2-pyridyl ethyl ester **4** exhibits a base peak at *m/e* 79. The spectra of the 2-pyridyl methyl ester **1** (see Figure 1) and several other 2-substituted pyridine compounds investigated in this study also show a base peak or a strong peak at *m/e* 79. A strong peak at *m/e* 79 generally results from a hydrogen transfer from the 2 substituent to the ring nitrogen followed by a cleavage of the bond attached to the 2 position. The presence of a strong peak at *m/e* 79 and a weak molecular ion peak may be of diagnostic value in identifying the 2-substituted pyridine compounds.

Picolinamide, Nicotinamide, and Isonicotinamide. As shown in Figure 3, the difference between the spectrum of picolinamide (7) and those of nicotinamide (8) and isonicotinamide (9) is evident. The difference is primarily due to the interaction of the ring nitrogen with the side chain in picolinamide. This interaction results in a hydrogen transfer to the ring nitrogen in a five-membered transition state and elimi-



7 e, *m/e* 79

nation of isocyanic acid to yield the base peak ion e (*m/e* 79). The expulsion of isocyanic acid from **7** is analogous to the loss of CO_2 from 2-pyridinecarboxylic acids.[7] The other major

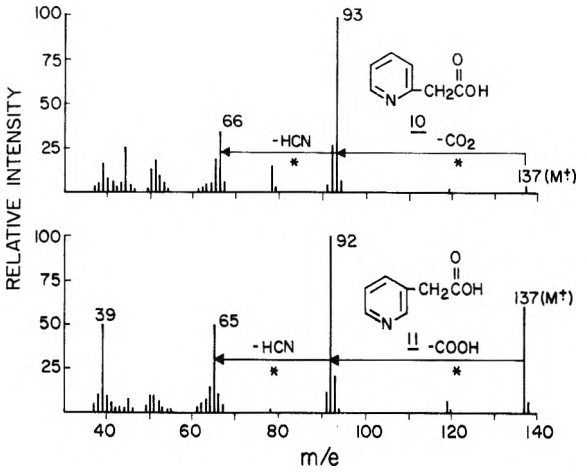


Figure 4. Mass spectra (70 eV) of 2-pyridylacetic acid (**10**) and 3-pyridylacetic acid (**11**).

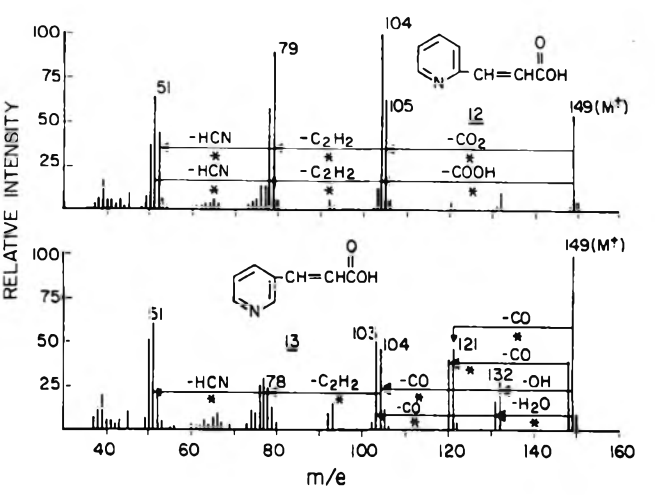
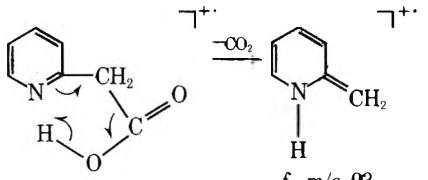


Figure 5. Mass spectra (70 eV) of 2-pyridylacrylic acid (**12**) and 3-pyridylacrylic acid (**13**).

fragmentations are shown in Figure 3. The spectra of nicotinamide and methyl nicotinate have been reported elsewhere.[9]

Pyridylacetic Acids. The striking differences between the mass spectra (Figure 4) of 2-pyridylacetic acid (**10**) and 3-pyridylacetic acid (**11**) are the following: **10** has a very weak molecular ion and a very strong M − CO_2 ion (*m/e* 93), whereas **11** has a strong molecular ion and a very strong M − COOH ion (*m/e* 92). The weak molecular ion and the facile loss of carbon dioxide from the molecular ion in the spectrum of **10** are attributed to the interaction of the substituent at the



10

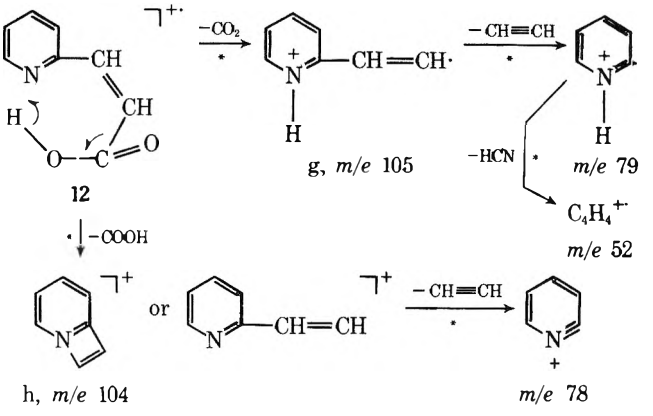
2 position with the ring nitrogen. The interaction is initiated by a transfer of the carboxylic hydrogen to the ring nitrogen in a six-membered ring transition state and expulsion of carbon dioxide yielding ion f (*m/e* 93). Moser and Brown[7] have reported earlier the loss of carbon dioxide from a number of substituted 2-pyridinecarboxylic acid molecular ions and attributed this loss to an interaction of the ring nitrogen and the carboxyl group.

A metastable peak measured by scanning in the metastable mode was observed for the transition from *m/e* 137 (M) to *m/e* 93 (M − CO_2) for compound **10.** This indicates that at least part of M − CO_2 is due to electron impact. The chemical ionization mass spectrum of **10** shows an intense M + 1 peak at *m/e* 138. This suggests that at least a substantial part of **10** is not thermally decomposed prior to ionization.

Pyridylacrylic Acids. The mass spectra of 2-pyridylacrylic acid (**12**) and 3-pyridylacrylic acid (**13**) are shown in Figure 5. Again differences are evident between the spectra of the two isomers. The major fragmentation pathways of **12** are illustrated in Scheme I. Note that the elimination of CO_2 to yield a strong ion g (*m/e* 105) is initiated by a seven-membered ring hydrogen transfer to the pyridine nitrogen. The corresponding peak (*m/e* 105) is weak in the spectrum of **13.** The possible involvement of the side chain in the cyclization to the ring nitrogen to give an ion h (see Scheme I) may contribute to the formation of a very strong ion at *m/e* 104 (M − COOH).

The mass spectrum of 3-pyridylacrylic acid displays two strong peaks at *m/e* 121 and 120 corresponding to the loss of

Scheme I



CO and HCO from the molecular ion, respectively. The elemental compositions of these two ions have been substantiated by high-resolution mass measurements. Other fragmentation pathways are shown in Figure 5.

In summary, mass spectra of 2-substituted pyridine compounds investigated in this study are different from those of their corresponding 3 or 4 isomers. The differences are attributable to the participation of the ring nitrogen in the fragmentation of the 2 isomers.

Experimental Section

All the compounds except methyl picolinate, picolinamide, and 2-pyridylacrylic acid were purchased from Aldrich Chemical Co. Methyl picolinate and picolinamide were obtained from Chemicals Procurement Laboratories. 2-Pyridylacrylic acid was purchased from Research Organic/Inorganic Chemical Corp. 2-Pyridylacetic acid was obtained as its hydrochloride salt. It was converted to free base and its mass spectrum was obtained without storage of sample. Ethyl-*1,1-d*$_2$ picolinate was prepared from ethyl-*1,1-d*$_2$ alcohol and picolinic acid by a method similar to the procedure used by Badgett et al.[10] for octyl nicotinate. The purity of samples was checked by GC, ir, or NMR. In the cases where impurities were found, the samples were purified by either recrystallization or gas chromatography.

Mass spectra were obtained on a CEC 21-104 mass spectrometer at 70 eV, 10 μA, and 2400 V ion accelerating voltage. Samples were introduced via the direct insertion probe. The accurate mass measurements were done on a CEC 21-110B mass spectrometer with a resolution of about 10 000. The metastable peaks were measured by the accelerating voltage scan method similar to the one used by Schulze and Burlingame.[11] The chemical ionization mass spectrum was obtained on a Du Pont 21-490 mass spectrometer using isobutane as the reagent gas.

Registry No.—1, 2459-07-6; 2, 93-60-7; 3, 2459-09-8; 4, 2524-52-9; 5, 614-18-6; 6, 1570-45-2; 7, 1452-77-3; 8, 98-92-0; 9, 1453-82-3; 10, 13115-43-0; 11, 501-81-5; 12, 7340-22-9; 13, 1126-74-5; 2-pyridylacetic acid HCl, 16179-97-8.

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Reactions of Perhaloacetones with Dihydropyridines and Other Electron Donors

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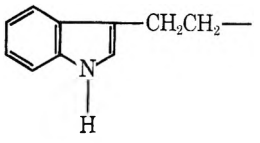
The kinetics of the reduction of hexachloroacetone by 3-substituted 1-benzyl-1,4-dihydropyridines is first order in each reactant. The rate of reduction is sensitive to the electron-withdrawing power of the 3 substituent. Attachment of an indole moiety at either the 3 or the 1 position of the dihydropyridine ring resulted at most in a small decrease in the rate. Activation energies for reduction by the 3-carbamoyl- and 3-cyanodihydropyridines are low (5–7 kcal mol^{-1}) and the entropies of activation are very negative (−46, −47 eu). Reduction by the 3-carbamoyl derivative proceeds 33 times more rapidly in acetonitrile than in benzene. The isotope effect (k_H/k_D) in the product-forming step in reactions of hexachloroacetone, pentachloroacetone, and *sym*-tetrachloroacetone with 1-benzyl-3-carbamoyl-1,4-dihydropyridine-*4-d* is essentially invariant with the nature of the halo ketone. Changes in the ultraviolet–visible spectra are observed when dihydropyridines and halo ketones are mixed, suggesting the possible intervention of intermediate complexes in the reduction. Although electron spin resonance studies indicated the lack of detectable radicals in these reactions, one-electron transfer occurs from *N,N,N',N'*-tetramethyl-*p*-phenylenediamine to hexafluoroacetone to yield the cation radical of the amine. Pentachloroacetone is the product from hexachloroacetone and the diamine. 1,4,4-Trimethyl-1,4-dihydropyridine in acetonitrile gives highly colored solutions when mixed either with hexachloroacetone or chloranil. It was not possible to identify products from these reactions.

The efficient, nonenzymic reductions of thiobenzophenones[1] and halo ketones[2] by 1-substituted 1,4-dihydronicotinamides are approximations to the biological reductions of simple carbonyl groups by the coenzyme, NADH. Electronegative halogen atoms enhance the ease of reduction of the carbonyl group in the halo ketones, a finding consistent with the increase in the rate of reduction of the thiocarbonyl groups in thiobenzophenones when electron-withdrawing substituents are present[1] and in the reduction of electron-deficient nitro and nitroso groups by NADH models.[3,4] Recently, Creighton and Sigman found that complexation of the carbonyl group of 1,10-phenanthroline-2-carboxaldehyde by zinc ions allows its efficient reduction by 1-*n*-propyl-1,4-dihydronicotinamide.[5] Metal ions also facilitate the reduction of pyridoxal phosphate,[6] the reduction of α-hydroxy ketones, and the stereoselective reduction of esters of pyruvic and benzoylformic acids[7] by NADH models. In none of the model systems for the biological reduction of a carbonyl group by dihydronicotinamides has a simple, unactivated carbonyl group been reduced efficiently: metal ions or highly electronegative carbonyl compounds are required.

These above examples involve hydrogen transfers from NADH models to a substrate. The NADH models are capable also of electron donation,[8] and one-electron transfers to tetracyanoethylene,[9] quinones,[10] *N*-methylphenazinium methosulfate,[11] and pyocyanine[11] have been observed. The kinetic isotope effects in the reduction of trifluoroacetophenone by various 1-substituted 1,4-dihydronicotinamides have been explained on the basis of an intermediate, possibly of the charge transfer type, in which partial electron transfer may have occurred.[2e] Charge transfer interactions of trifluoroacetophenone with aromatic electron donors are especially important in the photoreductions of that ketone as compared with acetophenone.[12] The possible intervention of charge transfer complexes in hydrogen transfers from NADH has been suggested,[13] and the possible involvement of the halo ketones in such complexes prior to their reduction by NADH models has been noted.[2b] An oriented complex has been suggested to account for the regioselectivity of the addition of a halomethyl anion produced in a haloform-like cleavage of the product of reduction of 1,1,3-trichloro-1,3,3-trifluoro-2-propanone by 1-benzyl-3-cyano-1,4-dihydropyridine.[14]

Reduction of Hexachloroacetone by Dihydropyridines. The reduction of hexachloroacetone in acetonitrile by 1-benzyl-1,4-dihydronicotinamide is first order in both reactants, the kinetics being followed by noting the decrease in absorbance of the dihydro compound. No change in rate was observed when the reaction was done in a degassed cell; and the addition of *tert*-butylcatechol, a free-radical inhibitor, had little effect. For convenience, excess ketone was used so that

Table I. Rate Constants for the Reduction of Hexachloroacetone (1×10^{-2} M) by Substituted Dihydropyridines[a] in Acetonitrile at 26.6 °C



R

Registry no.	1-Subst	3-Subst	k_{obsd},[b] s^{-1}
59547-43-2	$PhCH_2$	$CON(CH_3)_2$	2.34×10^{-2}
952-92-1	$PhCH_2$	$CONH_2$	2.71×10^{-3}
	$PhCH_2$	$CONH_2$	3.69×10^{-3} [c]
	$PhCH_2$	$CONH_2$	5.06×10^{-3} [d]
	$PhCH_2$	$CONH_2$	6.75×10^{-3} [e]
	$PhCH_2$	$CONH_2$	1.68×10^{-3} [f]
	$PhCH_2$	$CONH_2$	3.55×10^{-4} [g]
	$PhCH_2$	$CONH_2$	8.21×10^{-5} [h]
19350-64-2	$PhCH_2$	$COCH_3$	4.65×10^{-4}
37589-77-8	$PhCH_2$	CN	4.76×10^{-5}
59547-44-3	CH_3	$CONHCH_3$	7.53×10^{-3} [i]
59547-45-4	CH_3 (1)	CONHR	6.33×10^{-3} [i]
59547-46-5	R (2)	$CONH_2$	7.29×10^{-3} [i]

[a] Concentrations in 10^{-4} M range. [b] Pseudo-first-order constant. [c] Ketone concentration 1.5×10^{-2} M. [d] Ketone concentration 2.0×10^{-2} M. [e] Ketone concentration 2.5×10^{-2} M. [f] 4,4-d_2; ketone concentration 2.55×10^{-2} M. [g] In presence of 5×10^{-3} M $ZnCl_2$. [h] In benzene solvent. [i] 26.1 ± 0.2 °C.

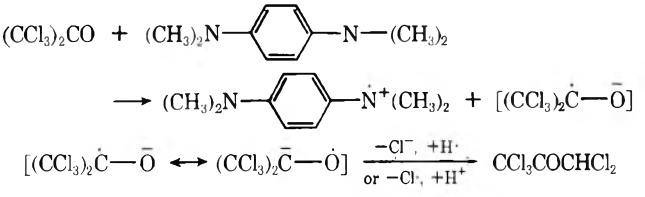
pseudo-first-order kinetics was observed. The rate constant, however, showed first-order dependence on the halo ketone concentration. Table I summarizes the rate data. The rate constant varies by more than 2×10^3 on going from a 3-*N,N*-dimethylcarbamoyl to a 3-cyano substituent. Attachment of an indole moiety to the dihydronicotinamide results, at most, in an 18% decrease in the rate constant from that of 1-methyl-3-methylcarbamoyl-1,4-dihydropyridine. The interpretation of such a small effect is difficult: it may be caused by a steric effect of the bulky indolylethyl substituent, by a small, electron-withdrawing effect of that group, or by complexation of the dihydropyridine with the indole ring. That an interaction can occur between the pyridine and indole rings is indicated by fluorescent emission at 430 nm from the dihydropyridine ring of 1 when the indole chromophore is excited at 300 nm. A similar behavior of 2 was reported by Shifrin a number of years ago.[15] Charge-transfer complexation frequently affects rates; for example, the rate of reaction of pyridine with 3,5-dinitrophthalic anhydride is reduced (ca. 15–50%) by the electron donor, acenaphthene, which stabilizes the anhydride.[16]

Data on the effect of solvents are limited. Protic solvents are unsatisfactory because they react with hexachloroacetone. The reduction proceeds 33 times faster in acetonitrile than in benzene, a reasonable finding in view of the formation of charged molecules from neutral ones. The experimental energies of activation in acetonitrile are 5.2 and 7.2 ± 0.6 kcal mol^{-1}, respectively, for the 3-carbamoyl- and 3-cyano-1,4-dihydropyridines. Entropies of activation are −45.5 and −47.2 ± 0.2 eu, respectively. These activation energies are low compared with those for the reduction of aliphatic ketones by sodium borohydride (9.3–14.9 kcal mol^{-1}).[17] Reduction of riboflavin by 1-*n*-propyl-1,4-dihydronicotinamide has a low activation energy, which prompted the suggestion of complex formation prior to reduction.[18] While experimental energies of activation may be lowered by complex formation,[19] the low activation energies encountered in the reductions of hexachloroacetone may be a consequence of the negative entropies of activation attendant the formation of charged species in an aprotic solvent.[20]

The product isotope effect, k_H/k_D, for the reduction of hexachloroacetone, pentachloroacetone, and *sym*-tetrachloroacetone by 1-benzyl-1,4-dihydronicotinamide is 3.7 ± 0.2, 3.8 ± 0.2, and 3.7 ± 0.2, respectively. The isotope effect was obtained by determination of the amount of deuterium in the alcohol formed by reduction of the ketone by the 4-monodeuteriodihydronicotinamide. The kinetic isotope effect obtained from the comparison of the rates of 1-benzyl-4,4-dideuterio-1,4-dihydronicotinamide with the undeuterated isomer was ca. 4.0 (k_{HH}/k_{DD} = 3.96 ± 0.28), essentially the same as the product isotope effect. The magnitude of the product isotope effect is coincidentally almost the same as that reported (3.8 ± 0.3) for the reduction of trifluoroacetophenone by 1-benzyl- or 1-*n*-propyl-1,4-dihydronicotinamide.[2e]

Effect of Zinc(II) Ions. Zinc ions (5×10^{-3} M) decrease (by a factor of ca. 7) the rate of reduction of hexachloroacetone (1×10^{-2} M) in acetonitrile by 1-benzyl-1,4-dihydronicotinamide (1.5×10^{-4} M), in contrast to the zinc ion accelerated reductions of other carbonyl compounds,[5-7] because of complexation of the zinc with the nicotinamide derivative. The zinc ions not only cause a bathochromic shift from the normal absorption for the dihydro compound at 348 nm but also cause an increase in the absorbance of about 50%. These changes seem too large to be accounted for by a change in solvent polarity on addition of the small amount of zinc chloride. Difference spectra of solutions of the dihydronicotinamide and zinc chloride indicate that the complex has absorption at 389 nm. Because of the closeness of the absorption maxima for complexed and uncomplexed substrate, the equilibrium constant could not be determined accurately. If the rate of reaction of the complexed species is assumed to be small relative to the rate of the uncomplexed species, a dissociation constant of 0.136 is obtained from kinetics.[21] Complexation may occur through the amide group,[22] or it may be of the charge transfer type. Complexation of the electropositive zinc ion with the dihydronicotinamide would be expected to decrease its reducing power in the same manner as attachment of a more electron-withdrawing substituent group.

Reactions with Tetramethyl-*p*-phenylenediamine and with 1,4,4-Trimethyl-1,4-dihydropyridine. Treatment of hexachloroacetone or hexafluoroacetone with *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine in acetonitrile gives a deep blue color, identified as Würster's blue by its ultraviolet absorption spectrum at 568 and 617 nm[23] and by electron spin resonance.[24] The ketyl radical (below in brackets) was not observed by ESR; in any case, its lifetime is short.[25] Pentachloroacetone is formed in about 30% yield; chloride ions were detected by silver nitrate. Tetrachloroacetone (15%) also was obtained.



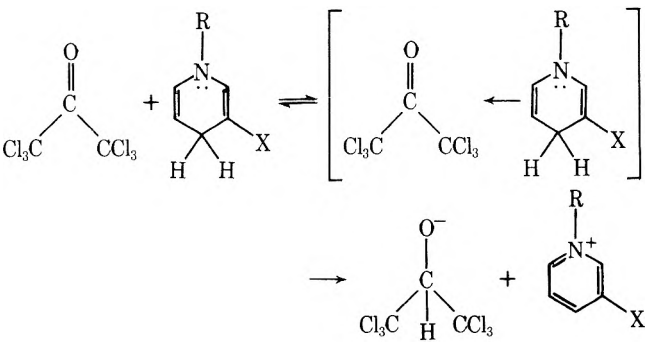
When hexafluoroacetone and the diamine are mixed, a transient, instantaneously produced absorption at 402 nm was observed before the appearance of the blue color of the cation radical of the diamine. An orange color was seen which within a few seconds gave way to the blue of the cation radical. In cyclohexane, the mixture of diamine and hexafluoroacetone showed a broad, new absorption centered at 400 nm and no further change was observed. It seems that a solvent more polar than cyclohexane is required for the electron transfer, which produces ions. The new absorption band may be caused

by formation of a charge-transfer complex. For example, absorption at 843 nm not attributable to any other reactant or product was suggested as being caused by a charge-transfer complex of the diamine and chloranil.[23c]

Just after hexachloroacetone and 1-benzyl-1,4-dihydronicotinamide are mixed in acetonitrile, a transient absorption is observed at higher wavelength (ca. 380 nm) than the absorption for the dihydro compound alone.[26] When 1,4,4-trimethyl-1,4-dihydropyridine, which cannot transfer hydrogen because there is none at the 4 position, is treated with hexachloroacetone in acetonitrile, the solution became yellow at first and then purple. New absorptions appeared at 384 and 540 nm. A purple solution (λ_{max} 586, 720 nm) also appeared when the trimethyldihydropyridine was treated with chloranil. An amorphous, purple solid was obtained from this solution, but the solid was unable to be characterized. Its broad and featureless infrared spectrum and its lack of solubility in both polar and nonpolar solvents suggest a polymer. The new absorptions produced when dihydropyridines are mixed with halo ketones may indicate formation of either a complex, a radical intermediate, or an adduct. No ESR signals could be observed in either hexane or acetonitrile when the reactants were mixed in a special cell immediately prior to the ESR measurement. The trimethyldihydropyridine has been reported to form a charge-transfer complex with maleic anhydride.[27]

Discussion

Charge transfer complexation and one-electron transfers involving hexachloro- or hexafluoroacetone are possibilities which must be considered when examining reductions of these ketones by models for the pyridine nucleotide coenzymes. Previous observations have indicated that free-radical inhibitors do not affect the reduction of the carbonyl group, but one-electron transfers within complexes cannot be ruled out.[2b] The requirement of an obligatory intermediate to explain isotope effects in the reduction of trifluoroacetophenone supports a more complex mechanism than a simple, one-step hydride ion transfer.[2e] Our finding that the kinetic isotope effect with hexachloroacetone and 1-benzyl-4,4-dideuterio-1,4-dihydronicotinamide is essentially the same as the product isotope effect contrasts with the studies on trifluoroacetophenone for which the two isotope effects differed. This result is consistent both with a mechanism of hydrogen transfer involving an intermediate complex (provided the same reasonable assumptions are made concerning the magnitudes of rate constants as was made in the trifluoroacetophenone work)[2e] and with a mechanism involving no intermediates. The significant involvement of charge-transfer complexation in the photoreduction of trifluoroacetophenone[12] lends credence to the suggestion of intermediate complexes, probably of the donor–acceptor type. As mentioned previously, the regioselectivity of reactions of an unsymmetrically substituted perhaloacetone with a dihydropyridine derivative may be interpreted on the basis of an oriented, intermediate complex.[14] Oriented complexes or transition states have been suggested to explain the stereospecificity of certain dehydrogenase enzymic reductions,[13,28] and preliminary, stereospecific complexation may occur in the recently reported zinc-catalyzed reduction of α-keto esters by chiral NADH models.[7] Complexation may be especially important for highly electron-deficient substrates, and the spectroscopic observations with perhaloacetones and 1,4,4-trimethyl-1,4-dihydropyridine and 1-benzyl-1,4-dihydronicotinamide may be considered as indications of complex formation although, as indicated above, other possibilities, or combinations of them, may explain the results. The scheme for the reduction of hexachloroacetone via a complex is illustrated:



Experimental Section[29]

Materials. Acetonitrile (Matheson Coleman and Bell, Spectroquality) was refluxed over calcium hydride for 2 h and distilled from the hydride. The halo ketones were obtained commercially and were purified by distillation. Hexafluoroacetone was used as obtained. 1-Benzyl-3-carbamoyl-1,4-dihydropyridine and its mono-4-deuterio analogue were prepared as previously described.[30] *N,N,N′,N′*-Tetramethyl-*p*-phenylenediamine was prepared from the dihydrochloride.[31] 1,4,4-Trimethyl-1,4-dihydropyridine was prepared as described previously.[27] 1-(β-Ethyl-3-indolyl)-3-carbonyl-1,4-dihydropyridine[15] was prepared as described previously. 1-Benzyl-4,4-dideuterio-1,4-dihydronicotinamide was prepared according to the directions of Mauzerall and Westheimer[32] by reduction of 1-benzyl-3-carbamoyl-4-deuteriopyridinium chloride in D_2O. ^1H NMR analysis of the intermediate, methyl 4-deuterionicotinate, showed only 2–3% of protium at the 4 position.

1-Benzyl-3-acetyl-1,4-dihydropyridine. Reduction of 1-benzyl-3-acetylpyridinium chloride by sodium dithionite was done as described previously.[2b,33] A better yield was obtained when the reduction was done at 0 °C for 7 h, during which time the dihydropyridine precipitated. Precipitation was encouraged by refrigeration of the reaction mixture overnight. Recrystallization from ethanol provides off-white crystals (85% yield), mp 64–66 °C dec (lit.[33] mp 61–67 °C).

1-Benzyl-3-cyano-1,4-dihydropyridine. 3-Cyanopyridine (30 g, 0.288 mol) and benzyl chloride (36.5 g, 0.288 mol) were refluxed for 22 h in 150 ml of absolute ethanol in a 300-ml, one-necked, round-bottomed flask equipped with a condenser and drying tube. No precipitation of product was observed upon cooling even at freezer temperatures. A small amount of the solution (ca. 2 ml) was placed in a test tube, and anhydrous ether was added. A white precipitate formed and these crystals were used to seed the main body of the reaction solution. Precipitation then occurred rapidly to give white 1-benzyl-3-cyanopyridinium chloride (41 g, 62%). The material starts to darken in color at ca. 185 °C and becomes red just before melting: mp 207–209 °C dec; ir (KBr) 2250 (w), 1640 (s), 1580 (w), 1490 cm^{-1} (s); uv (methanol) 268 nm (ε 3900); NMR (D_2O) δ 9.4 (s, 1 H), 9.15 (complex doublet, 1 H), 8.8 (complex doublet, 1 H), 8.26 (quartet, 1 H), 7.31 (complex multiplet, 5 H), 5.8 (s, 2 H).

Anal. Calcd for $C_{13}H_{11}ClN_2$: C, 67.7; H, 4.77; N, 12.1. Found: C, 67.8; H, 5.05; N, 12.1.

Sodium dithionite (34.8 g, 0.2 mol) and sodium carbonate (17.7 g, 0.167 mol) were dissolved in 250 ml of distilled water in a 500-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer and a 60-ml addition funnel. 1-Benzyl-3-cyanopyridinium chloride (11.5 g, 0.05 mol) dissolved in 50 ml of distilled water was added dropwise to the vigorously stirred solution by means of the addition funnel. The solution immediately became yellow but no precipitation occurred throughout the entire addition of the salt which took 30 min. After ca. 90 min more, a yellow precipitate formed. Stirring was halted when it appeared that precipitation had been completed. The solid was collected by filtration and recrystallized from ethanol–water (no heating). Bright yellow needles (7 g, 71%) were obtained and dried in a vacuum oven for 1 h at 35–40 °C: mp 52–53 °C dec; ir (KBr) 2200 (s), 1680 (s), 1610 (s), 1495 cm^{-1} (m); uv (CH_3CN) 340 nm (ε 5600); NMR ($CDCl_3$) δ 7.31 (s, 5 H), 6.51 (d, $J_{2,6}$ = 1.5 Hz, 1 H), 5.68 (pair of quartets, 1 H), 4.58 (pair of triplets, 1 H), 4.18 (s, 2 H), 3.02 (broad quartet, 2 H).

Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.51; H, 6.12; N, 14.28. Found: C, 79.38; H, 6.02; N, 14.45.

1-Benzyl-3-(*N,N*-dimethylcarbamoyl)-1,4-dihydropyridine. *N,N*-Dimethylnicotinamide (25 g, 0.17 mol) and benzyl chloride (21.5 g, 0.17 mol) were refluxed for 8 h in 100 ml of ethanol in a 200-ml, round-bottomed, one-necked flask equipped with a condenser and

drying tube. No precipitation occurred upon cooling. Because of the hygroscopicity of the salt no attempt was made to obtain the 1-benzyl-3-(*N,N*-dimethylcarbamoyl)pyridinium chloride as a solid, and 100 ml of water was added to the oil obtained by evaporation of solvent. The yield of salt was estimated to be ca. 35 g (75%). A NMR spectrum of the water solution was consistent with the presence of a pyridinium salt: δ 9.26 (s, 1 H), 9.16 (d, 1 H), 8.70 (d, 1 H), 8.24 (quartet, 1 H), 7.44 (broad singlet, 5 H), 5.9 (s, 2 H), 3.05 (s, 3 H), 2.95 (s, 3 H).

The reduction was carried out directly on half of the aqueous solution of pyridinium salt (ca. 17 g, 0.062 mol) at 0 °C. Sodium dithionite (41.8 g, 0.24 mol) and sodium carbonate (21.2 g, 0.20 mol) were dissolved in 200 ml of distilled water in a 500-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer and a 60-ml addition funnel. To this vigorously stirred solution, the salt solution was added dropwise over a period of 1 h. The solution turned yellow immediately, and 1 h after the salt addition had been completed, a yellow precipitate formed. The reaction was put under nitrogen to prevent decomposition of the dihydro compound. The reaction was allowed to proceed for a total of 6 h. The solid was collected by filtration under nitrogen, crude mp 38–50 °C. This compound decomposed very quickly in air to give a dark brown oil. Purification was accomplished by eight recrystallizations (material dissolved in ethanol without heating, water added to the cloud point, then cooling). The yield after all recrystallizations was 4 g (37%): mp 56–58 °C; ir ($CHCl_3$) 1675 (s), 1600 (vs), 1490 cm^{-1} (s); uv (ethanol) 345 nm (ϵ 4300); NMR ($CDCl_3$) δ 7.3 (s, 5 H), 6.23 (d, $J_{2,6}$ = 1.5 Hz, 1 H), 4.59 (pair of triplets, 1 H), 4.22 (s, 2 H), 3.17 (broad doublet, 2 H), 2.97 (s, 6 H).

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.39; H, 7.44; N, 11.58. Found: C, 74.21; H, 7.08; N, 11.36.

1-Methyl-3-(*N*-methylcarbamoyl)-1,4-dihydropyridine. Sodium carbonate (21.2 g, 0.20 mol) and 1-methyl-3-(*N*-methylcarbamoyl)pyridinium iodide[34] (6.8 g, 0.0274 mol) were dissolved in water (150 ml). The solution was cooled to 4 °C and sodium dithionite (13.0 g, 0.07 mol) was added. The mixture was stirred at 4 °C for 3 h and the solid was removed by filtration. Recrystallization of the solid from hot water (60–70 °C) gave a light yellow solid (2.1 g, 0.0138 mol, 50.4%): mp 77–79 °C; uv (CH_3CN) 347 nm (ϵ 5485); NMR ($CDCl_3$) δ 2.75 (s, 3 H), 2.90 (s, 3 H), 3.06 (m, 2 H), 3.33 (s, 1 H), 4.63 (m, 1 H), 5.70 (m, 1 H), 6.86 (m, 1 H).

1-Methyl-3-(*N*-β-ethyl-3-indolyl)carbamoylpyridinium Iodide. Nicotinic acid tryptamide[35] (2.50 g, 0.009 mol) and methyl iodide (5.11 g, 0.036 mol) were dissolved in absolute ethanol (50 ml). The mixture was refluxed for 20 h and cooled. Ethyl ether was added to the cloud point, and cooling to −20 °C precipitated the yellow product (2.0 g, 0.0049 mol, 54%): mp 204–206 °C; NMR (Me_2SO-d_6) δ 2.9–3.18 (m, 2 H), 3.45–3.70 (m, 2 H), 3.78 (m, 1 H), 4.41 (s, 3 H), 6.83–7.67 (m, 5 H), 8.08–8.33 (m, 1 H), 8.81–8.95 (m, 1 H), 9.05–9.15 (m, 1 H), 9.38 (m, 1 H).

Anal. Calcd for $C_{17}H_{18}IN_3O$: C, 50.12; H, 4.42; N, 10.31. Found: C, 50.38; H, 4.41; N, 10.13.

1-Methyl-3-(*N*-β-ethyl-3-indolyl)carbamoyl-1,4-dihydropyridine. Sodium carbonate (0.636 g, 0.006 mol) and 1-methyl-3-(*N*-β-ethyl-3-indolyl)carbamoylpyridinium iodide were dissolved with stirring in water (350 ml) in an atmosphere of nitrogen. Sodium dithionite (1.74 g, 0.01 mol) was added in several portions and the solution became bright yellow. Stirring was continued for 1 h and the solution was extracted with methylene chloride (3 × 100 ml). Drying ($NaSO_4$) and removal of the solvent at reduced pressure gave an amorphous yellow solid (0.58 g, 0.0021 mol, 68.8%): mp 197–201 °C; NMR (CD_3CN) δ 2.81 (s, 3 H), 2.98 (m, 4 H), 3.50 (m, 2 H), 5.66 (m, 1 H), 6.08 (m, 1 H), 6.86–7.66 (m, 6 H); uv (CH_3CN) 347 nm (ϵ 5850). An analysis was not performed because the compound is extremely sensitive to air and heat: the material turns to an oil and becomes progressively dark red.

Table II. Variation of k_{obsd} with Temperature for the Reduction of Hexachloroacetone[a] by 1-Benzyl-3- carbamoyl-1,4-dihydropyridine[b] in Acetonitrile

Temp, K	$10^3 k_{obsd}$ s^{-1}
299.6	2.52
309.6	3.32
319.6	4.41

[a] 1.00 × 10^{-2} M. [b] 1.08 × 10^{-4} M.

Table III. Interactions of *N,N,N',N'*-Tetramethyl-*p*-phenylenediamine and 1,4,4-Trimethyl-1,4-dihydropyridine with Electron Acceptors in CH_3CN

Donor[a]	Registry no.	Acceptor[b]	Registry no.	ESR signal	Color	λ_{max}, nm
TMPD	100-21-1	HFA	684-16-2	Yes	Blue	402,[c] 568, 617
TMPD		HCA			Blue	404, 568, 620
TMPD		HFA				380–450[d]
TMPD		DDQ	84-58-2		Blue	430, 568, 611
TMPD		CA	118-75-2		Blue	450, 568, 620
TDP	59547-47-6	HCA	116-16-5	No	Blue-red	540[e]
TDP		CA		No	Purple	586, 720

[a] TMPD = *N,N,N',N'*-tetramethyl-*p*-phenylenediamine; TDP = 1,4,4-trimethyl-1,4-dihydropyridine. [b] HFA = hexafluoroacetone; HCA = hexachloroacetone; DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; CA = chloranil. [c] Disappears after 10 min as absorption at 568 and 617 nm reaches maximum intensity. [d] Hexane solvent; broad, weak absorption. [e] New absorption first appears at 382 nm slowly giving way to the absorption at 540 nm.

Kinetics and Isotope Effects. Spectrophotometric measurements were done on a Perkin-Elmer ultraviolet–visible spectrophotometer, Model 202, equipped with a controlled temperature cell mount and a time-drive accessory with interchangeable motors.

The dihydro compound was weighed out on a Cahn ratio balance and was transferred to a volumetric flask, and the flask was filled to the mark with acetonitrile. The halo ketone was weighed directly into a volumetric flask and the flask was then filled to the mark with solvent.

In a typical run the sample and reference cells were placed in the thermostated cell mount which was maintained at 26.6 ± 0.05 °C. The time-drive accessory was locked on the wavelength of maximum absorption of the dihydropyridine. The reference cell contained pure solvent. Products of the reaction, the pyridinium ion and the alkoxide ion, were not needed in the reference cell at the concentrations used since they did not interfere with the band being followed. A syringe equipped with a Chaney adapter was used to deliver 2 ml of the halo ketone solution into the sample cell. The same syringe was then washed and dried thoroughly and used to deliver 2 ml of the dihydropyridine solution into the halo ketone solution in the sample cell. Mixing was instantaneous; the cell compartment cover was closed quickly and locked, and the time drive motor was started. The speed of the time drive motor used was chosen on the basis of a length of time sufficient to allow 65% or more reaction to occur. Control experiments showed that solvent evaporation was negligible for periods up to 1 h.

The infinity values of the absorbance (A_∞) were obtained in two ways. At the conclusion of a run the reaction solution was transferred from the sample cell to a 10-ml volumetric flask. The flask was sealed and placed in a constant-temperature bath for the required time (ca. 20 half-lives). At the end of that time the solution was returned to the sample cell and its spectrum was recorded. The other method used was to mix equal volumes of the reaction solutions in a 10-ml volumetric flask which was then sealed and placed in a thermostated bath. After the required time, the t_∞ spectrum of the solution was recorded.

Rate constants (pseudo-first-order) were calculated from the slope of the line obtained by plotting log $(A_t - A_\infty)$ against time, where A_t is the absorbance at time t. The absorption of the dihydropyridines obeys Beer's law. Table II gives the data from which the experimental energies and entropies of activation were obtained.

The NMR spectrum taken immediately after mixing chloroform-*d*

solutions (room temperature) of 1-benzyl-1,4-dihydronicotinamide and hexachloroacetone showed the absence of absorption at δ 3.10 for the methylene protons at the 4 position of the dihydro compound and appearance of absorption at δ 4.81 for the 2 proton of 1,1,1,3,3,3-hexachloro-2-propanol.[36] Protons for the formation of hexachloro-2-propanol from the alkoxide presumably are donated by solvent or by the amide group.

The rate of reaction of hexachloroacetone with 1-benzyl-1,4-dihydronicotinamide in the absence of atmospheric oxygen was determined spectrophotometrically in a Pyrex ultraviolet cell equipped with a side bulb and an attached joint for evacuation of the cell and side arm by means of a high vacuum system. A solution of the halo ketone was placed in the cell and a solution of the dihydronicotinamide was placed in the side bulb. The solutions were frozen in a bath of dry ice–trichloroethylene and the system was degassed ($<10^{-3}$ mm). The observed rate constant for a reaction mixture 1.0×10^{-2} M in halo ketone and 1.0×10^{-4} M in dihydronicotinamide at 26.6 °C was 2.58×10^{-3} s^{-1}, in satisfactory agreement with the average value of 2.71×10^{-3} s^{-1} obtained when no precautions were taken to exclude air.

The halo-2-propanols were isolated from reactions in acetonitrile of 1-benzyl-4-deuterio-1,4-dihydronicotinamide with hexachloroacetone, pentachloroacetone, and *sym*-tetrachloroacetone. Control experiments show that exchange of deuterium from the alcohol does not occur either during workup or under the conditions of reduction (e.g., 2-deuteriohexachloro-2-propanol does not lose its deuterium when it was put through the workup procedure consisting of evaporation of the acetonitrile solution and chromatography of the residue on Florisil with elution by 2:1 hexane–ether or when it was added to a mixture of *sym*-tetrachloroacetone and 1-benzyl-1,4-dihydronicotinamide in acetonitrile.) Deuterium analysis was done on the acetates of the alcohols (prepared by treating the alcohol with acetic anhydride plus 2 drops of concentrated sulfuric acid) by mass spectrometry (with the exception of pentachloroisopropyl alcohol, which was analyzed without conversion to an acetate). The values of k_H/k_D thus obtained were 3.7, 3.8, and 3.7, respectively. A sample of 1,1,3,3-tetrachloro-2-propyl acetate also was analyzed by the combustion–falling drop technique[37] to give a value of k_H/k_D of 3.9, within experimental error (0.2) of the values obtained by mass spectrometry.

Interaction of *N,N,N',N'*-Tetramethyl-*p*-phenylenediamine and 1,4,4-Trimethyl-1,4-dihydropyridine with Halo Ketones. The observations are summarized in Table III. Gas chromatography [on a 5 ft × 0.25 in. glass column of 20% Dow-Corning Silicone Oil 550 on Chromosorb P (80/100 mesh)] of the reaction of diamine and hexachloroacetone showed the formation of pentachloroacetone whose infrared spectrum (of an isolated sample) was identical with that of an authentic sample. Tetrachloroacetone and unreacted hexachloroacetone also were detected. In a comparison of the gas chromatographic behavior of the reaction mixture with that of a mixture of authentic hexachloroacetone, pentachloroacetone, and tetrachloroacetone, one can estimate that the reaction mixture contained roughly 15% hexachloroacetone, 25% pentachloroacetone, and 15% tetrachloroacetone. Water (20 ml) was added to the reaction mixture and nonpolar organic compounds were extracted with ether (20 ml) twice. The aqueous solution was acidified and addition of aqueous silver nitrate gave an immediate precipitate of silver chloride (ca. 1 mol of chloride ions were produced per mole of hexachloroacetone).

A purple, amorphous product was obtained from the reaction of chloranil with 1,4,4-trimethyl-1,4-dihydropyridine: ir, broad and featureless; NMR (Me_2SO-d_6) δ 1.23 (m), 2.20 (s), 2.60 (s), 2.90 (m), 3.60 (m).

Spectroscopic Observations on Mixtures of Halo Ketones and 1-Benzyl-1,4-dihydronicotinamide. Alone, hexachloroacetone and hexafluoroacetone each have an absorption maximum in acetonitrile at 296 and 290 nm, respectively. Solutions of halo ketone and 1-benzyl-1,4-dihydronicotinamide in acetonitrile were mixed, and the ultraviolet spectrum was immediately taken in the region above 330 nm. The absorbance (beyond 350 nm) of the mixture was always greater than the sum of the absorbances of the reactants. The concentration of halo ketone was much greater than the concentration of dihydropyridine. A 1 M solution of hexachloroacetone and a 10^{-4} M solution of 1-benzyl-1,4-dihydronicotinamide showed new absorption (difference spectrum) at 382 nm.[26] This absorption disappears as the reduction proceeds. Pentachloroacetone and *sym*-tetrachloroacetone (both 5×10^{-2} M) with 10^{-4} M dihydro compound gave new maxima in the difference spectra at 371 and 362 nm, respectively. 1,1,1-Trichloroacetone (50% by volume) and chloroacetone (neat) showed no change in the ultraviolet spectrum when mixed with a 10^{-4} or 10^{-3} M solution of 1-benzyl-1,4-dihydronicotinamide.

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Registry No.—3-Cyanopyridine, 100-54-9; benzyl chloride, 100-44-7; 1-benzyl-3-cyanopyridinium chloride, 14535-08-1; *N,N*-dimethylnicotinamide, 6972-69-6; 1-benzyl-3-(*N,N*-dimethylcarbamoyl)pyridinium chloride, 58287-39-1; 1-methyl-3-(*N*-methylcarbamoyl)pyridinium iodide, 58287-40-4; 1-methyl-3-(*N*-β-ethyl-3-indolyl) carbamoylpyridinium iodide, 59547-48-7; nicotinic acid, 59-67-6; tryptamide, 61-54-1.

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Alkyl Nitrate Nitration of Active Methylene Compounds. Nitration of Arylidene and of Alkylidene Phenylhydrazines[1]

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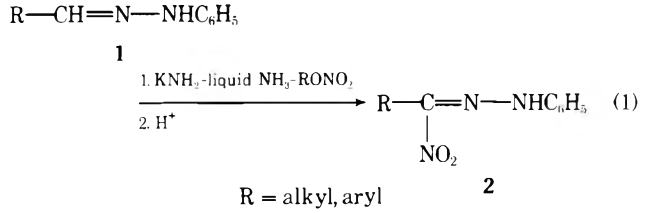
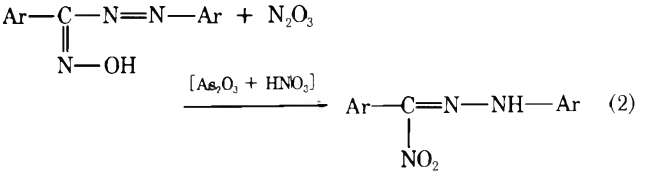
The alkyl nitrate nitration of arylidene and alkylidene phenylhydrazines affords the corresponding α-nitroarylidene and α-nitroalkylidene phenylhydrazines. Exclusive nitration on carbon is observed. This is in contrast to alkylation and acylation reactions which occur on nitrogen. The NMR spectra of the nitro compounds show the presence of both the *Z* and *E* isomers. The ratio of the isomers varies with the polarity of the solvent, the *Z* configuration predominating in nonpolar media owing to intramolecular hydrogen bonding.

In continuation[2] of our studies of the alkyl nitration, we are now reporting on its application to the synthesis of α-nitroarylidene and α-nitroalkylidene phenylhydrazines (eq 1).

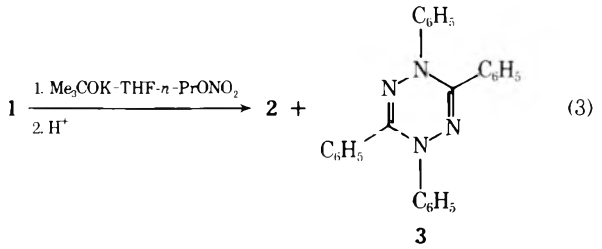


R = alkyl, aryl

Previously, the only available method for preparing these compounds involved the coupling of diazonium compounds with salts of primary nitro compounds.[3,4] The method has afforded moderate yields and suffered because substituted arylnitromethanes are not readily available. α-Nitroarylidene phenylhydrazines have also been obtained in low yields from the oxidation of arylazoaldoximes[5] (eq 2).



The nitration reaction in eq 1 was studied in several base–solvent systems with **1** (R = C_6H_5) as the model compound; the results are summarized in Table I. Highest yields (91%) of α-nitrobenzylidene phenylhydrazine (**2**) (R = C_6H_5) were obtained in the potassium amide–liquid ammonia system when the molar ratio of **1** to base to nitrating agent was 1:1:2. In the potassium *tert*-butoxide–tetrahydrofuran (THF) system, the yield of **2** was 80% but the reaction was accompanied by the formation of 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (**3**) (eq 3). It is very likely that **2** is the precursor in the formation of **3** for **2** was converted into **3** on heating in ethanolic potassium hydroxide or methanolic sodium methoxide.[6]



When the nitration of **1** was carried out in the *n*-butyllithium–ethyl ether system, 1-phenylazo-1-phenylpentane (**4**) was the major product (40%) and **2** the minor product (30%) (eq 4). Compound **4** arose from a nucleophilic attack of *n*-butyllithium on the azomethine carbon of **1**, followed by air oxidation, a reaction which is well documented.[7]

The generality of the reaction in the potassium amide–liquid ammonia system was established by its application to a variety of compounds **1** including those derived from heterocyclic carboxaldehydes. As indicated by the data shown in Table II, the yields of some of the nitro compounds were substantially higher when reactions were carried out in a more concentrated medium. For instance, the yield of α-nitroethylidene phenylhydrazine (**5**) was increased by 53% when the concentration of potassium amide was increased from 0.3 to 0.7 M. This phenomenon was previously observed in the nitration of alkylsulfonate esters[8] and alkyl-substituted heterocyclics.[9]

However, nitrations in a more concentrated medium did not improve the yields of α-nitro-1-naphthylidene phenylhydrazine and α-nitro-3-picolylidene phenylhydrazine.

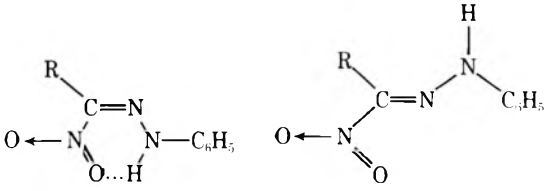
The low yields of compounds **2** (R = alkyl), with the exception of compound **5**, are very likely due to the instability of the starting materials.

Spectra of Compounds 2. A detailed study of the NMR spectra of compounds **2** indicated that in solution, both *E* and *Z* isomers were present. In relatively nonpolar solvents, the *Z* isomer predominated. This can be explained on the basis of its increased stability due to intramolecular hydrogen bonding. For example, the spectrum of **2** (R = C_6H_5) in $CDCl_3$ showed two NH absorptions at δ 12.0 and 8.0, which integrated to a value of 0.7 and 0.3 protons, respectively. The signals at δ 12.0 and 8.0 were assigned to the *Z* and *E* isomers, respectively. In a recent NMR study of these compounds, the authors reported only one NH signal in $CDCl_3$ at δ 11.73–11.89 and assigned it to the *Z* isomer.[10] The absorption peak at 12.0

Table I. Effect of Various Base–Solvent Systems on the Nitration of Benzylidene Phenylhydrazine [a] (1, R = C_6H_5)

Base–solvent	α-Nitrobenzylidene phenylhydrazine yield, %	Recovered 1 yield, %
KNH_2–liquid NH_3	91	3
$NaNH_2$–liquid NH_3	45 [b]	45
$LiNH_2$–liquid NH_3	2	90
$(CH_3)_3COK$–THF	80	c
n-BuLi–Et_2O	33	21 [d]

[a] In all experiments the molar ratio of 1 to base to n-propyl nitrate was maintained at 1.0:1.0:2.0 in approximately 300 ml of solvent. [b] When the molar ratio of 1 to sodium amide was 1.0:2.0, the yield of 2 was unchanged. [c] A 20% yield of 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (3) was isolated. [d] A 40% yield of 1-phenyl-1-phenylazopentane (4) was obtained.



Z isomer *E* isomer

R = H, alkyl, aryl

ppm corresponds very closely to the NH absorptions observed by Karabatsos in the o-nitrophenylhydrazine derivatives of several aldehydes and ketones where intramolecular hydrogen bonding was evident.[11]

In Me_2SO-d_6 the equilibrium of the *Z* and *E* isomers in **2** (R = C_6H_5) was found to be in favor of the latter. The NH signal at δ 12.0 now integrated to 0.3 protons while that of the *E* isomer was shifted downfield from δ 8.0 to δ 10.50 and integrated to 0.7 protons. Apparently, the shift in the equilibrium to the thermodynamically more stable *E* isomer was favored by the intermolecular hydrogen bonding between the NH and the solvent. Similarly in **2** (R = alkyl) the equilibrium was in favor of the *Z* isomer in $CDCl_3$ and of the *E* isomer in Me_2SO-d_6.

Evidence for the rapid interconversion of the *E* and *Z* isomers in these nitro compounds was found when the spectrum of **2** (R = C_6H_5) was investigated at various temperatures. When a Me_2SO-d_6 solution of **2** was heated to 55 °C, the two NH signals at δ 12.0 and 10.51 coalesced into a single broad absorption between δ 12.0 and 10.5.[12] At this temperature integration of the spectrum over the range of δ 10.5–12.0 resulted in a constant value of one proton. On cooling the solution to 40 °C, the two NH signals reappeared at δ 12.0 and 10.51 which integrated to 0.3 and 0.70 protons, respectively.

The extended conjugation in these compounds was indicated in their infrared spectra by the absorption of the azomethine linkage at 1560–1580 cm^{-1} and of the nitro group at 1500 and 1300 cm^{-1}. In compounds **1**, the azomethine absorption occurred near 1600 cm^{-1}. Unconjugated nitro groups usually absorb at 1550 and 1350 cm^{-1}.

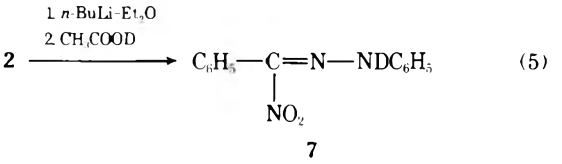
The mass spectra of compounds **2** showed molecular ions as well as the preferential loss of nitrous acid rather than of the nitro group. In each case, the synchronous loss of nitrous acid was accompanied by the presence of a metastable ion. It was established that the loss of nitrous acid involved the amino hydrogen for the mass spectrum of *N*-deuterio-α-nitrobenzylidene phenylhydrazine (**7**) showed the loss of deuterated nitrous acid which again was accompanied by the presence of a metastable ion. Compound **7** was prepared by

Table II. Preparation of $RC(NO_2)=N-NHC_6H_5$ [a,b]

R	Yield, %[c]	Mp, °C
2-$MeOC_6H_4$	28 (65)[d]	120–125
4-$MeOC_6H_4$	74	112–113
2-MeC_6H_4	70	98–100
4-MeC_6H_4	94	118–120
2-ClC_6H_4	21 (45)[d]	124–126
4-ClC_6H_4	73	127.5–129
4-BrC_6H_4	16 (58)[d]	125–126 dec
4-$Me_2CHC_6H_4$	94	103–104
4-$CF_3C_6H_4$	83	127.5–130 dec
1-Naphthyl	14 (14)[d]	124–126
2-Naphthyl	46	129–131
2-Furyl	19 (47)[d]	110–111
2-Thienyl	83	124–126.5 dec
3-Pyridyl	38	117–119
H	70	98–100
Me	30 (83)[d]	142–144
Pr	30 (15)[d]	63–65

[a] Satisfactory analytical data were reported for all new compounds listed in this table. [b] Unless otherwise noted, the nitrations were carried out at −33 °C in ca. 0.3 M solution of potassium amide. The nitro compounds were obtained upon aqueous acidification of their crude nitronate salts with acetic acid. Recrystallizations were carried out with 95% ethanol. [c] Yields are based on starting materials. [d] Nitrations were performed at −33 °C in ca. 0.7 M solution of potassium amide.

treating **2** (R = C_6H_5) with n-butyllithium followed by the addition of deuterated acetic acid (eq 5).



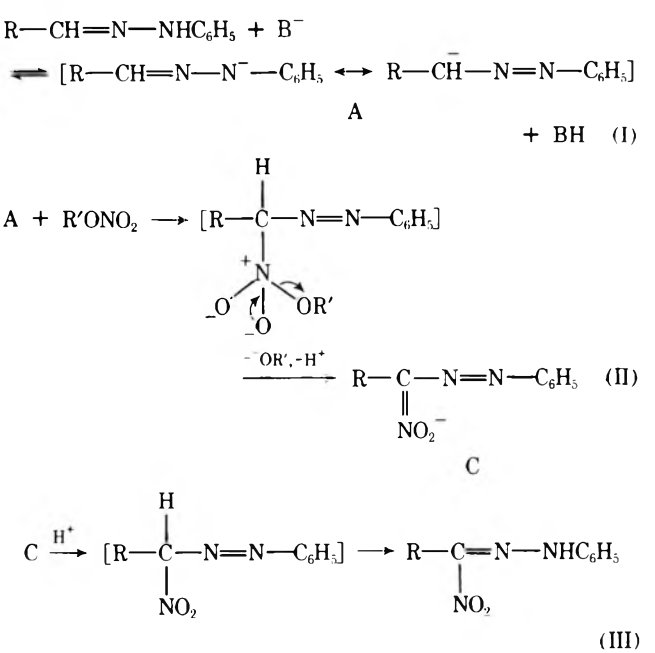
(5)

7

Discussion

This investigation has shown that the alkyl nitration of compounds **1** affords only *C*-nitro compounds. The formation of these products can be envisioned by the mechanism shown in Scheme I. The initial reaction involves proton abstraction

Scheme I



(I)

(II)

(III)

(step I) with the formation of a resonance stabilized ambident anion. The remaining steps have been discussed previously.[2]

The exclusive formation of *C*-nitro compounds might be a consequence of the greater nucleophilicity of the carbanion over the anilide ion (step II). Moreover, a nitroamino compound resulting from an electrophilic attack of nitrate ester on nitrogen would probably revert to starting material because it could not be stabilized by salt formation.

Exclusive attack on carbon has also been observed in nitrosations of compounds **1** with alkyl nitrites under alkaline conditions.[5] Subsequently, the nitroso compounds tautomerized to the corresponding oximes. On the other hand nitrosations of compounds **1** (R = C_6H_5) under acidic conditions have afforded *N*-nitrosoarylidene phenylhydrazines which, in base, rearranged to their isomeric arylazoaldoximes.[13]

In order to establish that such rearrangement was not involved in the formation of **2** (R = C_6H_5) during the alkyl nitrate nitration, attempts were made to prepare a *N*-nitroarylidene phenylhydrazine. When a dry toluene solution of *N*-nitrosobenzylidene 4-bromophenylhydrazine[13] (**8**) was subjected to a stream of oxygen at room temperature, instead of the nitramine there was obtained a 45% yield of α-nitrobenzylidene 4-bromophenylhydrazine[4] (**9**) (eq 6). The

$$\underset{\text{NO}}{\underset{|}{\text{C}_6\text{H}_5\text{CH=N-N-C}_6\text{H}_4\text{Br-}p}} \quad \mathbf{8}$$

$$\xrightarrow[\text{R.T.}]{\text{toluene, O}_2} \underset{\text{NO}_2}{\underset{|}{\text{C}_6\text{H}_5\text{C=N-NH-C}_6\text{H}_4\text{Br-}p}} \quad \mathbf{9} \qquad (6)$$

transformation might occur by the pathway shown in Scheme II. In step I, **8** dissociates into the resonance stabilized radical

Scheme II

$$\mathbf{8} \longrightarrow \underset{\text{E}}{\text{C}_6\text{H}_5\text{CH=N-}\dot{\text{N}}\text{-C}_6\text{H}_4\text{Br-}p} + \text{NO} \qquad \text{(I)}$$

$$\text{NO} \xrightarrow{[\text{O}]} \text{NO}_2 \qquad \text{(II)}$$

$$\text{E} + \text{NO}_2 \longrightarrow \mathbf{9} \qquad \text{(III)}$$

E and nitric oxide which is oxidized to nitrogen dioxide in step II. Combination of the latter with E in step III then affords **9**.[14] Some evidence of step I was obtained when, in the absence of oxygen, a toluene solution of **8** kept at room temperature for 24 h afforded a 12% yield of 1,4-dibenzal-2,3-di(*p*-bromophenyl)tetrazabutane (**10**) (84% of **8** was recovered) (eq 7).

$$\mathbf{8} \xrightarrow[\text{R.T.}]{\text{toluene}} \underset{\text{NO}}{\underset{|}{(\text{C}_6\text{H}_5\text{CH=N-N-C}_6\text{H}_4\text{Br-}p)_2}} \quad \mathbf{10} \qquad (7)$$

Compound **10** was also formed when **8** was kept for 3 weeks in a vacuum desiccator. The mass spectrum of **10** gave molecular ions at *m/e* 548, 546, and 544 in a ratio of 1:2:1 which indicated the presence of two bromine atoms.

The instability of *N*-nitrosobenzylidene phenylhydrazine has already been noticed by Busch and Kunder[13] who reported that on standing the compound was converted to 1,4-dibenzal-2,3-diphenyltetrazabutane.

The exclusive substitution on carbon in the alkyl nitration and nitrosation of compounds **1** is in contrast to alkylation reactions which in alkaline media lead to exclusive substitution on nitrogen.[15] Apparently these reactions are less influenced by the nucleophilicity of the anion. This conclusion was further substantiated by experiments in which certain compounds **1** did not undergo the alkyl nitration but readily underwent alkylation. For example, 3-nitrobenzylidene phenylhydrazine (**11**) was recovered unchanged from nitrations in the potassium amide–liquid ammonia or potassium *tert*-butoxide–THF system. However, when methyl iodide was added to the reaction mixture, a quantitative yield of 3-nitrobenzylidene *N*-methylphenylhydrazine[16] (**12**) was obtained (eq 8).

$$3\text{-NO}_2\text{C}_6\text{H}_4\text{CH=N-NHC}_6\text{H}_5 \quad \mathbf{11}$$

$$\xrightarrow[\text{2. MeI 3. H}^+]{\text{1. K-}t\text{-OBu-THF-PrONO}_2} 3\text{-NO}_2\text{C}_6\text{H}_4\text{CH=N-}\underset{\text{CH}_3}{\underset{|}{\text{N}}}\text{C}_6\text{H}_5 \quad \mathbf{12} \qquad (8)$$

Experimental Section

Apparatus. Nitrations were performed in a thoroughly dried 500-ml four-necked flask equipped with a dry ice condenser, mechanical stirrer, thermometer, and pressure equalizing dropping funnel.

α-Nitrobenzylidene Phenylhydrazine (2, R = C_6H_5). A. Employing Potassium Amide in Liquid Ammonia. The following experiment is typical of the procedure employed in the potassium amide–liquid ammonia system. To a freshly prepared solution of potassium amide (0.075 mol) in 300 ml of ammonia was added 14.7 g (0.075 mol) of benzylidene phenylhydrazine (**1**, R = C_6H_5) rapidly at −33 °C. After stirring for 45 min, 15.75 g (0.15 mol) of *n*-propyl nitrate was added as rapidly as possible while the temperature was kept at −33 °C.[17] The solution was stirred for an additional 30 min, the ammonia gradually replaced with absolute ether, and the reaction mixture filtered after room temperature was reached (3–4 h).

The crude potassium phenylazophenylmethanenitronate was dried in vacuo, dissolved in 300 ml of water, filtered, and acidified to pH 6 with glacial acetic acid at room temperature. Filtering and washing with water afforded 16.3 g (91%) of α-nitrobenzylidene phenylhydrazine as red-orange plates (95% C_2H_5OH): mp 103–104 °C (lit.[5] mp 102–103 °C); uv max (95% C_2H_5OH) 403 nm (log ε 3.89); NMR ($CDCl_3$) δ 7.0–7.8 (m, 10, ring H), 8.0 (s, 0.3, NH), and 12.0 (s, 0.7, NH); ir (KBr) 3226 (NH), 1567 (C=N), and 1502 and 1304 cm^{-1} (NO_2); mass spectrum (75 eV) *m/e* (rel intensity) 241 (36.1), 195 (20.7), and 194 (100.0).

Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.61; H, 4.59; N, 17.54.

The ethereal filtrate was concentrated in vacuo to give 2.2 g (15%) of **1** (R = C_6H_5), mp 154–156 °C (lit.[18] mp 156 °C).

B. Employing Potassium *tert*-Butoxide in THF. To a suspension of sublimed potassium *t*ert-butoxide (0.075 mol) in 250 ml of dry THF was added 14.7 g (0.075 mol) of **1** (R = C_6H_5) at −50 °C under nitrogen. After stirring for 45 min, 15.75 g (0.15 mol) of *n*-propyl nitrate was added rapidly at −30 °C. Stirring was continued for 30 min at −30 °C, and the solution was warmed to −10 °C and acidified with 9.0 g (0.15 mol) of glacial acetic acid dissolved in 10 ml of THF. The suspension was warmed to room temperature and filtered, the ethereal layer concentrated in vacuo, and the residue refluxed in 200 ml of 95% ethanol. Filtration gave 0.75 g (20%) of 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (**3**): mp 203–205 °C (lit.[6] mp 203–204 °C); ir (KBr) 1600 cm^{-1} (C=N); NMR ($CDCl_3$) δ 6.9–7.5 (m, ring H).

The ethanolic solution was cooled to afford 14.5 g (80%) of **2** (R = C_6H_5), mp 103–104 °C.

C. Employing *n*-Butyllithium in Absolute Ether. To a solution of *n*-butyllithium (0.05 mol in 20 ml of hexane) in 100 ml of absolute ether was added 9.8 g (0.05 mol) of **1** (R = C_6H_5) at 5 °C under nitrogen. The solution was stirred for 45 min and cooled to −70 °C, and 10.5 g (0.10 mol) of *n*-propyl nitrate was rapidly added. The reaction mixture was warmed to 0 °C and poured into 300 ml of water, and the ethereal layer separated. The aqueous layer was acidified with glacial acetic acid and filtered to give 4.0 g (33%) of **2** (R = C_6H_5), mp 103–104 °C.

The ethereal solution was concentrated in vacuo to give a semisolid. Addition of *n*-hexane followed by filtration gave 2.0 g (21%) of **1** (R = C_6H_5), mp 154–156 °C, mass spectrum (75 eV) *m/e* 196.

The hexane solution was evaporated in vacuo to give 4.6 g (40%) of 1-phenylazo-1-phenylpentane (4): bp 120 °C (0.15 mm); ir (neat) 1600 cm^{-1} (N=N); NMR ($CDCl_3$) δ 0.8 (t, 3, CH_3CH_2), 1.0–2.0 (m, 4, CH_2CH_2), 2.1 (m, 2, CH_2), 4.6 (t, 1, $CHCH_2$), and 6.6–7.8 (m, 10, ring H); mass spectrum (75 eV) *m/e* 252.

α-Nitrobenzylidene 4-Bromophenylhydrazine (9). A. Employing *N*-Nitrosobenzylidene 4-Bromophenylhydrazine (8). To 100 ml of oxygen-free toluene was added 0.5 g (1.6 mmol) of *N*-nitrosobenzylidene 4-bromophenylhydrazine[13] at room temperature with stirring. Oxygen was then introduced to the solution via a balloon. Stirring was continued for 24 h at room temperature and then the solution was concentrated in vacuo. The orange solid was recrystallized from petroleum ether (bp 30–60 °C) to give 0.25 g (45%) of α-nitrobenzylidine 4-bromophenylhydrazine (9): mp 127–128 °C (lit.[4] mp 128 °C); ir (KBr) 3250 (NH), 1570 (C=N), and 1490 and 1300 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 7.0–7.7 (m, 9, ring H) and 11.9 (s, 1, NH).

B. Employing Compound 2 (R = C_6H_5). To a solution of 3.0 g (0.012 mol) of **2** in 15 ml of glacial acetic acid was added dropwise at room temperature 3.0 g (0.018 mol) of bromine. Addition of 25 ml of water gave a red precipitate. Recrystallization from 95% ethanol afforded 3.5 g (87%) of **9**, mp 128 °C.

1,4-Dibenzal-2,3-di(4-bromophenyl)tetrazabutane (10). To 100 ml of oxygen-free toluene was added with stirring 0.5 g (1.6 mmol) of compound **8** at room temperature. Stirring was continued for 24 h and then the reaction vessel was opened to the atmosphere. Oxides of nitrogen were detected by a positive potassium iodide–starch paper test. Concentration of the reaction mixture in vacuo gave a yellow oil. Addition of 20 ml of a 1:1 mixture of ether–petroleum ether (bp 30–60 °C) to the oil gave a precipitate. Filtration afforded 0.05 g (12%) of 1,4-dibenzal-2,3-di(4-bromophenyl)tetrazabutane:[13] mp 170–175 °C; ir (KBr) 1590 cm^{-1} (C=N); NMR (Me_2SO-d_6) δ 7.0–8.0 (m, ring H and CH); mass spectrum (75 eV) *m/e* (rel intensity) 548 (31.6), 546 (63.0), 54.4 (31.6), 378 (41.5), 376 (41.5), 171 (100.0), and 169 (100.0).

The filtrate was concentrated in vacuo to give 0.42 g (84%) of recovered **8**: mp 68 °C (lit.[13] mp 68–69 °C); ir (KBr) 1447 cm^{-1} (N–N=O).

***N*-Deuterio-α-nitrobenzylidene Phenylhydrazine (7).** To 0.01 mol of *n*-butyllithium dissolved in 20 ml of *n*-hexane was added 2.41 g (0.01 mol) of compound **2** (R = C_6H_5) with stirring at −20 °C under nitrogen. Stirring was continued for 30 min at 0 °C and then 1.0 g (0.016 mol) of deuterated acetic acid was added dropwise. The suspension was filtered at room temperature and dried ($MgSO_4$), and the solvent was removed in vacuo. Recrystallization of the residue from *n*-hexane gave 2.2 g (91%) of *N*-deuterio-α-nitrobenzylidene phenylhydrazine: mp 103–104 °C; NMR ($CDCl_3$) δ 7.0–7.8 (m, ring H) and 12.1 (s, 0.1, NH); mass spectrum (75 eV) *m/e* (rel intensity) 244 (1.66), 243 (15.3), 242 (100.0), and 241 (20.5).

Benzamidrazone Hydrochloride. A 75-ml absolute ethanol solution containing 1.0 g (0.004 mol) of **2** (R = C_6H_5) and 0.1 g of 60% palladium chloride was treated with hydrogen under a pressure of 40 psi for 3 h. Filtration and concentration of the solution in vacuo gave an oil. It was dissolved in anhydrous ether and treated with hydrogen chloride at 10 °C. A white precipitate formed which was filtered and dried in vacuo to give 1.0 g (98%) of benzamidrazone hydrochloride: mp 123–125 °C dec (lit.[19] mp 124 °C dec); ir (KBr) 3400–2500 ($-NH_3^+$) and 1605 cm^{-1} (C=N).

3-Nitrobenzylidene Methylphenylhydrazine (12). The general procedure was used as described in experiment B except that 8.4 g (0.075 mol) of potassium *tert*-butoxide, 18.1 g (0.075 mol) of 3-nitrobenzylidene phenylhydrazine (**11**), and 15.75 g (0.15 mol) of *n*-propyl nitrate were employed in 250 ml of THF. No apparent reaction occurred upon the addition of *n*-propyl nitrate as judged by the lack in color change of the reaction mixture. After 30 min, the reaction mixture was cooled to −40 °C and 21.4 g (0.15 mol) of methyl iodide added dropwise. After 30 min, the solution was warmed to −10 °C and 9.0 g 0.15 mol) of glacial acetic acid added. The green suspension was filtered at room temperature and the filtrate concentrated in vacuo to afford 13.0 g (100%) of 3-nitrobenzylidene methylphenylhydrazine (95% C_2H_5OH): mp 111–112 °C (lit.[18] mp 112 °C); NMR ($CDCl_3$) δ 3.36 (s, 3, NCH_3) and 6.8–8.1 (m, 10, ring H and CH).

Acknowledgment. We are indebted to our colleague Professor John Grutzner for his helpful discussions of the NMR data.

Registry No.—**1** (R = C_6H_5), 588-64-7; **1** (R = 2-$MeOC_6H_4$), 21968-29-6; **1** (R = 4-$MeOC_6H_4$), 622-73-1; **1** (R = 2-MeC_6H_4), 59473-50-6; **1** (R = 4-MeC_6H_4), 2829-25-6; **1** (R = 2-ClC_6H_4), 34158-76-4; **1** (R = 4-ClC_6H_4), 2829-26-7; **1** (R = 4-BrC_6H_4), 16917-42-3; **1** (R = 4-$Me_2CHC_6H_4$), 10407-16-6; **1** (R = 4-$CF_3C_6H_4$), 59473-51-7; **1** (R = 1-naphthyl), 24090-98-0; **1** (R = 2-naphthyl), 24091-13-2; **1** (R = 2-furyl), 2216-75-3; **1** (R = 2-thienyl), 39677-96-8; **1** (R = 3-pyridyl), 57023-37-7; **1** (R = H), 6228-40-6; **1** (R = Me), 935-07-9; **1** (R = Pr), 940-54-5; *E*-**2** (R = C_6H_5), 59473-52-8; *Z*-**2** (R = C_6H_5), 55849-26-8; *E*-**2** (R = 2-$MeOC_6H_4$), 59473-53-9; *Z*-**2** (R = 2-$MeOC_6H_4$), 59473-54-0; *E*-**2** (R = 4-$MeOC_6H_4$), 59473-55-1; *Z*-**2** (R = 4-$MeOC_6H_4$), 59473-56-2; *E*-**2** (R = 2-MeC_6H_4), 59473-57-3; *Z*-**2** (R = 2-MeC_6H_4), 59473-58-4; *E*-**2** (R = 4-MeC_6H_4), 59473-59-5; *Z*-**2** (R = 4-MeC_6H_4), 59473-60-8; *E*-**2** (R = 2-ClC_6H_4), 59473-61-9; *Z*-**2** (R = 2-ClC_6H_4), 59473-62-0; *E*-**2** (R = 4-ClC_6H_4), 59473-63-1; *Z*-**2** (R = 4-ClC_6H_4), 59473-64-2; *E*-**2** (R = 4-BrC_6H_4), 59473-65-3; *Z*-**2** (R = 4-BrC_6H_4), 59473-66-4; *E*-**2** (R = 4-$Me_2CHC_6H_4$), 59473-67-5; *Z*-**2** (R = 4-$Me_2CHC_6H_4$), 59473-68-6; *E*-**2** (R = 4-$CF_3C_6H_4$), 59473-69-7; *Z*-**2** (R = 4-$CF_3C_6H_4$), 59473-70-0; *E*-**2** (R = 1-naphthyl), 59473-71-1; *Z*-**2** (R = 1-naphthyl, 59473-72-2; *E*-**2** (R = 2-naphthyl), 59473-73-3; *Z*-**2** (R = 2-naphthyl), 59473-74-4; *E*-**2** (R = 2-furyl), 59473-75-5; *Z*-**2** (R = 2-furyl), 59473-76-6; *E*-**2** (R = 2-thienyl), 59473-77-7; *Z*-**2** (R = 2-thienyl), 59473-78-8; *E*-**2** (R = 3-pyridyl), 59473-79-9; *Z*-**2** (R = 3-pyridyl), 59473-80-2; *E*-**2** (R = H), 59473-81-3; *Z*-**2** (R = H), 59473-82-4; *E*-**2** (R = Me), 55849-27-9; *Z*-**2** (R = Me), 55849-23-5; *E*-**2** (R = Pr), 55849-29-1; *Z*-**2** (R = Pr), 55849-25-7; **3**, 17355-78-1; **4**, 59473-83-5; **7**, 59473-84-6; **8**, 59473-85-7; **9**, 59473-86-8; **10**, 59473-87-9; **11**, 7539-23-3; **12**, 23718-95-8; benzamidrazone HCl, 39696-43-0.

Supplementary Material Available. Full analytical and spectroscopic data (ir, uv, NMR, mass spectra) for compounds **2** listed in Table II are presented (6 pages). Ordering information is given on any current masthead page.

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Aralkylation of Potassium Ethylnitrosolate. Ring Closure of Nitrosolic Acid Esters

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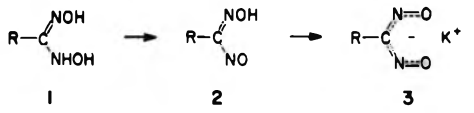
The aralkylation of potassium ethylnitrosolate has been examined as a synthetic route to nitrosolic acid esters. The reaction of potassium ethylnitrosolate with representative benzylic halides did not stop at the ester stage but resulted in the formation of heterocyclic *N*-oxides derived from the 1,2,4-oxadiazole ring system. The product was shown to be the N-4 rather than the N-2 oxide on the basis of NMR studies. A formal mechanism is proposed involving intramolecular reaction of the nitroso group of an intermediate nitrosolic acid ester with the benzylic methylene, followed by oxidation to the observed product. The sequence provides a new route to unsymmetrically substituted 1,2,4-oxadiazole 4-oxides. When the benzylic methylene is further substituted, as in the case of triphenylmethyl chloride, reaction with potassium ethylnitrosolate terminates at the corresponding ester.

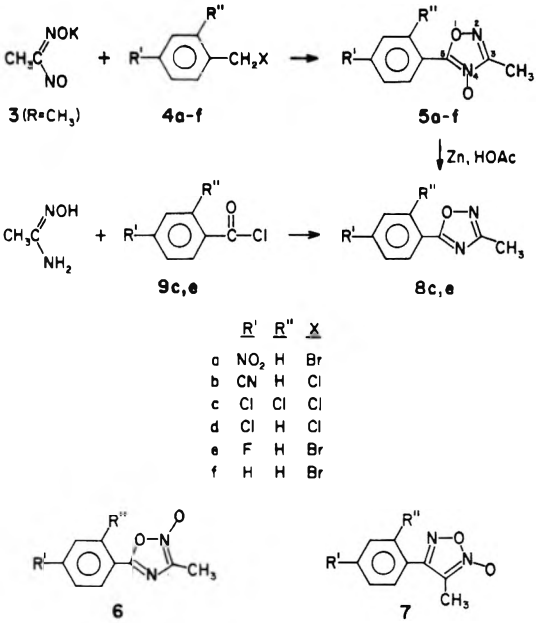
Nitrosolic acids (**2**) constitute a rather obscure class of functionality even though the first examples were reported by Wieland[1] in the early 1900's. They have been prepared from oxyamide oximes (**1**) by disproportionation[1] or, more recently, by periodate oxidation.[2] Although the acids themselves are not sufficiently stable to permit facile isolation, the metal salts (**3**) of the acid are easily prepared and are sufficiently stable to be isolated. The chemical properties and reactivity of the nitrosolic acid salts have not been studied, although electrochemical reactions have been investigated and the pK_a's of a series of acids have been determined.[3] We were interested in the potential reactivity of the nitrosolic acid esters, a class of compounds not heretofore prepared. Of the routes considered for the synthesis of the desired esters, oxidation of an *O*-alkyl oxyamide oxime or O-alkylation of a nitrosolate salt appeared the most straightforward, and we chose to examine the latter route. Alkylation of oxime anions is known to result in N- or O-alkylation, and O-alkylation can be favored through selection of appropriate reaction conditions.[4] C-Alkylation is theoretically possible but has not been detected. The possibility of C-alkylation in nitrosolates might be greater than for their oxime analogues because of the second electron-withdrawing group.[5] Therefore, C-alkylation had to be considered as an additional possibility. We report here the reaction of potassium ethylnitrosolate (**3**, R = CH_3) with several aralkyl halides and the preparation of the trityl ester.



1 **2** **3**

Results and Discussion

Potassium ethylnitrosolate (**3**, R = CH_3) is a blue, crystalline solid which can be stored at 0 °C for several weeks without decomposition. When *p*-nitrobenzyl bromide and potassium ethylnitrosolate were allowed to react in acetone, the acid salt was rapidly consumed. A yellow, crystalline compound was isolated from the reaction mixture, but it quickly became apparent to us that this was not the desired *p*-nitrobenzyl ester. The mass spectrum of the compound gave a molecular ion at *m/e* 221 instead of 223 as expected. The NMR spectrum showed only an A_2B_2 pattern in the aromatic region and a three-hydrogen signal for a methyl group (δ 2.80); there was no signal for benzylic protons. Analytical data were consistent with the formula $C_9H_7N_3O_4$ but not with the expected formula $C_9H_9N_3O_4$. One structure compatible with these data is that of 3-methyl-5-(4-nitrophenyl)-1,2,4-oxadiazole 4-oxide (**5a**). The isomeric 1,2,4-oxadiazole 2-oxide (**6**) was also a plausible structure, but appeared less likely, and so far as we could determine no N-2 oxides of this ring system have been reported. The isomeric furazan (**7**) was unlikely on the basis of mass spectral evidence.[6] Reduction of the product to the known 3-methyl-5-(4-nitrophenyl)-1,2,4-oxadiazole would serve to confirm the heterocyclic ring structure. However, the sensitivity of the nitro group to reduction would make this a difficult transformation. Therefore, we prepared the 2,4-dichlorophenyl analogue (**5c**) by the reaction of α,2,4-trichlorotoluene with potassium ethylnitrosolate. Treatment of this *N*-oxide with Zn/HOAc[7] resulted in the formation of 5-(2,4-dichlorophenyl)-3-methyl-1,2,4-oxadiazole (**8c**) identical



with an authentic sample (melting point, TLC, and NMR) prepared from **9c** by the method of Tieman and Kruger.[8] This confirmed the structure of the heterocyclic ring, the presence of an *N*-oxide, and limited the possible structures to **5** and **6**.

The position of the *N*-oxide function was identified through a comparison of the NMR spectra of compound **8c** and its *N*-oxide precursor. The resonance of the 6-H in the 2,4-dichlorophenyl ring could be assigned in both compounds from the values of the coupling constants.[9] In **8c** the 6-H appears at δ 8.10, while in the *N*-oxide this hydrogen is found at δ 9.10; i.e., there is a downfield shift of 1.00 ppm in the *N*-oxide. A shift of this magnitude cannot be due to inductive effects in view of the small change in the chemical shifts of the 3- and 5-H's (~0.03 ppm further downfield in the *N*-oxide) and in

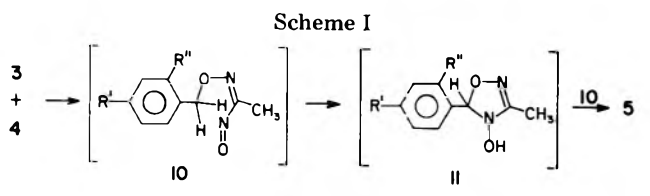
the methyl protons (~0.05 ppm further downfield in the *N*-oxide). The strong deshielding effect must be due to anisotropy of the *N*-oxide[10] or to van der Waals deshielding[11] rather than inductive effects. Models clearly indicate that the preferred conformations of the N-2 oxide place the *N*-oxide oxygen at a relatively large distance from the 6-H. The N-4 oxide however, would have strong steric interaction with the 2-Cl, restricting the system to conformations where the two rings are not coplanar, or where coplanarity of the rings forces the *N*-oxide very close to the 6-H. The large change in the chemical shift of the 6-H in the *N*-oxide relative to the parent heterocyclic ring system (**8c**) is very good evidence for proximity of the 6-H and the *N*-oxide function, and thus forms the basis for the assignment of structure **5** to the *N*-oxides isolated from the reaction **3** + **4a–f**.

Further support for this assignment as the N-4 oxide was found with the *p*-fluorophenyl analogue **5e** prepared from the reaction of *p*-fluorobenzyl bromide with potassium ethylnitrosolate. The proton resonances of this compound could be assigned on the basis of J_{FH} values.[12] The protons ortho to fluorine appear at δ 7.43 as a pseudotriplet (J_{FH} = 9, J_{HH} = 9 Hz) while the protons meta to the fluorine appear at δ 8.68 as a quartet (J_{FH} = 5, J_{HH} = 9 Hz).[12b] Reduction of the *N*-oxide with Zn/HOAc afforded 5-(*p*-fluorophenyl)-3-methyl-1,2,4-oxadiazole (**8e**), identical with an authentic sample (melting point, TLC, and NMR) prepared according to the method of Tieman and Krüger.[8a,13] The phenyl protons were again assigned on the basis of their J_{FH} values (3-, 5-H's at 7.37, J_{FH} = 9, J_{HH} = 9 Hz; 2-, 6-H's at 8.17, J_{FH} = 6, J_{HH} = 9 Hz). In this pair, there is a downfield shift of 0.51 ppm for the 2 and 6 protons of the *N*-oxide (**5e**) relative to the reduced form (**8e**). Although this is a smaller $\Delta\delta$ than found for the 2,4-dichlorophenyl compounds, a shift of this magnitude would be predicted if the deshielding effect of the *N*-oxide were averaged over both ortho protons in the absence of a bulky group at the 2 position. Accordingly, on the basis of the NMR data for both sets of compounds, the products of the general reaction, **3** + **4**, are clearly of structure **5**.

The condensation of *O*-acyl amidoximes[8] provides an easy entry to the 1,2,4-oxadiazole system and numerous examples of substituted oxadiazoles have been reported.[13] A literature survey revealed that N-4 oxides of this system have also been prepared[14] although apparently not via direct oxidation of the parent oxadiazole.[15] The reported 1,2,4-oxadiazole 4-oxides were obtained from the dimerization of nitrile oxides. Because furazans are frequently the major product of nitrile oxide dimerization[16] and because dimerization provides only heterocycles with identical substituents in the 3 and 5 positions, this new route to substituted 1,2,4-oxadiazole 4-oxides is of supplementary interest. We have examined this reaction with additional substituted benzylic halides (**4a–f**) to illustrate generality. With benzylic halides bearing strong electron-withdrawing groups, e.g., nitro or cyano, the reaction proceeds in good yield at room temperature in acetone, while reactions with benzylic halides bearing less strongly electron-withdrawing groups, e.g. Cl, F (or H), required higher temperatures or a more polar solvent.

The following reaction sequence can account for the formation of oxadiazole 4-oxides in this reaction (Scheme I). Under the conditions which we employed, O-alkylation would be expected, resulting in a benzylic ester (**10**) of nitrosolic acid. The free nitroso group of this ester presumably reacts with the benzylic methylene to produce the intermediate hydroxylamine **11**, which is then oxidized by a second mole of ester to afford the observed product. The alternative dehydration of **11** to an oxadiazole and subsequent oxidation was ruled out when it was determined that authentic samples of oxadiazoles were not oxidized under these conditions by the nitrosolic acid salt.

Scheme I



The actual oxidant involved in this reaction may be a second mole of the nitrosolic acid ester (**10**), for in experiments in which 2 mol of potassium ethylnitrosolate was added per mole of halide, 1 molar equiv of the salt was recovered unchanged. Our presumptive evidence for the presence of reduction products of **10** was supported by mass spectral data. Substitution of an alternative oxidant would be attractive because it would reduce the ratio of 2 equiv of starting material per equivalent of product to a one-to-one ratio and would not be destructive of the less accessible starting material. However, attempts to employ air, nitrosobenzene, or potassium periodate as the alternative oxidant did not result in increased yield.

There are several precedents for the proposed reaction scheme. The intermolecular reaction of an aromatic nitroso compound with an active methylene is known to afford either a nitrone, an imine, or a mixture.[17] Precedent for the proposed intramolecular condensation (**10** → **11**) is found in the reaction of benzylic halides with aromatic nitroso compounds to afford nitrones, presumed to arise via condensation to an hydroxylamine and loss of HX.[18] The isolation of 1,3-dimethylalloxazine 10-oxide upon attempted nitrosation of 1,3-dimethyl-6-anilinouracil is analogous to the oxidation of **11**, and in this case it was suggested that excess nitrous acid served as an oxidant of an intermediate hydroxylamine.[19]

The isolation of these 1,2,4-oxadiazole 4-oxides indicates that C-alkylation is not a significant process under the stated reaction conditions. The possibility of an N-alkylated intermediate resulting in the oxadiazole 4-oxide appears remote, unless there is a facile rearrangement to the *O*-aralkyl ester[20] or unless such an N-alkylated intermediate serves only as an oxidant.

In order to take advantage of the foregoing knowledge for the preparation of an isolable nitrosolic acid ester, we ran the reaction of triphenylmethyl chloride with potassium ethylnitrosolate. A green crystalline solid was obtained in ca. 60% yield following purification by chromatography on silica gel. The assignment of the structure as $CH_3(ON)C{=}NOCPh_3$ (**12**) was supported by infrared and mass spectral data, including a $(C_6H_5)_3COH^+$ ion even in the field desorption spectrum.[21] The ester is stable at 0 °C but appears to undergo slow decomposition at room temperature.

Our experiments provide sufficient encouragement for continued investigation of nitrosolic acid derivatives.

Experimental Section

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. The NMR spectra were recorded on a Varian Associates A-60 or HA-100 spectrometer using tetramethylsilane as an internal standard. The ultraviolet spectra were obtained on a Beckman Acta MVI spectrophotometer, and the infrared spectra were obtained on a Perkin-Elmer Model 337 infrared spectrophotometer. Microanalyses were performed by Mr. Josef Nemeth and associates, who also weighed samples for the quantitative electronic absorption spectra. Low-resolution mass spectra were obtained by Mr. J. Wrona on a Varian-MAT CH-5 spectrometer coupled with a 620i computer and STATOS recorder.

Potassium Ethylnitrosolate (3, R = CH_3). Potassium ethylnitrosolate was prepared through the following sequence. Acetamidoxime was prepared by the condensation of hydroxylamine[22] and acetonitrile according to the procedure of Lenaers et al.,[23] mp 133–134

°C (lit.[23] 135 °C). The acetamidoxime was treated with hydroxylamine hydrochloride according to the procedure of Armand[24] to afford acetoxyamidoxime (1, R = CH_3), which was isolated as its hydrochloride salt, mp 154–155 °C (lit.[24] 156 °C). Potassium ethylnitrosolate was prepared by periodate oxidation of acetoxyamidoxime according to the procedure of Armand.[2] After acidification to pH 6 with saturated sodium dihydrogen phosphate solution, the nitrosolic acid was extracted with ether, and the combined ether extracts were dried (Na_2SO_4) and then treated with a solution of 1 equiv of potassium *tert*-butoxide in methanol. Careful scratching[25] resulted in the formation of a blue, crystalline solid which was then collected by filtration, mp 205 °C dec (lit.[1] 207 °C dec).

3-Methyl-5-(*p*-nitrophenyl)-1,2,4-oxadiazole 4-Oxide (5a). *p*-Nitrobenzyl bromide (432 mg, 2 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2 mmol) in acetone (30 ml). The blue color quickly disappeared (≈10 min), resulting in a yellow solution and a white precipitate. The reaction mixture was stirred overnight under nitrogen at 20 °C. Filtration and evaporation of the filtrate to dryness resulted in a yellow solid. Crystallization from acetone afforded 139 mg of fine yellow needles. Further concentration of the mother liquor resulted in a second crop (60 mg) bringing the total yield to 92% (based on *p*-nitrobenzyl bromide and assuming consumption of 2 mol of the nitrosolic ester per mole of product): mp 177–178 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 347 (8.88), 254 (11.8); NMR [$(CD_3)_2CO$] δ 2.50 (s, 3, CH_3), 8.49 (d, 2, J = 9 Hz, 3-, 5-H's), 8.85 (d, 2, J = 9 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 221 (52, M^+), 205 (10, $M^+ - O$), 150 (100, $O_2NC_6H_4CO^+$).

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.87; H, 3.19; N, 19.00. Found: C, 49.20; H, 3.34; N, 19.30.

5-(4-Cyanophenyl)-3-methyl-1,2,4-oxadiazole 4-Oxide (5b). α-Bromo-*p*-tolunitrile (392 mg, 2.0 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2.0 mmol) in acetone and the mixture was stirred overnight at room temperature. The mixture was then filtered and the filtrate was concentrated in vacuo to a thin oil. Addition of ether and filtration gave **5b** (151 mg, 75%) as a white solid, recrystallized from acetone as colorless needles: mp 172–173 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$), 332 (10.8), 250 (14.5); NMR [$(CD_3)_2CO$] δ 2.50 (s, 3, CH_3), 8.06 (d, 2, J = 8 Hz, 3-, 5-H's), 8.76 (d, 2, J = 8 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 201 (4, M^+), 130 (100, $NCC_6H_4CO^+$).

Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.81; H, 3.71; N, 20.86.

5-(2,4-Dichlorophenyl)-3-methyl-1,2,4-oxadiazole 4-Oxide (5c). α,2,4-Trichlorotoluene (391 mg, 2.0 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2.0 mmol) in acetone (25 ml) and the resulting mixture was heated at reflux for ~1.5 h. The mixture was then filtered to remove KCl and the filtrate was evaporated to dryness in vacuo. The residue was purified by column chromatography on silica gel (5% acetone/$CHCl_3$) to afford 193 mg (79%) of **5c** as colorless crystals, recrystallized from acetone: mp 146–147 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 315 (7.74), 240 (10.0); NMR [$(CD_3)_2CO$] δ 2.49 (s, 3, CH_3), 7.65 (dd, 1, J = 2.2, 8.8 Hz, 5-H), 7.78 (dd, 1, J = 0.5, 2.2 Hz, 3-H), 9.10 (dd, 1, J = 0.5, 8.8 Hz, 6-H); mass spectrum (70 eV) *m/e* (rel intensity), 248 (3, M^+), 246 (17, M^+), 244 (26, M^+) 177 (12, $Cl_2C_6H_3CO^+$), 175 (67, $Cl_2C_6H_3CO^+$), 173 (100, $Cl_2C_6H_3CO^+$).

Anal. Calcd for $C_9H_6Cl_2N_2O_2$: C, 44.11; H, 2.47; N, 11.43. Found: C, 43.95; H, 2.55; N, 11.31.

5-(2,4-Dichlorophenyl)-3-methyl-1,2,4-oxadiazole (8c). Method A. A sample prepared from 2,4-dichlorobenzoyl chloride and acetamidoxime according to the general procedure of Tieman[8,13] was crystallized from ethanol: yield, 79%; mp 79–80 °C; NMR [$(CD_3)_2CO$] δ 2.43 (s, 3, CH_3), 7.61 (dd, J = 2.0, 8.4 Hz, 5-H), 7.74 (dd, 1, J = 0.4, 2.0 Hz, 3-H), 8.10 (dd, 1, J = 0.4, 8.4 Hz, 6-H); mass spectrum (70 eV) *m/e* (rel intensity) 232 (8, M^+), 230 (44, M^+), 228 (69, M^+), 175 (17, $Cl_2C_6H_3CN^+$), 173 (74, $Cl_2C_6H_3CN^+$), 171 (100, $Cl_2C_6H_3CN^+$).

Anal. Calcd for $C_9H_6Cl_2N_2O$: C, 47.19; H, 2.64; N, 12.22. Found: C, 46.99; H, 2.82; N, 12.09.

Method B. Zinc dust was added to a solution of **5c** (12 mg, 0.05 mmol) in acetic acid (2 ml) and the mixture was stirred at room temperature for 1 h, then heated at reflux for 30 min. The mixture was filtered and the filtrate was evaporated in vacuo to give 12 mg (~100%) of **8c**, identical with the material from method A by melting point, TLC, and NMR.

5-(4-Chlorophenyl)-3-methyl-1,2,4-oxadiazole 4-Oxide (5d). α,*p*-Dichlorotoluene (322 mg, 2.0 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2.0 mmol) in acetone and the resulting mixture was heated at reflux for 16 h. Workup in the usual manner and column chromatography gave **5d** (185 mg, 88%) as a white, crystalline solid: mp 145–146 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$), 317 (11.9), 242 (12.5), 228 (sh, 6.96); NMR [$(CD_3)_2CO$] δ 2.46 (s, 3, CH_3), 7.67 (d, 2, J = 9 Hz, 3-, 5-H's), 8.58 (d, 2, J = 9 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity), 212 (8, M^+), 210 (23, M^+), 141 (33, $ClC_6H_4CO^+$), 139 (100, $ClC_6H_4CO^+$).

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.44; H, 3.48; N, 13.13.

5-(4-Fluorophenyl)-3-methyl-1,2,4-oxadiazole 4-Oxide (5e). 4-Fluorobenzyl bromide[26] (1.34 g, 7.1 mmol) was added to a suspension of potassium ethylnitrosolate (0.89 g, 7.1 mmol) in methanol. The reaction mixture was stirred at room temperature for ~16 h, filtered to remove KBr, and evaporated to dryness in vacuo. The residue was purified by column chromatography on silica gel (5% acetone/$CHCl_3$) to afford **5e** (544 mg, 79%), recrystallized from ethanol: mp 138–139 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 310 (9.87), 243 (9.52), 226 (sh, 7.62); NMR [$(CD_3)_2CO$] δ 2.46 (s, 3, CH_3), 7.42 (dd, 2, J = 9, 9 Hz, 3-, 5-H's), 8.68 (dd, 2, J = 5, 9 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 194 (18, M^+), 123 (100, $FC_6H_4CO^+$).

Anal. Calcd for $C_9H_7FN_2O_2$: C, 55.67; H, 3.63; N, 14.43. Found: C, 55.38; H, 3.58; N, 14.50.

5-(*p*-Fluorophenyl)-3-methyl-1,2,4-oxadiazole (8e). Method A. A sample was prepared from *p*-fluorobenzoyl chloride and acetamidoxime according to the general procedure of Tieman[8,13] and purified by column chromatography on silica gel ($CHCl_3$ eluent): yield 62%; mp 80–81 °C; NMR [$(CD_3)_2CO$] δ 2.38 (s, 3, CH_3), 7.37 (t, 2, J = 9, 9 Hz, 3-, 5-H's), 8.17 (dd, 2, J = 6, 9 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 178 (87, M^+), 121 (100, $FC_6H_4CN^+$).

Anal. Calcd for $C_9H_7FN_2O$: C, 60.67; H, 3.96; N, 15.72. Found: C, 60.53; H, 4.01; N, 15.76.

Method B. Zinc dust was added to a solution of **5e** (15 mg, 0.08 mmol) in acetic acid (2 ml) and the mixture was heated at reflux for 30 min. Analysis by TLC indicated that complete reduction had occurred. The reaction mixture was filtered and the filtrate was evaporated to dryness in vacuo to afford **8e** (14 mg, ~100%). This material was identical with that obtained from method A by melting point, TLC, and NMR.

3-Methyl-5-phenyl-1,2,4-oxadiazole 4-Oxide (5f). Benzyl bromide (342 mg, 2.0 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2.0 mmol) in methanol and the resulting mixture was stirred at room temperature for 1 h. Workup in the usual manner and purification by column chromatography gave 132 mg (75%) of **5f** as a white solid, recrystallized from ethanol: mp 120–121°; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 311 (8.64), 243 (8.90), 220 (sh, 6.89); NMR [$(CD_3)_2CO$] δ 2.46 (s, 3, CH_3), 7.58–7.74 (m, 3, 3-, 4-, and 5-H's), 8.52–8.64 (m, 2, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 176 (7, M^+), 105 (85, $C_6H_5CO^+$), 77 (100, $C_6H_5^+$).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.49; H, 4.68; N, 16.09.

Triphenylmethyl Ethylnitrosolate (12). Triphenylmethyl chloride (279 mg, 1.0 mmol) was added to a suspension of potassium ethylnitrosolate (126 mg, 1.0 mmol) in acetone and the resulting mixture was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was evaporated to dryness in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$ eluent) to afford 176 mg (61%) of **12** as a green, crystalline solid: mp 108–112 °C dec; ir 1500 cm^{-1}; NMR (CCl_4) δ 1.58 (s, 3, CH_3), 7.10–7.50 [m, 15, $(C_6H_5)_3C$–]; field desorption mass spectrum *m/e* 260 [$(C_6H_5)_3COH^+$], 243 [$(C_6H_5)_3C^+$].

Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.58; H, 5.34; N, 7.38.

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Registry No.—**3** (R = CH_3), 59562-60-6; **4a**, 100-11-8; **4b**, 17201-43-3; **4c**, 94-99-5; **4d**, 104-83-6; **4e**, 459-46-1; **4f**, 100-39-0; **5a**, 59562-61-7; **5b**, 59562-62-8; **5c**, 59562-63-9; **5d**, 59562-64-0; **5e**, 59562-65-1; **5f**, 59562-66-2; **8c**, 59562-67-3; **8e**, 59562-68-4; **12**, 59562-69-5; triphenylmethyl chloride, 76-83-5.

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A New Synthetic Approach to the 3-Benzazepine Skeleton through Pinacol–Pinacolone Rearrangement

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Treatment of 2′-(β-*N*-benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene oxide (**13**), prepared from laudanosine (**9**) via 2′-(β-*N*-benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene (**11**), with methanolic potassium hydroxide gave the diol **1**, and the epoxide **13** and diol **1** were treated with acetic acid in the presence of *p*-toluenesulfonic acid to afford 2,3-dihydro-7,8-dimethoxy-5-(3,4-dimethoxyphenyl)-3-methyl-1*H*-3-benzazepine (**17**). 2,3-Dihydro-3-methyl-7,8-methylenedioxy-5-(3,4-methylenedioxyphenyl)-1*H*-3-benzazepine (**18**) was also obtained from 2-methyl-6,7-methylenedioxy-1-(3,4-methylenedioxybenzyl)isoquinoline through stilbene **12**, epoxide **14**, and diol **2**.

The 3-benzazepine skeleton is observed in the rhoeadine, isopavine, and cephalotaxine alkaloids[1,2] and is found to be an important intermediate for the total syntheses of these alkaloids. Several synthetic methods for the 3-benzazepine skeleton have been applied to the total synthesis of alkaloids.[3] We have now investigated application of the pinacol rearrangement and related epoxide reactions[4,5] for the synthesis of these benzazepine alkaloids. Three types of products appeared possible from pinacol rearrangement of unsymmetrical stilbene diol as shown in Scheme I.[6]

Laudanosine (**9**) was treated with benzyloxycarbonyl chloride in the presence of aqueous sodium hydroxide to give the stilbene **11**, which indicated a *trans*-stilbene chromophore at 330 nm[7] in the uv spectrum (MeOH) and a urethane system at 1680 cm^{-1} in the ir spectrum ($CHCl_3$). Oxidation of the stilbene **11** with *m*-chloroperbenzoic acid proceeded smoothly to afford the epoxide **13**, which on treatment with methanolic potassium hydroxide solution yielded the dihydroxyurethane **1**. The NMR spectrum ($CDCl_3$) revealed the presence of two protons attached to hydroxyl and phenyl groups (δ 4.75 as broad singlet) and the ir spectrum showed hydroxyl and urethane groups at 3400 and 1680 cm^{-1}, respectively. The compound **1** was treated with acetone in the presence of perchloric acid to give the acetonide **15**, whose ir spectrum showed urethane at 1680 cm^{-1}, and the NMR spectrum revealed the presence of two methyl groups due to an acetonide (δ 1.70 as singlet), which suggested that two phenyl groups were located trans to each other because of the same chemical shift of two methyl groups on an acetonide. The compound **2** was obtained by the same way as described for the compound **1** from benzylisoquinoline **10** through the stilbene **12** and the epoxide **14**. The diol **2** was also converted into the acetonide **16**.

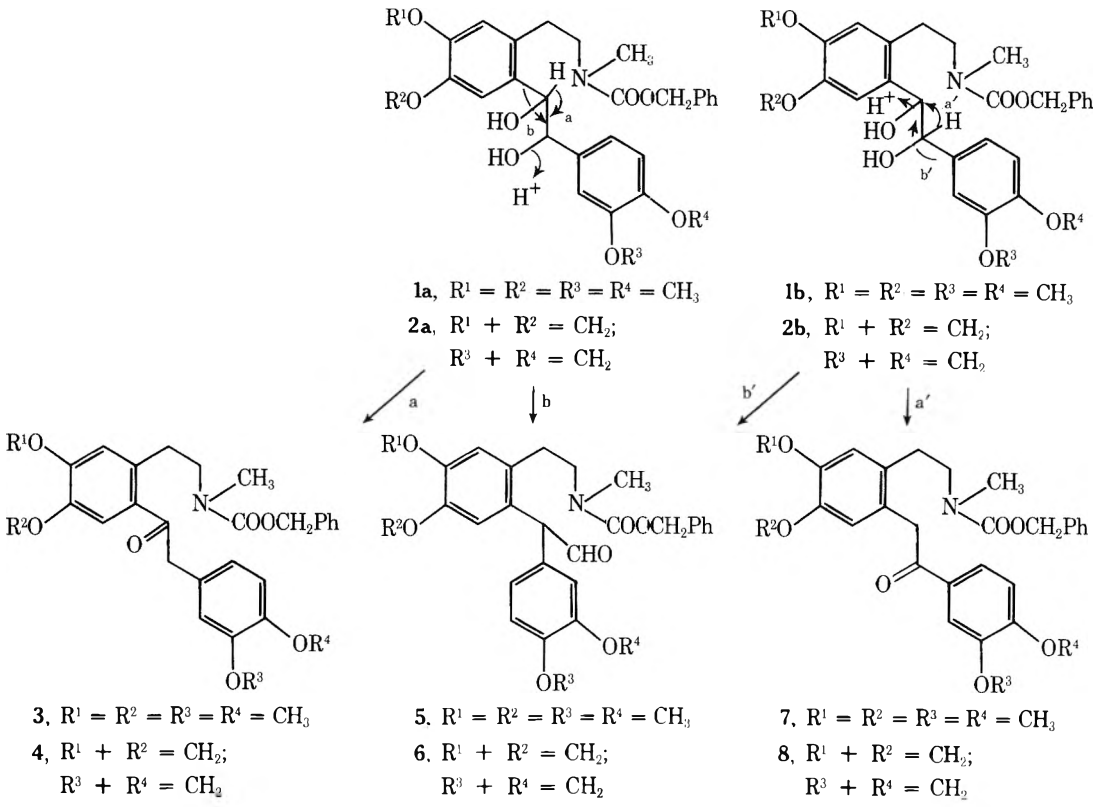
Compounds **1** and **13** were, independently, treated with acetic acid in the presence of *p*-toluenesulfonic acid to afford the same compound **17** in 46 and 25.3% yield, respectively, whose NMR spectrum showed the presence of an *N*-methyl group (δ 2.90). The uv spectrum showed λ_{max} 306 nm which shifted to 298 nm on addition of concentrated hydrochloric acid. This shift indicated the presence of a conjugated enamine system. All spectral data of the product **17** were identical with those of an authentic sample.[8] The diol **2** was also treated under the same condition as described above to give the compound **18** in 11.6% yield.

Experimental Section

Melting points are uncorrected. NMR spectra were measured with a JNM-PMX-60 spectrometer (tetramethylsilane as an internal reference), ir spectra with a Hitachi 215 spectrophotometer, uv spectra with a Hitachi 124 spectrophotometer, and mass spectra with a Hitachi RMU-7 spectrometer.

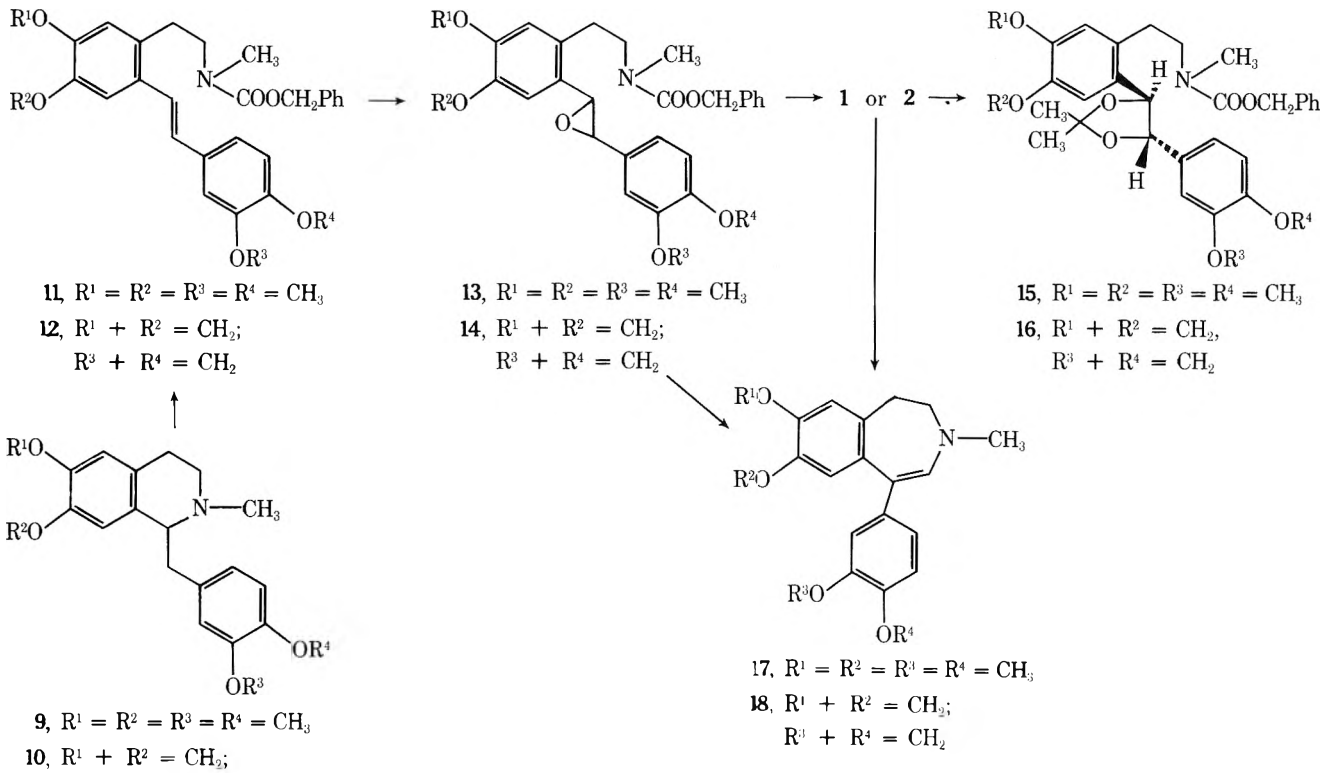
2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene (11). To a stirred solution of laudanosine (**9**, 25 g) in methylene chloride (200 ml) were added in portions a solution of benzyloxycarbonyl chloride (13.2 g) in methylene chloride (200 ml) and a solution of sodium hydroxide (3.4 g) in water (100 ml) separately within 1 h at room temperature. After the stirring had been continued for 1 h at room temperature, the organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water, dried over Na_2SO_4, and evaporated to leave an orange, viscous oil, which was triturated with ethanol to give the stilbene **11** (25.9 g, 75.3%) as colorless prisms: mp 126–127 °C; uv (MeOH) 295 and 330 nm; ir ($CHCl_3$) 1680 cm^{-1}

Scheme I



1a, $R^1 = R^2 = R^3 = R^4 = CH_3$
2a, $R^1 + R^2 = CH_2$; $R^3 + R^4 = CH_2$
1b, $R^1 = R^2 = R^3 = R^4 = CH_3$
2b, $R^1 + R^2 = CH_2$; $R^3 + R^4 = CH_2$
3, $R^1 = R^2 = R^3 = R^4 = CH_3$
4, $R^1 + R^2 = CH_2$; $R^3 + R^4 = CH_2$
5, $R^1 = R^2 = R^3 = R^4 = CH_3$
6, $R^1 + R^2 = CH_2$; $R^3 + R^4 = CH_2$
7, $R^1 = R^2 = R^3 = R^4 = CH_3$
8, $R^1 + R^2 = CH_2$; $R^3 + R^4 = CH_2$

Scheme II



11, $R^1 = R^2 = R^3 = R^4 = CH_3$
12, $R^1 + R^2 = CH_2$; $R^3 + R^4 = CH_2$
13, $R^1 = R^2 = R^3 = R^4 = CH_3$
14, $R^1 + R^2 = CH_2$; $R^3 + R^4 = CH_2$
15, $R^1 = R^2 = R^3 = R^4 = CH_3$
16, $R^1 + R^2 = CH_2$, $R^3 + R^4 = CH_2$
9, $R^1 = R^2 = R^3 = R^4 = CH_3$
10, $R^1 + R^2 = CH_2$; $R^3 + R^4 = CH_2$
17, $R^1 = R^2 = R^3 = R^4 = CH_3$
18, $R^1 + R^2 = CH_2$; $R^3 + R^4 = CH_2$

(C=O); NMR ($CDCl_3$) δ 2.88 (3 H, s, NCH_3) and 5.08 ppm (2 H, s, CO_2CH_2Ph); mass spectrum *m/e* 491 (M^+).

Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.85; H, 6.77; N, 2.85. Found: C, 70.95; H, 6.81; N, 2.83.

2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-dimethylenedioxystilbene (12). 1,2,3,4-Tetrahydro-2-methyl-6,7-methylenedioxy-1-(3,4-methylenedioxybenzyl)isoquinoline (**10**, 10.2 g) was treated with benzyloxycarbonyl chloride (5.6 g) and a solution of sodium hydroxide (1.57 g) in water (40 ml) by the same way as described for compound **11** to give the stilbene **12** (10.9 g, 75.7%) as colorless prisms: mp 114–115 °C; uv (MeOH) 293 and 340 nm; ir ($CHCl_3$) 1680 cm^{-1} (C=O); NMR (CCl_4) δ 2.82 (3 H, s, NCH_3), 5.01 (2 H, s, CO_2CH_2Ph), and 5.83 and 5.86 ppm (4 H, each s, 2 OCH_2O).

Anal. Calcd for $C_{27}H_{25}NO_6$: C, 70.57; H, 5.49; N, 3.05. Found: C, 70.36; H, 5.50; N, 2.98.

2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene Oxide (13). To a stirred solution of stilbene

11 (2 g) in methylene chloride (50 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (1 g) in methylene chloride (50 ml) at 0 °C. After the stirring had been continued for 4 h at room temperature, a saturated sodium sulfite aqueous solution (50 ml) was added to the above reaction mixture. The methylene chloride layer was separated and washed with potassium carbonate aqueous solution and water, dried over K_2CO_3, and evaporated to give a brownish, viscous oil, which was chromatographed on silica gel (50 g). Elution with chloroform afforded the epoxide **13** (1.86 g, 89.9%) as a pale brown oil: uv (MeOH) 280 nm; ir ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.77 (3 H, s, NCH_3), 4.99 (2 H, s, CO_2CH_2Ph), and 6.30–8.0 ppm (10 H, m, aromatic protons); mass spectrum *m/e* 507 (M^+).

2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-dimethylenedioxystilbene Oxide (14). Stilbene **12** (5 g) was treated with *m*-chloroperbenzoic acid (4.4 g) as described above to give the epoxide **14** (3.5 g, 67.7%) as a pale brown oil: uv (MeOH) 287 nm; ir ($CHCl_3$) 1680 cm^{-1} (C=O); NMR (CCl_4) δ 2.81 (3 H, s, NCH_3), 5.05 (2 H, s, CO_2CH_2Ph), 5.80, 5.83 (4 H, each s, 2 OCH_2O), and 6.33–7.96 ppm (10 H, m, aromatic protons).

Reaction of 2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene Oxide (13) with Potassium Hydroxide in Methanol. A solution of stilbene oxide **13** (1.58 g) in 1 N methanolic potassium hydroxide (10 ml) was refluxed for 1.5 h. After the solvent had been distilled off under reduced pressure, the residue was dissolved in chloroform. The chloroform layer was washed with water, dried over K_2CO_3, and evaporated to leave a brown oil, which was chromatographed on silica gel (30 g). Elution with chloroform afforded the diol **1** (1.172 g, 71.4%) as a pale brown oil: ir ($CHCl_3$) 3400 (OH) and 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.74 (3 H, s, NCH_3), 3.60, 3.70, 3.74, 3.82 (12 H, each s, 4 OCH_3), 4.0–4.6 br (2 H, s, 2 OH, disappeared by D_2O exchange), 4.75 [2 H, broad s, CH(OH)CH(OH)], 4.96 (2 H, CO_2CH_2Ph), and 6.25–7.5 ppm (10 H, m, aromatic protons); mass spectrum *m/e* 507 ($M^+ - 18$).

Anal. Calcd for $C_{29}H_{35}NO_8$: C, 66.27; H, 6.71; N, 2.67. Found: C, 66.15; H, 6.93; N, 2.62.

The diol **1** (399 mg) was converted to the acetonide **15** with acetone–perchloric acid in a usual way. The resulting crude acetonide was chromatographed on silica gel (30 g). Elution with benzene–ethyl acetate (3:1) afforded the acetonide **15** (170 mg, 39.6%) as an oil: ir ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.70 [6 H, s, $O_2C(CH_3)_2$], 2.68 (3 H, s, NCH_3), 4.5–5.0 (2 H, m, OCHCHO), 5.10 (2 H, s, CO_2CH_2Ph), and 6.3–7.5 ppm (10 H, m, aromatic protons); mass spectrum *m/e* 565 (M^+).

Anal. Calcd for $C_{32}H_{39}NO_8$: C, 67.94; H, 6.95; N, 2.48. Found: C, 67.75; H, 6.85; N, 2.27.

Reaction of 2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-dimethylenedioxystilbene Oxide (14) with Potassium Hydroxide in Methanol. Stilbene oxide **14** (3.5 g) was similarly treated with 1 N methanolic potassium hydroxide (60 ml) to afford the diol **2** (2.2 g, 60.6%) as a pale brown oil: ir ($CHCl_3$) 3400 (OH) and 1680 cm^{-1} (C=O); NMR (CCl_4) δ 2.70 (3 H, s, NCH_3), 4.0–4.4 br (2 H, s, 2 OH), 4.55 br [2 H, s, CH(OH)CH(OH)], 4.96 (2 H, s, CO_2CH_2Ph), 5.85, 5.88 (4 H, each s, 2 OCH_2O), and 6.36–7.4 ppm (10 H, m, aromatic protons).

Anal. Calcd for $C_{27}H_{27}NO_8$: C, 65.71; H, 5.52; N, 2.84. Found: C, 65.35; H, 5.50; N, 3.16.

The diol **2** (500 mg) was converted into the acetonide **16** with acetone–perchloric acid in a usual way to afford the acetonide **16** (340 mg, 62.9%) as an oil: ir ($CHCl_3$) 1680 cm^{-1} (C=O); NMR (CCl_4) δ 1.55 [6 H, s, $O_2C(CH_3)_2$], 2.66 (3 H, s, NCH_3), 4.3–4.9 (2 H, m, OCHCHO), 5.06 (2 H, s, CO_2CH_2Ph), 5.65, 5.63 (4 H, each s, 2 OCH_2O), and 6.41–7.6 ppm (10 H, m, aromatic protons).

Anal. Calcd for $C_{30}H_{31}NO_8 \cdot 1.5CHCl_3$: C, 62.40; H, 5.40; N, 2.31. Found: C, 61.95; H, 5.20; N, 2.33.

Reaction of Diol 1 with *p*-Toluenesulfonic Acid in Acetic Acid. A solution of diol **1** (772 mg) and *p*-toluenesulfonic acid (1 g) in acetic acid (20 ml) was refluxed for 2 h. After the solvent had been distilled off under reduced pressure, the residue was dissolved in chloroform.

The organic layer was washed with 10% sodium hydroxide and water, dried over K_2CO_3, and evaporated to afford a brown oil, which was triturated with methanol to give the azepine **17** (240 mg, 46%) as colorless needles: mp 116–117 °C; uv (MeOH) 306 nm; NMR ($CDCl_3$) δ 2.90 (3 H, s, NCH_3), 3.60, 3.81, 3.86, 3.90 (12 H, each s, 4 OCH_3), and 6.20–6.81 ppm (6 H, m, aromatic and olefinic protons); mass spectrum *m/e* 355 (M^+). This was identical with an authentic specimen[8] (mixture melting point and comparison of spectroscopic data).

Reaction of 2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene Oxide (13) with *p*-Toluenesulfonic Acid in Acetic Acid. A solution of stilbene oxide **13** (1.86 g) was treated with *p*-toluenesulfonic acid (1 g) in acetic acid (30 ml) under the same conditions as described for the diol **1** to give the azepine **17** (330 mg, 25.4%) as needles, mp 116–117 °C, identical with the authentic sample as described above.

Reaction of Diol 2 with *p*-Toluenesulfonic Acid in Acetic Acid. A solution of diol **2** (1 g) was similarly treated with *p*-toluenesulfonic acid (1 g) in acetic acid (40 ml) to afford the azepine **18** (76.2 mg, 11.6%) as a glass: uv (MeOH) 315 nm; NMR (CCl_4) δ 2.83 (3 H, s, NCH_3), 5.73, 5.83 (4 H, each s, 2 OCH_2O), and 6.0–7.2 ppm (6 H, m, aromatic and olefinic protons); mass spectrum *m/e* 323 (M^+).

Anal. Calcd for $C_{19}H_{17}NO_4 \cdot 0.5H_2O$: C, 68.66; H, 5.46. Found: C, 68.49; H, 5.21.

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Registry No.—**1**, 59643-46-8; **2**, 59643-47-9; **9**, 20412-65-1; **10**, 7688-68-8; **11**, 59643-48-0; **12**, 59643-49-1; **13**, 59643-50-4; **14**, 59643-51-5; **15**, 59643-52-6; **16**, 59643-53-7; **17**, 32407-74-2; **18**, 59643-54-8; benzyloxycarbonyl chloride, 501-53-1.

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Preparation of Intermediates for Uroporphyrin Synthesis

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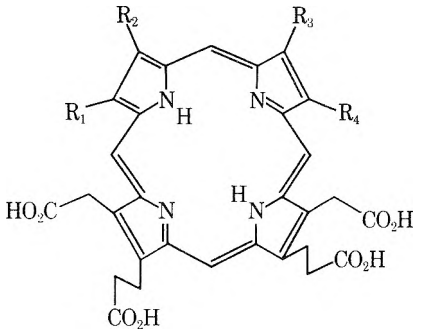
The obtention of dipyrrylmethanes necessary for the synthesis of uroporphyrins III, IV, and II (as octamethyl esters) is described. The necessary pyrroles were prepared by transesterification of the corresponding tribenzyl esters with methanol and sulfuric acid, which produced the transesterification of the side chain esters, but not of the nuclear benzyloxycarbonyl groups. The dimethyl esters of the 2-methyl-5-benzyloxycarbonylpyrroles thus obtained were converted into their 2-chloromethyl derivatives, which were condensed at 180 °C with the dimethyl esters of the 5-free 2-benzyloxycarbonylpyrroles. The tetramethyl esters of the 5,5′-dibenzyloxycarbonyldipyrrylmethanes thus prepared were converted by hydrogenolysis into the corresponding 5,5′-dicarboxydipyrrylmethanes, which were condensed with the tetramethyl ester of a 5,5′-diformyldipyrrylmethane to afford the above-mentioned uroporphyrin esters. The 5,5′-free dipyrrylmethane necessary for the synthesis of the 5,5′-diformyldipyrrylmethane was obtained by hydrogenolysis of a 5,5′-dibenzyloxycarbonyldipyrrylmethane, decarboxylation with iodine of the resulting 5,5′-diacid, and reduction of the 5,5′-diiododipyrrylmethane with hydrogen.

Uroporphyrins are valuable synthetic products since some of their reduced derivatives (e.g., uroporphyrinogens III and IV) are important biosynthetic intermediates of the porphyrin metabolism.[1] Uroporphyrin isomers are best prepared by MacDonald's procedure, which consists in an acid-catalyzed condensation of a 5,5′-diformyldipyrrylmethane and a 5,5′-free dipyrrylmethane.[2,3] By using the recently introduced refinements of this condensation technique,[4] it was possible to increase the simplicity of the reaction for the synthesis of uroporphyrins III **1**, IV **2**, and II **3** (see Experimental Section).



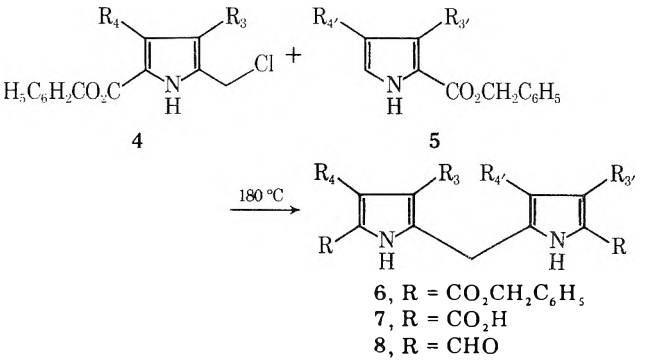
1, $R_1 = R_3 = CH_2CO_2H$; $R_2 = R_4 = CH_2CH_2CO_2H$
2, $R_1 = R_4 = CH_2CH_2CO_2H$; $R_2 = R_3 = CH_2CO_2H$
3, $R_1 = R_4 = CH_2CO_2H$; $R_2 = R_3 = CH_2CH_2CO_2H$

An efficient and versatile synthesis of the required pyrrylmethane intermediates is hence the main objective for a preparative synthesis of the three uroporphyrin isomers. It is also of interest for biosynthetic studies that each pyrrole unit of the uroporphyrin ring should be built into the structure independently of the other three rings, allowing in this way a differential labeling of the substituents of each ring. Hence, the synthesis of symmetrically substituted dipyrrylmethanes should be carried out following the pattern of an asymmetric dipyrrylmethane synthesis, avoiding the so-called dimerization reactions of 2-halomethylpyrroles to give symmetrical dipyrrylmethanes.[3]

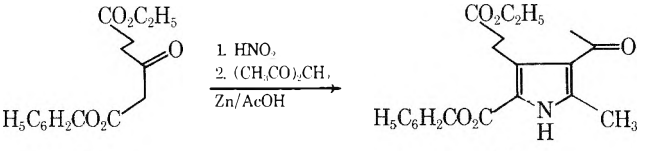
The outline of the method which we propose for the synthesis of the required dipyrrylmethanes (Scheme I) is based on the asymmetric condensation of 2-chloromethyl-5-benzyloxycarbonylpyrroles **4** with 2-benzyloxycarbonylpyrroles **5** to obtain the 5,5′-benzyloxycarbonyldipyrrylmethanes **6**. Hydrogenolysis of the benzyl groups then gave the 5,5′-carboxydipyrrylmethanes **7**, which were then directly condensed with a 5,5′-diformyldipyrrylmethane **8** (also derived from **7**) to obtain the desired uroporphyrins.

The building blocks for the synthesis of the required dipyrrylmethanes were the dimethyl esters of the 5-benzyloxycarbonylpyrroles. Benzyl δ-ethyl-β-oxoadipate (**9**), readily obtained by transesterification of diethyl β-ketoadipate,[5] was oximinated with sodium nitrite and then condensed with 2,4-pentanedione to give the β-acetylpyrrole **10**.

Scheme I

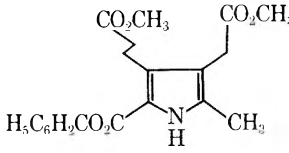


6, R = $CO_2CH_2C_6H_5$
7, R = CO_2H
8, R = CHO



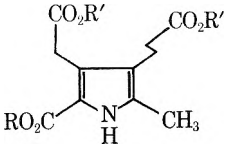
9 **10**

Oxidation of **10** with thallium(III) nitrate in methanol[6] gave the dimethylbenzylpyrrole **11** in 61% yield.



11

The isomeric dimethylbenzylpyrrole **12** was obtained by an acid-catalyzed transesterification with methanol of the tribenzyl ester **13**[7]. While the base-catalyzed transesterification

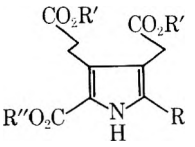


12, R = $CH_2C_6H_5$; R′ = CH_3
13, R = R′ = $CH_2C_6H_5$

of **13** with methanol met with considerable difficulties (see ref 7 and discussion therein), the acid-catalyzed transesterification afforded **12** in 84% yield. Moreover, the procedure was

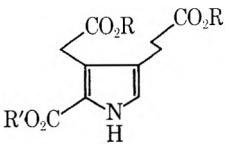
found to be a general one for all the analogous tribenzyl esters (see below).

Dimethyl benzyl esters of the α-free pyrroles were prepared by a similar pattern. The readily available[6] dimethylethylpyrrole **14** was oxidized to the acid **15**, the latter was decarboxylated by iodination, and the 2-iodopyrrole **16** was reduced to the α-free triester **17**. Saponification of the ester groups, followed by treatment of the triacid **18** with α-diazotoluene, afforded the tribenzyl ester **19** in 68% yield. Acid-catalyzed transesterification of **19** with methanol gave the dimethylbenzyl ester **20** in 70% yield.



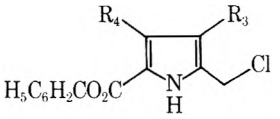
14, R = CH_3; R′ = CH_3; R″ = C_2H_5
15, R = CO_2H; R′ = CH_3; R″ = C_2H_5
16, R = I; R′ = CH_3; R″ = C_2H_5
17, R = H; R′ = CH_3; R″ = C_2H_5
18, R = R′ = R″ = H
19, R = H; R′ = R″ = $CH_2C_6H_5$
20, R = H; R′ = CH_3; R″ = $CH_2C_6H_5$

Analogously, by saponification of the isomeric triethyl ester **21**, followed by treatment of the triacid **22** with α-diazotoluene, the tribenzyl ester **23** was obtained. Acid-catalyzed transesterification of **23** gave the dimethylbenzyl ester **24** in 69% yield.



21, R = R′ = C_2H_5
22, R = R′ = H
23, R = R′ = $CH_2C_6H_5$
24, R = CH_3; R′ = $CH_2C_6H_5$

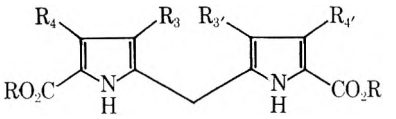
The 2-methylpyrroles **11** and **12** were transformed into their 2-chloromethylpyrroles **25** and **26** by using sulfuryl chloride, and the latter were condensed with the α-free pyrroles **20** and **24**.



25, R_3 = $CH_2CO_2CH_3$; R_4 = $CH_2CH_2CO_2CH_3$
26, R_3 = $CH_2CH_2CO_2CH_3$; R_4 = $CH_2CO_2CH_3$

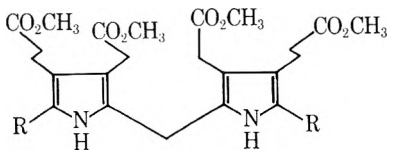
The condensation reaction was carried out in glacial acetic acid containing 1% of sodium acetate. To overcome the deactivation produced by the 2-benzyloxycarbonyl substituents in **20** and **24** it was necessary to carry out the reaction at 180 °C in a closed vessel. Under those conditions, no randomization of the reaction products took place, no "irrational" dipyrrylmethanes were obtained,[3] and the desired dipyrrylmethanes were isolated in approximately 70% yield. By condensation of **25** and **24**, the dipyrrylmethane **27** was obtained; by condensation of **25** and **20** the dipyrrylmethane **28** was obtained; and by condensation of **26** and **24** the dipyrrylmethane **29** was obtained.

For the synthesis of uroporphyrins III, IV, and II, it was necessary to prepare the 5,5′-diformyldipyrrylmethane **30**. This was achieved by using dipyrrylmethane **28** as a starting material. Hydrogenolysis of the benzyl esters, followed by treatment of the resulting diacid **31** with iodine, afforded the 5,5′-diiododipyrrylmethane **32** in good yield. Hydrogenolysis of **32** gave the 5,5′-free dipyrrylmethane **33**, which was



27, R_3 = $R_{4'}$ = $CH_2CO_2CH_3$; R_4 = $R_{3'}$ = $CH_2CH_2CO_2CH_3$; R = $CH_2C_6H_5$
28, R_3 = $R_{3'}$ = $CH_2CO_2CH_3$; R_4 = $R_{4'}$ = $CH_2CH_2CO_2CH_3$; R = $CH_2C_6H_5$
29, R_3 = $R_{3'}$ = $CH_2CH_2CO_2CH_3$; R_4 = $R_{4'}$ = $CH_2CO_2CH_3$; R = $CH_2C_6H_5$
31, R_3 = $R_{3'}$ = $CH_2CO_2CH_3$; R_4 = $R_{4'}$ = $CH_2CH_2CO_2CH_3$; R = H
34, R_3 = $R_{4'}$ = $CH_2CO_2CH_3$; R_4 = $R_{3'}$ = $CH_2CH_2CO_2CH_3$; R = H
35, R_3 = $R_{3'}$ = $CH_2CH_2CO_2CH_3$; R_4 = $R_{4'}$ = $CH_2CO_2CH_3$; R = H

transformed into the 5,5′-diformyldipyrrylmethane **30** by using the Vilsmaier–Haack procedure[8]. The attempted thermal decarboxylation of the diacid **31** to **33** gave very poor yields, while attempts made by using trifluoroacetic acid lead to extensive decomposition of the dipyrrylmethanes.



30, R = CHO
32, R = I
33, R = H

Uroporphyrins III **1**, IV **2**, and II **3** (as octamethyl esters) were obtained by condensing the diformyldipyrrylmethane **30** with the diacids **31**, **34**, and **35** obtained "in situ" after hydrogenolysis of the benzyl esters of **27**, **28**, and **29**. The *p*-toluenesulfonic acid catalyzed condensations were performed in methylene chloride[4] and there was no need to carry out a previous decarboxylation of the diacids **31**, **34**, and **35**, since analogous yields (approximately 30–50%) were obtained when the reactions were carried out with the 5,5′-free dipyrrylmethanes. Decarboxylation of the uroporphyrins to coproporphyrins and TLC analysis of the latter[9,10] indicated that the obtained uroporphyrins were the pure isomers.

Experimental Section[11]

Benzyl 2-Methyl-3-acetyl-4-(β-ethoxycarbonylethyl)-5-pyrrolecarboxylate (10). A solution of 18 g of sodium nitrite in 60 ml of water was slowly added to a stirred mixture of 67 g (0.24 mol) of α-benzyl δ-ethyl-β-ketoadipate (**9**) and 100 ml of glacial acetic acid, while the temperature was kept at 10 °C. After the addition was completed, the mixture was kept overnight at 5 °C, and then added to a constantly stirred mixture of 24.5 g (0.24 mol) of 2,4-pentanedione, 44 g of zinc, and 44 g of sodium acetate in 100 ml of acetic acid. A supplemental amount of 44 g of zinc was added in small portions during the addition of the isonitroso derivative. The resulting mixture was kept at 65 °C during 60 min with constant stirring, and was then poured into 1 l. of ice water. The precipitate was filtered and crystallized from methanol–water: 57.5 g (65%); mp 100–101 °C; NMR ($CDCl_3$) 1.2 (t, *J* = 7 Hz, 3, CH_2CH_3), 2.4, 2.5 (s, 3, 3, $COCH_3$, CH_3), 2.5, 3.4 (m, 2, 2, $-CH_2CH_2-$), 4.15 (q, 2, CH_2CH_3), 5.3 (s, 2, CH_2Ph), 7.3 ppm (b, 5, Ph).

Anal. Calcd for $C_{20}H_{23}O_5N$: C, 67.2; H, 6.4; N, 4.0. Found: C, 67.3; H, 6.5; N, 4.0.

Benzyl 2-Methyl-3-(methoxycarbonylmethyl)-4-(β-methoxycarbonylethyl)-5-pyrrolecarboxylate (11). Thalium(III) nitrate (12 g, 30 mmol) was added to a solution of 5.75 g (16 mmol) of the β-acetylpyrrole **10** in 200 ml of anhydrous methanol and 40 ml of 70% perchloric acid. The mixture was kept at 20 °C during 5 h, then poured over 500 ml of water, and the aqueous solution was extracted with chloroform (3 × 50 ml). The chloroform solution was washed with a sodium bicarbonate solution, then with water, dried (Na_2SO_4), and evaporated to dryness in vacuo. The residue was dissolved in a small volume of 10% methanol in benzene, and was filtered through a column (3.5 × 40 cm) of TLC silica gel, packed and prewashed with the

same solvent. The pyrrole **11** was eluted by applying a small pressure, the eluate was evaporated to dryness in vacuo, and the residue was crystallized from cyclohexane: 3.7 g (61%); mp 78 °C (lit.[7] 78 °C, mmp 78 °C); NMR ($CDCl_3$) 2.2 (s, 3, CH_3), 2.7 (m, 4, CH_2CH_2), 3.4 (s, 2, CH_2CO), 3.55, 3.6 (s, 3, 3, OCH_3), 5.2 (s, 2, $CH_2C_6H_5$), 7.3 ppm (s, 5, C_6H_5).

Benzyl 2-Methyl-3-(methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-5-pyrrolecarboxylate (12). Concentrated sulfuric acid (30 ml) was added to a solution of 6.2 g of the tribenzyl ester **13** in 600 ml of anhydrous methanol, while it was kept at 5 °C with constant stirring. The mixture was further kept at 20 °C during 8 h, then poured over 2 l. of ice–water. The precipitate was filtered, dried, and crystallized from cyclohexane: 3.7 g (84%); mp 111 °C (lit[7] mp 111 °C, mmp 111 °C); NMR ($CDCl_3$) 2.2 (s, 3, CH_3), 3.5, 3.6 (s, 3, 3, OCH_3), 5.2 (s, 2, $CH_2C_6H_5$), 7.2 ppm (s, 5, C_6H_5).

Ethyl 2-Carboxy-3-(methoxycarbonylmethyl)-4-(methoxycarbonylethyl)-5-pyrrolecarboxylate (15). Freshly distilled sulfuryl chloride (4 ml, 192 mmol) was added to 20 g (64 mmol) of the dimethyl ethyl ester **14** dissolved in 200 ml of anhydrous methylene chloride, while keeping the solution at 5 °C with constant stirring. The mixture was further kept at 20 °C during 30 min, the solvent was then evaporated to dryness in vacuo, 60 g of sodium acetate dissolved in 1 l. of warm water was added, and the mixture was boiled during 5 min. Sodium bicarbonate was added to the cooled suspension, the alkaline solution was extracted with ether (3 × 100 ml), and the aqueous phase was adjusted to pH 2 with concentrated hydrochloric acid. The precipitated acid was filtered, dried, and crystallized from ethanol–water, 14 g (63%), mp 186–187 °C.

Anal. Calcd for $C_{15}H_{19}NO_8$: C, 52.8; H, 5.6; N, 4.1. Found: C, 52.8; H, 5.5; N, 4.0.

Ethyl 2-Iodo-3-(methoxycarbonylmethyl)-4-(methoxycarbonylethyl)-5-pyrrolecarboxylate (16). A solution of 17.5 g of the acid **15** and 33 g of sodium bicarbonate in 260 ml of water was added to a stirred solution of 41 g of potassium iodide and 16.4 g of iodine in 26 ml of water. The mixture was stirred and heated at 75 °C during 1 h. After that period it was cooled at 5 °C during several hours, and the precipitate was filtered and crystallized from ethanol, 18.6 g (85%), mp 133 °C.

Anal. Calcd for $C_{14}H_{18}NO_6I$: C, 40.0; H, 4.2; N, 3.3. Found: C, 39.9; H, 4.1; N, 3.3.

Ethyl 3-(Methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-2-pyrrolecarboxylate (17). Anhydrous sodium acetate (18 g) was added to a solution of 18 g of **16** in 150 ml of ethanol, and the mixture was reduced with hydrogen at 30 psi during 2 h over 3.6 g of 10% palladium on charcoal. The catalyst was filtered, the solution was evaporated to dryness in vacuo, the residue was dissolved in 250 ml of water, and the aqueous solution was extracted with chloroform (3 × 100 ml). The chloroform extracts were washed first with 10% thiosulfate, then with water, dried (Na_2SO_4), and evaporated to dryness. The oily residue crystallized from cyclohexane: 10 g (78%); mp 47–48 °C (benzene–petroleum ether); NMR ($CDCl_3$) 1.3 (t, J = 7 Hz, 3, CH_2CH_3), 2.7 (m, 4, CH_2CH_2), 3.5 (s, 2, CH_2CO), 3.6, 3.65 (s, 3, 3, OCH_3), 4.2 (q, J = 7 Hz, 2, CH_2CH_3), 6.8 ppm (b, 1, H_5).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.1; N, 4.9. Found: C, 56.5; H, 6.0; N, 4.8.

Benzyl 3-(Benzyloxycarbonylethyl)-4-(benzyloxycarbonylmethyl)-2-pyrrolecarboxylate (19). The triester **17** (6.8 g) was dissolved in a mixture of 80 ml of ethanol and 80 ml of 10% sodium hydroxide, and the solution was evaporated to dryness at 110 °C in an open flask. The residue was dissolved in 60 ml of water, the solution was adjusted to pH 2 with concentrated hydrochloric acid, and the precipitated triacid **18** was filtered and dried. Without further purification it was dissolved in methanol and distilled (60 °C, 0.2 mm). α-Diazotoluene[12] was added dropwise until Ehrlich's reaction was negative in the cold. The excess of α-diazotoluene was destroyed with acetic acid, the solution was evaporated to dryness in vacuo, and the residue was crystallized from cyclohexane: 8 g (68%); mp 81–82 °C (from methanol); NMR ($CDCl_3$) 2.9 (m, 4, CH_2CH_2), 3.6 (s, 2, CH_2CO), 5.2, 5.3 (s, 4, CH_2Ph), 5.45 (s, 2, nuclear CO_2CH_2Ph), 7.55 (b, 15, Ph) 6.8 ppm (b, 1, H_5).

Anal. Calcd for $C_{31}H_{29}NO_6$: C, 72.8; H, 5.7; N, 2.7. Found: C, 72.7; H, 5.6; N, 2.8.

Benzyl 3-(Methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-2-pyrrolecarboxylate (20). The tribenzyl ester **19** (10 g) was transesterified by using 1 l. of anhydrous methanol and 200 ml of concentrated sulfuric acid, as desribed in the preparation of **12.** The obtained product was dissolved in a small volume of 3% methanol in benzene, and was filtered through a silica gel column (3 × 40 cm) packed and eluted with the same solvent under slight pressure. The fractions containing the pyrrole **20** were collected and evaporated to dryness in vacuo, and the residue was crystallized from benzene–cyclohexane: 4.9 g (70%); mp 61–63 °C (lit.[13] mp 60–63 or 49–52 °C); NMR ($CDCl_3$) 2.8 (m, 4, CH_2CH_2), 3.5 (s, 2, CH_2CO), 3.6, 3.65 (s, 6, OCH_3), 5.3 (s, 2, CH_2Ph), 6.8 (b, 1, H_5), 7.4 ppm (b, 5, Ph).

Anal. Calcd for $C_{19}H_{21}O_6N$: C, 63.5; H, 5.9; N, 3.9. Found: C, 63.4; H, 5.7; N, 3.8.

Benzyl 3-(Benzyloxycarbonylmethyl)-4-(benzyloxycarbonylethyl)-2-pyrrolecarboxylate (23). The triethyl ester **21**[3] (4 g) was saponified to the acid **22** and esterified with α-diazotoluene as described for the preparation of the isomer **19.** The product was dissolved in 1% methanol in benzene and was filtered through a silica gel column (4 × 40 cm) packed and eluted with the same solvent under slight pressure. The eluates containing the tribenzyl ester were pooled and evaporated to dryness, and the oily residue was crystallized from benzene–cyclohexane: 3.3 g (52%); mp 59–61 °C; NMR ($CDCl_3$) 2.7 (m, 4, CH_2CH_2), 3.9 (s, 2, CH_2CO), 5.05, 5.07 (s, 4, CH_2Ph), 5.25 (s, 2, nuclear CO_2CH_2Ph), 6.65 (b, 1, H_5), 7.3 ppm (b, 15, Ph).

Anal. Calcd for $C_{31}H_{29}NO_6$: C, 72.8; H, 5.7; N, 2.7. Found: C, 72.8; H, 5.6; N, 2.6.

Benzyl 3-(Methoxycarbonylmethyl)-4-(methoxycarbonylethyl)-2-pyrrolecarboxylate (24). The tribenzyl ester **23** (3.1 g) was transesterified with a mixture of 320 ml of anhydrous methanol and 64 ml of concentrated sulfuric acid by following the procedure described for **12.** The product was crystallized from benzene–cyclohexane: 1.52 g (69%); mp 63–65 °C (lit.[13] mp 63.5–66 °C); NMR ($CDCl_3$) 2.6 (m, 4, CH_2CH_2), 3.6, 3.65 (s, 6, OCH_3), 3.75 (s, 2, CH_2CO), 5.3 (s, 2, CH_2Ph), 6.7 (b, 1, H_5), 7.3 ppm (b, 5, Ph).

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.5; H, 5.9; N, 3.9. Found: C, 63.4; H, 5.8; N, 3.9.

2-Chloromethyl-3-(methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-5-benzyloxycarbonylpyrrole (26). Sulfuryl chloride (0.28 ml, 3.5 mmol) was added to a solution of **13** (1.34 g, 3.5 mmol) in 13 ml of anhydrous methylene chloride, while the solution was kept at 5 °C with constant stirring. The mixture was further stirred at 20 °C during 30 min, then evaporated to dryness in vacuo, and the residue was crystallized from benzene–hexane or from methylene chloride–petroleum ether: 1.2 g (82%); mp 89–91 °C; NMR ($CDCl_3$) 2.7 (m, 4, CH_2CH_2), 3.6, 3.65 (s, 6, OCH_3), 3.8 (s, 2, CH_2CO), 4.6 (s, 2, CH_2Cl), 5.3 (s, 2, CH_2Ph), 7.4 ppm (b, 5, Ph).

Anal. Calcd for $C_{20}H_{22}NO_6Cl$: C, 58.9; H, 5.4; N, 3.4; Cl, 8.7. Found: C, 58.9; H, 5.5; N, 3.5; Cl, 8.5.

Dibenzyl 3,4′-(Methoxycarbonylmethyl)-4,3′-(methoxycarbonylethyl)-5,5′-pyrrylmethanedicarboxylate (27). 2-Chloromethylpyrrole **25**[7] (500 mg, 1.22 mmol) and 450 mg (1.22 mmol) of dimethylbenzylpyrrole **24** were dissolved in 16 ml of glacial acetic acid containing 1% of sodium acetate, the solution was placed in a glass vessel, and the vessel was thoroughly deaerated while the solution was kept frozen (−10 °C). The vessel was closed (or sealed) under vacuum (0.1–0.2 mm), and heated at 180 °C during 90 min. After cooling the vessel it was opened, the solution was evaporated to dryness, and the residue was crystallized from methanol–water: 590 mg (65%); mp 96–97 °C; NMR ($CDCl_3$) 2.7 (m, 8, CH_2CH_2), 3.55, 3.64, 3.66 (s, 14, OCH_3, C_3CH_2CO), 3.8 (s, 2, C_4, CH_2CO), 3.95 (s, 2, $-CH_2-$), 5.3 (s, 4, CH_2Ph), 7.3 ppm (b, 10, Ph).

Anal. Calcd for $C_{39}H_{42}N_2O_{12}$: C, 64.1; H, 5.8; N, 3.8. Found: C, 64.0; H, 5.7; N, 3.7.

TLC analysis using 3% methanol in benzene indicated that **27** (R_f 0.60) was pure, and not contaminated with either **28** (R_f 0.80) or **29** (R_f 0.50).

Dibenzyl 3,3′-(Methoxycarbonylmethyl)-4,4′-(methoxycarbonylethyl)-5,5′-pyrrylmethanedicarboxylate (28). 2-Chloromethylpyrrole **25** (338 mg, 0.83 mmol) was condensed with the dimethylbenzylpyrrole **20** (300 mg, 0.83 mmol) in 18 ml of glacial acetic acid containing 1% of sodium acetate, following the technique described for **27.** Crystallization of **28** from methanol gave 490 mg (80%): mp 144–147 °C; NMR ($CDCl_3$) 2.7 (m, 8, CH_2CH_2), 3.55 (b, 16, OCH_3, CH_2CO), 3.8 (s, 2, $-CH_2-$), 5.2 (s, 4, CH_2Ph), 7.3 ppm (b, 10, Ph).

Anal. Calcd for $C_{39}H_{42}N_2O_{12}$: C, 64.1; H, 5.8; N, 3.8. Found: C, 63.9; H, 5.8; N, 3.9.

It was pure by TLC analysis (3% methanol in benzene).

Dibenzyl 3,3′-(Methoxycarbonylethyl)-4,4′-(methoxycarbonylmethyl)-5,5′-pyrrylmethanedicarboxylate (29) was prepared following the method described for **27** and **28.** From 330 mg of 2-chloromethylpyrrole **26** and 253 mg of pyrrole **24** was obtained 400 mg (78%) of **29**: mp 133–135 °C (from methanol); NMR ($CDCl_3$) 2.6 (m, 8, CH_2CH_2), 3.5 (b, 12, OCH_3), 3.7 (b, 4, CH_2CO), 3.95 (b, 2, $-CH_2-$), 5.2 (s, 4, CH_2Ph), 7.3 ppm (b, 10, Ph).

Anal. Calcd for $C_{39}H_{42}N_2O_{12}$: C, 64.1; H, 5.8; N, 3.8. Found: C, 64.4; H, 5.8; N, 3.9.

It was pure by TLC analysis (3% methanol in benzene).

3,3'-Bis(methoxycarbonylmethyl)-4,4'-(methoxycarbonylethyl)-5,5'-diiodopyrrylmethane (32). Dibenzyl ester **28** (700 mg) dissolved in 150 ml of glacial acetic acid was reduced with hydrogen over 500 mg of 10% palladium on charcoal at 50 psi during 2 h. The catalyst was filtered, the solvent was evaporated in vacuo at 40 °C, and the obtained diacid **31** was suspended in methanol and filtered (420 mg, 80%). The crude diacid **31** was dissolved in a mixture of 20 ml of ethanol, 16 ml of water, and 400 mg of sodium bicarbonate. A solution of 400 mg of iodine in 16 ml of ethanol was then dropwise added to the aforementioned solution with constant stirring, the precipitate formed after completion of the addition was redissolved with gentle heating, and the mixture was cooled at 5 °C. The precipitate of crude **32** was filtered and used in the next step, 490 mg (94%). For analysis it was crystallized from methanol–water, mp 135–136 °C.

Anal. Calcd for $C_{23}H_{28}N_2O_8I_2$: C, 38.6; H, 3.9; N, 3.9. Found: C, 38.6; H, 3.8; N, 4.0.

3,3'-Bis(methoxycarbonylmethyl)-4,4'-(methoxycarbonylethyl)dipyrrylmethane (33). A solution of the diiodopyrrylmethane **32** (490 mg) and 500 mg of sodium acetate in 100 ml of ethanol was reduced with hydrogen over 250 mg of 10% palladium on charcoal at 30 psi during 2 h. The catalyst was filtered, the solution was evaporated to dryness in vacuo, and the residue was crystallized from ethanol–water: 200 mg (63%); mp 102–104 °C (from hexane, lit.[2] 103.5–105 °C); NMR ($CDCl_3$) 2.7 (m, 8, CH_2CH_2), 3.5 (b, 4, CH_2CO), 3.65, 3.75 (s, 14, OCH_3, $-CH_2-$), 6.5 ppm (b, 2, H_5 and $H_{5'}$).

Anal. Calcd for $C_{23}H_{30}N_2O_8$: C, 59.7; H, 6.5; N, 6.1. Found: C, 59.6; H, 6.4; N, 6.1.

Uroporphyrin III Octamethyl Ester (1). A solution of 480 mg of the dibenzyl ester **27** in 150 ml of glacial acetic acid was reduced with hydrogen over 400 mg of 10% palladium on charcoal at 50 psi during 2 h. The catalyst was filtered, the solution was evaporated to dryness in vacuo, and the obtained diacid **34** was suspended in methanol and filtered (282 mg, 0.48 mmol, 77%). It was dissolved in a mixture of 240 ml of dry methylene chloride and 30 ml of methanol, 270 mg (0.48 mmol) of dialdehyde **30** (obtained from **33** as described elsewhere[8]) was added followed by 700 mg of *p*-toluenesulfonic acid, and the mixture was kept in the dark during 24 h at 20 °C. Methanol (30 ml) saturated with zinc acetate dihydrate was then added, and the mixture was kept for an additional 48 h; it was then evaporated to dryness at 40 °C, and the residue was dissolved in 150 ml of a 5% sulfuric acid in methanol solution. The solution was kept during 16 h at 20 °C in the dark; it was then diluted with 400 ml of chloroform and washed with water (200 ml), then with a 5% sodium carbonate solution (200 ml), again with water (200 ml), dried (Na_2SO_4), and evaporated to dryness at 40 °C. The residue was dissolved in a small volume of a 1% methanol–chloroform solution and was filtered through a column (2 × 30 cm) of silica gel, packed and prewashed with the same solvent. The porphyrin containing eluates were crystallized from chloroform–methanol: 240 mg (50%); mp 264–266 °C (lit.[3] mp 258–260 °C); NMR (0.05 M in $CDCl_3$) 3.3 (m, 8, CH_2CH_2CO), 3.7, 3.8 (b, 24, OCH_3), 4.3 (m, 8, CH_2CH_2CO), 5.05 (b, 8, CH_2CO), 10.2 ppm (b, 4, CH).

Anal. Calcd for: $C_{48}H_{54}N_4O_{16}$: C, 61.1; H, 5.7; N, 5.9. Found: C, 61.3; H, 5.8; N, 6.1.

When a sample of **1** was decarboxylated to coproporphyrin III, the latter was found to be the pure isomer by TLC analysis.[10]

Uroporphyrin IV octamethyl ester (2) was obtained following the procedure described for **1**. Hydrogenolysis of 640 mg of the dibenzyl ester **29** afforded 300 mg (62%) of the diacid **35**. The latter was condensed with 250 mg of the dialdehyde **30** as described above, and 135 mg (30%) of uroporphyrin IV octamethyl ester (**2**) was obtained: mp 257–258 °C (benzene–cyclohexane) (lit.[2] mp 254–257 °C); NMR ($CDCl_3$) 3.3 (m, 8, CH_2CH_2CO), 3.68, 3.70, 3.77, 3.8 (s, 24, OCH_3), 4.3 (m, 8, CH_2CH_2CO), 4.9, 5.0 (b, 8, CH_2CO), 10.0 ppm (b, 4, CH).

Anal. Calcd for $C_{48}H_{54}N_4O_{16}$: C, 61.1; H, 5.7; N, 5.9. Found: C, 61.0; H, 5.6; N, 5.8.

When a sample of **2** was decarboxylated to coproporphyrin IV, the latter was found to be pure by TLC analysis.[10]

Uroporphyrin II octamethyl ester (3) was obtained following the procedure described for **1** and **2**. By condensation of 360 mg of the diacid **31** and 300 mg of the dialdehyde **30** was obtained 201.6 mg (37%) of uroporphyrin II octamethyl ester (**3**): mp 310–312 °C (from chloroform–acetone) (lit.[2] 307–312 °C); NMR ($CDCl_3$) 3.3 (m, 8, CH_2CH_2CO), 3.7, 3.9 (s, 24, OCH_3), 4.4 (m, 8, CH_2CH_2CO), 5.1 (b, 8, CH_2CO), 10.2 ppm (b, 4, CH).

Anal. Calcd for $C_{48}H_{54}N_4O_{16}$: C, 61.1; H, 5.7; N, 5.9. Found: C, 61.3; H, 5.9; N, 6.0.

By decarboxylation to coproporphyrin II and analysis of the latter by TLC[9] it was found to be the pure isomer.

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Registry No.—**1**, 553-18-4; **2**, 613-02-5; **3**, 531-42-0; **9**, 59562-70-8; **10**, 59562-71-9; **11**, 50622-64-5; **12**, 50622-78-1; **13**, 38252-61-8; **14**, 40515-71-7; **15**, 59562-72-0; **16**, 59562-73-1; **17**, 59562-74-2; **18**, 59562-75-3; **19**, 59562-76-4; **20**, 50622-60-1; **21**, 53700-90-6; **22**, 59562-77-5; **23**, 59562-78-6; **24**, 50622-82-7; **25**, 50622-68-9; **26**, 51912-03-9; **27**, 57907-57-0; **28**, 55305-15-2; **29**, 55305-18-5; **30**, 55258-98-5; **31**, 58950-41-7; **32**, 59562-79-7; **33**, 55374-15-7; **34**, 58950-42-8; **35**, 59562-80-0; sodium nitrite, 7632-00-0; 2,4-pentanedione, 123-54-6; α-diazotoluene, 766-91-6.

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Studies on Biologically Active Nucleosides and Nucleotides. 1. Reactions of Tetraacetoxysilane with Pyrimidine Ribonucleosides

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Tetraacetoxysilane was found to react with 5′-*O*-acetyluridine to give 3′,5′-di-*O*-acetyluridine as a major product. When the reaction was carried out in the presence of $ZnCl_2$, 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)uracil (**6a**) was obtained in good yield. A similar treatment of uridine also afforded **6a**. The reaction of tetrachlorosilane with uridine in acetic acid gave, after hydrolysis, 2′-chloro-2′-deoxyuridine. In the case of 5-bromouridine followed by hydrolysis, 2′-chloro-2′-deoxy-5-bromouridine and 1-(3′-chloro-3′-deoxy-β-D-xylofuranosyl)-5-bromouracil were obtained in 34 and 2% yields, respectively. The structure of the latter was confirmed by its chemical conversion to 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil. An alternative method for the syntheses of 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine and the 5-bromo analogue was also achieved by using these reagents.

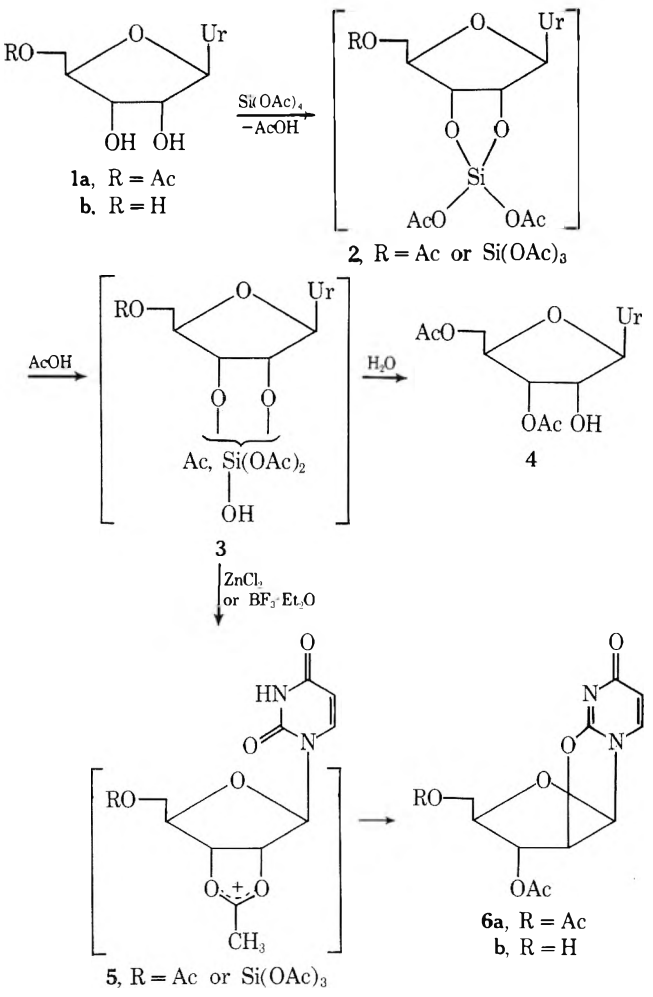
Introduction of a silyl group has been widely exploited in the nucleoside and nucleotide chemistry as a valuable synthetic tool. However, its use is limited mainly to the protection[1] of the hydroxyl group and the activation[2] of the heterocyclic base. Little attention has been devoted to the chemical alterations of nucleosides by using silyl compounds such as tetrachlorosilane and tetraacetoxysilane.

Tetraacetoxysilane[3] was first prepared in 1868 by Friedel and Landenburg[4] from tetrachlorosilane and acetic anhydride, and has been demonstrated to function as an acetylating agent.[5] Dorgov and co-workers[6] reported that aliphatic alcohols react with tetraacetoxysilane to give tetraalkoxy- or alkoxyacetoxysilanes and acetic acid depending on the reaction conditions. They also stated that when the reactions were carried out at the elevated temperatures, the products were the corresponding alkyl acetates and a silicopolymer gel. Mehrotra and Pant[7] isolated spiro alkoxysilanes by treating simple 1,2-glycols with tetraacetoxysilane. In view of the reactivities of tetraacetoxysilane toward hydroxy compounds, especially 1,2-glycols, it was of interest to investigate its reactions with ribonucleosides, since one could expect a selective acylation of the glycosyl hydroxyl groups. In this paper we describe the application of the reagents to the selective transformations of pyrimidine ribonucleosides, and discuss the reaction mechanisms.

Results and Discussion

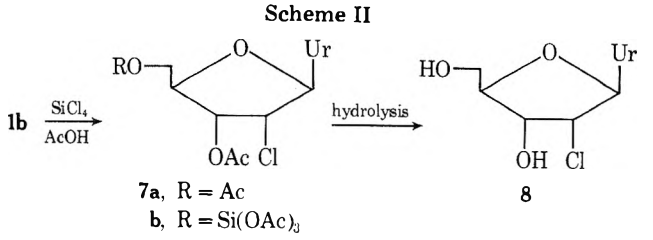
Reactions with Uridine Derivatives. It has been shown that the treatment of 5′-*O*-acetyluridine[8,9] (**1a**) with 1 equiv of acetic anhydride afforded a roughly equimolar mixture of 3′,5′-di-*O*-acetyluridine, 2′,3′,5′-tri-*O*-acetyluridine, and the unchanged starting material.[8,9] In order to study the reactivity of tetraacetoxysilane with nucleoside cis glycol, **1a** was first chosen as a model compound which could avoid the complexity in the analysis of the result. Treatment of **1a** with 2 equiv of tetraacetoxysilane at 90–95 °C in acetic acid for 2 h followed by mild hydrolysis of the product afforded two products, which were separated by silica gel column chromatography. The major product, isolated in 57% yield, proved to be 3′,5′-di-*O*-acetyluridine (**4**);[8,9] the minor component, isolated only in 8% yield, was determined to be 2,2′-anhydro-1-(3′-5′-di-*O*-acetyl-β-D-arabinofuranosyl)uracil (**6a**).[10] A mechanistic explanation of the monoacetylation would involve initial formation of a 1,3-dioxa-2-silacyclopentane derivative (**2**)[11] which could give rise to a mixture of 2′ (and 3′),5′-di-*O*-acetyluridines probably via a silylated intermediate **3**. Crystallization of the crude mixture from a polar solvent led to equilibration of the acetyl function and isolation of pure **4**.[9,12] As a result, in contrast to acetic anhydride, the monoacetylation took place even in the presence of the excess reagent. An effective method for the monoacetylation of a ribonucleoside via 2′,3′-*O*-stannylene intermediate has been reported by Moffatt et al.[13] In fact, the intermediate was isolated and characterized by spectral analyses. However, our effort to isolate a corresponding intermediate (**2**) was unsuccessful. It is interesting to note the concomitant formation of **6a**, though in low yield, under the relatively mild acidic condition. This product could be derived from **2** through an acetoxonium ion **5** which has been proposed as an intermediate under more acidic conditions in the preparation of 2,2′-anhydro-1-β-D-arabinofuranosylpyrimidines.[14] The formation of a similar acetoxonium ion from the 1,3-dioxa-2-silacyclopentane derivative of pinacol has been demonstrated by Magnuson et al.[15] In an attempt to determine the effect of an acidic catalyst, the above reaction mixture was further heated with 2 equiv of zinc chloride. Examination of the reaction by thin layer chromatography (TLC) and ultraviolet (uv) spectral analysis showed the exclusive formation of **6a**. In practice, the treatment of **1a** with 2 equiv of tetraacetoxysilane in the presence of 2 equiv of zinc chloride in acetic acid[16] afforded **6a** in 78% yield as the sole product. As was shown by Holý,[17] anhydro linkage of a 2,2′-anhydro-3′,5′-di-*O*-acyluridine is cleaved by Lewis acid (boron trifluoride etherate) catalysis. It is noteworthy that such a cleavage could not be observed in our zinc chloride catalyzed cyclization. To obtain more information concerning the unusual stability of the anhydro linkage of **6a** under our reaction conditions, **6a** was treated with 2 equiv of zinc chloride in acetic acid at 80 °C for 30 min. The uv absorption maxima at 224 and 251 nm shifted to 260 nm indicating the occurrence of the cleavage. In contrast, the treatment of **6a** with 2 equiv of zinc chloride in the presence of 2 equiv of tetraacetoxysilane under the same conditions showed no change of the uv spectrum. These results strongly suggest that the unexpected stability of **6a** is due to the interaction between zinc chloride and tetraacetoxysilane, which prevented the activation[17] of the C-2′. Similar result was obtained from the reaction of uridine (**1b**) with tetraacetoxysilane. The reaction of **1b** with 2 equiv of tetraacetoxysilane in the presence of 2 equiv of zinc chloride was performed in acetic acid at 75–80 °C for 15 h. The NMR spectrum of the crude product indicated it to be a roughly equal mixture of **6a** and 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil (**6b**).[14a] By a combination of fractional crystallization and preparative TLC, **6a** and **6b** were isolated in yields of 21 and 30%, respectively. The latter would result from the hydrolysis of a C-5′ silyloxy derivative [**6**, R = $Si(OAc)_3$], indicating that the acetylation of the cis glycol group proceeded faster than that of the C-5′ hydroxyl group. Prolongation of the reaction to 48 h led to a completion of the acetylation at the C-5′ hydroxyl group, and only **6a** was obtained in 54% yield. When boron trifluoride etherate, which is a stronger Lewis acid than zinc chloride,[18] was employed as the catalyst, the reaction was

Scheme I



completed at a lower temperature (50–55 °C) within 7 h; **6a** was obtained together with 2′,3′,5′-tri-*O*-acetyluridine[8a] in yields of 65 and 11%, respectively. The overall scheme for the above reactions is shown in Scheme I. It has previously been shown by several authors[19] that 2,2′-anhydropyrimidine nucleosides react with hydrogen halides to give 2′-halogeno-2′-deoxy nucleosides. Therefore, the use of tetrachlorosilane, which generates tetraacetoxysilane and hydrogen chloride in situ in the reaction with acetic acid,[4,20] was expected to give **8** as a final product. Thus, the treatment of **1b** with 2 equiv of tetrachlorosilane in boiling acetic acid for 3 h led to the formation of a mixture of two major products on TLC. These were presumed to be 3′,5′-di-*O*-acetyl-2′-chloro-2′-deoxyuridine (**7a**)[21] and 3′-*O*-acetyl-5′-*O*-triacetoxysilyl-2′-chloro-2′-deoxyuridine (**7b**)[22] from the mechanistic considerations and the following experimental result. Mild alkaline hydrolysis of the mixture afforded 2′-chloro-2′-deoxyuridine (**8**)[19] in 58% yield, and no other halogenated nucleoside was detected in the reaction (Scheme II). A plausible mechanism would involve the formation of the protonated anhydro nucleoside via the corresponding acetoxonium intermediate, followed by the anhydro bond cleavage by the attack of chloride ion on C-2′[19] to produce **7a** and **7b**.

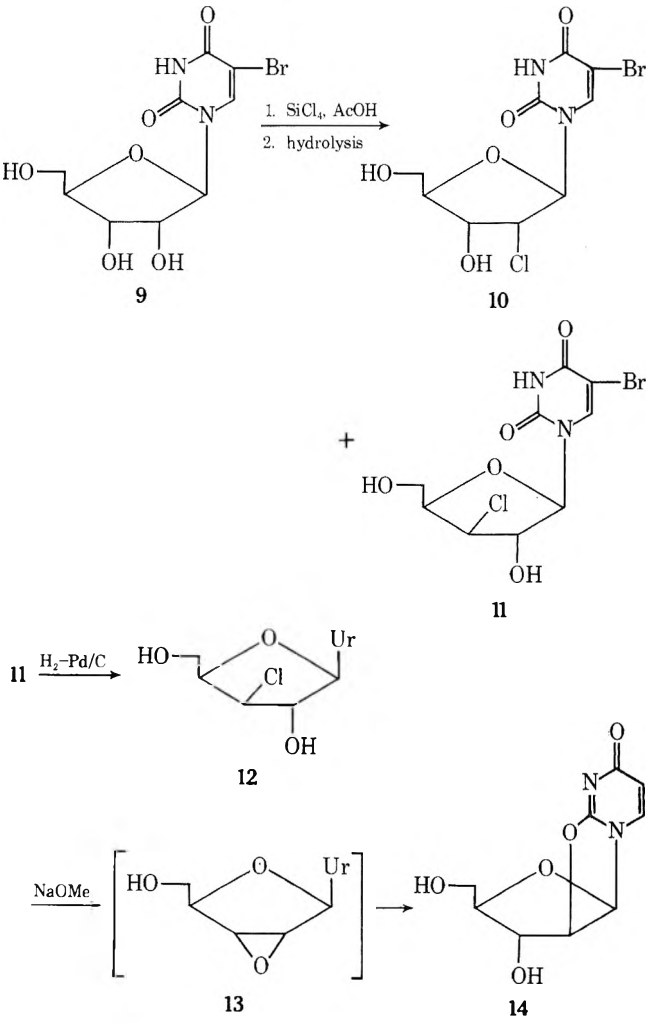
Scheme II



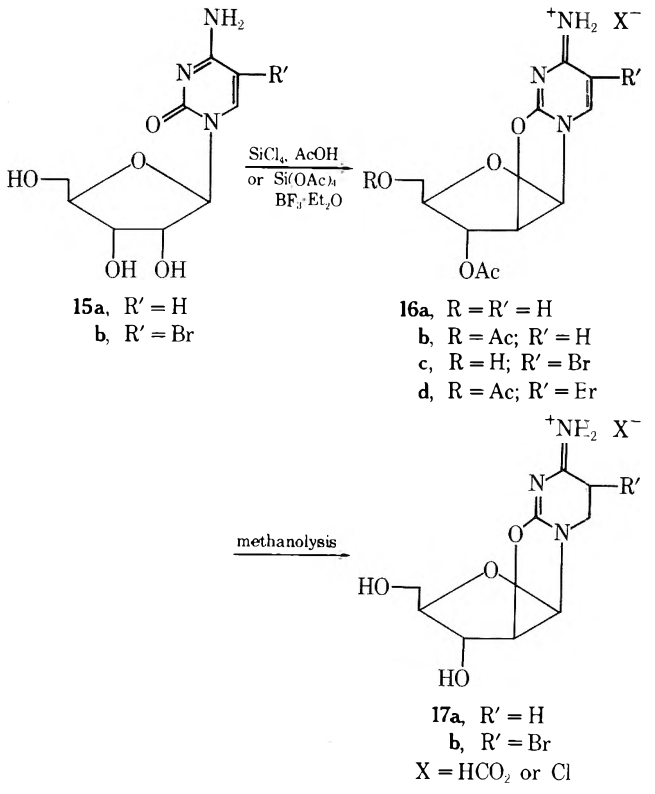
Treatment of 5-bromouridine (**9**)[23] with tetrachlorosilane under the same condition followed by the mild acid hydrolysis led to the formation of a roughly 4:1 (NMR) mixture of two products. By fractional crystallization of the mixture, the major component, 2′-chloro-2′-deoxy-5-bromouridine (**10**), was obtained in 34% yield. The minor product, isolated only in 2% yield, proved to be 1-(3′-chloro-3′-deoxy-β-D-xylofuranosyl)-5-bromouracil (**11**) (Scheme III). The NMR spectrum of **11** in Me_2SO-d_6 showed the signals assignable to the C-3′ and C-4′ protons which were shifted downfield, while the C-2′ proton was shifted upfield relative to **10**. These data support the location of the chloro function at the C-3′.

Recently Zemlicka and Horwitz[24] demonstrated that the C-5′ oxygen atom is one of the factors influencing the C-6 proton chemical shift in pyrimidine nucleosides. They suggested that a gauche–gauche (g,g) conformation at the C-4′–C-5′ bond brought the C-5′ oxygen in close proximity to the C-6 proton and resulted in enhancement of deshielding effect, compared with other conformers. The signal for the C-6 proton in **11** was observed roughly 0.4 ppm upfield compared to that in **10**. This suggests the up configuration of the C-3′ chloro function, because the decrease or the lack of the deshielding may be explained by an inability to attain the g,g conformation due to the bulkiness of the C-3′ substituent in the up configuration. The xylo configuration of **11** was further established on the basis of the chemical conversion of **11** into 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (**14**).[25] Thus, selective catalytic hydrogenation of **11** in the presence of 5% Pd/C gave 1-(3′-chloro-3′-deoxy-β-D-xylofuranosyl)uracil (**12**) in 74% yield. Treatment of **12** with 2 equiv of methanolic sodium methoxide at room temperature led to the formation of

Scheme III



Scheme IV



15a, R′ = H
b, R′ = Br

16a, R = R′ = H
b, R = Ac; R′ = H
c, R = H; R′ = Br
d, R = Ac; R′ = Er

17a, R′ = H
b, R′ = Br
X = HCO_2 or Cl

14 in 64% yield. The formation of **14** would be explained by the base-catalyzed rearrangement of a transient intermediate, 1-(2′,3′-anhydro-β-D-ribofuranosyl)uracil (**13**),[26,27] providing strong support for the xylo configuration of **11** and **12**. The formation of **11** would be due to the competitive attack of chloride ion from the β face on the C-3′ of the acetoxonium ion intermediate, while in the case of **1b** preferential attack of the C-2 carbonyl occurred and the corresponding 3′-chloro-3′-deoxy isomer could not be obtained. Accordingly, this differences would be attributed to the decreased nucleophilicity of the C-2 carbonyl caused by the inductive effect of the bromo group.

Reactions with Cytidine Derivatives. From a viewpoint of medicinal chemistry, the application of this reaction to cytidine derivatives was of great interest, since 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine derivatives have been known to have marked antileukemic activity.[28] Treatment of cytidine (**15a**) with 2 equiv of tetrachlorosilane in acetic acid, followed by column chromatographic separation of the reaction products, afforded 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**16a**, X = Cl)[14a] and 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)-cytosine hydrochloride (**16b**, X = Cl)[14b] in yields of 32 and 14%, respectively. When the mixture of the crude products was treated with hot methanol on a cation exchange resin, the acetyl groups were easily removed, and 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine formate (**17a**, X = HCO_2)[29] was obtained in 72% yield by the elution of the resin with pyridinium formate buffer (Scheme IV). Addition of boron trifluoride etherate to the reaction effected again the acetylation of the C-5′ hydroxyl group, giving **16b** in 48% yield as a sole product. Treatment of **15a** with 2 equiv of tetraacetoxysilane and boron trifluoride etherate in acetic acid at reflux temperature for 30 min followed by the methanolysis of the crude product afforded **17a** (X = HCO_2) in 61% yield. Similarly, the reaction of 5-bromocytidine (**15b**)[14c,30] with tetrachlorosilane in acetic acid followed by solvolysis in methanol yielded 2,2′-anhydro-1-(β-D-arabinofuranosyl)-5-bromocytosine formate (**17b**, X = HCO_2)[14c] in 43% yield.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R20A spectrometer and are reported in parts per million downfield from an internal standard of tetramethylsilane. Me_2SO-d_6 was used as the solvent in every case. Uv spectra were measured on a Hitachi EPS-3T spectrometer. Thin layer chromatography (TLC) was performed on Merck silica gel $60F_{254}$ and preparative TLC on Merck silica gel GF_{254}. Spots were detected by uv examination. Column chromatography was done using Merck silica gel 60.

Reaction of 5′-*O*-Acetyluridine (1a) with Tetraacetoxysilane. A. Without Lewis Acid. To a solution of **1a**[9] (1.0 g, 3.5 mmol) in dry AcOH (20 ml) was added $Si(OAc)_4$[32] (1.86 g, 7.0 mmol). The mixture was heated with stirring at 65–70 °C for 1 h, and then at 90–95 °C for 2 h. The reaction mixture was concentrated to dryness in vacuo and the residue was triturated with ice–water. The resulting mixture was evaporated in vacuo below 45 °C and the residue was coevaporated with H_2O twice. The final residue was slurried with $CHCl_3$ and the slurry was added to the top of a column of silica gel (100 g). Elution with $CHCl_3$–MeOH (95:5) gave 1.0 g of a mixture of 2′(3′),5′-di-*O*-acetyluridines (2′:3′ roughly 1:3 by NMR)[33] as a syrup in the first fraction. Crystallization of the syrup from *i*-PrOH gave 0.65 g (57%) of 3′,5′-di-*O*-acetyluridine (**4**) with mp 143–145 °C. An analytical sample from *i*-PrOH had mp 145–146 °C (reported mp 138–140,[6a] 152–154 °C[9]); λ_{max} (EtOH) 260 nm (ε 8900); NMR 2.09 (s, 3, OAc), 2.11 (s, 3, OAc), 4.6–3.9 (m, 4, $C_{2'}$ H, $C_{4'}$ H, $C_{5'}$ H_2), 4.9–5.2 (m, 1, $C_{3'}$ H), 5.5–6.0 (br s, 1, $C_{2'}$ OH), 5.73 (d, J = 8 Hz, 1, C_5 H), 5.77 (d, J = 5.5 Hz, 1, $C_{1'}$ H), 7.70 ppm (d, J = 8 Hz, 1, C_6 H). Anal. Calcd for $C_{13}H_{16}N_2O_8$ (328.31): C, 47.56; H, 4.91; N, 8.53. Found: C, 47.32; H, 5.05; N, 8.52. Evaporation of the second fraction followed by crystallization of the residue from *i*-PrOH gave 90 mg (8%) of 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)uracil (**6a**): mp 185–186 °C (reported mp 186–187,[10a] 178–179 °C[10b]); λ_{max} (pH 6.8) 224 nm (ε 8400), 251 (8200); NMR 1.91 (s, 3, OAc), 2.12 (s, 3, OAc), 3.9–4.2 (m, 2, $C_{5'}$ H_2), 4.5–4.7 (m, 1, $C_{4'}$ H), 5.32 (d, J = 1.5 Hz, 1, $C_{3'}$ H), 5.54 (d, J = 6 Hz, 1, $C_{2'}$ H), 5.90 (d, J = 8 Hz, 1, C_5 H), 6.43 (d, J = 6 Hz, 1, $C_{1'}$ H), 7.88 ppm (d, J = 8 Hz, 1, C_6 H). Anal. Calcd for $C_{13}H_{14}N_2O_7$ (310.26): C, 50.32; H, 4.55; N, 9.03. Found: C, 50.14; H, 4.42; N, 9.05. The third fraction contained 30 mg (3%) of the starting material **1a** with mp 162–164 °C.

B. With Lewis Acid. To a solution of **1a** (2.0 g, 7.0 mmol) in dry AcOH (80 ml) were added $Si(OAc)_4$ (3.7 g, 14.0 mmol) and $ZnCl_2$ (1.9 g, 14.0 mmol). This mixture was heated at 75–80 °C for 6 h with stirring and then evaporated to dryness in vacuo. The residue was dissolved in cold H_2O (100 ml) and the solution was adjusted to pH 6.2 with $NaHCO_3$ (7 g). The resulting precipitate was removed by filtration (Celite) and the filtrate was applied to a column of activated charcoal (20 g). The column was washed with H_2O (1.5 l.) and eluted with EtOH–pyridine (4:1). The eluate (165 g) was evaporated to dryness in vacuo and the residue was crystallized from EtOH, giving 1.7 g (78%) of **6a** with mp 182–184 °C. This product was identical with the authentic sample prepared as above.

Reactions of Uridine (1b) with Tetraacetoxysilane in the Presence of Zinc Chloride. A. For 15 h. To a solution of uridine (2.0 g, 8.2 mmol) in dry AcOH (80 ml) were added $Si(OAc)_4$ (4.3 g, 16.4 mmol) and $ZnCl_2$ (2.2 g, 16.4 mmol). This mixture was heated at 75–80 °C for 15 h with stirring and evaporated to dryness in vacuo. The residue was worked up as described above to give a crystalline solid (**6a**:**6b** roughly 1:1 by NMR). This material was recrystallized from EtOH (50 ml) to give 0.52 g of pure 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil (**6b**). The mother liquor from the recrystallization was concentrated to dryness, and crystallization from H_2O (8 ml) gave 0.24 g of **6a** identical with the authentic sample obtained above. The combined mother liquors were separated into two major bands on preparative TLC by five developments with $CHCl_3$–MeOH (9:1). Elution of the faster moving band gave a further 0.29 g of **6a** (total yield 0.53 g, 21%). Elution of the slower moving band afforded a further 0.14 g of **6b** (total yield 0.66 g, 30%): mp 189–192 °C (reported[4a] mp 202–204 °C); λ_{max} (MeOH) 224 nm (ε 9700), 251 (7900); NMR δ 2.13 (s, 1, OAc), 2.4–2.6 (m, 2, $C_{5'}$ H_2), 4.2–4.5 (m, 1, $C_{4'}$ H), 5.12 (t, J = 4.5 Hz, $C_{5'}$ OH), 5.36 (br s, 1, $C_{3'}$ H), 5.46 (d, J = 6 Hz, 1, $C_{2'}$ H), 5.86 (d, J = 7.5 Hz, C_5 H), 6.40 (d, J = 6 Hz, 1, $C_{1'}$ H), 7.84 (d, J = 7.5 Hz, C_6 H). Anal. Calcd for $C_{11}H_{12}N_2O_6$ (268.22): C, 49.25; H, 4.51; N, 10.45. Found: C, 49.23; H, 4.63; N, 10.41.

B. For 48 h. To a solution of uridine (5.0 g, 0.021 mol) in dry AcOH (200 ml) were added $Si(OAc)_4$ (10.8 g, 0.041 mol) and $ZnCl_2$ (5.6 g, 0.041 mol). This mixture was heated at 75–80 °C for 48 h with stirring and evaporated to dryness in vacuo. The residue was processed in the usual way to give a syrup. Crystallization from EtOH gave 3.7 g (54%) of **6a**, mp 183–185 °C, identical with that above.

Reaction of Uridine with Tetraacetoxysilane in the Presence of Boron Trifluoride Etherate. To a stirred mixture of uridine (1.0 g, 4.1 mmol) and $Si(OAc)_4$ (2.2 g, 8.2 mmol) in dry AcOH (20 ml) was added BF_3·Et_2O (0.52 ml, 4.1 mmol). This mixture was heated at 50–55 °C for 7 h and then the solvent was evaporated to dryness in vacuo. The residue was dissolved in cold H_2O (30 ml) and the solution was adjusted to pH 6.0 with $NaHCO_3$. The mixture was evaporated to dryness in vacuo below 45 °C and the residue was triturated with hot MeOH (2 × 15 ml). The combined MeOH extract were filtered and concentrated in vacuo. The residual syrup was purified by preparative TLC using two developments with *n*-BuOH–H_2O (84:16) giving two major bands. Elution of the slower moving band with EtOH gave 0.83 g (65%) of **6a** with mp 179–182 °C and identical with that above. Elution of the faster moving band with the same solvent, followed by crystallization from *i*-PrOH, gave 0.17 g (11%) of 2′,3′,5′-tri-*O*-acetyluridine with mp 126–127 °C (reported[8] mp 128–130 °C). This material was identical with an authentic sample prepared by an alternate route.[8]

2′-Chloro-2′-deoxyuridine (8). To a solution of uridine (500 mg, 2.1 mmol) in dry AcOH (20 ml) was added $SiCl_4$ (0.47 ml, 4.1 mmol). The mixture was heated at 60–70 °C for 20 min with stirring and then refluxed for 3 h. The resulting clear solution was concentrated to dryness in vacuo and the residue was dissolved in 2 N NaOH (10 ml). After standing at room temperature for 1 h, the solution was neutralized with 2 N AcOH and the resulting mixture was filtered (Celite). The filtrate was passed through a column of Diaion SK-1B (H^+, 20 ml) and the column was washed with H_2O (300 ml). The combined eluate and washings were evaporated in vacuo to give a crystalline solid, which was recrystallized from MeOH to give 308 mg (58%) of **8**: mp 204–205 °C (reported mp 207–212,[19] 206–207 °C[14a]); λ_{max} (H_2O) 260 nm (ε 9800); NMR 3.5–3.8 (m, 2, $C_{5'}$ H_2), 3.8–4.1 (m, 1, $C_{4'}$ H), 4.1–4.4 (m, 1, $C_{3'}$ H), 4.4–4.7 (m, 1, $C_{2'}$ H), 5.22 (t, *J* = 5 Hz, 1, $C_{5'}$ OH), 5.70 (d, *J* = 8 Hz, 1, C_5 H), 5.85 (d, *J* = 5 Hz, 1, $C_{3'}$ OH), 6.04 ppm (d, *J* = 5 Hz, 1, $C_{1'}$ H). Anal. Calcd for $C_9H_{11}N_2O_5Cl$ (262.66): C, 41.15; H, 4.22; N, 10.66; Cl, 13.49. Found: C, 41.53; H, 4.35; N, 10.85; Cl, 13.45.

Reaction of 5-Bromouridine (9) with Tetrachlorosilane in Acetic Acid. To a suspension of **9**[23] (10 g, 0.031 mol) in dry AcOH (200 ml) was added $SiCl_4$ (7.1 ml, 0.062 mol). This mixture was refluxed for 6 h and then evaporated to dryness in vacuo. The residue was dissolved in 1 N HCl (200 ml) and the solution was heated at 90–95 °C for 30 min. The solvent was evaporated in vacuo and the residue was coevaporated several times with EtOH. The final residue was extracted with hot MeOH and the extract was filtered. Evaporation of the filtrate gave a syrup which was found to be a mixture of 2′-deoxy-2′-chloro-5-bromouridine (**10**) and 1-(3′-chloro-3′-deoxy-β-D-xylofuranosyl)-5-bromouracil (**11**) in a ratio of roughly 4:1 by NMR. Crystallization from H_2O followed by recrystallization from MeOH gave 3.17 g of pure **10**: mp 210–211 °C; λ_{max} (pH 6.9) 279 nm (ε 9700); NMR δ 3.70 (br s, 2, $C_{5'}$ H_2), 3.8–4.1 (m, 1, $C_{4'}$ H), 4.1–4.5 (m, 1, $C_{3'}$ H), 4.5–4.7 (m, 1, $C_{2'}$ H), 5.40 (t, *J* = 4 Hz, 1, $C_{5'}$ OH), 5.83 (d, *J* = 5 Hz, 1, $C_{3'}$ OH), 5.99 (d, *J* = 4 Hz, 1, $C_{1'}$ H), 8.55 (s, 1, C_6 H), 11.88 (br s, 1, NH). Anal. Calcd for $C_9H_{10}N_2O_5BrCl$ (341.58): C, 31.65; H, 2.95; N, 8.20. Found: C, 31.80; H, 3.11; H, 8.27. Storage of the original H_2O washings in a refrigerator gave 0.08 g of **11**, mp 207–208 °C. Recrystallization from MeOH gave analytically pure **11**: mp 208–209 °C; λ_{max} (pH 6.9) 280 nm (ε 9200); NMR 3.74 (br s, 2, $C_{5'}$ H_2), 4.2–4.6 (m, 3, $C_{2'}$ H, $C_{3'}$ H, and $C_{4'}$ H), 5.2 (br s, 1, OH), 5.70 (d, *J* = 3 Hz, 1, $C_{1'}$ H), 6.3 (br s, 1, OH), 8.18 (s, 1, C_6 H), 11.9 (br s, 1, NH). Anal. Calcd for $C_9H_{10}N_2O_5BrCl$: C, 31.65; H, 2.95; N, 8.20. Found: C, 31.67; H, 3.09; N, 8.28. The repeated fractional crystallization of the crystals recovered from the combined mother liquors gave a further 0.42 g of **10** (total yield 3.59 g, 34%) and 0.11 g of **11** (total yield 0.19 g, 2%).

1-(3′-Chloro-3′-deoxy-β-D-xylofuranosyl)uracil (12). To a solution of **11** (510 mg, 1.49 mmol) in MeOH (100 ml) were added $BaCO_3$ (440 mg) and 5% palladium on charcoal (180 mg). This mixture was hydrogenated under atmospheric pressure at 25 °C for 1 h. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was dissolved in H_2O and the solution was applied to a column of activated charcoal (4 g). The column was washed with H_2O (300 ml) and eluted with EtOH–pyridine (4:1). The eluate (100 g) was concentrated to dryness in vacuo and the residue was dissolved in $CHCl_3$. The solution was applied to a column of silica gel (5 g) and the desired product was eluted with $CHCl_3$–MeOH (9:1) giving 290 mg (74%) of **12**. An analytical sample from methyl *n*-propyl ketone had mp 171–172 °C; λ_{max} (MeOH) nm 262 (ε 10 600); NMR 3.77 (br s, 2, $C_{5'}$ H_2), 4.2–4.6 (m, 3, $C_{2'}$ H, $C_{3'}$ H, and $C_{4'}$ H), 5.07 (t, *J* = 5 Hz, $C_{5'}$ OH), 5.63 (d, *J* = 4 Hz, 1, $C_{1'}$ H), 5.68 (d, *J* = 8.5 Hz, 1, C_5 H), 6.27 (d, *J* = 5 Hz, 1, $C_{2'}$ OH), 7.74 (d, *J* = 8.5 Hz, C_6 H), 11.38 (br s, 1, NH). Anal. Calcd for $C_9H_{11}N_2O_5Cl$ (262.67): C, 41.15; H, 4.22; N, 10.66; Cl, 13.50. Found: C, 41.42; H, 4.34; N, 10.52; Cl, 13.86.

Reaction of 12 with Sodium Methoxide. To a suspension of **12** (100 mg, 0.39 mmol) in MeOH (0.5 ml) was added 2 N methanolic MeONa (0.38 ml, 0.76 mmol). The resulting clear solution was stirred at room temperature for 48 h, acidified with AcOH, and evaporated in vacuo. The residue was crystallized from H_2O to give 55 mg (64%) of **14**, mp 238–239 °C dec. This material was identical with an authentic sample of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil prepared by a different route[9] in the criteria of infrared and ultraviolet spectra.

Reactions of Cytidine with Tetrachlorosilane. A. Without Lewis Acid. To a solution of cytidine (3 g, 0.012 mol) in dry AcOH (30 ml) was added with stirring $SiCl_4$ (2.84 ml, 0.025 mol). The mixture was heated at 60–70 °C for 30 min and then refluxed for 3 h. The solvent was evaporated to dryness in vacuo and the residue was applied to a column of silica gel (90 g). The column was eluted with *n*-BuOH–H_2O–AcOH (5:2:1, 700 ml). The eluate was evaporated in vacuo below 40 °C and the residue was repeatedly coevaporated with H_2O. Crystallization of the residue from EtOH gave 1.2 g (32%) of 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**16a**, X = Cl): mp 243–244 °C dec (reported mp 254–255 °C dec[12c]); λ_{max} (EtOH) 234 nm (ε 10 000), 265 (10 900); NMR δ 3.3–3.6 (m, 2, $C_{5'}$ H_2), 4.48 (br s, 1, $C_{4'}$ H), 5.40 (br s, 1, $C_{3'}$ H), 5.68 (d, *J* = 6 Hz, 1, $C_{2'}$ H), 6.64 (d, *J* = 6 Hz, 1, $C_{1'}$ H), 6.75 (d, *J* = 7.5 Hz, 1, C_5 H), 8.32 (d, *J* = 7.5 Hz, C_6 H). Anal. Calcd for $C_{11}H_{14}N_3O_5Cl$ (303.7): C, 43.50; H, 4.65; N, 13.84; Cl, 11.68. Found: C, 43.34; H, 4.82; N, 13.62; Cl, 11.18. The mother liquors from the crystallization were evaporated and the residue was chromatographed on a column of silica gel (80 g). The required fraction was eluted with $CHCl_3$–MeOH (3:1, 600 ml). The eluate was evaporated and the residue was crystallized from EtOH, giving 0.41 g (14%) of 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**16b**) with mp 217–219 °C dec. Recrystallization from EtOH gave analytically pure **16b**: mp 220–222 °C dec; λ_{max} (EtOH) 236 nm (ε 10 300), 264 (11 500); NMR δ 1.88 (s, 1, OAc), 2.12 (s, 1, OAc), 4.07 (br s, 1, $C_{5'}$ H_2), 4.5–4.8 (br s, 1, $C_{4'}$ OH), 5.40 (br s, 1, $C_{3'}$ H), 5.77 (d, *J* = 6 Hz, 1, $C_{2'}$ H), 6.67 (d, *J* = 6 Hz, 1, $C_{1'}$ H), 6.82 (d, *J* = 7.5 Hz, 1, C_5 H), 8.39 (d, *J* = 5 Hz, 1, C_6 H). Anal. Calcd for $C_{13}H_{16}N_3O_6Cl$ (345.75): C, 45.16; H, 4.67; N, 12.15; Cl, 10.26. Found: C, 45.14; H, 4.89; N, 12.00; Cl, 10.25. In a separate experiment, the crude product from the reaction of cytidine with $SiCl_4$ in AcOH was dissolved in H_2O (50 ml). The solution was applied to a column of Diaion SK-1B (H^+, 200 ml). The column was washed with H_2O (4 l.) and then with MeOH (1 l.). The resin was suspended in MeOH (250 ml). The mixture was refluxed with vigorous stirring for 30 min and cooled, and the resin was packed again in a column. The column was eluted with 0.5 M pyridinium formate (pH 4.8, 3 l.), and evaporation of the eluate gave a solid foam which was crystallized from EtOH to give 8.1 g (72%) of 2,2′-anhydro-1-(β-D-arabinofuranosyl)-cytosine formate (**17a**, X = HCO_2): mp 173–176 °C dec (reported mp 173–174 °C dec[26]); uv λ_{max} (MeOH) 233 nm (ε 12 300), 264 (13 000); NMR δ 3.37 (br s, 2, $C_{5'}$ H_2), 4.24 (br s, 1, $C_{4'}$ H), 4.52 (br s, 1, $C_{3'}$ H), 5.45 (d, *J* = 6 Hz, 1, $C_{2'}$ H), 6.55 (d, *J* = 6 Hz, 1, $C_{1'}$ H), 6.68 (d, *J* = 7 Hz, 1, C_5 H), 7.1–8.7 (br s, 2, OH), 8.27 (d, *J* = 7 Hz, 1, C_6 H), 8.52 (s, 1, HCO_2). Anal. Calcd for $C_{10}H_{13}O_6N_3$ (271.23): C, 44.28; H, 4.83; N, 15.49. Found: C, 44.28; H, 5.02; N, 15.37.

B. With Lewis Acid. To a solution of cytidine (2 g, 8.2 mmol) in dry AcOH (120 ml) was added with stirring $SiCl_4$ (1.89 ml, 16.5 mmol). The mixture was refluxed for 1 h and then BF_3·Et_2O (1.04 ml, 8.23 mmol) was added. Refluxing was continued for 1 h and the solvent was evaporated in vacuo. The residue was applied to a column of silica gel (60 g). Elution with $CHCl_3$–MeOH (7:3, 400 ml) gave an oily material, which was dissolved in H_2O (15 ml). The solution was passed through a column of Diaion SA-11B (Cl^-, 50 ml) and the column was washed with H_2O (150 ml). The combined eluate and washings were evaporated to dryness in vacuo and crystallization of the residue from EtOH gave 1.36 g (48%) of **16b** with mp 217–218 °C. This compound was identical with the sample prepared as above.

Reaction of Cytidine with Tetraacetoxysilane. To a solution of cytidine (10 g, 0.0412 mol) in dry AcOH (400 ml) was added with stirring $Si(OAc)_4$ (21.8 g, 0.0824 mol) and BF_3·Et_2O (7.8 ml, 0.0618 mol). The mixture was heated at 60–70 °C for 30 min and then refluxed for 30 min. The solvent was evaporated to dryness in vacuo and the residue was dissolved in ice–water (200 ml). The solution was filtered (Celite) and the filtrate was worked up as above to give 5.5 g of **17a** (X = HCO_2) with mp 173–174 °C dec which was identical with a sample prepared as above. Evaporation of the mother liquors from the crystallization of **17a** (X = HCO_2) followed by fractional crystallization from EtOH gave a further 1.2 g of **17a** (X = HCO_2) (total yield 6.7 g, 61%).

2,2′-Anhydro-1-(β-D-arabinofuranosyl)-5-bromocytidine

(17b). To a solution of **15b**[30] (5.0 g, 15.5 mmol) in dry AcOH (50 ml) was added with stirring $SiCl_4$ (3.6 ml, 31 mmol). The mixture was heated at 60–70 °C for 20 min and then refluxed for 2.5 h. The mixture was proccessed as described for the preparation of **17a** (X = HCO_2) to give 3.0 g of crude **17b** (X = HCO_2). The formate was dissolved in H_2O (15 ml) and passed through a column of Amberlite IRA-400 (Cl^-, 100 ml), and the column was washed with H_2O (150 ml). The combined eluate and washings were evaporated, and the residue was recrystallized from 80% EtOH to give 2.3 g (43%) of **17b** (X = Cl): mp 218–220 °C dec (reported mp 217 °C dec,[31a] 230 °C dec[14c]); λ_{max} (pH 7.2) 235 nm (sh, ϵ 8500), 280 (9600); NMR 3.3–3.5 (m, 2, $C_{5'}$ H_2), 4.1–4.4 (m, 1, $C_{4'}$ H), 4.4–4.6 (m, 1, $C_{3'}$ H), 5.12 (t, J = 5 Hz, 1, $C_{5'}$ OH), 5.49 (d, J = 6 Hz, 1, $C_{2'}$ H), 6.29 (d, J = 4.5 Hz, 1, $C_{3'}$ OH), 6.58 (d, J = 6 Hz, 1, $C_{1'}$ H), 8.00 (s, 1, C_6H). Anal. Calcd for $C_9H_{11}N_3O_4BrCl$ (340.59): C, 31.73; H, 3.25; N, 12.33. Found: C, 31.90; H, 3.33; N, 12.26.

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Registry No. —**1a,** 6773-44-0; **1b,** 58-96-8; **4,** 6773-48-4; **6a,** 28309-53-7; **6b,** 38642-32-9; **8,** 4753-04-2; **9,** 957-75-5; **10,** 55612-19-6; **11,** 59588-21-5; **12,** 59588-22-6; **14,** 3736-77-4; **15a,** 65-46-3; **15b,** 3066-86-2; **16a** (X = Cl), 50896-83-8; **16b** (X = Cl), 50896-84-9; **17a** (X = HCO_2), 26790-12-5; **17b** (X = Cl), 40502-95-2; **17b** (X = HCO_2), 59653-50-8; $Si(OAc)_4$, 562-90-3; 2′,3′,5′-tri-*O*-acetyluridine, 4105-38-8; $SiCl_4$, 10026-04-7.

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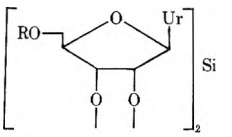

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C-Glycosyl Nucleosides. 9.[1] An Approach to the Synthesis of Purine-Related C-Glycosides

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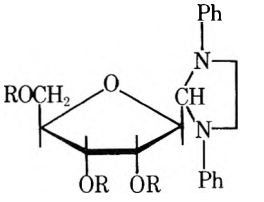
Several approaches to the synthesis of 4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-3(5)-carbomethoxypyrazole (**4b**) have been investigated. One route involves conversion of 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose to the C-glycosyl acrylate **3** via a Wittig reaction followed by cycloaddition of diazomethane and dehydrogenation with chlorine. Alternatively **4b** could be directly prepared via cycloaddition of diazomethane to methyl 3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)propiolate (**16a**). Condensation of 2,3,5-tri-*O*-benzyl-D-ribose with a Grignard reagent derived from propiolic acid gave, after esterification, an essentially stereoselective synthesis of methyl 5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*altro*-oct-2-ynonate (**7a**). Reaction of this material with diazomethane followed by acid-catalyzed cyclization gave the desired **4b**. While acid-catalyzed cyclization of **7a** was unsuccessful, reaction with methyltriphenoxyphosphonium iodide gave **16a** together with a number of isomeric products. Characterization of these substances was achieved by conversion to pyrazole derivatives and by use of ^{13}C NMR spectroscopy. The pyrazole ester **4b** was converted into a 3-aminopyrazole via a Curtius reaction on the acyl azide. Cyclization with phenoxycarbonyl isocyanate followed by debenzylation with boron trichloride gave the purine-related C-glycoside 2,4-dioxo-8-β-D-ribofuranosyl-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine.

The natural occurrence of a number of *C*-glycosyl nucleosides,[3] some of which possess antibiotic or antitumor activities, has stimulated much recent effort toward the synthesis of this class of compound. In some cases a direct forging of the critical C–C glycosyl linkage has been successfully accomplished via condensation of an appropriate carbohydrate derivative with a suitably activated heterocyclic component.[4] A much more versatile route, however, involves the synthesis of functionally substituted anhydro sugar derivatives, already containing the elusive *C*-glycosyl bond, that can be further elaborated into a variety of heterocyclic substituents.[5] Our own activities have centered about this latter approach and have led to the development of efficient syntheses of a number of differently protected derivatives of 2,5-anhydro-D-allose.[6] The latter compounds have then been elaborated into a variety of maleimide,[1,7] pyrazole,[8] isoxazole,[9] and 1,2,4-oxadiazole[8b] *C*-glycosides. In addition, we have developed stereochemically controlled methods for the synthesis of other functionally substituted anhydro sugars.[10] These compounds, which have also been briefly reported on by others,[11] provide attractive intermediates for the synthesis of further *C*-glycosyl nucleosides.[12]

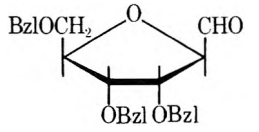
While the above methods have been rather successful for the synthesis of five- and six-membered heterocyclic ring *C*-glycosides, the development of routes leading to condensed heterocyclic *C*-glycosides related to purine nucleosides has been considerably more difficult. Quite facile routes to 2- and 8-ribofuranosyladenines and their sugar analogues are available,[13] but the preparation of the more interesting purine nucleoside analogues in which the *C*-glycosyl linkage is adjacent to the heterocyclic ring junction is challenging. Toward this end, elegant syntheses of formycin B[5a] and oxoformycin[5c] have been achieved.

One attractive approach to the above problem involves the annulation of a fused pyrimidine ring onto one of the 4-(β-D-ribofuranosyl)pyrazoles that we have previously described.[8] The readily available 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3(5)-carbomethoxypyrazole (**4a**) appeared to be a suitable starting material if the carbomethoxyl group could be converted into an amino function via the Curtius reaction.[14] Unfortunately, as has been pointed out previously,[8] the carbomethoxyl group of **4a** is relatively nonreactive toward amidation and accordingly we have been unable to convert **4a** into the requisite hydrazide. Upon reaction with hydrazine under a variety of conditions a number of products were obtained, presumably due to side reactions with the benzoate functions. Accordingly, it was decided to prepare 4-(tri-*O*-benzyl-β-D-rihofuranosyl)-3(5)-carbomethoxypyrazole (**4b**), a compound in which the sugar protecting groups should be completely stable.

We have previously described the preparation of 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose (**2**) via benzylation of



1a, R = H
b, R = $CH_2C_6H_5$(Bzl)
c, R = COC_6H_5



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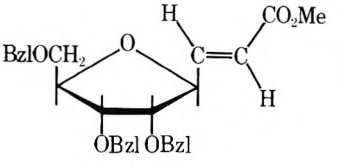

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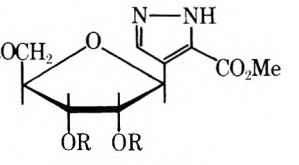


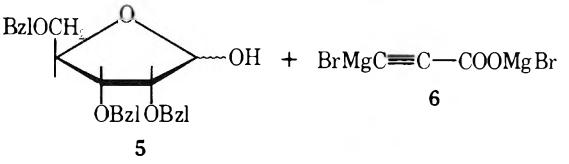
4a, R = COC_6H_5
b, R = $CH_2C_6H_5$
c, R = H

1,3-diphenyl-2-(β-D-ribofuranosyl)imidazolidine (**1a**) using benzyl chloride and sodium hydride in dimethyl sulfoxide followed by mild acidic hydrolysis.[6] This method, however, required purification of the fully protected intermediate **1b** by chromatography on silicic acid. We have now found that by conducting the benzylation with benzyl bromide in dimethylformamide at room temperature the chromatographic step is unnecessary and crystalline **1b** can be directly obtained in 84% yield. An improved procedure for the preparation of **1a** from its tri-*O*-benzoyl precursor **1c** without the necessity of chromatography is also to be found in the Experimental Section. The free aldehyde **2** was liberated from its imidazolidine derivative **1b** by treatment with *p*-toluenesulfonic acid monohydrate[6] and reacted with carbomethoxymethylenetriphenylphosphorane giving methyl *trans*-4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*allo*-oct-2-enonate (**3**) in essentially quantitative yield. The ^1H NMR spectrum of **3** confirms that the trans olefin ($J_{2,3}$ = 15.5 Hz) was the predominant product. Subsequent treatment of **3** with an excess of diazomethane in ether at room temperature gave an in-

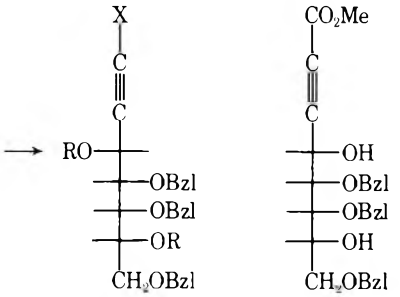
termediate 2-pyrazoline that was not purified, but rather directly treated with chlorine in carbon tetrachloride[8a] giving 4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-3(5)-carbomethoxypyrazole (**4b**) in 72% yield. The ^{1}H NMR spectrum of **4b** shows the pyrazole ring proton[15] as a singlet at 7.91 ppm, a figure very similar to that previously reported for **4a** (7.87 ppm)[8] and supporting the well-established principal mode of 1,3-dipolar cycloaddition.[16] There was no indication of any product resulting from inverse addition of diazomethane giving a 4-methoxycarbonyl-3-β-D-ribofuranosylpyrazole. Debenzylation of **4b** using boron trichloride in methylene chloride at −78 °C gave crystalline **4c** identical with that prepared from the tribenzoate[8] in 77% yield.

While the procedure described above for the preparation of **4b** via the glycosylacrylate **3** was quite efficient on a small scale, we have found the chlorine oxidation of the intermediate pyrazoline to be rather capricious, giving quite variable yields of **4b** when scaled up. Accordingly, we were also interested in examining an alternate synthesis via direct 1,3-dipolar cycloaddition of diazomethane to an acetylenic ester. In a previous paper[8] we reported an attempt to prepare such a 3-β-D-ribofuranosylpropiolate via condensation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide with the silver derivative of methyl propiolate. The 2-*O*-benzoyl group, however, participated in the displacement of the 1-bromide and a 1,2-α-ethynylbenzylidene derivative was formed rather than the desired glycosylethyne. The use of a 2-*O*-benzyl protecting group should avoid this problem, but recent extensive work by Buchanan et al.[17] has shown that the condensation of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl halides with either Grignard or silver derivatives of acetylenes leads predominantly to the undesired α-D-ribofuranosylalkynes. On the other hand, subsequent to completion of our work, it has recently been reported that the related condensation of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl chloride with the silver derivative of ethyl propiolate leads primarily to the desired 3-β-D-ribofuranosylpropiolate.[18]

The probability that condensations of metal derivatives of propiolates with 2,3,5-tri-*O*-benzyl-D-ribofuranosyl halides will lead to α-*C*-glycosides[17] led us to first explore an alternate route in which the first step would be the reaction of 2,3,5-tri-*O*-benzyl-D-ribofuranose (**5**)[19] with the Grignard reagent derived from methyl propiolate. Preliminary experiments using the reagent prepared from equimolar amounts of methyl propiolate and ethylmagnesium bromide, however, suggest that side reactions are prevalent, probably due to self-condensation. Accordingly, we have preferred to react **5** with the reagent **6**[20] derived from propiolic acid and 2 equiv of ethylmagnesium bromide. The crude, acidic product **7c** from this reaction at room temperature was directly converted to its methyl esters by treatment with methanol and benzene in the presence of *p*-toluenesulfonic acid and then purified by chromatography on silicic acid. In this way an analytically pure, but noncrystalline, adduct was isolated in 73% yield. Unfortunately, the ^{1}H NMR spectrum of this substance is rather unrevealing since the benzyl resonances are superimposed upon those of several of the sugar protons. Only a single methyl ester singlet was apparent at 3.73 ppm, and while the compound appears homogeneous we could not rule out the presence of a trace of a second isomer. The ^{13}C NMR spectrum run on a rather large sample was very clean and gave no indication of the presence of a second isomer. Acetylation of the acetylenic ester **7a** with acetic anhydride and pyridine was relatively slow and accompanied by formation of some unidentified by-products. On the other hand, a comparable acetylation in the presence of a catalytic amount of 4-dimethylaminopyridine[21] was complete within 1 h at room temperature and gave a single spot product by TLC analysis. Following chromatographic isolation a TLC homogeneous diacetate was isolated as an oil in 82% yield and once again appeared to be a single isomer by ^{1}H and ^{13}C NMR analysis. Only the presence of a very small signal at 1.99 ppm in the ^{1}H NMR spectrum suggested the possible existence of another acetylated species. The closely related condensation of **5** with ethynylmagnesium bromide has been shown by degradative studies to lead predominantly (70%) to the D-*altro*-ethynylpentitol **7d**[17a] and this has been rationalized by consideration



5 **6**



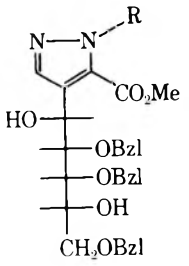
7a, X = CO_2Me, R = H
b, X = CO_2Me, R = Ac
c, X = COOH, R = H
d, X, R = H

8

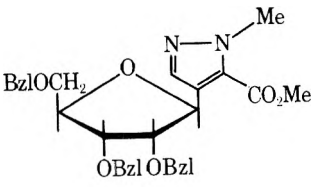
of the rules of asymmetric induction derived by Cram[22a] and Karabatsos.[22b] A direct extrapolation of these considerations leads us to believe that the present compound is essentially pure methyl 5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*altro*-oct-2-ynonate (**7a**), although the presence of a trace of the D-allo isomer cannot be excluded.

In an effort to confirm the stereochemistry of **7a** we have attempted to decarboxylate the precursor acetylenic acid **7c** to the previously characterized **7d**.[17a] Upon heating **7c** in benzene under reflux, however, a number of neutral products were formed and no conclusions could be reached. Various attempts to acetylate the free hydroxyl groups in **7c** under either basic or acidic conditions led to extensive decomposition.

A copious literature exists concerning the cyclization of 1,4-diols to the corresponding tetrahydrofurans via treatment with anhydrous acids[23] or suitable sulfonyl chlorides in the presence of a base.[17,24] The acid-catalyzed cyclization is particularly facile when one of the hydroxyl groups is activated by being benzylic or allylic in nature.[4a] Unfortunately, treatment of **7a** with either *p*-toluenesulfonic acid in benzene under reflux or with 2.2 equiv of *p*-toluenesulfonyl chloride in pyridine at 60 °C[17] led to mixtures of products most of which no longer contained an acetylene function as judged from their infrared spectra. Accordingly, **7a** was first reacted with an excess of diazomethane in ether at 0 °C giving two pyrazoles in a ratio of roughly 10:1. These compounds were separated by preparative TLC and the major product was isolated in 76% yield. By a combination of the usual spectroscopic and analytical techniques this crystalline compound was shown to be the expected 4-(2,3,5-tri-*O*-benzyloxy-1,4-dihydroxy-D-*altro*-pent-1-yl)-3(5)-carbomethoxypyrazole (**9a**). The D-altro configuration of **9a** is based upon the assumed structure of **7a** and is supported by its ORD spectrum. It is well established that the ORD spectra of a variety of heterocyclic polyols derived from sugars are predominantly dependent upon the chirality of the carbinol adjacent to the heterocycle,[25] those with an *R* configuration showing a negative Cotton effect. The ORD spectrum of **9a** only showed a large trough at 267 nm, the low-wavelength region being



9a, R = H
b, R = Me



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poorly defined, probably due to the presence of the benzyl ethers. This nevertheless suggests a negative Cotton effect centered about 220 nm (λ_{max} for **4c** is 219 nm[8a]) and supports the D-altro configuration for **7a**. A second pyrazole was also isolated in 7% yield and shown by ^{1}H NMR spectroscopy to contain an *N*-methyl group which appeared as a singlet at 4.06 ppm. It is well known that N-methylation of pyrazoles can be achieved using a variety of alkylating agents including diazomethane.[16] In particular, the methylation of pyrazoles bearing electron-withdrawing substituents at the 3(5) position almost inevitably occurs on the nitrogen adjacent to that substituent.[16] Hence we consider this by-product to be the 1-methyl derivative **9b** arising by methylation of the initially formed **9a** by excess diazomethane. In support of this, we find that treatment of **7a** with an excess of diazomethane at room temperature for longer periods leads to the formation of the *N*-methylpyrazole **9b**. Further confirmation of the site of N-methylation will be presented later in this paper.

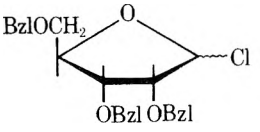
While acid-catalyzed cyclization of **7a** was not successful, treatment of **9a** with an excess of *p*-toluenesulfonic acid monohydrate in benzene under reflux for 17 h led to the smooth formation of a less polar product that no longer showed hydroxyl absorptions in its ir spectrum. By chromatography on silicic acid an 85% yield of the β-D-ribofuranosylpyrazole **4b** was isolated and shown to be identical (ir, ^{1}H and ^{13}C NMR spectra) with the compound prepared via the 3-β-D-ribofuranosylacrylate **3**. This identity confirms the β-D-ribofuranosyl structure for **4b**, the route of synthesis via **5** → **9** → **4b** being quite competitive or even superior to that via **2** and **3**.

The related cyclization of **9b** was also achieved using *p*-toluenesulfonic acid in benzene and gave crystalline 4-(2,3,5-tri-*O*-benzyl-5-carbomethoxymethyl-1-methylpyrazole (**10**) in 77% yield. The latter compound was found to be identical with the product slowly formed, and isolated in 42% yield, from the reaction of **4b** with an excess of diazomethane at room temperature for 3 days.

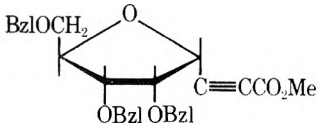
Recently, ^{13}C NMR spectroscopy has been shown to provide a convenient tool for determination of the position of N-alkylation in heterocycles.[26] Thus alkylation of a nitrogen leads to a substantial upfield shift of the adjacent carbons (α shift) and to a variable downfield shift of the β carbons. In the present case, the ^{13}C chemical shifts of the pyrazole ring carbons in **4b** are readily assigned by comparison with the spectra of other pyrazoles.[27] C_3 being immediately identified by being the only doublet in the nondecoupled spectrum. The *N*-methyl derivative (**10**) showed a 7.94-ppm upfield shift of C_5 and a 5.42-ppm downfield shift of C_3, both being related to the shifts reported for 1-methylpyrazole[27] and confirming the site of alkylation. It should also be noted that while the ^{13}C NMR spectrum of **9b** and **10** showed very sharp signals for the pyrazole ring carbons, the spectra of the nonmethylated compounds (e.g., **9a**) showed broadened signals, presumably as a consequence of tautomeric equilibria.

It is interesting to note that acid-catalyzed cyclization of **9a** and **9b** to the β-D-ribofuranosylpyrazoles **4b** and **10** appears to be a stereoselective process leading to inversion of configuration at $C_{1'}$. This same observation was previously reported during acid-catalyzed cyclization of 5-(D-*altro*-pentahydroxypentyl)uracil to β-pseudouridine.[4a] In the uracil series, cyclization of the related D-*allo*-pentitol led predominantly to α-pseudouridine, suggesting that the cyclization involved direct SN2 displacement of the protonated $C_{1'}$ hydroxyl rather than proceeding through a common, allylically stabilized carbonium ion. In the present work we have not had the D-allo isomer of **9a** available and hence can come to no firm conclusions regarding the mechanism of this cyclization.

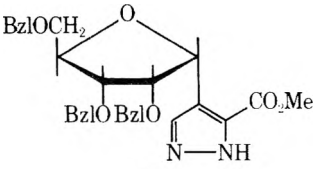
In the pseudouridine series, acid-catalyzed cyclization was followed by a slower anomerization of the *C*-glycosyl linkage.[4a,28] We observed no comparable isomerization of **4b** to its α anomer (**13**) during cyclization of **9a**, but in order to clarify this point it was of interest to have a sample of pure 4-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)-3(5)-carbomethoxypyrazole (**13**) available. Previous work[17] has shown that condensation of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride (**11**, largely β)[29] with metal acetylides leads predominantly to the α-D-ribofuranosylalkynes. Accordingly, **11** was reacted with the propiolic acid Grignard derivative **6** in tetrahydrofuran at room temperature. Following the isolation of acidic materials by a partition process the crude reaction product was then converted into the methyl esters by treatment with methanol and benzene in the presence of *p*-toluenesulfonic acid. The overall yield of neutral products was not very good in this process and preparative TLC allowed the isolation of a hydroxyl-free acetylenic ester in only 27% yield. This reaction has not, however, been optimized. The product was homogeneous by TLC and NMR (^{1}H and ^{13}C) and by analogy with the work of Buchanan is considered to be methyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*altro*-oct-2-ynonate (**12**). Very recently,[17b] Buchanan et al. have briefly described the condensation of **11** with the silver derivative of methyl propiolate and obtained **12**, and its D-allo isomer **16a**, in a ratio of 2:1.



11



12

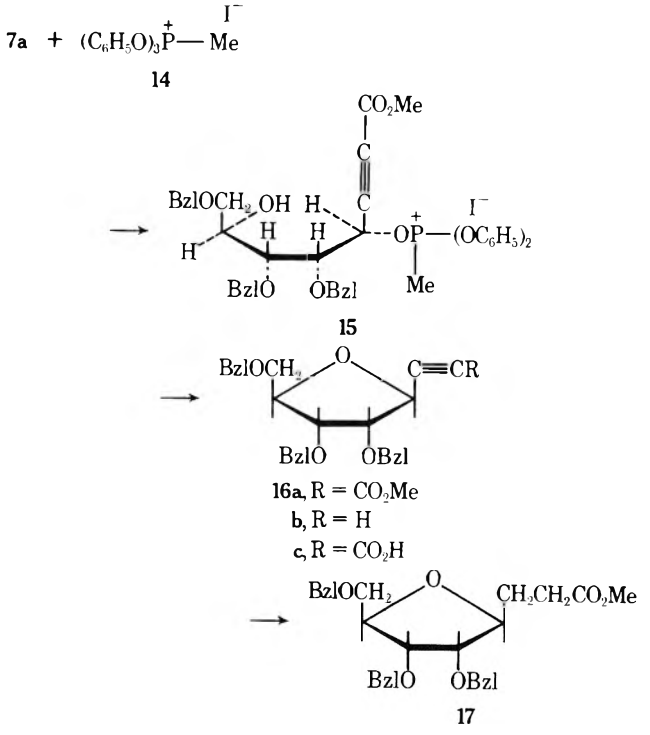


13

Treatment of **12** with diazomethane in ether at 0 °C led to the isolation, in 58% yield, of 4-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)-3(5)-carbomethoxypyrazole (**13**). The latter compound was clearly separable from its less polar β anomer **4b** by TLC and, since the method of synthesis would be expected to lead to structural ambiguity only at the "anomeric" carbon, its assigned α-D-ribofuranosyl structure seems assured. No equilibration of **4b** and **13** was observed upon treatment of either compound with *p*-toluenesulfonic acid in benzene under reflux for 16 h.

While attempted conversion of **7a** to furanose ring derivatives via treatment with either *p*-toluenesulfonic acid in benzene or *p*-toluenesulfonyl chloride in pyridine were unsuccessful, we considered that this transformation might be accomplished by conversion of one of the hydroxyl groups to a reactive, positively charged derivative. With this in mind **7a** was reacted with methyltriphenoxyphosphonium iodide (**14**)[30] in dimethylformamide at room temperature but led to only

a complex mixture of products. A comparable reaction between **7a** and **14** in methylene chloride was considerably

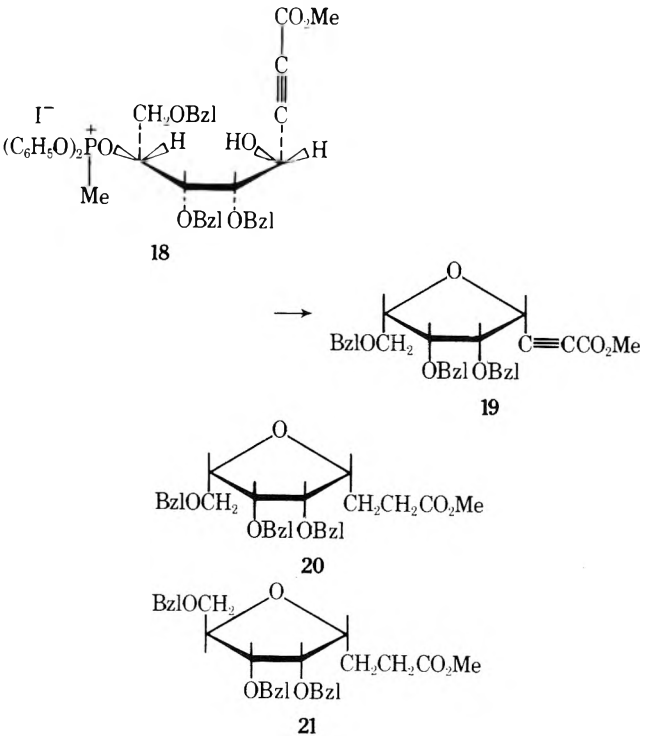


slower but led to the clean formation of two major and three minor carbohydrate products together with the expected diphenyl methylphosphonate and phenol. By chromatography on silicic acid the carbohydrate products were isolated in homogeneous form, and three of them were shown by ir and NMR (^{1}h and ^{13}C) analysis to correspond to the desired tetrahydrofuran derivatives. The two major products, isolated in yields of 33 and 19%, corresponded to the most polar and least polar of these products, respectively, while three minor products were of intermediate mobility.

The authentic α-D-ribofuranosylpropiolate **12**[31] corresponded to one of the minor products upon TLC and NMR examination and was obtained in only 2% yield. The less polar of the major products was shown to be the desired β-D-ribofuranosylpropiolate **16a** by several means. Thus, reduction of **16a** with diimide,[32] generated from potassium azodicarboxylate and acetic acid in pyridine,[33] was shown to give the same methyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*allo*-octonate (**17**) that was obtained by comparable reduction of the acrylate **3**. Also, the reaction of **16a** with diazomethane gave, in 83% yield, a pyrazole that was chromatographically and spectroscopically identical with **4b**. Finally, **16a** was hydrolyzed and the resulting propiolic acid was decarboxylated by heating in benzene as described by Buchanan et al.[17b] The resulting crystalline 3,6-anhydro-4,5,7-tri-*O*-benzyl-1,2-dideoxy-D-*allo*-hept-1-ynitol (**16b**) was found to be identical (ir, NMR, TLC, and melting point) with an authentic sample kindly provided by Dr. Buchanan.[17a] It therefore appears that the stereochemistry of the 3-ribofuranosylpropiolates with the α (**12**) and β (**16a**) configurations obtained in the above cyclization reaction is on safe grounds. It should be noted, however, that the optical rotation observed for **16a** was 25° less positive than that reported by Buchanan et al.[17b] The rotation we report has been consistent from several different preparations and we cannot readily explain this difference. It may be noted, however, that the values of $[\alpha]_D$ for these compounds vary widely in different solvents.

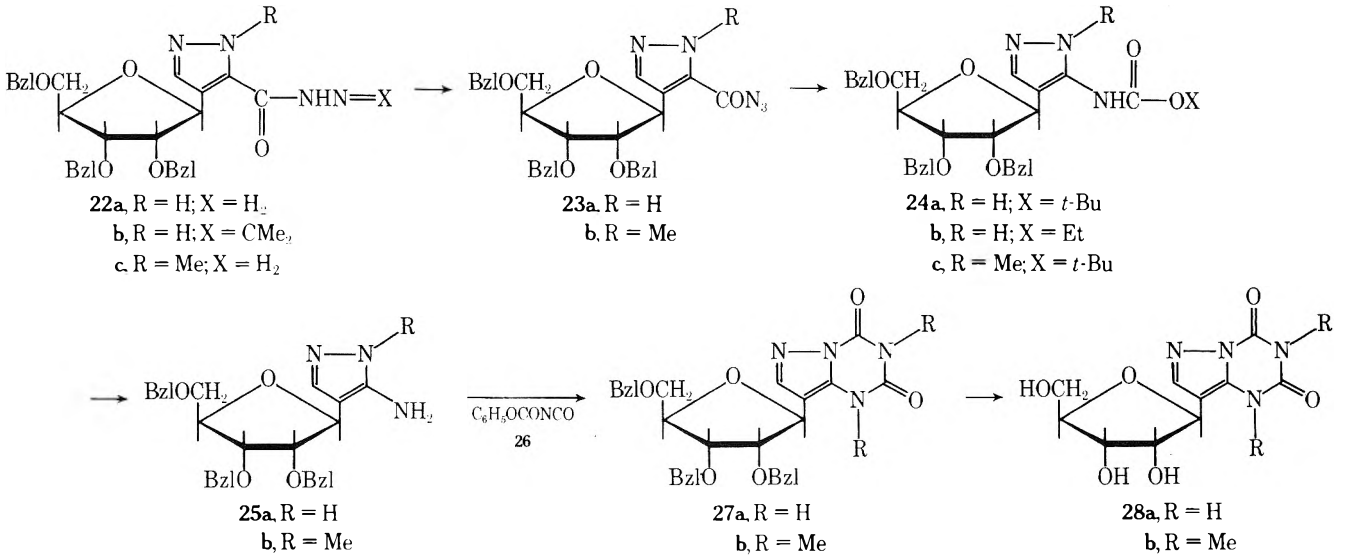
The two remaining minor products, each isolated in only 1% yield, were shown by ir spectroscopy to still contain a free hydroxyl group. While these compounds have not been rigorously characterized, one would appear to be an iodo sugar since its ^{13}C NMR spectrum showed a resonance at unusually high field (2.7 ppm).[34] The second product showed the presence of both an acetylene (ir 2240 cm^{-1}) and a vinyl proton as a doublet at 6.97 ppm. Purely on the basis of this evidence we tentatively suggest this compound to be methyl 5,6,8-tri-*O*-benzyl-2,3,4-trideoxy-D-*erythro*-oct-4-en-2-ynonate resulting from an elimination reaction.

The mechanism of the above cyclization must proceed through initial reaction between a free hydroxyl group of **7a** and the reagent **14** giving an oxyphosphonium intermediate such as **15**. Both the inductive effect of the acetylene and its relatively small steric bulk suggested to us that the C_4 hydroxyl of **7a** would be the principal site of reaction with **14** leading to the intermediate **15**. Direct SN2 displacement of diphenyl methylphosphonate by the C_7 hydroxyl group would then give the β-D-ribofuranosyl product **16a**. A similar activation of the C_4 hydroxyl group in any of the D-allo compound **8** that could be present as a minor contaminant of **7a** would lead to the α-D-ribofuranosyl product **12**. The possibility that cyclization proceeds via initial conversion of **15** to the 4-iodo compound with inversion of configuration seems unlikely since the major product from **7a** by this pathway would be **12**. Alternatively, reagent **14** could attack the C_7 hydroxyl of **7a** giving the intermediate **18**, and subsequent SN2 attack at C_7



by the C_4 hydroxyl of **18** would then lead to methyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-L-*galacto*-oct-2-ynonate (**19**, 3-β-L-lyxofuranosyl propiolate). Neither of these pathways is clearly predominant since **16a** and **19** are both formed in substantial amounts in this reaction. Once again, diimide reduction of **19** and **12** cleanly gave the saturated esters **20** and **21**, respectively.

Unfortunately, the use of ^{1}H NMR spectroscopy has proved to be of minimal use for configurational assignments to the compounds described in the present work. The methylene protons of the benzyl ethers are generally nonequivalent and the resulting doublets are superimposed over a large portion of the pertinent sugar proton resonances. With the exception of well-defined signals due to methyl esters, and sometimes $C_{5'}$ and $C_{1'}$ protons, it is usually difficult to even ensure



chemical homogeneity from the ^1H NMR spectra alone. Hence the use of ^{13}C NMR spectra has been of critical importance in determination of chemical purity since resonances due to most of the nonbenzylic carbons are well separated and the presence of extraneous signals is readily detected. It is not always possible, however, to make specific assignments to all carbon resonances since the poorly defined ^1H NMR signals preclude comprehensive single frequency decoupling. The ^{13}C chemical shifts for pertinent compounds are shown in Table I, figures in parentheses being tentative assignments not supported by decoupling data. Regardless of specific assignments, the precise chemical shifts provide a useful fingerprint for comparative purposes.

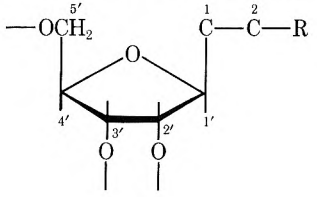
It is well known that the chemical shift of a carbon substituent on a five-membered ring is sensitive to steric crowding, especially by oxygen-containing neighbors, a cis orientation leading to upfield shifts relative to the trans counterpart.[35] We, and others, have made extensive use of this empirical rule in assignments of $C_{1'}$ and $C_{4'}$ configurations in pairs of nucleosides and *C*-glycosides where both isomers are available.[10,35b] In the case of the *C*-glycosyl propiolates **12, 16a,** and **19,** ^{13}C NMR was not of analytical value in assigning configurations at C_4 ("anomeric") and C_7. Thus the chemical shifts of C_3 in these three compounds were essentially identical (84.73 ± 0.05 ppm), probably as a result of the very small steric bulk and rigid geometry of such an acetylenic carbon. Unfortunately, the C_8 chemical shifts were also too close to be of diagnostic value. The fully reduced products **17, 20,** and **21** arising from diimide reduction of **16a, 19,** and **12,** respectively, were more amenable to ^{13}C analysis of "anomeric" configuration. As expected, the chemical shift of C_3 in the cis oriented *altro*-octonate **21** appeared 3.67 ppm upfield of the same carbon in the *allo*-octonate **17** which bears a trans vicinal substituent. Similarly, C_3 in **20** appeared at 26.23 ppm, which is 2.67 ppm upfield of C_3 in **17** and strongly supports the cis configuration in this compound and in its precursor **19.** Once again the chemical shifts of C_8 in **17, 20,** and **21** were too similar to allow confirmation of the configuration at C_7 in **20,** but previous arguments (see above) leave no doubt that its precursor (**19**) belonged to the L-lyxo series. This, together with the NMR assignment of "anomeric" configuration above, provides substantive evidence that the β-L-lyxo configuration of **19** predicted on mechanistic grounds is indeed true.

Since **4b** was available by several different routes described in this paper, we proceeded with attempts to convert this compound to purine-related *C*-glycosides via the route **22** → **28.** Thus **4b** was converted in 86% yield into the syrupy hydrazide **22a** by reaction with anhydrous hydrazine in methanol under reflux. Various attempts to convert **4a** into the corresponding hydrazide were unsuccessful owing to the lability of the benzoyl functions. For characterization, **22a** was readily transformed into the crystalline isopropylidene derivative **22b** by treatment with acetone. The hydrazide **22a** was converted into the acyl azide **23a** upon treatment with dilute hydrochloric acid and sodium nitrite in a mixture of aqueous acetic acid and ether at −10 °C. Without purification, **23a** was subjected to a Curtius rearrangement[14] by heating under reflux with *tert*-butyl alcohol, giving, after purification by chromatography on silicic acid, a 71% yield of 4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl-3(5)-*tert*-butoxycarboxamido)-pyrazole (**24a**). A similar treatment of **23a** with ethanol gave the corresponding urethane **24b** in 76% yield. In essentially identical ways the *N*-methylpyrazole **10** was converted into the *tert*-butoxycarboxamido derivative **24c** via the intermediate hydrazide **22c** and azide **23b.**

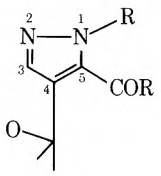
Treatment of **24a** with aqueous trifluoroacetic acid at room temperature for 7 h led to clean cleavage of the *tert*-butyl ester and decarboxylation of the resulting carbamic acid giving 3(5)-amino-4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole (**25a**) in 94% yield. Similar treatment of **24c** gave the corresponding crystalline *N*-methyl derivative **25b** in 65% yield. The aminopyrazole **25a** could also be obtained by alkaline hydrolysis of the urethane **24b,** but in this case the conditions were quite vigorous and the yield of **25a** was only 39%. While **25a** gave satisfactory ^1H and ^{13}C NMR spectra, it appeared to be unstable and quite rapidly gave several spots on TLC analysis. It was therefore used directly in the following steps. The N-methylated analogue **25b** was, on the other hand, a stable, crystalline substance.

Numerous examples of the cyclization of amino heterocycles to fused ring products by reaction with alkoxy- or aryloxycarbonyl isothiocyanates are to be found in the literature.[36] In particular, the reaction of 3-aminopyrazole with ethoxycarbonyl isothiocyanate to give 2-oxo-4-thiono-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine[37] provides a close analogy for the type of cyclization that we desired. Accordingly, **25a** was reacted in dioxane with phenoxycarbonyl isocyanate (**26**),[38] a reagent that has found considerable use in this laboratory for other heterocyclic syntheses.[39] Without isolation of the acyclic ureido intermediate, crystalline 2,4-dioxo-8-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**27a**) was isolated in 50% yield. Debenzylation of **27a** was readily accomplished by treatment with boron trichloride in methylene chloride at −78 °C giving the crystalline, unprotected nucleoside **28a** in 73% yield. The latter compound was chromatographically homogeneous and had an electrophoretic mobility in pH 9.2 borate buffer very similar to that of β-pseudouridine.[4a] It is, of course, a C-gly-

Table I. 22.62-MHz ^{13}C NMR Chemical Shifts (ppm from Me_4Si)[a]



a



b

Compd	Solvent[b]	Pentose[c] C_1'	C_2'	C_3'	C_4'	C_5'	Side chain[c] C_1	C_2	Ester CO	OMe	Other[d]
3	C	(80.04)	(81.40)	(77.53)	(81.86)	70.22	121.62	145.90	166.87	51.62	
4b	C	76.88	81.89	76.88	79.97	69.21			162.58	51.85	125.06 (C_4), 132.08 (C_3), 137.16 (C_5)
4c	D	76.66	(76.66)	(70.48)	(83.45)	61.48			162.06	51.40	121.67 (C_5), 124.64 (C_4), 131.99 (C_3)
7a	C	62.35	(80.23)	(79.36)	(70.84)	70.84	86.86	77.14	153.74	52.83	
7b	C	62.78	(77.11)	(79.19)	68.37	71.81	83.00	77.89	153.25	52.83	169.93, 169.47 (COMe), 21.10, 20.64 ($COCH_3$)
9a	C	66.94	(80.17)	(80.92)	70.32	71.29			163.00	52.08	127.01 (C_4), 131.99 (C_3), 136.70 (C_5)
9b	C	66.87	(80.23)	(80.65)	70.35	71.16			160.43	51.85	40.41 (NMe), 129.39 (C_5 or C_4), 138.20 (C_3)[e]
10	C	76.27	82.61	77.44	80.65	69.76			160.58	52.02	40.28 (NMe), 126.71 (C_4), 129.21 (C_5), 137.50 (C_3)
12	B	70.58	79.26	78.48	81.86	69.80	84.69	79.68	153.87	52.05	
13	C	(75.97)	(79.55)	(77.44)	(80.62)	70.35			162.74	51.82	122.40 (C_4), 132.87 (C_3)[e]
16a	C	70.74	(82.11)	(78.19)	(81.86)	69.93	84.72	(77.93)	153.67	52.79	
16b	C	70.90	(82.12)	(78.19)	(81.76)	70.22	81.66	74.97			
17	C	79.84	80.95	77.66	81.57	70.64	28.90	30.23	173.99	51.66	
19	C	68.63	(79.84)	(77.47)	(80.43)	69.44	84.78	(78.41)	153.93	52.60	
20	C	(77.96)	(79.13)	(78.15)	(79.55)	70.25	26.23	30.62	174.38	51.49	
21	C	(78.09)	(79.84)	(79.29)	(79.84)	70.32	25.23	30.53	174.19	51.53	
22a	C	(76.69)	(81.47)	(76.43)	(80.56)	69.38			162.55		122.0 (C_4), 132.5 (C_3)[e]
24a	C	(77.89)	(82.05)	(76.79)	(81.76)	69.08			153.15		28.25 (CMe_3), 102.89 (Me_3C)
25a	C	(77.86)	(81.76)	(76.40)	(81.11)	70.22					130.00 (pyrazole)

							Heterocycle C_2	C_4	C_7	C_8	C_9	
27a	C	(77.33)	(81.89)	(76.69)	(80.85)	67.75	(143.53)	(148.02)	144.50	103.74	136.96	
28a	D	(76.10)	(75.03)	(71.32)	84.39	61.38	(144.18)	(148.27)	144.18	103.18	137.84	
28b	D	(75.48)	(74.02)	(70.97)	85.21	61.64	(144.54)	(148.73)	144.73	104.06	138.03	29.13, 31.83 (NMe)

[a] Assignments that are ambiguous and could not be confirmed by single frequency decoupling are written in parentheses. [b] Solvents are C, $CDCl_3$; D, Me_2SO-d_6; B, benzene-d_6. [c] In an effort at consistency, the various non-N-heterocyclic sugar derivatives, including the acyclic compounds **7** and **9**, are numbered as in a. The pyrazole derivatives are all numbered as in b in order to be consistent with the nontautomeric *N*-methyl derivatives (**9b**, **10**). [d] In addition, all tribenzyl derivatives showed three signals (OCH_2Ar) at 71.59–74.51 ppm, nine overlapping aryl carbons at 127–129 ppm, and three aryl C_1 carbons at 136–138 ppm in the spectra in $CDCl_3$. [e] One pyrazole carbon is masked by aryl resonances.

coside analogue of xanthosine in which N^9 is transposed to a bridgehead position and represents one of the few reported syntheses of purine-related *C*-glycosides.[5a,5c,13] The heterocyclic base related to **28a** has recently been prepared[37] and considerable interest has centered upon the synthesis of *N*-glycosides derived from purine nucleoside analogues bearing a bridgehead nitrogen.[40] Debenzylation of **27a** by treatment with sodium in liquid ammonia required the use of a charcoal adsorption and elution step in order to free the produce from inorganic materials. The resulting product was found to consist of a mixture of the desired **28a** and an isomeric material with a similar, but different, chromatographic mobility. These substances could be cleanly separated by borate electrophoresis and the second product was found to have a mobility similar to that of α-pseudouridine. Presumably under the strongly basic conditions of the sodium in ammonia reduction, **28a** underwent partial isomerization to the corresponding α nucleoside via a mechanism similar to that previously proposed for pseudouridine.[28] There was, however, no indication of the formation of pyranosides. Fortunately, no similar isomerization was observed under the mild conditions for debenzylation with boron trichloride.

The similarity of the ^{13}C chemical shifts of urea and oxygen substituted azomethine carbons makes an unequivocal assignment of tautomeric structure for **27a** and **28a** difficult. The ^{13}C NMR spectra of both compounds show signals for C_2, C_4, C_7, and C_9 all between 137 and 148 ppm, making it difficult to reach any conclusions. Hence **28a** was treated with methyl iodide and potassium carbonate to give the crystalline N^1,N^3-dimethyl compound **27b** in >90% yield. Debenzylation of **27b** with boron trichloride proceeded readily giving crystalline 2,4-dioxo-1,3-dimethyl-8-β-D-ribofuranosylpyrazolo[1,5-*a*]-1,3,5-triazine (**28b**) in 61% yield. The ^1H NMR spectra of **27b** and **28b** left the site of alkylation ambiguous, but the ^{13}C NMR spectrum of **28b** clearly indicated that methylation had, as expected, occurred on nitrogen rather than oxygen. Thus the new methyl signals appeared at 29.13 and 31.83 ppm, positions compatible with those shown by N^1,N^3-dimethyluracil (27.5 and 36.8 ppm)[41] but distinctly different from those of aryl methyl ethers (55–60 ppm).[34,41]

The uv spectra of **28a** and **28b** were quite similar with both showing maxima at 253–254 nm. The N^1,N^3-dimethyl compound **28b**, however, showed a second maxima at 240 nm while **28a** only had a shoulder at 231 nm. Since these lower wavelength peaks are rather close to the beginning of intense end absorption it is difficult to reach firm conclusions regarding tautomeric structure without careful study on the pH dependence of the uv spectra. Finally, it is interesting to note that the ir spectra of **27a** and **28a** show intense carbonyl absorptions at roughly 1770 and 1710 cm^{-1}. The former are at rather high frequency when compared with other ketonucleosides[42a] such as xanthosine (1715 and 1690 cm^{-1})[42b] and are much closer to those exhibited by 2,4-dioxo-1,3,5-triazines such as substituted 5-azauracils (~1750 cm^{-1} in dioxane).[42c] The N^1,N^3-dimethyl derivatives **27b** and **28b** showed similar long-wavelength carbonyl absorptions which futher support the dioxo structures for the parent nucleosides.

In the present paper we have outlined a number of different routes for the preparation of selected pentofuranosylpropiolates. These compounds can, in turn, be converted into functionally substituted *C*-glycosylpyrazoles which are useful precursors of bicyclic *C*-glycosides related to purine nucleosides. In forthcoming papers in this series we hope to describe the preparation of other compounds of the latter class.

Experimental Section

General Methods. The general methods used are similar to those described previously.[7] Only limited ^1H NMR data are presented owing to the frequent complexity of the spectra of tri-*O*-benzylribose derivatives. In Table I, ^{13}C NMR data are accumulated and assignments are made based upon off-resonance and, whenever possible, single frequency proton decoupling studies. We are most grateful to Dr. M. L. Maddox for his help with ^{13}C NMR spectroscopy.

1,3-Diphenyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)imidazolidine (1b). A solution of **1c** (27.0 g, 40.4 mmol) in chloroform (275 ml) was added to methanolic sodium hydroxide (275 ml of 0.075 M) and stirred at room temperature for 2.5 h. After neutralization with Dowex 50 (H^+) resin the mixture was filtered and evaporated leaving a gum that was triturated with ether to remove methyl benzoate. The solid was crystallized from aqueous methanol giving 10.3 g (72%) of **1a**.[6] A solution of **1a** (14.25 g, 40 mmol) in anhydrous DMF (30 ml) was added dropwise at 0 °C under nitrogen to a suspension of 100% sodium hydride (4.8 g, 0.2 mol)[43] in DMF (35 ml). The mixture was stirred at room temperature for 2 h and then cooled to 0–5 °C while a solution of benzyl bromide (22.6 ml, 190 mmol) in DMF (15 ml) was added over 30 min. After 2 h at room temperature methanol (20 ml) was added and the solution was poured onto a mixture of ice water and ether. The aqueous phase was further extracted with ether and the combined organic layers were washed with water (three times), dried ($MgSO_4$), and evaporated. The residue was triturated with petroleum ether (bp 30–60 °C) and the solid residue was crystallized from ether–hexane giving 20.97 g (84%) of **1b** with mp 93–94 °C and in all ways identical with an authentic sample.[6]

Methyl *trans*-4,7-Anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*allo*-oct-2-enonate (3). The aldehyde **2** was regenerated from **1b** (9.0 g, 14.4 mmol) with *p*-toluenesulfonic acid as previously described[6] and directly reacted with carbomethoxymethylenetriphenylphosphorane (9.6 g, 28.8 mmol) in methylene chloride (180 ml) at room temperature for 2 h. The solution was washed three times with water, diluted with ether, and filtered. The evaporated filtrate was chromatographed on a column of silicic acid using ether–hexane (1:1) giving 6.45 g (92%) of **3** as a colorless oil: $[\alpha]^{25}D$ −13.7° (*c* 1.0, $CHCl_3$); ν_{max} (film) 1725 cm^{-1} (CO); ^1H NMR ($CDCl_3$) inter alia 6.16 (dd, 1, $J_{2,3}$ = 15.5, $J_{2,4}$ = 2 Hz, C_2H), 6.92 ppm (dd, 1 $J_{3,4}$ = 5 Hz, C_3H); ^{13}C NMR (see Table I) showed the presence of a little (5–10%) of the cis isomer by minor peaks at 148.9 (C_3), 120.0 (C_2), 80.5, 79.0, 77.9, 71.3, 69.3, and 51.5 ppm (OCH_3).

Anal. Calcd for $C_{30}H_{32}O_6$ (488.59): C, 73.75; H, 6.60. Found: C, 73.52; H, 6.89.

4-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-3(5)-carbomethoxypyrazole (4b). A. A solution of **3** (1.2 g, 2.5 mmol) and diazomethane (from 1.0 g, 10 mmol, of *N*-nitroso-*N*-methylurea) in ether was stored at room temperature for 2.5 h and then evaporated to dryness. A solution of chlorine (0.3 g, 4.1 mmol) in carbon tetrachloride (50 ml) was added dropwise to a solution of the residue in carbon tetrachloride (10 ml). After 1.5 h at room temperature the solvent was evaporated and the residue was chromatographed on a column of silicic acid using ether–hexane (2:1) giving 0.95 g (72%) of **4b** as a TLC-homogeneous syrup: $[\alpha]^{25}D$ 95.1° (*c* 0.8, $CHCl_3$), 69.5° (*c* 0.4, MeOH); ORD (MeOH) $[\Phi]_{260}^{pk}$ 12 100°, $[\Phi]_{240}^{tr}$ 7500°, $[\Phi]_{232}^{pk}$ 9100°; λ_{max} (MeOH) 236 nm (sh, ϵ 5400); ^1H NMR ($CDCl_3$) 3.78 (s, 3, OMe), 5.62 (d, 1, $J_{1',2'}$ = 2 Hz, $C_{1'}H$), 7.91 ppm (s, 1, $C_{5(3)}H$).

Anal. Calcd for $C_{31}H_{32}N_2O_6$ (528.61): C, 70.44; H, 6.10; N, 5.30. Found: C, 70.46; H, 6.15; N, 5.33.

B. A solution of **9a** (1.7 g, 3.1 mmol) and *p*-toluenesulfonic acid (0.3 g, 1.6 mmol) in benzene (50 ml) was stirred and heated under reflux for 17 h. The solution was diluted with ether, washed with aqueous sodium bicarbonate (three times) and water, dried ($MgSO_4$), and evaporated. The residue was chromatographed as in A giving 1.4 g (86%) of **4b** that was identical with that above by TLC and ir analysis. By ^1H and ^{13}C NMR the product was shown to be at least 90–95% pure with only a few very small signals suggesting the presence of a trace of a second isomer.

C. A solution of **16a** (130 mg, 0.27 mmol) and diazomethane (from 250 mg, 2.4 mmol, of *N*-nitroso-*N*-methylurea) in ether (15 ml) was kept at 0 °C for 1.5 h. Purification by preparative TLC using ether–hexane (3:1) gave 120 mg (83%) of **4b** identical with that above.

4-β-D-Ribofuranosyl-3(5)-carbomethoxypyrazole (4c). A solution of **4b** (240 mg, 0.45 mmol) in methylene chloride (2 ml) was added to a solution of boron trichloride (~1 ml) in methylene chloride (5.5 ml) cooled to −78 °C. After 40 min at −78 °C a mixture of methanol and methylene chloride (1:1, 6 ml) was added and the mixture was warmed to room temperature and evaporated to dryness. The residue was coevaporated five times with methanol and then crystallized from methanol–ether giving 90 mg (77%) of **4c** with mp 183–184.5 °C. This material was identical with an authentic sample of **4c** (mp 186–188 °C, mmp 182–187 °C).[8a]

Methyl 5,6,8-Tri-*O*-benzyl-2,3-dideoxy-D-*altro*-oct-2-ynonate (7a). Ethylmagnesium bromide (141 ml of a 1.32 M solution in tet-

rahydrofuran, 186 mmol) was added dropwise to a stirred solution of propiolic acid (6.7 g, 95.7 mmol) in tetrahydrofuran (100 ml) at 0 °C and the mixture was warmed to room temperature for 1 h. A solution of **5** (7.7 g, 18.3 mmol) in tetrahydrofuran (50 ml) was added dropwise to the resulting **6** and stirred at room temperature for 20 h. Following addition of excess saturated aqueous ammonium chloride and 6 N hydrochloric acid (35 ml) the mixture was extracted (three times) with ether and the extracts were washed with water (three times) and evaporated to a syrup. A solution of the latter in saturated aqueous sodium bicarbonate was washed three times with ether, acidified with 6 N hydrochloric acid, and extracted with ether. The extracts were washed with water, dried ($MgSO_4$), and evaporated, leaving 9.7 g of crude acid that was dissolved in benzene–methanol (1:1, 100 ml) containing *p*-toluenesulfonic acid (1.0 g) and heated under reflux for 5.5 h. The cooled solution was diluted with ether and washed with water, aqueous sodium bicarbonate (three times), and water, dried ($MgSO_4$), and evaporated, leaving 8.9 g of crude **7a**. Chromatography on a column of silicic acid using ether–hexane (2:1) gave 6.78 g (73%) of TLC-homogeneous **7a** that appeared to be a single isomer by ^1H and ^{13}C NMR analysis: $[\alpha]^{25}D$ −33° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$) 3.73 ppm (s, 3, OMe); ir (film) 2240 (C≡C), 1720 cm^{-1} (CO).

Anal. Calcd for $C_{30}H_{32}O_7$ (504.59): C, 71.41; H, 6.39. Found: C, 71.01; H, 6.35.

Methyl 4,7-Di-*O*-acetyl-5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*altro*-oct-2-ynonate (7b). A solution of **7a** (2.0 g, 4 mmol), acetic anhydride (10 ml), and 4-dimethylaminopyridine (20 mg) in pyridine (30 ml) was stirred at room temperature for 1 h and then poured into ice water. After 30 min the mixture was extracted with ether and the extracts were washed with 2 N hydrochloric acid (three times), aqueous sodium bicarbonate, and water. The dried solution was evaporated and the residue was chromatographed on a column of silicic acid using ether–hexane (3:2) to give 1.9 g (82%) of **7b** as a TLC-homogeneous syrup: $[\alpha]^{25}D$ −33.6° (*c* 0.4, MeOH); ^1H NMR ($CDCl_3$) 1.93 and 2.04 (s, 3, OAc), 3.67 ppm (s, 3, OMe).

Anal. Calcd for $C_{34}H_{36}O_9$ (588.63): C, 69.37; H, 6.16. Found: C, 69.53; H, 6.29.

4-(2,3,5-Tribenzyloxy-1,4-dihydroxy-D-*altro*-pent-1-yl)-3(5)-carbomethoxypyrazole (9a). A solution of **7a** (0.52 g, 1.03 mmol) and diazomethane (from 0.8 g, 8 mmol, of *N*-nitroso-*N*-methylurea) in ether (50 ml) was stored at 0 °C for 2 h. After removal of excess diazomethane with a stream of nitrogen the solvent was evaporated and the residue was purified by preparative TLC using ether–methanol (19:1) giving 0.43 g (76%) of **9a** with mp 47–50 °C from benzene–hexane: $[\alpha]^{25}D$ −44.8° (*c* 1.0 MeOH); ORD (MeOH) $[\Phi]_{267}^{tr}$ −16 400°; λ_{max} (MeOH) 247 nm (sh, ϵ 4600); ^1H NMR ($CDCl_3$) 7.72 (s, 1, $C_{5(3)}$ H), 3.73 ppm (s, 3, OMe).

Anal. Calcd for $C_{31}H_{34}N_2O_7$ (546.62): C, 68.12; H, 6.27; N, 5.12. Found: C, 67.94; H, 6.44; N, 4.74.

Two by-products were also isolated by preparative TLC. The one less polar than **9a** (40 mg, 7%) was shown by ^1H NMR to be the *N*-methyl derivative (**9b**), ^1H NMR ($CDCl_3$) 7.68 (s, 1, $C_{5(3)}$ H), 3.69 (s, 3, OMe), 4.06 ppm (s, 3, NMe), while a more polar substance (15 mg) was not identified.

4-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-5-carbomethoxy-1-methylpyrazole (10). A solution of **9b** (280 mg, 0.5 mmol) and *p*-toluenesulfonic acid (60 mg, 0.25 mmol) in benzene (25 ml) was heated under reflux for 17 h, diluted with ether, and washed with aqueous sodium bicarbonate and water. The dried solution was evaporated and the residue was triturated with hexane giving 210 mg (77%) of **10**. An analytical sample from hexane had mp 98–99 °C: $[\alpha]^{25}D$ 56.9° (*c* 1.0, MeOH); λ_{max} (MeOH) 231 nm (ϵ 9400); ^1H NMR ($CDCl_3$) 3.85 (s, 3, OMe), 4.11 (s, 3, NMe), 5.51 (d, 1, $J_{1',2'}$ = 4 Hz, $C_{1'}$ H), 7.60 ppm (s, 1, C_3H).

Anal. Calcd for $C_{32}H_{34}N_2O_6$ (542.63): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.80; H, 6.36; N, 5.07.

Methyl 4,7-Anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*altro*-oct-2-ynonate (12). A solution of **11** (prepared from 1.9 g, 3.3 mmol, of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-ribose as previously described[29] and giving 81% of the theoretical *p*-nitrobenzoic acid) in dry tetrahydrofuran (15 ml) was added to a stirred suspension of **6** (prepared from 1.8 g, 25.7 mmol, of propiolic acid and 51.5 mmol of ethylmagnesium bromide as described for preparation of **7a**) in tetrahydrofuran (100 ml). After 16 h at room temperature excess saturated aqueous ammonium chloride and concentrated hydrochloric acid (20 ml) were added and the solution was extracted twice with ether. The extracts were washed with water and evaporated. A solution of the residue in aqueous sodium bicarbonate was washed with ether until the extracts were colorless, acidified with hydrochloric acid, and extracted with ether. The extracts were washed with water, dried ($MgSO_4$), and evaporated, leaving 1.3 g of crude acetylenic acid. A solution of this material in benzene (10 ml) and methanol (10 ml) containing *p*-toluenesulfonic acid (120 mg, 0.63 mmol) was heated under reflux for 5 h and then diluted with ether. The solution was washed twice with aqueous sodium bicarbonate and then with ice-cold water, dried ($MgSO_4$), and evaporated, leaving 780 mg of a light-colored oil. Preparative TLC using ether–hexane (3:1) gave 250 mg (15%) of **7a** and 430 mg (27%) of the less polar **12** as a homogeneous syrup. In various preparations the yield of **12** varied between 13 and 27%: $[\alpha]^{25}D$ 87.2° (*c* 0.1, $CHCl_3$) (reported[17b] $[\alpha]D$ 84.3°); ν_{max} (film) 2240 (C≡C), 1720 cm^{-1} (CO).

4-(2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl)-3(5)-carbomethoxypyrazole (13). A solution of **12** (130 mg, 0.27 mmol) in ether was treated with diazomethane as described for the preparation of **4b** (method C) giving 85 mg (58%) of homogeneous **13:** $[\alpha]^{25}D$ −25.0° (*c* 0.5, $CHCl_3$); $[\alpha]^{25}D$ −34.9° (*c* 0.5, MeOH); ORD (MeOH) $[\Phi]_{264}^{tr}$ −12 200°, $[\Phi]_{240}$ 0°; λ_{max} (MeOH) 230 nm (sh, ϵ 7000); ^1H NMR ($CDCl_3$) 3.76 (s, 3, OMe), 5.56 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{1'}$ H), 7.86 ppm (s, 1, $C_{3(5)}$ H).

Anal. Calcd for $C_{31}H_{32}N_2O_6$ (528.61): C, 70.44; H, 6.10; N, 5.30. Found: C, 70.11; H, 6.20; N, 5.20.

Reaction of 7a with Methyltriphenoxyphosphonium Iodide (14). A solution of **7a** (2.0 g, 4 mmol) and **14** (5.5 g, 12 mmol) in dry methylene chloride (240 ml) was stored at room temperature for 91 h. Methanol (50 ml) was then added and after 30 min the solution was evaporated. A solution of the residue in ether was washed with ice-cold 5% potassium hydroxide (3 × 50 ml) and water, dried ($MgSO_4$), and evaporated. The residue was separated into five pure components by a combination of chromatography on a column of silicic acid and preparative TLC using ether–hexane (1:1). In order of increasing polarity these were identified as follows.

(a) The least polar band contained 375 mg (19%) of the β-D-ribofuranosylpropiolate (**16a**) as a homogeneous syrup: $[\alpha]^{25}D$ −23.4° (*c* 0.8, MeOH), −8.7° (*c* 0.9, $CHCl_3$) (reported[17b] $[\alpha]D$ 16°, $CHCl_3$); ν_{max} (film) 2240 (C≡C), 1720 cm^{-1} (CO); ^1H NMR ($CDCl_3$) 3.73 (s, 3, OMe), 4.74 ppm (d, 1, $J_{4,5}$ = 4.5 Hz, C_4 H).

Anal. Calcd for $C_{30}H_{30}O_6$ (486.59): C, 74.06; H, 6.21. Found: C, 73.53; H, 6.02.

(b) The second band contained 30 mg (1%) of a compound that was considered on spectral grounds to be an iodo sugar: ν_{max} (film) 3300 (OH), 2240 (C≡C), 1730 cm^{-1} (CO); ^1H NMR ($CDCl_3$) 3.69 ppm (s, 3, OMe); ^{13}C NMR ($CDCl_3$) 2.7 (C_4), 52.7 (OMe), 69.4 (C_8), 77.4 (C_6), 80.7 (C_5), 81.4 (C_7), 84.5 (C_2), 153.8 ppm (C_1) (tentative carbohydrate assignments).

(c) The third band contained 15 mg (1%) of what is tentatively considered to be methyl 5,6,8-tri-*O*-benzyl-2,3,4-trideoxy-D-*erythro*-oct-4-en-2-ynonate: ν_{max} (film) 3400 (OH), 2240 (C≡C), 1720 (CO), 1630 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) 3.71 (s, 3, OMe), 6.97 ppm (d, 1, $J_{4,6}$ = 1.5 Hz, C_4 H).

(d) The next band contained 40 mg (2%) of the α-D-ribofuranosyl propiolate (**12**) that was identical with the sample prepared as above by ^1H and ^{13}C NMR and TLC analysis.

(e) The most polar band contained 630 mg (33%) of the β-L-lyxofuranosyl propiolate (**19**) as a homogeneous syrup: $[\alpha]^{25}D$ 69.7° (*c* 0.3, $CHCl_3$), 43.9° (*c* 0.3, MeOH); ν_{max} (film) 2240 (C≡C), 1725 cm^{-1} (CO); ^1H NMR ($CDCl_3$) 3.72 ppm (s, 3, OMe).

Anal. Calcd for $C_{30}H_{30}O_6$ (486.59): C, 74.06; H, 6.21. Found: C, 74.37; H, 6.04.

In another reaction similar to that above, the yields of the purified major products **16a** and **19** were 30 and 33%, respectively.

2,3,5-Tri-*O*-benzyl-β-D-ribofuranosylethyne (16b). A solution of **16a** (100 mg, 0.2 mmol) and aqueous potassium hydroxide (0.25 ml of 2 N) in dioxane (1.5 ml) was stirred at room temperature for 1 h and then evaporated to dryness. An aqueous solution of the residue was washed with ether, acidified to pH 4 with 2 N hydrochloric acid, and then extracted with chloroform (3 × 20 ml). The dried ($MgSO_4$) extracts were evaporated leaving 80 mg of the acid **16c** [ν_{max} 2240 (C≡C), 1715 cm^{-1} (CO_2H)] that was dissolved in benzene (10 ml) and heated under reflux for 27 h. The solution was diluted with ether, washed with aqueous sodium bicarbonate and water, dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC using ether–hexane (1:1) giving 45 mg (52%) of NMR and TLC homogeneous **16b** that was crystallized from hexane giving 30 mg of product with mp 63.5–64.5 °C (reported[17] mp 63–64 °C); $[\alpha]^{25}D$ 11.9° (*c* 0.4, $CHCl_3$); ν_{max} (film) 3280 cm^{-1} (C≡CH); ^1H NMR ($CDCl_3$) 2.47 (d, 1, $J_{1,3}$ = 2 Hz, C≡CH), 3.52 ppm (d, 2, $J_{6,7}$ = 4 Hz, C_7 H). This material was identical in all respects with a sample kindly provided by Professor J. G. Buchanan.

Methyl 4,7-Anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*allo*-octonate (17). A. A mixture of **3** (244 mg, 0.5 mmol), potassium azodicarboxylate (485 mg, 2.5 mmol), glacial acetic acid (0.28 ml, 5 mmol),

and pyridine (5 ml) was stirred under nitrogen at room temperature for 17 h. It was then diluted with methanol, filtered, and evaporated in vacuo, leaving a residue that was partitioned between ethyl acetate and water. The organic phase was washed with aqueous sodium bicarbonate (3 × 20 ml), 2 N hydrochloric acid (5 × 20 ml), and ice-cold water (2 × 20 ml), dried ($MgSO_4$), and evaporated, leaving 220 mg (90%) of pure **17** as a syrup: $[\alpha]^{25}D$ −18.3° (*c* 0.6, $CHCl_3$); ν_{max} (film) 1735 cm^{-1} (CO_2Me); ^1H NMR ($CDCl_3$) 2.39 (t, 2, C_2H_2), 3.60 ppm (s, 3, OMe).

Anal. Calcd for $C_{30}H_{34}O_6$ (490.60): C, 73.44; H, 6.98. Found: C, 73.11; H, 702.

B. The propiolate **16a** (120 mg, 0.25 mmol) was reduced with diimide as in A giving 130 mg of a red syrup the major component of which was identical with **17** by TLC. Purification by preparative TLC using ether–hexane (3:2) gave 50 mg (41%) of pure **17** that was identical with that from A by ^1H and ^{13}C NMR.

Methyl 4,7-Anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-L-*galacto*-octonate (20). Reduction of the propiolate **19** (120 mg, 0.25 mmol) with diimide was carried out as described for preparation of **17**. Purification of the red syrup by preparative TLC gave 70 mg (57%) of pure **20** as a colorless syrup: $[\alpha]^{25}D$ 9.0° (*c* 0.5, $CHCl_3$); ν_{max} (film) 1730 cm^{-1} (CO_2Me); ^1H NMR ($CDCl_3$) 2.42 (t, 2, C_2H_2), 3.60 ppm (s, 3, OMe).

Anal. Calcd for $C_{30}H_{34}O_6$ (490.60): C, 73.44; H, 6.98. Found: C, 72.99; H, 6.59.

Methyl 4,7-Anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-D-*altro*-octonate (21). The reduction of **12** (120 mg) with diimide was carried out as described for preparation of **17**. The resulting crude product was purified by preparative TLC using ether–hexane (1:1) to give 42 mg (35%) of **21** as a clear syrup: $[\alpha]^{25}D$ 37.6° (*c* 0.3, $CHCl_3$); ν_{max} (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) 3.58 ppm (s, 3, OMe).

Anal. Calcd for $C_{30}H_{34}O_6$ (490.60): C, 73.44; H, 6.98. Found: C, 73.84; H, 6.64.

4-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-3(5)-carboxylic Acid Hydrazide (22a). A solution of **4b** (8.0 g, 15.1 mmol) in anhydrous hydrazine (25 ml) and methanol (50 ml) was heated under reflux for 3 h and then evaporated to dryness. A solution of the residue in ether was washed with water (three times), dried, and evaporated. Purification of the residue by chromatography on a column of silicic acid using ether–methanol (19:1) gave 6.89 g (86%) of **22a** as a homogeneous (TLC and NMR) syrup: ^1H NMR ($CDCl_3$) 3.57 (dd, 1, J_{gem} = 11, $J_{4',5'a}$ = 3 Hz, $C_{5'a}$ H), 3.78 (dd, 1, $J_{4',5'b}$ = 2 Hz, $C_{5'b}$ H), 5.57 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}$ H), 7.70 (s, 1, $C_{5(3)}$ H).

The hydrazide **22a** reacted rapidly with acetone to give crystalline **22b** with mp 157–159 °C: $[\alpha]^{25}D$ 72.3° (*c* 0.2, MeOH); ORD (MeOH) $[\Phi]_{250}^{pk}$ 10 000°, $[\Phi]_{230}^{tr}$ 5900°; ^1H NMR 1.79 and 2.01 (s, 3, CMe_2), 5.58 (d, 1, $J_{1',2'}$ = 2 Hz, $C_{1'}$ H), 7.78 ppm (s, 1, $C_{5(3)}$ H).

Anal. Calcd for $C_{33}H_{36}N_4O_5$ (568.68): C, 69.70; H, 6.38; N, 9.85. Found: C, 69.39; H, 6.24; N, 9.80.

4-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-1-methylpyrazole-5-carboxylic Acid Hydrazide (22c). A solution of **10** (1.8 g, 3.3 mmol) and anhydrous hydrazine (5 ml) in methanol (20 ml) was heated under reflux for 7 h and then evaporated to dryness. The residue was partitioned between water and ether and the aqueous phase was extracted twice with ether. The combined ether phases were dried ($MgSO_4$) and evaporated, leaving a residue that was triturated with hexane. The solid residue was crystallized from ether–hexane giving 1.6 g (89%) of **22c** with mp 85–87.5 °C: $[\alpha]^{25}D$ −28.4° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$) 4.07 (s, 3, NMe), 5.03 ppm (d, 1, $J_{1',2'}$ = 7.5 Hz, $C_{1'}$ H).

Anal. Calcd for $C_{31}H_{34}N_4O_5$ (542.61): C, 68.81; H, 6.31; N, 10.32. Found: C, 69.12; H, 6.27; N, 9.84.

4-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-3(5)-*tert*-butoxycarboxamidopyrazole (24a). A solution of sodium nitrite (0.72 g, 10.4 mmol) in water (8 ml) was added dropwise to a stirred mixture of **22a** (1.2 g, 2.27 mmol), 2.5 N hydrochloric acid (20 ml), acetic acid (10 ml), and ether (30 ml) at −10 °C. After a further 5 min at −10 °C the ether layer was separated and the aqueous phase was extracted twice with ether. The combined ether phases were washed repeatedly with cold aqueous sodium bicarbonate and with water, dried, and evaporated below 10 °C giving crude **23a** as a pale yellow glass that was essentially pure by TLC using ether–methanol (19:1). A solution of this material in *tert*-butyl alcohol (20 ml) was heated under reflux for 7 h and then evaporated to dryness. The residue was purified by preparative TLC using ether–methanol (98:2) giving 940 mg (71%) of pure **24a** as a dry foam: $[\alpha]^{25}D$ −4.0° (*c* 1.0, MeOH); λ_{max} (MeOH) 228 nm (sh, ε 6400), 258 (850), 264 (700); ^1H NMR ($CDCl_3$) 1.42 (s, 9, *t*-Bu), 3.37 (dd, 1, J_{gem} = 10, $J_{4',5'a}$ = 1.5 Hz, $C_{5'a}$ H), 3.71 (dd, 1, $J_{4',5'b}$ = 3 Hz, $C_{5'b}$ H), 5.04 ppm (d, 1, $J_{1',2'}$ = 6.5 Hz, $C_{1'}$ H).

Anal. Calcd for $C_{34}H_{39}N_3O_6$ (585.70): C, 69.72; H, 6.71; N, 7.17. Found: C, 69.66; H, 6.68; N, 7.12.

4-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-3(5)-ethoxycarboxamidopyrazole (24b). The hydrazide **22a** (200 mg, 0.38 mmol) was converted as above into the acyl azide **23a.** This was dissolved in ethanol and heated under reflux for 2 h. Evaporation of the solvent left 170 mg (80%) of essentially pure **24b** that was characterized only by its ^1H NMR spectrum ($CDCl_3$): 1.15 (t, 3, CH_2CH_3), 3.39 (dd, 1, J_{gem} = 11, $J_{4',5'a}$ = 1.5 Hz, $C_{5'a}$ H), 5.05 ppm (d, 1, $J_{1',2'}$ = 6.5 Hz, $C_{1'}$ H).

4-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-1-methyl-5-*tert*-butoxycarboxamidopyrazole (24c). The hydrazide **22c** (250 mg, 0.46 mmol) was converted to the acyl azide (**23b**) and thence to the *tert*-butylurethane (**24c**) as described above for **22a → 24a.** The crude product was purified by preparative TLC using ether–methanol (99:1) giving 200 mg (72%) of **24c** as a homogeneous syrup: $[\alpha]^{25}D$ 3.9° (*c* 0.8, MeOH); λ_{max} (MeOH) 227 nm (sh, ε 6100), 257 (850), 263 (700); ^1H NMR ($CDCl_3$) 1.43 (s, 9, *t*-Bu), 3.49 (dd, 1, J_{gem} = 10, $J_{4',5'a}$ = 3 Hz, $C_{5'}$ H_a), 3.66 (dd, 1, $J_{4',5'b}$ = 4 Hz, $C_{5'b}$ H), 3.67 (s, 3, NMe), 3.93 (dd, 1, $J_{1',2'}$ = $J_{2',3'}$ = 5 Hz, $C_{2'}$ H), 4.00 (dd, 1, $J_{3',4'}$ = 8 Hz, $C_{3'}$ H), 4.22 (m, 1, $C_{4'}$ H), 4.4–4.75 (m, 6, OCH_2Ph), 4.99 (d, 1, $C_{1'}$ H), 7.7 (s, 16, Ar and C_3 H).

Anal. Calcd for $C_{35}H_{41}N_3O_6$ (599.74): C, 70.10; H, 6.89; N, 7.01. Found: C, 70.37, H, 6.72; N, 7.04.

A slightly more polar by-product (50 mg) was not identified.

3(5)-Amino-4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole (25a). A. A solution of **24a** (650 mg, 1.08 mmol) in trifluoroacetic acid (9 ml) and water (3 ml) was stirred at room temperature for 7 h. It was then diluted with water, neutralized with solid sodium bicarbonate, and extracted three times with ether. The extracts were dried ($MgSO_4$) and evaporated, leaving 490 mg (94%) of crude **25a** that was predominantly a single spot by TLC (ether–methanol, 19:1) and gave a clean ^{13}C NMR spectrum. It was, however, unstable and gradually decomposed during several days' storage at room temperature. Attempts to isolate a crystalline salt were not successful and accordingly **25a** was generated and used directly in subsequent experiments.

B. A solution of **24b** (160 mg, 0.29 mmol) in ethanol (5 ml) and 5.3 M sodium hydroxide (1 ml) was heated under reflux for 19 h and then evaporated to dryness. The residue was then treated with 6 N hydrochloric acid and extracted three times with ether. The aqueous phase was made basic and extracted four times with chloroform. The extracts were washed with water, dried ($MgSO_4$), and evaporated, leaving 55 mg (39%) of **25a** similar to that in A above.

5-Amino-4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-1-methylpyrazole (25b). A solution of **24c** (120 mg, 0.2 mmol) in trifluoroacetic acid (2 ml) and water (1 ml) was stirred at room temperature for 20 h and then worked up as for **25a.** After removal of a trace of unreacted **24c** by preparative TLC (ether–methanol, 98:2) crystallization from hexane gave 65 mg (65%) of **25b** with mp 82–83 °C: $[\alpha]^{25}D$ −31.4° (*c* 1.0, MeOH); λ_{max} (MeOH) 233 nm (ε 6000); ^1H NMR ($CDCl_3$) 3.49 ppm (dd, 1, J_{gem} = 10, $J_{4',5'a}$ = 3 Hz, $C_{5'a}$ H), 3.71 (dd, 1, $J_{4',5'b}$ = 3 Hz, $C_{5'b}$ H), 3.48 (s, 3, NMe), 3.78 (s, 2, NH_2), 3.91 (dd, 1, $J_{1',2'}$ = $J_{2',3'}$ = 6 Hz, $C_{2'}$ H), 3.99 (dd, 1, $J_{3',4'}$ = 7 Hz, $C_{3'}$ H), 4.20 (m, 1, $C_{4'}$ H), 4.35–4.75 (m, 6, OCH_2Ph), 4.94 (d, 1, $C_{1'}$ H), 7.13 (s, 1, C_3 H), 7.2–7.4 (m, 15, Ar).

Anal. Calcd for $C_{30}H_{33}N_3O_4$ (499.61): C, 72.12; H, 6.66; N, 8.41. Found: C, 72.15; H, 6.68; N, 8.37.

2,4-Dioxo-8-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-1*H*,-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (27a). A solution of phenoxycarbonyl isocyanate (**26**, 200 mg, 1.2 mmol) in dry dioxane (3 ml) was added over 20 min to a stirred solution of crude **25a** (390 mg, 0.8 mmol) at room temperature. After a further 22 h the solution was heated under reflux for 4.5 h and then evaporated in vacuo. The residue was triturated with ether giving a solid that was further washed with ether and crystallized from chloroform–ether giving 220 mg (50%) of **27a** with mp 195–201°: $[\alpha]^{25}D$ −64.3° (*c* 0.24, MeOH); λ_{max} (MeOH) 235 nm (sh, ε 5400), 252 (5300), 257 (5300); ν_{max} (KBr) 1775, 1705, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) 3.47 (br d, 1, J_{gem} = 11, $J_{4',5'a}$ ~ 2 Hz, $C_{5'a}$ H), 5.00 (d, 1, $J_{1',2'}$ = 4 Hz, $C_{1'}$ H), 7.46 (s, 1, C_7 H).

Anal. Calcd for $C_{31}H_{30}N_4O_6$ (554.61): C, 67.14; H, 5.45; N, 10.10. Found: C, 66.81; H, 5.34; N, 10.20.

2,4-Dioxo-8-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-1,3-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine (27b). A solution of **27a** (200 mg, 0.36 mmol) and methyl iodide (1.0 ml) in acetone (7 ml) was stirred for 16 h at room temperature in the presence of anhydrous potassium carbonate (200 mg, 0.36 mmol). The mixture was then filtered and the filtrate was evaporated leaving a residue that was triturated with water. The resulting solid was crystallized from chloroform–hexane, giving 165 mg (79%) of **27b** with mp 111–112 °C: $[\alpha]^{25}D$ −27.7° (*c* 0.4, MeOH); λ_{max} (MeOH) 239 nm (ε 5600), 252 (5800), 258 (6000); ν_{max} (KBr) 1755, 1685, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) 3.46 and 3.60 ppm (s, 3, NMe), 5.09 (d, 1, $J_{1',2'}$ = 7.5 Hz, $C_{1'}$ H), 7.61 (s, 1, C_7 H).

Anal. Calcd for $C_{33}H_{34}N_4O_6$ (582.66): C, 68.03; H, 5.88; N, 9.62. Found: C, 68.28; H, 5.73; N, 9.67.

2,4-Dioxo-8-β-D-ribofuranosyl-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (28a). A. A solution of **27a** (200 mg, 0.36 mmol) in methylene chloride (2 ml) was added to a solution of boron trichloride (~1 ml) in methylene chloride (8 ml) at −78 °C and the mixture was stored at −78 °C for 1.5 h. A mixture of methanol (4 ml) and methylene chloride (4 ml) was then added dropwise and the mixture was allowed to warm to room temperature and evaporated in vacuo. The residue was coevaporated six times with methanol (10 ml) and crystallized from acetone–hexane, giving 75 mg (73%) of **28a** with mp 184–186 °C dec: $[\alpha]^{25}D$ −50.4° (*c* 0.36, MeOH); λ_{max} (MeOH) 231 nm (sh, ϵ 4900), 253 (4300); λ_{max} (KBr) 1765, 1715, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6) 4.69 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}$ H), 7.80 ppm (s, 1, C_7 H).

Anal. Calcd for $C_{10}H_{12}N_4O_6$ (284.24): C, 42.26; H, 4.26. Found, 42.23; H, 4.50.

This material showed a single spot on paper chromatography using 2-propanol–concentrated NH_4OH–water (7:1:2) and 1-butanol–acetic acid–water (5:2:3). Paper electrophoresis using pH 9.2 borate buffer showed a single spot with the same mobility as pseudouridine C.

B. Sodium (75 mg, 3 mmol) was added portionwise to a solution of **27a** (100 mg, 0.18 mmol) in dioxane (3 ml) and liquid ammonia (2.5 ml) until a blue color persisted. Ammonium chloride (100 mg) was added and the ammonia was evaporated. An aqueous solution of the residue was neutralized with dilute hydrochloric acid and extracted with chloroform giving 15 mg of unreacted **27a**. The aqueous phase was passed through a column of activated charcoal[44] (1.5 *g*) and washed thoroughly with water. Elution with ethanol–water–concentrated NH_4OH (50:45:5) followed by evaporation of the eluates gave 20 mg (39%) of material that was shown by paper chromatography and borate electrophoresis as in A to be a mixture of **28a** and presumably its α anomer.

2,4-Dioxo-8-β-D-ribofuranosyl-1,3-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine (28b). Debenzylation of **27b** (170 mg, 0.29 mmol) with boron trichloride was done as described for **27b** above. Crystallization from methanol–ether gave 55 mg (61%) of **28b** with mp 184–184.5 °C: $[\alpha]^{25}D$ −31.0° (*c* 0.5, MeOH); λ_{max} (MeOH) 215 nm (ϵ 15 400), 240 (5600), 254 (5800); ν_{max} (KBr) 1750, 1670, 1600 cm^{-1}; ^1H NMR (Me_2SO-d_6) 3.25, 3.55 (s, 3, NMe), 4.80 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}$ H), 7.95 (s, 1, C_7 H).

Anal. Calcd for $C_{12}H_{16}N_4O_6$ (312.29): C, 46.15; H, 5.17; N, 17.94. Found: C, 45.70; H, 5.12; N, 17.81.

Registry No.—**1b,** 38821-04-4; **1c,** 39038-02-3; **2,** 37699-02-8; **3,** 59463-89-7; **4b,** 59463-90-0; **4c,** 50866-58-5; **7a,** 59463-91-1; **7b,** 59463-92-2; **9a,** 59463-93-3; **9b,** 59463-94-4; **10,** 59463-95-5; **11,** 16205-54-2; **12,** 57361-98-5; **13,** 59463-96-6; **14** isomer A, 17579-99-6; **14** isomer B, 4167-91-3; **16a,** 57361-95-2; **16b,** 3679-96-8; **16c,** 59463-97-7; **17,** 59463-98-8; **19,** 59463-99-9; **20,** 59464-00-5; **21,** 59464-01-6; **22a,** 59464-02-7; **22b,** 59464-03-8; **22c,** 59464-04-9; **24a,** 59464-05-0; **24b,** 59464-06-1; **24c,** 59492-70-5; **25a,** 59464-07-2; **25b,** 59464-08-3; **26,** 5843-43-6; **27a,** 59464-09-4; **27b,** 59464-10-7; **28a,** 59464-11-8; **28b,** 59492-71-6; benzyl bromide, 100-39-0; ethyl bromide, 74-96-4; propiolic acid, 471-25-0; acetic anhydride, 108-24-7; 5,6,8-tri-*O*-benzyl-2,3,4-trideoxy-D-*erythro*-oct-4-en-2-ynonate, 59464-12-9; acetone, 67-64-1; methyl iodide, 74-88-4.

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4′-Substituted Nucleosides. 3. Synthesis of Some 4′-Fluorouridine Derivatives[1]

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The reaction of 1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**1**) with iodine fluoride in methylene chloride leads to the stereospecific formation of 5′-deoxy-4′-fluoro-5′-iodo-2′,3′-*O*-isopropylideneuridine (**4a**) in almost quantitative yield. The 5′-iodo function of **4a** can be converted into the analogous 5′-azido derivative (**5a**) by vigorous treatment with lithium azide in dimethylformamide. Treatment of **5a** with nitrosyl tetrafluoroborate leads to the isolation of 2,5′-anhydro-4′-fluoro-2′,3′-*O*-isopropylideneuridine (**6a**) which can be readily hydrolyzed to 4′-fluoro-2′,3′-*O*-isopropylideneuridine (**7a**). The latter compound has been converted into 4′-fluoro-5′-*O*-sulfamoyluridine (**8b**), the uracil analogue of nucleocidin, by treatment with sulfamoyl chloride followed by mild acidic hydrolysis. The synthesis of 4′-fluorouridine 5′-phosphate (**8d**] has also been achieved via conversion of **7a** to its bis(2,2,2-trichloroethyl)phosphate ester followed by careful removal of protecting groups. The unusual stabilities of 4′-fluorouridine derivatives are discussed. In addition, it has been shown that treatment of 2′,3′-methoxymethylene- and 2′,3′-methoxyethylideneuridine derivatives with nitrosyl tetrafluoroborate leads to the formation of 2,2′-anhydro-1-β-D-arabinofuranosyluracils, presumably via 2′,3′-acyloxonium ions.

Recent work from this laboratory has explored methods for the introduction of substituents at $C_{4'}$ of the furanose ring in both purine and pyrimidine nucleosides.[3] While other types of substituents have subsequently been introduced via different routes,[4] addition reactions to 4′,5′-unsaturated nucleosides have proved to provide a facile route to 4′-fluoro[1] and 4′-methoxynucleosides.[5] Thus the reactions of various 2′,3′ derivatives of 1-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil with iodine in methanol have been shown to lead to 5′-iodo-4′-methoxynucleosides with both the β-D-ribo and α-L-lyxo configurations.[5] The nature of the substituents on the 2′- and 3′-hydroxyl groups exerted striking steric control upon the addition reaction, the isopropylidene derivative leading to the β-D-ribo and α-L-lyxo derivatives in a ratio of 3:2 while the 2′,3′-carbonate gave only the former. In a related study it was shown that the addition of iodine fluoride (from iodine and silver fluoride) to a suitably protected 4′,5′-unsaturated adenosine derivative led to the formation of the epimeric 4′-fluoro-5′-iodonucleosides. The β-D-ribo isomer from the above reaction constituted the key intermediate in the total synthesis of the nucleoside antibiotic nucleocidin.[1,6] In the present paper we extend the above work to a study of the preparation of 4′-fluorouridine derivatives including the uracil analogue of nucleocidin.

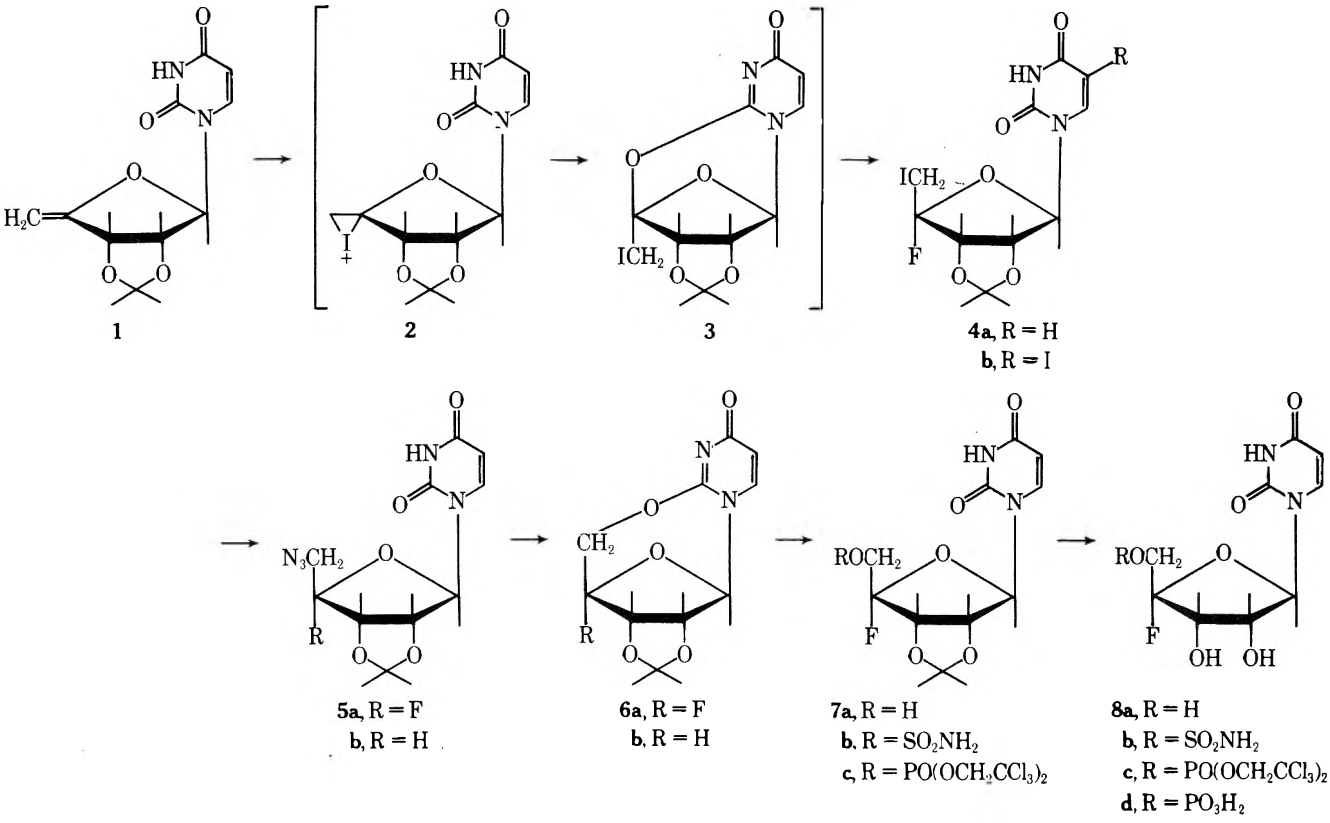
Our previous experience with the reactions of 4′,5′-unsaturated uridine derivatives with iodine and methanol suggested that the use of a 2′,3′-cyclic carbonate protecting group would probably be necessary in order to stereospecifically direct the addition of iodine fluoride so as to give the desired 4′-fluoro-β-D-ribofuranosyl configuration. As a prelude to this, however, we decided to examine the addition of iodine fluoride to 1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**1**).[7] Accordingly, a solution of iodine was gradually added to a solution of pure **1** in methylene chloride in the presence of an excess of finely divided silver fluoride. A rapid reaction ensued and was terminated once an iodine color persisted and the formation of a single new spot with an R_f just greater than that of **1** was shown by TLC.

By a simple workup this substance was isolated in quantitative yield and ^1H NMR analysis clearly showed that only a single isomer was present. This spectrum also strongly indicated that the product was only the desired 5′-deoxy-4′-fluoro-5′-iodo-2′,3′-*O*-isopropylideneuridine (**4a**) since our previous work in the adenosine series had allowed the development of several empirical rules distinguishing between 4′-fluoronucleosides in the β-D-ribofuranosyl and α-L-lyxofuranosyl series.[1] Thus the values of $J_{3',F}$ and $J_{1',F}$ were found to be 11.5 and 0 Hz, respectively, while the α-L-lyxofuranosyl epimer of **4a** would be expected to show values of roughly 5–6 and 2–2.5 Hz, respectively. In addition, the chemical shift difference between the isopropylidene methyl signals of **4a** was found to be 32 Hz, a figure similar to those observed for the 4′-fluoro-β-D-ribofuranosyl series (24–30 Hz) but quite unlike the α-L-lyxofuranosyl counterparts (16–19 Hz).[1] It is to be emphasized, however, that the chemical shift difference for isopropylidene groups is strongly solvent dependent, $\Delta\delta$ for **4a** being 32, 24, 21, and 16 Hz in deuterated benzene–acetone (3:1), pyridine, chloroform, and acetone, respectively. The rule appears to be reliable in chloroform and pyridine, but caution must be used in extrapolations to other solvents. The surprising stereoselectivity of this addition reaction suggests the participation of the uracil ring in its mechanism. Thus, opening of the presumed initial iodonium ion (**2**), or its oxonium counterpart, by the C_2 carbonyl of the uracil ring would form the O^2,4′-cyclonucleoside (**3**) which could be opened by fluoride ion to give exclusively the β-D-ribo compound **4a.** The 5′-bromo analogue of **3** has recently been isolated by Sasaki et al.[8] and opened with methanol, although the latter reaction appears to involve a subsequent epimerization.[5] The absence of comparable steric control during reaction of **1** with iodine in methanol[5] suggests that when methanol is the reaction solvent it can favorably compete with the uracil ring for direct attack at $C_{4'}$ of **2.**

It should be noted that if larger excesses of iodine (e.g., 8 equiv) and longer reaction times (e.g., 2 h) are used, a less polar by-product is also formed. This material has been separated in slightly impure form in 10–20% yields and on the basis of its uv, NMR, and mass spectra has been identified as the 5-iodouracil analogue **4b.** Formation of this substance has not been detected using the reaction conditions described in the Experimental Section.

As might be expected for a fluoro acetal, **4a** was quite labile toward both acid and base treatment. Thus, treatment of **4a** with 90% formic acid at room temperature for 1–2 h or with 1 M sodium hydroxide at 80° for 16 h led to uracil as the principal product. Further comments on the stabilities of 4′-fluoronucleosides have been noted[1] and others will appear later in this paper.

Previously, **1** has been prepared by treatment of the 5′-*O*-*p*-toluenesulfonyl[7a] or 5′-iodo[7b] derivatives of 2′3′-*O*-isopropylideneuridine in *tert*-butyl alcohol or dimethyl sulfoxide. While the yields of **1** are quite high, our experience has shown that the removal of several by-products requires careful chromatography and is hence awkward on a large scale. The



reaction of the readily available 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine[9] with potassium *tert*-butoxide in dioxane, however, leads to the rapid formation of **1** contaminated only with a little (5–10%) unreacted iodo compound. The latter creates no problem in the subsequent addition of iodine fluoride to crude **1** since it is quantitatively converted into O^2,5′-anhydro-2′,3′-*O*-isopropylideneuridine (**6b**)[9,10] which is removed during aqueous extraction. Using this approach it was possible to prepare essentially pure **1** (contaminated with only a trace of **6b**) in an overall yield of 91% from the iodonucleoside.

As was the case in the 4′-fluoro-5′-iodoadenosine series,[1] the iodo function of **4a** proved to be very resistant to nucleophilic displacement. Displacement by azide ion was possible under forcing conditions, but monitoring of this reaction has proved to be very difficult since we have been unable to find a TLC solvent system that separates **4a** from the resulting 5′-azido-4′-fluoronucleoside **5a**. It was, however, possible to follow the course of the reaction by NMR spectroscopy of worked-up aliquots since the chemical shifts of the $C_{5'}$ protons in **4a** and **5a** were found to be different (doublets at 3.47 and 3.54 ppm, respectively, in $CDCl_3$). By this technique a rough half-time of 1.5 h in dimethylformamide at 105 °C was observed. This is to be contrasted with a half-time of approximately 30 min for the conversion of 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine to its 5′-azido analogue with lithium azide in dimethylformamide at 21 °C. This indicates that the introduction of the 4′-fluoro substituent leads to about a 1000-fold decrease in the ease of displacement of the 5′-iodide. Based upon these guidelines the preparative conversion of **4a** to **5a** was conducted in dimethylformamide at 105 °C for 17 h. The reaction mixture rapidly became very dark colored, even under nitrogen, but most of the decomposition products appear to be water soluble and crystalline **5a** could be easily isolated in yields of 38–48%. All attempts to increase the yield of crystalline product have been unsuccessful. The ^1H (see Tables I and II) and ^{19}F NMR spectra of **5a** exhibit the same general characteristics shown by **4a** and further support the β-D-ribo configuration for these substances. It may be noted that the overall sequence from 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine to crystalline **5a** can be carried out in an overall yield of 37% without purification of any intermediates.

In the adenosine series the conversion of a 5′-azido-4′-fluoronucleoside analogous to **5a** to the desired 4′-fluoro-5′-hydroxyl counterpart was achieved via photolysis to the 5′-aldehyde followed by borohydride reduction.[1] An alternative route, based upon the work of Doyle and Wierenga,[11] involving reaction of the 5′-azido compound with nitrosyl tetrafluoroborate, led only to a complex mixture. It was our feeling, however, that this failure was predominantly due to side reactions with the adenine ring and, hence, it was of interest to see if the uracil counterpart would behave differently. As a model, 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**5b**) was reacted with 2 equiv of nitrosyl tetrafluoroborate in acetonitrile at 0 °C leading to a transient green color and gas evolution. Direct crystallization of the crude, extracted product gave not the expected 2′,3′-*O*-isopropylideneuridine, but rather O^2,5′-anhydro-2′,3′-*O*-isopropylideneuridine (**6b**)[9,10] in 75% yield. The suggested mechanism for this reaction[11] involves nitrosation of the azide and loss of nitrous oxide and nitrogen leading to a 5′-carbonium species. The latter must clearly undergo preferential intramolecular reaction with the C_2 oxygen of the uracil ring giving the cyclonucleoside **6b** rather than the 5′-alcohol. Since O^2,5′-cyclonucleosides such as **6b** are known to be readily hydrolyzed by both acid and base,[10] this approach seemed well suited to our purposes. Accordingly, **5a** was similarly treated with nitrosyl tetrafluoroborate and, while the reaction was somewhat slower than that with **5b**, it proceeded readily at room temperature giving amorphous O^2,5′-anhydro-4′-fluoro-2′,3′-*O*-isopropylideneuridine (**6a**) in 67% yield. The latter substance was pure by TLC and NMR analysis, and its unique uv spectrum (λ_{max} 237 nm) left no doubt as to its cyclonucleoside structure. While **6a** could be obtained in crystalline form, we prefer, because of its lability, to use the amorphous product directly in the next step.

The ^1H NMR spectrum of **6a** is quite unusual since the $C_{5'}$ protons appear as a sharp doublet (J_{gem} = 11.5 Hz), neither showing any coupling to the 4′-fluorine. Coupling of $C_{3'}$ H to

Table I. 100-MHz Proton Chemical Shifts (ppm)

Compd	Solvent[d]	$C_{1'}$ H	$C_{2'}$ H	$C_{3'}$ H	$C_{4'}$ H	$C_{5'}$ H_a	$C_{5'}$ H_b	C_5 H	C_6 H	Other
4a	B–A 3:1	5.51 (s)	4.85 (d)	5.08 (dd)		3.38 (d)		5.29 (d)	6.67 (d)	1.21 and 1.53 (s, 3, CMe_2)
4b	C	5.67 (s)	5.1 (m)	5.1 (m)		3.48 (ABX)			7.66 (s)	1.36 and 1.57 (s, 3, CMe_2)
5a	B–A 3:1	5.57 (br s)	4.85 (d)	5.08 (dd)		3.33 (d)		5.33 (d)	6.73 (d)	1.22 and 1.53 (s, 3, CMe_2)
6a	P	6.18 (s)	4.91 (d)[b]	5.02 (dd)[b]		4.41 (d)	4.72 (d)	6.10 (d)	7.90 (d)	1.30 and 1.47 (s, 3, CMe_2)
6b	P	5.94 (s)	5.02 (d)	4.94 (d)	4.76 (m)	4.24 (dd)	4.51 (dd)	6.10 (d)	7.83 (d)	1.31 and 1.48 (s, 3, CMe_2)
7a	D	6.15 (br s)	5.01 (d)	4.99 (dd)		3.44 (dd)	3.56 (dd)	5.61 (d)	7.66 (d)	1.29 and 1.46 (s, 3, CMe_2)
7b	P	6.38 (d)	5.30 (dd)	5.57 (dd)		4.82 (ABX)[a]	4.85 (ABX)[a]	5.77 (d)	7.69 (d)	1.37 and 1.63 (s, 3, CMe_2)
7c	C	5.69 (d)	5.07 (dd)	5.23 (dd)		4.9 (m)		5.74 (d)	7.22 (d)	1.37 and 1.58 (s, 3, CMe_2), 4.69 (d, 4, $POCH_2$)
8b	P	6.82 (d)	4.91 (dd)	5.15 (dd)		4.99 (d)		5.75 (d)	7.79 (d)	
8c	P	6.62 (d)	4.92 (dd)	5.20 (dd)		4.9 (m)		5.80 (d)	7.74 (d)	5.03 (d, 4, $POCH_2$)
9a	C	5.69 (s)	5.0 (m)	5.0 (m)		3.0 (m)		5.72 (d)	7.23 (d)	1.37 and 1.58 (s, 3, CMe_2)
9b	P	6.25 (br s)	5.29 (dd)	5.54 (dd)		3.91 (ddd)	4.17 (ddd)	5.75 (d)	7.62 (d)	1.33 and 1.63 (s, 3, CMe_2), 2.07 (s, 3, NAc)
11	C	5.81 (d)	5.25 (dd)	4.98 (dd)		3.5 (ABX)		5.74 (d)	7.19 (d)	3.41 (s, 3, OMe), 5.95 (d, 1, **H**COMe), 9.5 (br s, NH)
13b	D	6.45 (d)	5.37 (dd)	4.47 (dd)		3.60 (dd)[c]	3.82 (dd)	5.90 (d)	7.92 (d)	
16a	D	6.28 (d)	5.17 (d)	4.35 (d)	4.06 (dt)	3.25 (m)		5.81 (d)	7.82 (d)	
16c	P	6.69 (d)	5.71 (d)	5.84 (d)	4.65 (dt)	3.81 (dd)	3.98 (dd)	6.11 (d)	7.82 (d)	1.98 (s, 3, OAc)

[a] Via computer analysis of the ABX pattern by Dr. M. L. Maddox. [b] After addition of D_2O. In pyridine-d_5 alone, $C_{2'}$ H and $C_{3'}$ H are not resolved. [c] Partially obscured by HDO. [d] B = benzene-d_5; A = acetone-d_6; P = pyridine-d_5; C = $CDCl_3$; D = dimethyl sulfoxide-d_6.

Table II. First-Order Coupling Constants (Hz)

Compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5,6}$	Other
4a	0	6	11.5	16	16	0	7.5	
4b	0	*a*	*a*	*a*	*a*	*a*		
5a	~0.5	6	12	13.5	13.5	0	8	
6a	0	6	1.5	0	0	11.5	7.5	
6b	0	5.5	0	1	2	12.5	7	
7a	~0.5	6	11	7	1.5	13	7.5	
7b	1	6	12	10.3[b]	16.2[b]	11[b]	8	
7c	1	6	11.5	*a*	*a*	*a*	8	J_{POCH} = 6.5
8b	2	6.5	18	7	7	0	8	
8c	2	6	18	7.5	7.5	0	8	J_{POCH} = 6.5
9a	0	*a*	*a*	*a*	*a*	*a*	8	
9b	~0.5	0	13	14	8	14	8	$J_{5'a,NH}$ = 6, $J_{5'b,NH}$ = 6.5
11	2	7.5	7.5	*a*	*a*	*a*	8	$J_{HCOMe,F}$ = 1.5
13b	6.5	4	18	11	5	9	7.5	
16a	5.5	0	1.5	5	5	*a*	7.5	
16c	6	0	1.5	4	4	12	7	

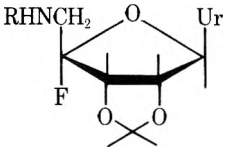
[a] Unresolved. [b] Via computer analysis of the ABX pattern by Dr. M. L. Maddox.

fluorine was also very small (1.5 Hz), and the surprisingly small magnitude of H–F couplings was confirmed by the ^{19}F NMR spectrum of **6a**, which showed only a slightly broadened singlet. These results are not readily predicted from a consideration of the known angular dependence of H–F couplings.[12] They are less surprising, however, when compared with the ^1H NMR spectrum of **6b**, which shows $J_{3',4'} = 0$ and only very small (1 and 2 Hz) 4′,5′ couplings. This suggests that cyclonucleosides such as **6a** and **6b** can adopt a conformation in solution that is not readily predicted from molecular models.

As expected, the 4′-fluorocyclonucleoside **6a** was rapidly hydrolyzed under acidic conditions and some care had to be taken to avoid partial spontaneous hydrolysis during reaction workup or chromatography. The course of the acidic hydrolysis could be readily followed by ultraviolet spectroscopy of aliquots in methanol, the initial spectrum of **6a** (λ_{max} 237 nm) rapidly changing to that of a uridine derivative (λ_{max} 256 nm).

In water adjusted to pH 2.0 with hydrochloric acid the half-times for hydrolysis of **6a** and **6b** were roughly 3.5 and 6 min, respectively. The similarities of these rates strongly suggest that it is the uracil C_2–oxygen bond that is undergoing cleavage rather than the $C_{5'}$–oxygen bond since the presence of the 4′-fluorine might be expected to exert a greater influence on the latter. In support of this, it was shown that treatment of **6a** with 1% trifluoroacetic acid in methanol at room temperature for 30 min led to the accumulation of a relatively stable component with λ_{max} 228 and 248 nm, very similar to the spectrum of O^2-methyluridine derivatives.[10] For preparative purposes the hydrolysis of **6a** could be readily accomplished using either very dilute (0.01–0.05 N) hydrochloric or trifluoroacetic acids in aqueous tetrahydrofuran or dioxane. Using, e.g., 0.05 N trifluoroacetic acid in tetrahydrofuran–water (9:1), the hydrolysis was shown to be essentially complete within 15 min at room temperature and 4′-fluoro-2′,3′-*O*-isopropylideneuridine (**7a**) could be isolated by preparative TLC in 75% yield. While we have been unable to obtain **7a** in crystalline form, it is an analytically and spectrally pure substance that can be purified and stored without undue difficulty. For preparative purposes it is advantageous to directly hydrolyze crude **6a,** and in this way pure **7a** can be obtained in 58% overall yield from **5a.**

It may be noted that in one larger scale preparation of **7a** as above a minor crystalline by-product with a TLC mobility just slower than that of **6a** was isolated in 5% yield. This substance was readily characterized as 5′-acetamido-5′-deoxy-4′-fluoro-2′,3′-*O*-isopropylideneuridine (**9b**) by the presence of a three-proton singlet at 2.07 ppm in its ^{1}H NMR spectrum in addition to the other usual features of a 4′-fluoronucleoside. The spectrum in pyridine-d_5 showed the 5′ protons as a very complex multiplet due to coupling with the $C_{5'}$ NH as well as the normal H_1 F and geminal couplings. Upon addition of D_2O this pattern collapsed to a pair of readily analyzed ABX signals. The same compound could also be obtained by palladium-catalyzed reduction of **5a** to give the 5′-amino-4′-fluoronucleoside **9a,** which was then acetylated with acetic anhydride. The formation of acetamide by-products has previously been observed during reactions of azides with nitrosyl tetrafluoroborate[11] and has been explained via trapping of the generated carbonium ion by the solvent acetonitrile. In smaller scale reactions, particularly when temperature control is stringent, the formation of **9b** seems negligible.

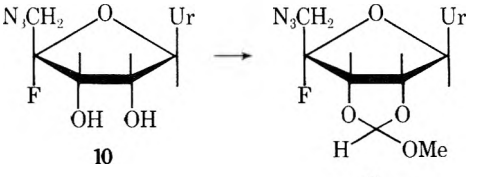


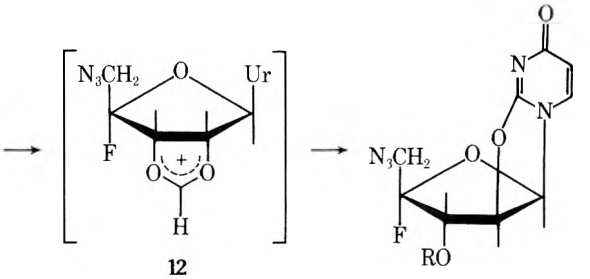
9a, R = H
b, R = $COCH_3$

The availability of **7a** made it attractive to undertake the synthesis of the 5′-*O*-sulfamoyl derivative, the uracil analogue of the antibiotic nucleocidin. In previous work, sulfamoylation of the adenine analogue of **7a** could only be readily accomplished via intermediate formation of an intermediate 5′-*O*-tributylstannyl derivative.[1] In the present case it was found that treatment of **7a** with an excess of sulfamoyl chloride in dioxane in the presence of a mixture of Linde 4A and AW-500 molecular sieves led to the isolation of the 5′-*O*-sulfamoyl derivative (**7b**) in 69% yield by chromatography on silicic acid. A similar method was used previously for the sulfamoylation of 2′,3′-di-*O*-acetyluridine by Shuman et al.[13] Hydrolysis of the isopropylidene function from **7b** could be accomplished by treatment with 90% formic acid at room temperature but was accompanied by considerable concomitant glycosidic cleavage giving uracil. By preparative TLC, however, chromatographically homogeneous 4′-fluoro-5′-*O*-sulfamoyluridine (**8b**) could be isolated in 45% yield. While the latter compound was homogeneous by ^{1}H NMR analysis, it could not be obtained in crystalline form and we have been unable to remove some contaminating silicic acid that was simultaneously eluted from the preparative TLC plate. Elemental analysis showed that there was a fortuitous 1 molar equiv of silica contaminating the product. We have, as yet, found no way of removing this impurity largely due to the alkaline and, to a lesser degree, acidic lability of **8b,** which precludes a number of possible methods. The impetus to achieve this goal was diminished by the finding that **8b** showed much reduced antibacterial and cytotoxic properties in comparison with those of nucleocidin itself.[14]

As was the case in the adenosine series, the stability of 4′-fluorouridine derivatives is strongly dependent upon the presence and nature of substituents on the 2′-, 3′- and 5′-hydroxyl groups. Thus, fully blocked compounds such as **4, 5a, 7b,** and **9** are reasonably stable compounds that can readily be chromatographed and stored without decomposition. In the presence of a suitable 5′ substituent the 2′,3′-diol derivatives (e.g., **8b**) are still reasonably stable, but the fully deblocked nucleoside **8a** is quite unstable. Thus **7a** was treated under a variety of acidic conditions in an effort to remove the isopropylidene group but inevitably uracil was the major product. For example, treatment of **7a** with 90% formic acid for 10 min at room temperature gave roughly 40% unreacted **7a,** 35% uracil, and only 25% of the desired **8a** as judged by TLC. Clearly, the rate of glycosidic cleavage is greater than that for acetal hydrolysis, and as yet we have not been successful in isolating a pure sample of **8a.**

The 5′-azido function does, however, provide a stabilizing influence on the glycosidic bond, and treatment of **5a** with 90% formic acid at room temperature for 105 min led to satisfactory formation of 5′-azido-5′-deoxy-4′-fluorouridine (**10**). The crude lyophilized product was not, however, completely pure by TLC and NMR analysis although no uracil was present as a contaminant. Attempted purification by chromatography on silicic acid led to partial decomposition giving uracil and hence crude **10** was used directly in subsequent steps. Attempted reaction of **10** with nitrosyl tetrafluoroborate did not look at all promising and was complicated by formation of uracil and the difficulty of separating the desired labile, water-soluble **8a** from inorganic salts. Hence it seemed necessary to use a 2′,3′-protecting group that is more acid labile than the isopropylidene function. Crude **10** was accordingly treated with methyl orthoformate in the presence of *p*-toluenesulfonic acid[15] giving the crystalline 2′,3′-*O*-methoxy-

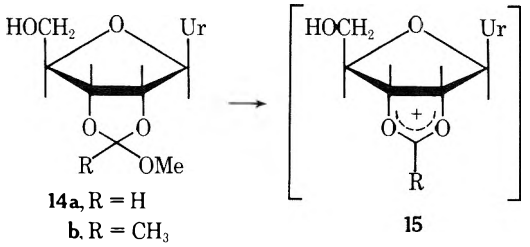




methylene derivative (11) in an overall yield of 52% from **5a**. As obtained, crystalline **11** appeared to be a single diastereomer as judged by its ^{1}H NMR spectrum.

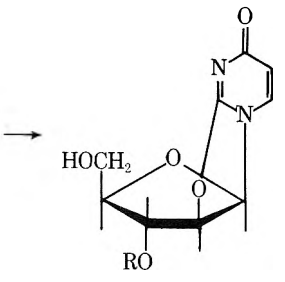
The reaction between 11 and a small excess of nitrosyl tetrafluoroborate proceeded rapidly at 0 °C giving a rather complex mixture of products. The major component could be separated from the others by virtue of its remaining in the aqueous phase during partitioning with chloroform. Subsequent desalting and preparative TLC led to the isolation of this substance in roughly 35% yield. While it still contained traces of silicic acid or other inorganic impurities that precluded obtaining an acceptable elemental analysis, this compound was clearly shown by spectral methods to be 2,2′-anhydro-1-(5′-azido-5′-deoxy-4′-fluoro-β-D-arabinofuranosyl)uracil (**13b**) rather than the expected 2′,3′-*O*-methoxymethylene analogue of **6a**. Thus **13b** was shown to have the typical ultraviolet spectrum of O^2,2′-cyclouridine derivatives (λ_{max} 223 and 247 nm).[16] In addition, its ^{1}H NMR spectrum was very similar to that of O^2,2′-cyclouridine except that both the $C_{3'}$ and $C_{5'}$ protons showed clear-cut H,F couplings and the $C_{5'}$ protons were somewhat deshielded by the presence of the azido substituent. The continued presence of the azido group was apparent from the ir spectrum (2110 cm^{-1}), and the mass spectrum of **13b** showed a molecular ion at *m/e* 269. The formation of **13b** suggests that nitrosyl tetrafluoroborate must react preferentially with the methoxymethylene group rather than with the azide. Collapse of an intermediate species, for which several possibilities exist, would then give the oxonium ion **12**, which in turn would be opened by intramolecular attack by the C_2 carbonyl oxygen of the uracil ring giving **13a**. The formate ester was presumably hydrolyzed during workup giving the observed **13b**. Ample precedent for the formation of O^2,2′-cyclonucleosides via collapse of 2′,3′-acyloxonium ions has been developed in this laboratory,[17] and the generation of oxonium ions from orthoesters in the presence of Lewis acids and related species has been documented.[18]

In order to cast further light on the generality of this unexpected reaction, we have also reacted 2′,3′-*O*-methoxymethyleneuridine (**14a**) with nitrosyl tetrafluoroborate in



14a, R = H
b, R = CH_3

15

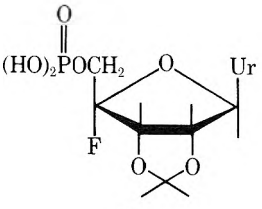


16a, R = H
b, R = CHO
c, R = $COCH_3$

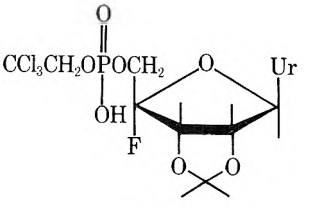
acetonitrile at 0–20 °C and obtained crystalline 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (**16a**) in 84% yield. The latter compound was in all ways identical with an authentic sample prepared by an independent route.[19] Once again, an intermediate 3′-*O*-formate (**16b**) was presumably lost by spontaneous hydrolysis during workup. A similar, but somewhat less efficient, conversion of **14a** to **16a** was also achieved using boron trifluoride etherate rather than nitrosyl tetrafluoroborate in acetonitrile at room temperature. In a closely related study, 2′,3′-*O*-methoxyethylideneuridine (**14b**)[20] was reacted with nitrosyl tetrafluoroborate at 0 °C and, following preparative TLC, crystalline 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil (**16c**) was isolated in 82% yield. The latter compound was identical by NMR, uv, and infrared analysis to a previously prepared sample of this compound.[17a] The presence of the 3′-*O*-acetyl group strongly supports the formation of **16** via the suggested 2′,3′-oxonium ion (**15**). Once again, the conversion of **14b** to **16c** could also be achieved using boron trifluoride etherate, the yield in this case being 68%.

Since the 5′-*O*-sulfamoyl group was found to exert a favorable influence on the stability of **8b**, it was of interest to see whether a phosphate ester would have a similar effect. Since 4′-fluorouridine 5′-phosphate (**8d**) was still expected to be fairly labile, the choice of phosphorylating agents was limited to those leading to products from which protecting groups could be removed under mildly acidic conditions. Accordingly, **7a** was reacted with commercially available bis(2,2,2-trichloroethyl) phosphorochloridate[21] in pyridine at room temperature for 1.5 h giving 4′-fluoro-2′,3′-*O*-isopropylideneuridine 5′-*O*-bis(2,2,2-trichloroethyl)phosphate (**7c**). Following removal of some unreacted **7a** and by-products by preparative TLC, **7c** was isolated as a foam in 50–80% yields. A somewhat better yield (90%) of **7c** was obtained by condensation of **7a** and bis(2,2,2-trichloroethyl)phosphoric acid,[22] prepared by hydrolysis of the phosphorochloridate, in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride. The latter reagent has previously been used with success for the condensation of nucleosides with mono(2,2,2-trichloroethyl)phosphoric acid.[23]

In small-scale experiments it was clear that the trichloroethyl groups could be largely removed from **7c** by treatment with zinc dust and acetic acid in dimethylformamide for 30 min at room temperature.[21,24] Analysis of the reaction product showed it to consist of 90% of the desired dianion (**17**) and 10%



17



18

of a monoanion, presumably the mono(trichloroethyl) ester (**18**). Similar accumulation of minor amounts of stubbornly resistant monoanions has previously been encountered in related reactions.[21,24c] Attempted hydrolysis of the isopropylidene group from crude **17** by treatment with 90% formic acid at room temperature was accompanied by extensive glycosidic cleavage giving uracil.

On the other hand, treatment of the phosphotriester **7c** with 90% formic acid led to removal of the isopropylidene group accompanied by relatively little glycosidic cleavage. The reaction had to be monitored rather carefully by TLC, and, since uracil formation became significant during the later stages, it was worked up before all **7c** had disappeared. By this technique it was possible to isolate the pure diol (**8c**) in 54–65% yields by preparative TLC. Treatment of **8c** with zinc dust and acetic acid in aqueous dimethylformamide was investigated under a number of conditions and the addition of a catalytic amount of silver acetate seemed to be advantageous.[25] Under all conditions the reaction appeared to stop while 5–15% of a monoanion species (presumably the diol related to **18**) still remained but formation of uracil was not significant. Pre-

liminary attempts to purify the major product (**8d**) by ion exchange chromatography were not promising. An effective separation of **8d** from the contaminating monoanion was achieved on columns of DEAE Sephadex (HCO_3^-) but some degradation to uracil accompanied evaporation of the aqueous triethylammonium bicarbonate eluents.

Fortunately, a separation of **8d** from the contaminating monoanion was readily accomplished as its barium salt. Following removal of zinc ions from the reaction mixture using Dowex 50 (NH_4^+) resin, an excess of barium acetate was added, followed by three volumes of ethanol. The resulting precipitated barium salts still contained some monoanion but reprecipitation using only two volumes of ethanol gave pure **8d** in a yield of 44% from **8c**. Once isolated in this way the barium salt seems reasonably stable and does not undergo decomposition upon storage at room temperature for several months.

The availability of pure **8d** allowed us to briefly examine its chemical stability. Its rate of alkaline hydrolysis was readily followed by uv spectroscopy since the hydrolysis product, uracil, has λ_{max} 284 nm in alkali while **8d** has very low absorption at that wavelength. Using this simple technique it was found that in 0.01 N sodium hydroxide at room temperature **8d** underwent roughly 20% hydrolysis to uracil in 45 min. In 0.05 N sodium hydroxide there was approximately 37% hydrolysis to uracil in 30 min. Under acidic conditions **8d** was considerably more stable as judged by the decrease in absorption at 260 nm in proceeding from a typical uridine spectrum (ϵ_{260} 10 000) to that of uracil (ϵ_{260} 7800). Thus, **8d** underwent no significant hydrolysis in 1 N hydrochloric acid at room temperature for 15 min, but was roughly 58% hydrolyzed in that acid after 30 min at 60 °C. It should be pointed out that these studies were done using the barium salt of **8d** and do not take into account any catalytic effects of the divalent metal ion. By way of comparison, 4′-fluoro-2′,3′-*O*-isopropylideneuridine (**7a**) is considerably more stable toward alkali, treatment with 0.6 N sodium hydroxide at room temperature giving roughly 50% uracil only after 2 h. It may be noted that the hydrolysis of **7a** cannot be followed by changes in the uv spectrum since there is generation of unknown uv absorbing by-products, probably via base-catalyzed eliminations on the initially formed 4-keto sugar. Clearly, the stabilizing effects of substituents on the different hydroxyl groups of 4′-fluorouridine vary widely and must be taken into consideration if **8d** is to be incorporated into other more complex molecules. Certainly syntheses of nucleoside polyphosphate and nucleotide coenzyme analogues derived from 4′-fluorouridine would be of interest for enzymological study. The present paper provides a sound foundation upon which to design such syntheses.

Experimental Section

General Methods. Thin layer chromatography (TLC) was done using 250-μ layers of silica gel GF obtained from Analtech, Inc., Newark, Del., and preparative TLC on 20 × 100 cm glass plates coated with a 1.3 mm layer of Merck silica gel HF. Column chromatography was done using the short column technique[26] with Merck silica gel GF. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian HA-100 instrument and are recorded in parts per million downfield of an internal standard of tetramethylsilane. Mass spectra were obtained on an Atlas CH-4 instrument fitted with a direct inlet system. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson and to Dr. L. Tökés for their continuous help with NMR and mass spectrometry. Most other analytical data were obtained by the staff of the Analytical Laboratories of Syntex Research, to whom we extend our thanks. Melting points were determined using a hot-stage microscope and are corrected.

5′-Deoxy-4′-fluoro-5′-iodo-2′,3′-*O*-isopropylideneuridine (4a). A. A saturated solution of iodine (2.72 g, 10.7 mmol) in methylene chloride (~50 ml) was added dropwise over 10 min to a stirred solution of purified **1** (1.33 g, 5 mmol)[7] in methylene chloride (100 ml) in the presence of finely divided silver fluoride (3.175 g, 25 mmol) until a permanent iodine color persisted. An aqueous solution (100 ml) containing 5% sodium bicarbonate and 5% sodium thiosulfate was then added and the mixture was filtered through a bed of Celite and washed with chloroform. The aqueous phase was extracted with chloroform and the combined organic phases were washed with the bicarbonate–thiosulfate solution and with water, dried ($MgSO_4$), and evaporated, leaving 2.04 g (99%) of **4a** as a dry foam that could not be crystallized. Analytical TLC separation of **4a** from **1** could be achieved using two developments with toluene–ethyl acetate–acetone (3:1:1) and ^1H NMR showed the presence of a single isomer.[27] An analytical sample prepared by preparative TLC (chloroform–methanol, 9:1) had λ_{max} (MeOH) 257 nm (ϵ 9400); mass spectrum (70 eV) *m/e* 412 (M^+), 397 ($M^+ - CH_3$), 354 (M^+ − acetone), 301 (M^+ − base), 243 (*m/e* 301 − acetone); ^{19}F NMR ($CDCl_3$) 101.8 ppm upfield of $CFCl_3$.

Anal. Calcd for $C_{12}H_{14}FIN_2O_5$ (412.16): C, 34.97; H, 3.42; N, 6.80. Found: C, 34.87; H, 3.53; N, 6.70.

B. A solution of potassium *tert*-butoxide (38 g, 340 mmol) in dioxane (1 l.) was added over 20 min to a stirred solution of 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine (66 g, 168 mmol)[9] in dioxane (1 l.). After a further 20 min a solution of sodium dihydrogen phosphate (138 g, 1 mol) in water (250 ml) was added with vigorous stirring and the resulting solution was partitioned between methylene chloride (1 l.) and water (1 l.). The organic phase was washed twice with water (1 l.), dried ($MgSO_4$), and evaporated, leaving crude **1** (~50 g) contaminated with ~10% unreacted iodo compound. A portion purified by preparative TLC (chloroform–methanol, 19:1) was identical with an authentic sample of **1**.[7b] Without purification crude **1** was dissolved in methylene chloride (3 l.) in the presence of finely divided silver fluoride (128 g, 1 mol) and solid iodine (89 g, 350 mmol) was added portionwise over 20 min. The reaction mixture was worked up as in A giving 63.2 g (91% from the iodo compound) of **4a** that was contaminated with only a faint trace of **6b**. The aqueous phase was shown by TLC to contain some cyclonucleoside (**6b**) that could be partially recovered by repeated extraction with chloroform. Following crystallization from ethanol it was shown to be identical with an authentic sample of **6b** (see later).

5′-Azido-5′-deoxy-4′-fluoro-2′,3′-*O*-isopropylideneuridine (5a). A. A solution of **4a** (13.6 g, 33 mmol) and lithium azide (8.3 g, 170 mmol) in dimethylformamide (300 ml) was stirred at 105 °C for 17 h. The mixture was then cooled and partitioned between chloroform (1.5 l.) and aqueous sodium bicarbonate (1 l.). The organic phase was then washed three times with water, dried ($MgSO_4$), and evaporated. The oily residue was crystallized from chloroform–hexane giving 3.82 g of pure **5a** with mp 153–153.5 °C. Chromatography of the mother liquors on a column of silicic acid using chloroform–methanol (99:1) gave a further 540 mg (total yield 40%) of crystalline **5a**: λ_{max} (MeOH) 256 nm (ϵ 9900); ^{19}F NMR ($CDCl_3$) 109.5 ppm upfield of $CFCl_3$; mass spectrum (70 eV) *m/e* 312 ($M^+ - CH_3$); ir (KBr) 2110 cm^{-1} (N_3).

Anal. Calcd for $C_{12}H_{14}FN_5O_5$ (327.27): C, 44.04; H, 4.31; N, 21.40. Found: C, 44.03; H, 4.32; N, 21.14.

B. The sequence 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine → **1** → **4a** → **5a** was carried out essentially as above starting with 66.45 g (168.6 mmol) of the 5′-iodonucleoside and without purification of any of the intermediates. In this way the overall yield of crystalline **5a** was 20.5 g (37%).

5′-Acetamido-5′-deoxy-4′-fluoro-2′,3′-*O*-isopropylideneuridine (9b). A solution of **5a** (654 mg, 2 mmol) in methanol (60 ml) was vigorously stirred for 2 h in an atmosphere of hydrogen in the presence of 10% palladium on carbon catalyst (500 mg). The mixture was filtered through Celite and the filtrate was evaporated leaving 586 mg (97%) of **9a** as a dry glass that failed to crystallize: ir (KBr) 3390 (NH_2), no N_3, 1680 cm^{-1}; mass spectrum (70 eV) *m/e* 300 ($M^+ - H$), 286 ($M^+ - CH_3$), 281 (M^+ − HF), 243 (M^+ − acetone). A portion of this material (301 mg, 1 mmol) was treated overnight with acetic anhydride (1 ml) in pyridine (10 ml). Following evaporation of the solvents the residue was purified by preparative TLC using chloroform–methanol (9:1). Crystallization from chloroform–hexane gave 247 mg (72%) of pure **9b**. An anlytical sample from chloroform–hexane and then ethyl acetate had mp 150.5–153.5 °C: λ_{max} (MeOH) 256 nm (ϵ 9400); mass spectrum (70 eV) *m/e* 328 ($M^+ - CH_3$), 323 (M^+ − HF), 285 (M^+ − acetone), 265 (M^+ − HF and acetone).

Anal. Calcd for $C_{14}H_{18}FN_3O_6$ (343.31): C, 48.98; H, 5.28. Found: C, 49.20; H, 5.40.

2,5′-Anhydro-2′,3′-*O*-isopropylideneuridine (6b). Solid nitrosyl tetrafluoroborate (300 mg, 2.6 mmol) was added to a solution of **5b** (309 mg, 1 mmol) in dry acetonitrile (5 ml) at 0 °C. Gas evolution took place as the nitrosyl salt dissolved leaving a pale yellow solution. After 15 min aqueous disodium hydrogen phosphate (5 ml of 1 M) was

added and the solution was extracted three times with chloroform. The extracts were dried ($MgSO_4$) and evaporated leaving 251 mg of a crystalline residue that was shown by TLC (chloroform–methanol, 9:1) to be **6b** contaminated with roughly 5% of 2′,3′-*O*-isopropylideneuridine. Crystallization from ethanol gave 175 mg of **6b** which sintered at 190 °C and slowly decomposed without melting until above 270 °C. Preparative TLC of the mother liquors followed by crystallization gave a further 25 mg (total yield 75%) of **6b:** λ_{max} (MeOH) 236 nm (ϵ 13 900) and NMR identical with that of an authentic sample.[9,10]

2,5′-Anhydro-4′-fluoro-2′,3′-*O*-isopropylideneuridine (6a). Solid nitrosyl tetrafluoroborate (700 mg, 6 mmol) was added to a stirred solution of **5a** (654 mg, 2 mmol) in anhydrous acetonitrile (10 ml). After 20 min at 0 °C the mixture was allowed to warm to room temperature and stirred for an additional 50 min with addition of a further 50 mg of nitrosyl salt after 45 min. At this point TLC (chloroform–methanol, 9:1) showed the starting material to have disappeared and a saturated aqueous solution of sodium chloride and disodium hydrogen phosphate (25 ml) was added. The aqueous phase was extracted three times with methylene chloride and the combined organic phases were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated, leaving 380 mg (67%) of **6a** as a foam that was homogeneous by TLC and NMR analysis. An analytical sample was crystallized from ethanol to give **6a** which slowly sintered and turned brown above 180 °C and melted with decomposition at 240–245 °C: λ_{max} (MeOH) 237 nm (ϵ 13 400); ^{19}F NMR (pyridine-d_5) 141.76 ppm upfield of $CFCl_3$.

Anal. Calcd for $C_{12}H_{13}FN_2O_5$ (284.24): C, 50.71; H, 4.61; N, 9.85. Found: C, 50.56; H, 4.68; N, 9.74.

4′-Fluoro-2′,3′-*O*-isopropylideneuridine (7a). A. Trifluoroacetic acid (0.015 ml) was added to a solution of **6a** (50 mg) in a mixture of tetrahydrofuran (2.7 ml) and water (0.3 ml). The reaction was monitored by examination of the uv spectra of 2-μl aliquots, the initial λ_{max} of 236 nm changing to λ_{max} 256 nm within 15 min. After 20 min the solvent was evaporated in vacuo at room temperature and the residue was coevaporated four times with methanol. The final residue was purified by preparative TLC using benzene–acetone (2:1), elution of the major band giving 40 mg (75%) of **7a** as a dry foam that could not be crystallized: λ_{max} (MeOH) 256 nm (ϵ 9300); mass spectrum (70 eV) *m/e* 287 ($M^+ - CH_3$).

Anal Calcd for $C_{12}H_{15}FN_2O_6$ (302.26): C, 47.67; H, 5.00; N, 9.27. Found: C, 47.45; H, 5.01; N, 9.06.

B. A solution of **5a** (3.27 g, 10 mmol) and nitrosyl tetrafluoroborate (2.40 g, 20 mmol) in acetonitrile (100 ml) was stored at 0 °C for 30 min and then at room temperature for 30 min. The reaction mixture was worked up as in A and the crude product was directly dissolved in dioxane–water (9:1) and made 0.01 N in hydrochloric acid. After 2 h at room temperature the solution was neutralized with ammonium hydroxide and evaporated to dryness. The residue was dissolved in chloroform–methanol (98:2), filtered, and applied to a column of silicic acid (120 g). Elution with 3% methanol in chloroform gave 1.74 g (58% from **5a**) of pure **7a** identical with that from A by TLC and NMR analysis.

In one experiment similar to B on an 8-mmol scale, a by-product with a TLC mobility just lower than that of **6a** was isolated in 5% yield by chromatography as above. This material was crystallized from chloroform and found to be identical with **9b**.

4′-Fluoro-2′,3′-*O*-isopropylidene-5′-*O*-sulfamoyluridine (7b). A solution of **7a** (1.6 g, 5.3 mmol) and sulfamoyl chloride (1.85 g, 16 mmol) in anhydrous dioxane (120 ml) was stirred at room temperature for 18 h in the presence of a 1:1 mixture (60 g) of Linde 4A and AW-500 molecular sieves. At this point TLC (chloroform–methanol, 9:1) showed the reaction to be essentially complete and ammonium hydroxide (1 M, 20 ml) was added. The mixture was filtered and the filtrate was evaporated leaving a syrup that was triturated with methanol and filtered to remove ammonium chloride. The evaporated filtrate was chromatographed on a column of silicic acid (80 g) using chloroform–methanol (19:1) giving 1.39 g (69%) of **7b** that was homogeneous by TLC and NMR analysis. An analytical sample was crystallized from acetone–hexane with mp 163.5–166.5 °C dec. In a separate experiment crystalline **7b** was isolated in 45% yield: λ_{max} (MeOH) 255 nm (ϵ 9700).

Anal. Calcd for $C_{12}H_{16}FN_3O_8S$ (381.34): C, 37.79; H, 4.23; N, 11.02. Found: C, 38.25; H, 4.50; N, 10.79.

4′-Fluoro-5′-*O*-sulfamoyluridine (8b). A solution of **7b** (1.25 g, 3.2 mmol) in 90% formic acid (10 ml) was stored at room temperature for 2 h and then evaporated to dryness. Following several coevaporations with ethanol the residue was purified by preparative TLC using chloroform–methanol (3:1). Elution of the major band with chloroform–methanol (1:2) gave 579 mg (45%) of **8b** as a colorless glass that contained a small amount of silicic acid that could not be removed. All attempts at crystallization were unsuccessful and analytical data were obtained on a sample lyophilized from water: λ_{max} (MeOH) 259 nm (ϵ 9600).

Anal. Calcd for $C_9H_{12}FN_3O_8S{\cdot}SiO_2$ (401.36): C, 26.93; H, 3.01; N, 10.47; residue, 14.97. Found: C, 26.68; H, 3.19; N, 10.37; residue, 16.17.

Bis(2,2,2-trichloroethyl) Phosphate. Water (0.80 ml, 44.5 mmol) was added with stirring to bis(2,2,2-trichloroethyl) phosphorochloridate (15.17 g, 40 mmol) that had been melted and maintained at 80–85 °C. After 30 min the mixture was thoroughly evacuated leaving a crystalline mass. Crystallization from hexane gave 12.58 g (87%) of bis(2,2,2-trichloroethyl) phosphate with mp 81–84 °C: NMR ($CDCl_3$) 4.61 ppm (d, 4, $J_{H,P}$ = 6.5 Hz, OCH_2), 11.5 (s, 1, POH).

Anal. Calcd for $C_4H_5Cl_6O_4P$ (360.77): C, 13.32; H, 1.40. Found: C, 13.22; H, 1.41.

4′-Fluoro-2′,3′-*O*-isopropylideneuridine 5′-*O*-Bis(2,2,2-trichloroethyl)phosphate (7c). A solution of **7a** (1.64 g, 5.4 mmol), bis(2,2,2-trichloroethyl) phosphate (2.35 g, 6.5 mmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (5.15 g, 17 mmol) in pyridine (40 ml) was stored at room temperature for 3 h and then quenched by addition of water (2 ml). After 30 min the solvent was evaporated and the residue was partitioned between chloroform and 10% aqueous sodium bicarbonate. The organic phase was washed with water, dried ($MgSO_4$), and evaporated, leaving a residue that was chromatographed on a column of silicic acid using chloroform–methanol (9:1). Evaporation of the major product left 3.12 g (90%) of **7c** as a TLC homogeneous foam: λ_{max} (MeOH) 255 nm (ϵ 9700).

Anal. Calcd for $C_{16}H_{18}Cl_6FN_2O_9P$ (645.02): C, 29.79; H, 2.81; N, 4.34. Found: C, 30.14; H, 3.13; N, 4.14.

4′-Fluorouridine 5′-*O*-Bis(2,2,2-trichloroethyl)phosphate (8c). A solution of **7c** (1.29 g, 2 mmol) in 90% formic acid (2 ml) was stored at room temperature, the hydrolysis being monitored by TLC using benzene–acetone (1:1). After 20 h the solvent was evaporated in vacuo and the residue was coevaporated several times with toluene–methanol. The residue was purified by preparative TLC using benzene–acetone (1:1) to separate unreacted **7c** (185 mg, 14%) and uracil (~10%) from the major product. Elution of the main band gave 655 mg (54%) of **8c** as a TLC homogeneous foam: λ_{max} (MeOH) 257 nm (ϵ 9600).

Anal. Calcd for $C_{13}H_{14}Cl_6FN_2O_9P$ (604.98): C, 25.81; H, 2.33; N, 4.63. Found: C, 25.87; H, 2.46; N, 4.20.

4′-Fluorouridine 5′-*O*-Phosphate (8d). Acetic acid (0.5 ml of 8.5 M) was added dropwise at room temperature over 2–3 min to a stirred solution of **8c** (121 mg, 0.2 mmol) in dimethylformamide (3 ml) and water (2 ml) in the presence of zinc powder (260 mg, 4 mmol)[28] and silver acetate (9 mg, 40 μmol). After 30 min paper electrophoresis at pH 7.5 showed the presence of a dianion and monoanion in a ratio of roughly 85:15 and this did not subsequently change. After 1.5 h Dowex 50 (NH_4^+) resin (2 ml) was added and the mixture was stirred and filtered. The filtrate was passed through a column of Dowex 50 (NH_4^+) resin (15 ml) and the eluates and water washings (1850 OD units at 259 nm) were carefully evaporated to dryness at 30 °C. The residue was dissolved in water (2 ml) and aqueous 1 M barium acetate (0.6 ml) was added followed by ethanol (8 ml). The resulting precipitate was reprecipitated twice using three volumes of ethanol to give 64 mg of **8d** that was shown by paper electrophoresis to still contain a small amount of a monoanion. Reprecipitation of this material from water (2 ml) by addition of two volumes of ethanol gave 45 mg (44%) of homogeneous **8d** as a dihydrate after careful drying in vacuo: λ_{max} (H_2O) 260 nm (ϵ 9600); P:uridine[29] = 1.03. An analytical sample was further reprecipitated to ensure the absence of inorganic salts.

Anal. Calcd for $C_9H_{10}FN_2O_9PBa{\cdot}2H_2O$ (513.54): C, 21.04; H, 2.75; N, 5.45. Found: C, 21.00; H, 2.78; N, 4.92.

5′-Azido-5′-deoxy-4′-fluoro-2′,3′-*O*-methoxymethyleneuridine (11). A solution of **5a** (654 mg, 2 mmol) in 90% formic acid (5 ml) was stored at room temperature, the reaction being monitored by TLC using chloroform–methanol (9:1). After 105 min the solution was evaporated to dryness in vacuo and the residue was lyophilized from water giving 640 mg of **10** as a dry glass that was essentially pure by TLC analysis. The product is not stable and attempted purification led to partial hydrolysis to uracil. The crude product was dissolved in a mixture of dioxane (8 ml) and methyl orthoformate (2 ml) together with *p*-toluenesulfonic acid (18 mg) and stored at room temperature. After 1 h the solution was neutralized by dropwise addition of methanolic sodium methoxide and then evaporated to dryness. A chloroform solution of the residue was washed with aqueous sodium bicarbonate and water, dried, and evaporated, leaving a crystalline solid. Crystallization from chloroform–hexane gave 344 mg (52% from **5a**) of a single diastereoisomer (^1H NMR) of **11** with mp 157–162 °C:

λ_{max} (MeOH) 256 nm (ϵ 9800); ν_{max} (KBr) 2110 (N_3), 1700 cm^{-1} (CO); mass spectrum (70 eV) *m/e* 329 (M^+), 298 ($M^+ - OCH_3$), 273 ($M^+ - CH_2N_3$), 218 (M^+ − uracil), 113 (uracil + 2 H).

Anal. Calcd for $C_{11}H_{12}FN_5O_6$ (329.24): C, 40.13; H, 3.67; N, 21.27. Found: C, 40.00; H, 3.72; N, 21.12.

Reaction of 11 with Nitrosyl Tetrafluoroborate. Nitrosyl tetrafluoroborate (82 mg, 0.7 mmol) was added to a stirred solution of **11** (165 mg, 0.5 mmol) in acetonitrile (10 ml) at 0 °C. After 30 min TLC analysis (chloroform–methanol, 9:1) showed **11** to be absent and saturated aqueous disodium hydrogen phosphate (15 ml) was added. The precipitated salts were removed by filtration and the aqueous phase was extracted repeatedly with chloroform. The major ultraviolet absorbing product remained in the aqueous phase, which was diluted with methanol and filtered to remove inorganic salts. The filtrate was evaporated and purified by preparative TLC using chloroform–methanol (9:1). The major uv absorbing band (R_f 0.17) was eluted with methanol and evaporated giving 50 mg of a glass with the typical uv spectrum of O^2,2′-cyclouridine: λ_{max} (MeOH) 223, 247 nm; λ_{min} 235 nm; ν_{max} (KBr) 2110 (N_3), 1660, 1630 cm^{-1}; mass spectrum (70 eV) *m/e* 269 (M^+), 213 ($M^+ - CH_2N_3$), 112 (uracil + H). See Tables I and II for ^1H NMR. The sample still contained traces of silica gel or inorganic salts and an acceptable elemental analysis was not obtained.

Reaction of 2′,3′-*O*-Methoxymethyleneuridine (14a) with Nitrosyl Tetrafluoroborate. Nitrosyl tetrafluoroborate (400 mg, 3.4 mmol) was added to a stirred solution of **14a** (572 mg, 2 mmol)[15] in acetonitrile (20 ml) at 0 °C and the mixture was allowed to warm to room temperature. After 20 min the mixture was concentrated to roughly 5 ml and directly purified by preparative TLC using chloroform–methanol (4:1). The major, broad, slow moving band was eluted with methanol–chloroform (1:1) giving 542 mg of a glass which was crystallized from methanol giving only 86 mg of **16a**. Rechromatography of the mother liquors using chloroform–methanol (3:1) followed by crystallization from methanol gave a further 291 mg (total yield 377 mg, 84%) of pure **16a** with mp 238–240 °C that was identical with an authentic sample by TLC, uv, and NMR.

2,2′-Anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil (16c). A. Nitrosyl tetrafluoroborate (400 mg, 3.4 mmol) was added to a solution of **14b** (600 mg, 2 mmol)[20] in acetonitrile (20 ml) at 0 °C. After 20 min a saturated solution of disodium hydrogen phosphate was added leading to separation of two phases. The upper phase was evaporated to dryness and purified by preparative TLC using chloroform–methanol (85:15) giving 611 mg of crude, crystalline **16c**. Recrystallization from ethanol gave 440 mg (82%) of **16b** with mp 200–202 °C and identical with an authentic sample[17a] by TLC, NMR, uv, and infrared analysis: λ_{max} (MeOH) 225 nm (ϵ 9300), 250 (7900).

B. Boron trifluoride etherate (0.28 ml, 2.2 mmol) was added to a solution of **14b** (300 mg, 1 mmol) in acetonitrile (10 ml) at 0 °C. After 15 min the mixture was worked up as in **A** giving 181 mg (68%) of **16c** identical with that above.

Registry No.—**1**, 17331-67-8; **4a**, 59462-99-6; **4b**, 59463-00-2; **5a**, 40764-48-5; **5b**, 15083-05-3; **6a**, 59463-01-3; **6b**, 3868-21-1; **7a**, 40654-03-3; **7b**, 59463-02-4; **7c**, 59463-03-5; **8b**, 59463-04-6; **8c**, 59463-05-7; **8d**, 59463-06-8; **9a**, 59463-07-9; **9b**, 59463-08-0; **11**, 59463-09-1; **13b**, 59463-10-4; **14a**, 16628-81-2; **14b**, 16667-57-5; **16a**, 3736-77-4; **16b**, 59463-11-5; **16c**, 38642-32-9; iodine, 7553-56-2; 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidenenuridine, 14671-65-9; lithium azide, 19597-69-4; acetic anhydride, 108-24-7; sulfamoyl chloride, 7778-42-9; bis(2,2,2-trichloroethyl) phosphate, 59463-12-6; bis(2,2-trichloroethyl) phosphorochloridate, 17672-53-6; nitrosyl tetrafluoroborate, 14635-75-7.

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Reactions of Ketene Acetals. 8.[1] Simple Syntheses of the Methyl Ester–Ethers of the Anthraquinones Endocrocin, Ptilometric Acid, and Clavorubin

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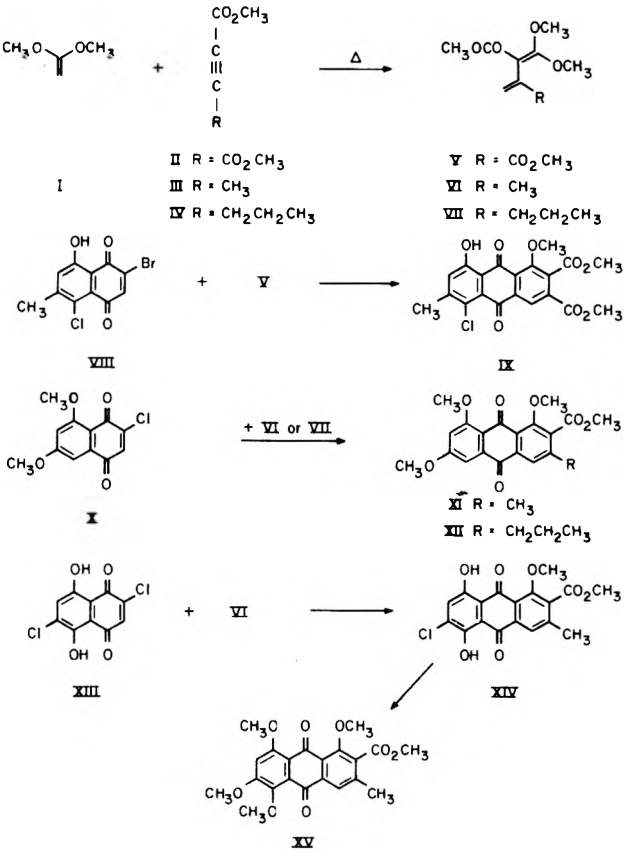
Appropriately substituted 1,1-dimethoxybutadienes (vinylketene acetals) obtained from ketene acetals and alkynoic esters were condensed with 2-chloro-6,8-dimethoxynaphthoquinone and gave directly tri-*O*-methylendocrocin methyl ester and methyl tri-*O*-methylptilometrate. An analogous reaction using 2,6-dichloronaphtazarin followed by substitution of the remaining chlorine by methoxide produced tetra-*O*-methylclavorubin methyl ester.

Ketene acetals have recently been used in order to simplify the preparation[2] of some naturally occurring anthraquinones or to elaborate some first total syntheses in this field.[1] Unsubstituted ketene acetals thus have given convenient syntheses of catenarin, helminthosporin, emodin, and indirectly of (±)-nalgiovensin (±)-isorhodoptilometrin, and (±)-rhodoptilometrin, whereas a simple conjugated reagent, isopropenylketene acetal, has been applied in the case of chrysophanol. Difficultly accessible substitution patterns as shown by the title compounds could in principle be obtained regiospecifically by the use of dienes analogous to those prepared by Brannock et al.[3]

It has been shown[3] that the reactions of ketene acetals with dimethyl acetylenedicarboxylate or methyl propiolate involved cycloadditions followed by electrocyclic processes since they eventually led to the formation of substituted 1,1-dialkoxybutadienes. The reactivity of such compounds toward 2-halonaphthoquinones was first tested using 2,3-dicarbomethoxy-1,1-dimethoxy-1,3-butadiene (V) obtained in a 47% yield from ketene dimethyl acetal (I) and dimethyl acetylenedicarboxylate (II). In spite of the presence of bulky electron-attracting groups in the diene, the latter proved to be quite reactive and a cycloaddition involving 2-bromo-5-chloro-8-hydroxy-6-methylnaphthaquinone (VIII) was complete in 1 h at 130 °C. Examination of the NMR spectrum of the crude reaction product revealed the presence of the expected anthraquinone and of another compound, probably the adduct, as indicated by aliphatic methoxyl signals at δ 3.21 and 3.29. A complete conversion to the desired product IX required an additional 3 h of heating at the same temperature.

The widely distributed metabolite endocrocin and the crinoid pigment ptilometric acid or their derivatives have until now only been synthesized by tedious means involving a large number of steps.[4-7] Attempts to prepare the appropriate dienes VI and VII from methyl tetrolate and methyl hex-2-ynoate according to the method used[3] for analogous products were unsuccessful. The reagents were, however, obtained in 35 and 28% yields, respectively, by prolonged heating (20–22 h) without solvent and at higher temperatures (145–160 °C) when large amounts (35–40%) of the unreacted esters could be recovered. By condensing these dienes with 2-chloro-6,8-dimethoxynaphthaquinone (X), which has only recently become available,[8] at 150–160 °C for 2–3 h, the permethylated derivatives of endocrocin and ptilometric acid were obtained in yields of 48 and 56%, respectively.

The minor ergot pigment clavorubin had previously been prepared by the manganese dioxide oxidation of endocrocin but only in low yield.[9] The most convenient starting material for the preparation of the completely methylated derivative of this quinone is undoubtedly 2,6-dichloronaphthazarin[10,11] (XIII). Condensation of this quinone with the diene VI as



before followed by pyrolysis at 150 °C for 1 h gave an excellent yield (87%) of the expected product XIV, thus confirming the previously observed favorable effect of peri-hydroxyl groups. The substitution of the remaining chlorine by methoxide could not be carried out in the usual manner[12,13] (CH_3ONa–CH_3OH) as the disodium salt of the substrate seems to be completely insoluble under these conditions, It could, however, be efficiently accomplished (75% after methylation) in a mixture of methanol and dimethylformamide in the presence of copper(I) iodide according to a recently published procedure.[14] Partial cleavage of the ethers is observed giving products strongly adsorbed during chromatography. The crude material was therefore methylated before purification. The resulting derivative XV has not been described earlier and an authentic sample of clavorubin could not be obtained. However, the general resemblance of the spectra of the three title compounds, the presence in the NMR spectrum of quinone XV of very characteristic signals corresponding to the protons in positions 4 and 7, and the fact that no trace of nonregiospecific products has ever been detected in this use

of ketene acetals leave very little doubt as to the precise structure of the synthetic substance.

Experimental Section

All melting points were taken for samples in capillary tubes with a Thomas-Hoover apparatus (calibrated thermometer). The ir and uv spectra were determined on Beckman Model IR-12 and Model DK-1A spectrophotometers, respectively. The NMR spectra were recorded on Varian A-60 and Bruker HX-90 spectrometers (tetramethylsilane as internal standard). Woelm silica gel, activity III, was used throughout for dry column chromatography.

2,3-Dicarbomethoxy-1,1-dimethoxy-1,3-butadiene (V). To a solution of dimethyl acetylenedicarboxylate (II, 9.50 g, 0.0668 mol) in dry acetonitrile (8 ml) was added dropwise (10 min) ketene dimethyl acetal (I,[15] 5.90 g, 0.0669 mol). The reaction mixture was stirred at room temperature (1 h), then refluxed (2 h) and evaporated. The residue was distilled under vacuum and gave the diene V (7.30 g, 48%): bp 104–106 °C (0.3 mm); n^{25}D 1.4838; ν_{max} (film) 1725 (ester) and 1600 cm^{-1} (broad, diene); δ (90 MHz, $CDCl_3$) 3.60, 3.66, 3.68 and 3.93 (4 × 3 H, 4 s, 1,1-OCH_3 and 2,3-CO_2CH_3), 5.35 and 6.26 (2 × 1 H, 2 d, J = 1.5 Hz, 4-H_2); m/e 230 (M^+). Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.08; H, 6.24.

2-Carbomethoxy-1,1-dimethoxy-3-methyl-1,3-butadiene (VI). A mixture of methyl tetrolate (III, 20.0 g, 0.204 mol) and ketene dimethyl acetal (I, 18.0 g, 0.204 mol) was heated in a sealed tube at 145 °C for 20 h and fractionated under vacuum, and gave unchanged methyl tetrolate (7.9 g, 38%), bp 50–60 °C (15 mm), and the diene VI (13.5 g, 35%): bp 106–112 °C (15 mm); n^{24}D 1.4774; ν_{max} (film) 1710 (ester), 1640 and 1601 cm^{-1} (diene); δ (60 MHz, neat) 1.83 (3 H, m, 3-CH_3), 3.60, 3.64, and 3.65 (3 × 3 H, 3 s, 1,1-OCH_3 and 2-CO_2CH_3), 4.75 and 4.97 (2 × 1 H, 2 m, 4-H_2). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.97; H, 7.64.

Methyl Hex-2-ynoate (IV). This compound was prepared from butanoyl chloride (125.6 g, 1.18 mol) and carbomethoxymethylenetriphenylphosphorane (404.8 g, 1.21 mol) according to the method described for the ethyl ester.[16] The intermediate 1-carbomethoxy-2-oxopentylidenetriphenylphosphorane (268 g) was pyrolyzed in 50-g portions (230 °C, 10 mm) and gave methyl hex-2-ynoate (IV, 45.0 g, 59%): bp 76–80 °C (25 mm) [lit.[17] bp 80–82 °C (23 mm)]; n^{20}D 1.4409; ν_{max} (film) 2241 (triple bond) and 1715 cm^{-1} (ester); δ (90 MHz, $CDCl_3$) 1.00 (3 H, t, J = 7.0 Hz, 6-H_3), 1.61 (2 H, sextuplet, J = 7.0 Hz, 5-H_2), 2.30 (2 H, t, J = 7.0 Hz, 4-H_2), 3.70 (3 H, s, 1-CO_2CH_3); m/e 216 (M^+). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.61; H, 7.99.

2-Carbomethoxy-1,1-dimethoxy-3-propyl-1,3-butadiene (VII). A mixture of methyl hex-2-ynoate (IV, 25.2 g, 0.200 mol) and ketene dimethyl acetal (I, 17.6 g, 0.200 mol) was heated in a sealed tube at 155–160 °C for 22 h and distilled under vacuum and gave unreacted methyl hex-2-ynoate (9.7 g, 39%), bp 76–78 °C (20 mm), and the diene VII (11.9 g, 28%): bp 70–72 °C (0.5 mm); n^{24}D 1.4730; ν_{max} (film) 1707 (ester) and 1607 cm^{-1} (diene); δ (60 MHz, neat) 0.88 (3 H, t, J = 7.0 Hz, 3′-H_3), 1.40 (2 H, m, 2′-H_2), 2.14 (2 H, m, 1′-H_2), 3.55 and 3.59 (2 × 3 H, 2 s, 1,1-OCH_3), 3.74 (3 H, s, 2-CO_2CH_3), 4.75 and 4.95 (2 H, 2 m, 4-H_2). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.05; H, 8.84.

4-Chloro-6,7-dicarbomethoxy-1-hydroxy-8-methoxy-3-methylanthraquinone (IX). A mixture of 2-bromo-5-chloro-8-hydroxy-6-methylnaphthoquinone[2] (VIII, 600 mg, 1.99 mmol) and 2,3-dicarbomethoxy-1,1-dimethoxy-1,3-butadiene (V, 920 mg, 3.99 mmol) in dry benzene (1 ml) was refluxed until it become homogeneous (10 min) and then evaporated. The residue was kept at 130 °C for 4 h, cooled, and chromatographed on silica gel (60 g) (dry column, benzene–ethyl acetate, 19:1) and gave the anthraquinone IX (743 mg, 89%), mp 183.5–184.0 °C (chloroform–methanol). An analytical sample was recrystallized four times from methanol: mp 187.5–188.0 °C; λ_{max} (ethanol) 247, 282 (sh), 345, 420 nm (log ϵ 4.45, 3.96, 3.55, 3.84); ν_{max} (KBr) 1735 (ester), 1680 (carbonyl), 1640 (chelated carbonyl), 1595 cm^{-1} (aryl); δ (90 MHz, $CDCl_3$) 2.50 (3 H, s, 3-CH_3), 3.98, 4.00, and 4.01 (3 × 3 H, 3 s, 8-OCH_3 and 6,7-CO_2CH_3), 7.19 broad (1 H, s, 2-H), 8.63 (1 H, s, 5-H), and 11.90 (1 H, s, 1-OH); m/e 418/420 (M^+). Anal. Calcd for $C_{20}H_{15}ClO_8$: C, 57.35; H, 3.61; Cl, 8.46. Found: C, 57.23; H, 3.66; Cl, 8.40.

2-Carbomethoxy-1,6,8-trimethoxy-3-methylanthraquinone (Tri-*O*-methylendocrocin Methyl Ester) (XI). To a suspension of 2-chloro-6,8-dimethoxynaphthoquinone,[8] mp 209.0–209.5 °C (600 mg, 2.37 mmol), in dry benzene (6 ml) was added 2-carbomethoxy-1,1-dimethoxy-3-methyl-1,3-butadiene (VI, 666 mg, 3.58 mmol). The reaction mixture was then refluxed for 2 h, evaporated, heated at 150–155 °C for 2 h, cooled, and chromatographed on silica gel (80 g) (dry column, chloroform–ethyl acetate 9:1), and gave the anthraquinone XI (423 mg, 48%): mp 227–228 °C (benzene) (lit.[4,18] mp 225–226 °C); λ_{max} (ethanol) 227, 241, 279, 343, 395 nm (log ϵ 4.40, 4.33, 4.44, 3.63, 3.75); ν_{max} (KBr) 1729 (ester), 1662 (carbonyl), 1596, 1570, 1447, 1390, 1321, 1244 cm^{-1}; δ (90 MHz, $CDCl_3$) 2.40 broad (3 H, s, 3-CH_3), 3.95–3.97 (4 × 3 H, 4 s, 1,6,8-OCH_3 and 2-CO_2CH_3), 6.79 (1 H, d, J = 2.5 Hz, 7-H), 7.35 (1 H, d, J = 2.5 Hz, 5-H), and 7.87 broad (1 H, s, 4-H); m/e 370 (M^+). Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 64.70; H, 4.88. (An authentic sample of this compound could not be obtained but the NMR spectrum in particular is in excellent agreement with that published by Venkataraman.[19])

2-Carbomethoxy-1,6,8-trimethoxy-3-propylanthraquinone (Methyl Tri-*O*-methylptilometrate) (XII). In an analogous reaction, a mixture of the naphthoquinone X (600 mg, 2.37 mmol), 2-carbomethoxy-1,1-dimethoxy-3-propyl-1,3-butadiene (VII, 1.520 g, 7.09 mmol), and benzene (2 ml) was refluxed for 30 min, evaporated, and heated at 160 °C for 3 h. Methanol (4 ml) was added to the cooled residue and the resulting suspension was filtered after 12 h giving the anthraquinone XII (454 mg), mp 149–150 °C. Chromatography of the mother liquor on silica gel (40 g) (dry column, chloroform–ethyl acetate, 9:1) provided another portion (78 mg) of the same substance, mp 150–151 °C (methanol) (total yield 56%). An analytical sample was recrystallized three times from the same solvent: mp 154.5–155.0 °C (lit.[20] 155–156,[6] 148.5–151.0 °C); λ_{max} (ethanol) 227, 243, 281, 345, 390 nm (log ϵ 4.38, 4.32, 4.41, 3.63, 3.73); ν_{max} (KBr) 1718 (ester), 1667 (carbonyl), and 1598 cm^{-1} (aryl); δ (90 MHz, $CDCl_3$) 0.96 (3 H, t, J = 7.0 Hz, 3′-H_3), 1.71 (2 H, m, 2′-H_2), 2.62 (2 H, t, J = 7.5 Hz, 1′-H_2), 3.93, 3.95, and 3.96 (3 H, 6 H and 3 H, 3 s, 1,6,8-OCH_3 and 2-CO_2CH_3), 6.75 (1 H, d, J = 2.5 Hz, 7-H), 7.32 (1 H, d, J = 2.5 Hz, 5-H) 7.89 broad (1 H, s, 4-H); m/e 398 (M^+). Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.08; H, 5.52. The synthetic substance was identical (mixture melting point, TLC in four solvent systems, and ir spectra) with an authentic sample kindly provided by Professor M. D. Sutherland.

2-Carbomethoxy-6-chloro-5,8-dihydroxy-1-methoxy-3-methylanthraquinone (XIV). A suspension of 2,6-dichloronaphthazarin (XIII, 1.000 g, 3.86 mmol) and the diene VI (1.080 g, 5.80 mmol) in dry benzene (3 ml) was refluxed until it becomes homogeneous. The mixture was then evaporated; the residue was heated at 150 °C for 1 h, refluxed in methanol (10 ml), cooled, and filtered and gave the anthraquinone XIV (1.263 g, 87%), mp 184–186 °C. An analytical sample was twice recrystallized from 1,2-dichloroethane: mp 187–188 °C; λ_{max} (ethanol) 234, 257, 294, 350, 470 nm (log ϵ 4.36, 4.32, 3.87, 3.31, 3.88); ν_{max} (KBr) 1718 (ester), 1618 (chelated carbonyl), and 1573 cm^{-1} (aryl); δ (90 MHz, $CDCl_3$) 2.45 (3 H, s, 3-CH_3), 3.97 and 4.00 (2 × 3 H, 2 s, 1-OCH_3 and 2-CO_2CH_3), 7.40 (1 H, s, 7-H), 8.03 broad (1 H, s, 4-H), 13.24 and 13.45 (2 × 1 H, 2 s, 5,8-OH); m/e 376/378 (M^+). Anal. Calcd for $C_{18}H_{13}ClO_7$: C, 57.38; H, 3.48; Cl, 9.41. Found: C, 57.53; H, 3.29, Cl, 9.45.

2-Carbomethoxy-1,5,6,8-tetramethoxy-3-methylanthraquinone (Tetra-*O*-methylclavorubin Methyl Ester) (XV). To a solution of sodium (2.00 g, 0.0869 mol) in absolute methanol (20 ml) was added dimethylformamide (20 ml), copper(I) iodide (200 mg), and the foregoing quinizarin XIV (200 mg, 0.531 mmol). The mixture was refluxed for 2 h, poured on ice (200 g), acidified with dilute hydrochloric acid, and filtered. The residue was methylated in the usual way with dimethyl sulfate (500 mg) and potassium carbonate (1.23 g) in refluxing acetone (20 ml, 10 h). The crude product was chromatographed on silica gel (60 g) (dry column, chloroform–ethyl acetate, 9:1) and gave the anthraquinone XV (160 mg, 75%): mp 191.5–192.0 °C (methanol); λ_{max} (ethanol) 230, 248, 282, 410 nm (log ϵ 4.37, 4.34, 4.17, 3.75); ν_{max} (KBr) 1722 (ester), 1666 (carbonyl), and 1588 cm^{-1} (aryl); δ (90 MHz, $CDCl_3$) 2.38 (3 H, s, 3-CH_3), 3.94, 3.95, and 3.98 (3 H, 3 H, and 9 H, 3 s, 1,5,6,8-OCH_3 and 2-CO_2CH_3), 6.81 (1 H, s, 7-H), and 7.75 (1 H, s, 4-H); m/e 400 (M^+). Anal. Calcd for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04. Found: C, 62.83; H, 5.04.

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Registry No.—I, 922-69-0; II, 762-42-5; III, 23326-27-4; IV, 18937-79-6; V, 59696-63-8; VI, 59696-64-9; VII, 59696-65-0; VIII, 52431-63-7; IX, 59711-76-1; X, 57165-99-8; XI, 59696-66-1; XII, 15939-13-6; XIII, 13719-93-2; XIV, 59696-67-2; XV, 59696-68-3; 1-carbomethoxy-2-oxopentyldenetriphenylphosphorane, 59696-69-4.

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Nickel-Promoted Isomerizations of Alkenes Bearing Polar Functional Groups

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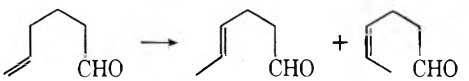
A catalyst derived from ethylenebis(tri-*o*-tolyl phosphite)nickel(0) (1) and hydrogen chloride has been found to isomerize a variety of alkenes bearing polar functional groups. Treatment of 5-hexenal and ethyl 4-pentenoate with the catalyst in hexane or toluene solution at 25 °C afforded essentially quantitative yields of the geometric isomer mixtures of 4-hexenal and of ethyl 3-pentenoate, respectively. High-yield catalytic conversions of 5-chloro-1-pentene and of 4-penten-1-ol to 5-chloro-2-pentene and 3-penten-1-ol, respectively, were also achieved. The configurationally specific conversion of allyl phenyl ether to phenyl *cis*-propenyl ether was accomplished in high yield. A number of allylic alcohols were isomerized to saturated carbonyl compounds by 1 and HCl. Allyl alcohol, 1-hexen-3-ol, 2-cyclohexen-1-ol, 2-methyl-2-propen-1-ol, 3-penten-2-ol, 2-buten-1-ol, and 1,4-pentadien-3-ol were converted to propanal, 3-hexanone, cyclohexanone, 2-methylpropanal, 2-pentanone, 1-butanal, and penten-3-one, respectively. The ethylenebis(tri-o-tolyl phosphite)nickel(0)–hydrogen chloride system catalyzed the skeletal rearrangement of *cis*-1,4-hexadiene to *trans*-2-methyl-1,3-pentadiene in 1-butanol and ethyl hexanoate solvents. This transformation was accompanied by the formation of *cis,cis*- and *trans,cis*-2,4-hexadienes. Treatment of 2,5-hexadien-1-ol with the catalyst system in hexane solvent afforded *trans*-4-methyl-2,4-pentadien-1-ol as major product along with lesser amounts of 5-hexenal. When 2,5-hexadien-1-ol was treated with the catalyst in ethylene-saturated hexane, *trans*-4-methyl-2,4-pentadien-1-ol, 5-hexenal, *cis*-4-hexenal, and *cis,cis*-2,4-hexadien-1-ol were formed.

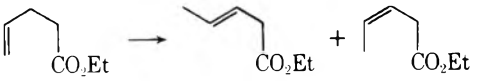
Soluble nickel-based catalysts can promote double bond positional isomerizations of simple alkenes[1] and polyenes[1c,2] as well as skeletal isomerizations of certain dienes.[2a,3] While the reactions of afunctional alkenes have been studied quite extensively, the applicability of the catalysts to isomerizations of alkenes bearing polar functional groups has not received much attention. In some cases, the natures of the catalyst precursors have been responsible for the limited scope of inquiry. For instance, the first catalysts which were found to cleave carbon–carbon σ bonds in dienes to afford rearranged products were derived from in situ reactions of nickel(II) complexes with alkylaluminum compounds.[2a,3] The aluminum cocatalysts react with most polar functional groups. Our findings that catalysts derived from ethylenebis(triarylphosphine)nickel(0) complexes and hydrogen halides accomplish both the 1,4-pentadiene to isoprene type rearrangement and alkene double bond migration reactions[3-5] offered the probability that isomerizations of functionally substituted alkenes could be achieved. The compatibility of this type of catalyst system with polar molecules was demonstrated by the successful isomerization of *cis*-1,4-hexadiene by ethylenebis(tri-*o*-tolyl phosphite)nickel(0) (1) and hydrogen chloride in 1-butanol solvent. During 5 min at room temperature, *trans*-2-methyl-1,3-pentadiene and *trans,cis*- and *cis,cis*-2,4-hexadienes were afforded in 26, 6, and 26% yields, respectively, at 78% conversion of the 1,4-diene to products when a 12:1:0.8 diene:Ni:HCl molar ratio was employed. Comparable results were obtained when ethyl hexanoate solvent was used. These results induced our discovery that a variety of alkenes bearing polar functional groups could be isomerized in high yield by the 1/HCl catalyst system.

Treatment of 5-hexenal with 1 and HCl in toluene or hexane solvents afforded essentially quantitative yields of *trans*- and *cis*-4-hexenal at 100% conversion when aldehyde:Ni ratios as high as 50:1 were employed, eq 1. In a like manner, ethyl 4-



(1)

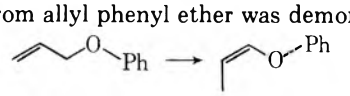
pentenoate was converted to a mixture of *trans*- and *cis*-ethyl 3-pentenoate in quantitative yield at 83% conversion, eq 2.



(2)

These reactions are synthetically useful since α,β-unsaturated carbonyl compounds are not generated, but the double bond migration can be controlled to produce nonconjugated products. High-yield catalytic isomerizations of 5-chloro-1-pentene and of 4-penten-1-ol were also achieved.

The configurationally specific catalytic generation of an enol ether from allyl phenyl ether was demonstrated, eq 3.



(3)

Table I. Alkene Isomerization Reactions Catalyzed by 1/HCl[a]

Expt	Registry no.	Alkene reactant	Reaction time, h	% conversion	Alkene products[b] % yield	
					Trans	Cis
1	764-59-0	5-Hexenal[c,d]	0.5	100	60	40
2		5-Hexenal[c]	1.0	96	53	45
3	1968-40-7	Ethyl 4-pentenoate	0.5	83	58	44
4	928-50-7	5-Chloro-1-pentene	0.5	95	55	45
5	821-09-0	4-Penten-1-ol	0.5	93	58	28
6	1746-13-0	Allyl phenyl ether	0.5	34	0	83

[a] Unless noted otherwise, all experiments were conducted under argon in dry deoxygenated hexane solutions at 25 °C with an alkene/Ni/HCl ratio of 50.0:1.0:0.8. [b] Experiment 1, 4-hexenal; 2, 4-hexenal; 3, ethyl-3-pentenoate; 4, 5-chloro-2-pentene; 5, 3-penten-1-ol; 6, phenyl propenyl ether. [c] The experiment was conducted in dry deoxygenated toluene. [d] Alkene/Ni/HCl ratio was 20.0:1.0:0.8.

Table II. Rearrangements of Allylic Alcohols by 1/HCl[a]

Registry no.	Alcohol	Time	Solvent	ROH/Ni/HCl	% conversion	% yield	Product
107-18-6	Allyl alcohol[b]	5 days	Xylene	20.0/1.0/0.8	100	100	Propanal
4978-44-1	1-Hexen-3-ol	2 days	Xylene	2.0/1.0/0.8	100	81	3-Hexanone
	1-Hexen-3-ol[c]	11 days	Xylene	20.0/1.0/0.8	99	74	3-Hexanone
822-67-3	2-Cyclohexen-1-ol	1 h	Pentane	2.0/1.0/1.0	26	51	Cyclohexanone
	2-Cyclohexen-1-ol	1 h	Et_2O	2.0/1.0/1.0	37	20	Cyclohexanone
513-42-8	2-Methyl-2-propen-1-ol	1 h	Toluene	2.0/1.0/0.8	65	30	2-Methylpropanal
	2-Methyl-2-propen-1-ol	1 h	Toluene	10.0/1.0/0.8	20	29	2-Methylpropanal
1569-50-2	3-Penten-2-ol[d]	1 h	Pentane	2.0/1.0/1.0	92	64	2-Pentanone
	3-Penten-2-ol[d]	1 h	Toluene	2.0/1.0/1.0	95	40	2-Pentanone
6117-91-5	2-Buten-1-ol[e]	2 h	Et_2O	5.0/1.0/1.0	79	33	Butanal
	2-Buten-1-ol[e]	2 h	Et_2O	2.0/1.0/1.4	98	80	Butanal
922-65-6	1,4-Pentadien-3-ol	1 h	Hexane	2.0/1.0/0.8	63	20	Penten-3-one

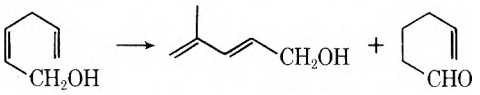
[a] Unless otherwise noted all reactions were conducted under argon in dry dexoygenated solvent at 25 °C. [b] 45 °C. [c] Reaction temperature was 50 °C. [d] 97% trans, 3% cis. [e] 95% trans, 5% cis.

Phenyl *cis*-propenyl ether was afforded in 83% yield at 34% conversion by the 1/HCl catalyst during 30 min in hexane. No trans isomer was detected in the product mixture. Yield and conversion data and descriptions of reaction conditions for these experiments are presented in Table I.

Although no attempt has been made to determine the maximum alkene:Ni ratio that is operable for each transformation described in Table I, experiments employing 5-chloro-1-pentene indicated that the achievable percent conversions decreased with increasing alkene:Ni ratio. Under conditions comparable to those given in Table I, 26% of 5-chloro-1-pentene was converted to 5-chloro-2-pentene in 98% yield when a 200:1 alkene:Ni ratio in hexane was used. An 82% yield of 5-chloro-2-pentene was afforded at 13.5% conversion in neat 5-chloro-1-pentene when a 1000:1 alkene:Ni ratio was employed. These data correspond to 51 and 111 catalytic cycles, respectively.

Only a few examples of the conversion in solution of allylic alcohols to saturated carbonyl compounds by transition metal complexes are known.[6] The capability of the 1/HCl system to accomplish such transformations was therefore investigated. Alcohols possessing unsubstituted double bonds were slowly converted in high yield to saturated carbonyl compounds when alcohol:Ni molar ratios as high as 20:1 were employed. The catalyst was not long lived in reactions of substituted allylic alcohols. While the initial rates of reaction were relatively high, the catalyst became deactivated during a 2-h period and only moderate yields of carbonyl products were afforded, even when very low alcohol:Ni ratios were employed. Data from these experiments are tabulated in Table II.

Treatment of 2,5-hexadien-1-ol with 1 and HCl (dienol:Ni:HCl, 5.0:1.0:0.8) afforded a skeletally isomeric alcohol as the major product along with lesser amounts of double bond migration products. During ca. 30 min in hexane solvent at 24–26 °C, 73–80% conversions of hexadienol to products were achieved and *trans*-4-methyl-2,4-pentadien-1-ol and 5-hexenal were formed in 30–40 and 7–10% yields, respectively, in a series of experiments, eq 4. Higher yields of the skeletal rearrangement product could be achieved when the experiments were conducted in ethylene-saturated hexane. Under this modified condition, 73% of the dienol was converted to product during ca. 30 min and *trans*-4-methyl-2,4-pentadien-1-ol, 5-hexenal, *cis*-4-hexenal, and *cis,cis*-2,4-hexadien-1-ol were afforded in 67, 6, 5, and 20% yields, respectively.



(4)

Previous studies of the 1/HCl and related catalyst systems indicate that the hydrogen transfer that accompanies these isomerizations should occur by a nickel hydride–alkene addition–elimination sequence.[1b,1e,3] The saturated carbonyl compounds which are generated from allylic alcohols would, therefore, be formed via enol intermediates. The generation of an enol ether from allyl phenyl ether supports this picture.

Experimental Section

All experiments employing ethylenebis(tri-*o*-tolyl phosphite)-nickel(0) were conducted under an argon atmosphere in deoxygenated solvents. Proton magnetic resonance spectra were recorded on a Varian A-60 instrument using tetramethylsilane as an internal standard in carbon tetrachloride solvent. Infrared spectra were obtained on a Beckman IR-12 spectrophotometer and mass spectra were recorded on a Du Pont 21-491 spectrometer.

Reaction solvents were dried over sodium–benzophenone and then distilled. All functionalized alkenes except 5-hexenal, ethyl 4-pentenoate, 1,4-pentadien-3-ol, and *cis*-2,5-hexadiene-1-ol were com-

mercially available. 5-Hexenal was prepared from the commercially available 5-hexen-1-ol by the method of Sheikh and Eadon.[7] Ethyl 4-pentenoate,[8] 1,4-pentadien-3-ol,[9] and *cis*-2,5-hexadien-1-ol[10] were also prepared by literature procedures. *cis*-1,4-Hexadiene was prepared by the procedure of Hata.[11] Ethylenebis(tri-o-tolyl phosphite)nickel(0) was prepared by the method of Seidel and Gosser.[12]

Typical Procedures for Alkene Isomerization Experiments. An ether solution, 0.08 ml, containing 0.065 mmol of hydrogen chloride was transferred via hypodermic syringe to a flask containing 0.081 mmol of ethylenebis(tri-o-tolyl phosphite)nickel(0) (1). 5-Chloro-1-pentene, 4.06 mmol, in 3 ml of hexane was then added to the amber-colored solution affording a solution that was orange-amber in color. The mixture was stirred under argon at room temperature and within 15 min, the color of the reaction solution had faded to a cloudy pale yellow. Thirty-microliter aliquots were removed periodically; they were quenched by exposure to air, and then analyzed by GLC on a 10 ft × 0.25 in., 20%, 1,2,3-tris(2-cyanoethoxy)propane on Chromosorb W column. On termination of an experiment, the volatile organic material was removed from the reaction flask in vacuo. The resulting hexane solution was then concentrated by distillation after which the reaction products were collected by preparative GLC.

Experiments involving other functionalized alkenes were conducted in a similar manner with the following exceptions. Isomerization reactions of all allylic alcohols except 1,4-pentadien-3-ol and *cis*-2,5-hexadien-1-ol were accomplished by adding the hydrogen chloride solution to a solution of **1**, the allyl alcohol, and the solvent. When 2,5-hexadien-1-ol was treated with **1** and HCl in the presence of ethylene, an ethylene-saturated solution of the alcohol in hexane was added to the flask containing 1 and HCl in ether–hexane. Ethylene was then passed through the reaction mixture for 5 min.

Product mixtures derived from reactions of allylic alcohols were analyzed by GLC on a 6 ft × 0.25 in. 20% Carbowax 20M on Chromosorb P column.

Determination of Product Yields. Percent conversions were based upon consumed alkene reactant and percent yields were defined as the percent of consumed starting material that was transformed into each product. Yield and conversion data were determined by GLC. In experiments employing allylic alcohols, standard mixtures of reactants and products were analyzed in order to determine the relationships between signal responses and molar amounts present. In each case, a known quantity of an internal standard, *m*-xylene, mesitylene, benzene, or *n*-hexane, was used, the choice depending upon the retention times of the reactants and products. Ratios of GLC peak areas were assumed to represent molar ratios of reactants and products in experiments involving double bond migrations in functionalized alkenes where the type of functional group was the same in both reactant and products.

It was found that the signal responses per mole of 2-buten-1-ol, 2-cyclohexen-1-ol, and 2,5-hexadien-1-ol decreased with increased time of use of the Carbowax 20M column. This situation was rectified by the periodic replacement of a portion of the column at the injection end with fresh Carbowax 20M on Chromosorb P packing. A 4-in. column extension was utilized for this purpose. It was necessary to monitor the column deterioration by periodic analyses of standard reactant–product mixtures.

Product Identifications. The structure assignments of the products described in Table I were based upon examination of the ^{1}H NMR, infrared, and mass spectra of each compound after isolation by preparative GLC. The parent ion peak in the mass spectrum of each compound corresponded with the assigned molecular weight. The multiplicities and chemical shifts of the proton resonances along with the ^{1}H NMR integrations were all consistent with the assigned structures. The geometry of the internal double bond was established by the alkene C–H out-of-plane deformation vibration, found near 10.3–10.42 μ for the trans isomers and 14.28–14.60 μ for the cis isomers.[1c,13] The GLC retention time of the cis isomer was found to be longer than that of the trans isomer in each case. The magnitude of the vinyl proton–proton coupling constant, J_{H-H} = 6.2 Hz, in phenyl *cis*-propenyl ether was used as a criterion for its configuration.[14]

The aldehyde and ketone products described in Table II were identified by comparisons of their ^{1}H NMR spectra and GLC retention times with those of authentic samples.

The identity of the skeletal rearrangement product derived from *cis*-2-5-hexadien-1-ol was established by its ^{1}H NMR, infrared, and mass spectra. The trans configuration of the internal double bond was evident from the strong band at 10.31 μ and from the magnitude of the alkene proton–proton coupling constant, J_{H-H} = 16.0 Hz, for the internal double bond protons. The configuration in *cis,cis*-2,4-hexadien-1-ol was established by comparing its ^{1}H NMR spectrum with that of *cis,cis*-2,4-hexadiene. The mass spectrum indicated the appropriate parent ion mass.

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Electron Transfer on Photolysis of 1-Chloronaphthalene in Alkane Solvents†

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Photoreduction of 1-chloronaphthalene to naphthalene is stimulated in the presence of electron donors such as triethylamine and 1,3-cyclohexadiene. These reactions are demonstrated by fluorescence measurements to involve the $^1\pi,\pi^*$ state of chloronaphthalene. In the absence of such compounds, 1-chloronaphthalene itself acts as a donor molecule, and excimers are involved.

Photolysis of 1-chloronaphthalene in solvents liable to hydrogen abstraction affords naphthalene and binaphthyls.[1] The distribution of these products varies widely with the experimental conditions; the observation that the efficiency of photolysis increases greatly in the presence of triethylamine (a known electron donor[2]) suggests a mechanism involving electron transfer to chloronaphthalene (eq 1, X = Et_3N) to be more likely than a simple C–Cl bond fission (eq 2).

$$C_{10}H_7Cl^* + X \rightarrow C_{10}H_7\cdot + Cl^- + X\cdot^+ \quad (1)$$

$$C_{10}H_7Cl^* \rightarrow C_{10}H_7\cdot + Cl\cdot \quad (2)$$

In this paper, we attempt to substantiate the above suggestion.

The mechanism under consideration is shown in full as Scheme I; it involves the radical anion of 1-chloronaphthalene as a central intermediate. Radical anions of haloaromatic compounds are known to expel halide ion and hence lead to reduction products.[3]

Scheme I

$$C_{10}H_7Cl \xrightarrow{h\nu} C_{10}H_7Cl^*$$

$$X + C_{10}H_7Cl^* \rightarrow C_{10}H_7Cl\cdot^- + X\cdot^+$$

$$C_{10}H_7Cl\cdot^- \rightarrow C_{10}H_7\cdot + Cl^-$$

$$C_{10}H_7\cdot + RH \rightarrow C_{10}H_8 + R\cdot$$

Reactions in the Presence of Triethylamine (TEA). In the photolysis of 1-chloronaphthalene, the presence of varying amounts of TEA greatly enhanced both naphthalene production and the quantum yield for decomposition: ϕ ([TEA] = 0) = 0.002; ϕ ([TEA] = 0.01 M) = 0.015. A plot of $[TEA]^{-1}$ vs. ϕ^0/ϕ is linear. The almost exclusive production of naphthalene at the higher TEA concentrations argues strongly against the simple homolysis of eq 2 on the grounds that the ratio of hydrogen abstraction to arylation[4] should be independent of [TEA] if both kinds of product derive from the same naphthyl radical. (However, this argument would be invalid if TEA not only enhanced the production of naphthyl radicals, but also scavenged them efficiently, thus making them unavailable for arylation.)

Correspondingly, the fluorescence of 1-chloronaphthalene (λ_{max} 335 nm)[5] is quenched upon addition of TEA and simultaneously a broad emission characteristic of an exciplex (λ_{max} 435 nm in isooctane) is observed (cf. ref 6). Triethylamine (up to 0.2 M) is without effect on the absorption spectrum of 1-chloronaphthalene in isooctane. It is thus likely that the amine-stimulated photoreduction derives from the singlet state of 1-chloronaphthalene, since it is improbable that TEA would simultaneously act upon excited 1-chloronaphthalene both to quench fluorescence and to enhance the reactivity of a reactive triplet. A similar conclusion has been reached for the TEA-assisted photoreduction of 4-chlorobiphenyl.[7] In addition, we have found that there is a complete parallel between the relative efficiency of an added substance for quenching the fluorescence of 1-chloronaphthalene and the efficacy of the same substance in promoting photoreduction; see Tables III and IV.

The effect of oxygen upon the reactivity of the 1-chloronaphthalene–TEA system is likewise consistent with the intervention of an exciplex. Degassed solutions react about three times as fast as aerated ones; these findings can be explained not in terms of a triplet reactive state, as we proposed previously,[1] but instead in terms of an exciplex intermediate, for Caldwell[8] has shown that oxygen is a quencher for exciplexes, albeit an inefficient one. Dimethyl acetylenedicarboxylate (DMA) quenches exciplexes much more efficiently,[8] and we find that this substance is an efficient quencher of both the photoreaction and the 1-chloronaphthalene–TEA exciplex emission. DMA also quenches the fluorescence of uncomplexed 1-chloronaphthalene at a comparable rate, perhaps demonstrating the establishment of a very rapid equilibrium between the exciplex and its components. When both TEA and DMA are present at high concentrations, the Stern-Volmer plots become curved; absorption spectroscopy indicates ground state complexation between DMA and TEA, causing quenching to be more efficient than would be expected if quenching resulted only from diffusion from the bulk of the solution.

The effect of solvent polarity supports the involvement of the exciplex intermediate. A polar solvent should be more effective at dissociating the radical cation–radical anion pair, thus allowing them to diffuse into the bulk of the solution. This will reduce the probability of back electron transfer, and enhance the likelihood of successful reaction. Both the direct and amine assisted reactions are speeded up when the solvent is an acetonitrile solution of an alkane, rather than a pure alkane. Likewise, no TEA–1-chloronaphthalene exciplex emission is seen in acetonitrile, though quenching of the fluorescence of uncomplexed 1-chloronaphthalene is still observed.

Direct Photolysis of 1-Chloronaphthalene. We have argued that in the TEA-assisted reaction, C–Cl bond cleavage is brought about by electron transfer from the amine to chloronaphthalene, followed by expulsion of chloride ion to leave a naphthyl radical. In the direct photolysis, we have to suggest a method for chlorine removal and to explain the substantial increase in biaryl formation. One mechanistic possibility might be that in the absence of the added electron donor, a second molecule of 1-chloronaphthalene may be able so to act (eq 1, X = $C_{10}H_7Cl$). Biaryls could then result from the attack of $C_{10}H_7Cl\cdot^+$ upon another aromatic species, as occurs in the anodic oxidation of aryl substrates.[9] Such a proposal implies excimer formation. This is known for other

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Table I. Concentration Dependence of Chloronaphthalene Photodegradation[a]

$C_{10}H_7Cl$, M	ϕ_{rel}
3.2×10^{-2}	1.00
3.2×10^{-3}	0.75
3.2×10^{-4}	0.57
3.2×10^{-5}	0.13

[a] In 3-methylpentane, irradiated at 254 nm.

Table II. Effect of Added 4-Chlorobiphenyl on the Efficiency of 1-Chloronaphthalene Photolysis[a]

$C_{12}H_9Cl$, M	ϕ_{rel}
0	1.0
1×10^{-6}	2.8
1×10^{-5}	7.6
1×10^{-4}	2.4
1×10^{-3}	0.8

[a] In 3-methylpentane, 1-chloronaphthalene concentration was 2.9×10^{-3} M.

simple naphthalene derivatives,[10] and is supported in the present work by the following evidence.

1. Concentrated solutions of 1-chloronaphthalene exhibit excimer emission at low temperatures. Thus at −59 °C a 0.059 M solution of 1-chloronaphthalene displayed two emission bands of approximately equal intensity, λ_{max} 335 and 410 nm, upon excitation at 290 nm. Correction for the monomer emission spectrum revealed the broad band characteristic of excimer emission over the range 350–500 nm with a maximum at 410 nm.

2. The quantum yield for 1-chloronaphthalene reactivity rises with increasing substrate concentration (Table I).

3. The efficiency of photolysis is also raised in the presence of 4-chlorobiphenyl as a foreign, but nonabsorbing aromatic compound (Table II). At very low concentrations of 4-chlorobiphenyl, almost all the light is absorbed by 1-chloronaphthalene (absorption spectrum), and no photoreduction of 4-chlorobiphenyl is observed. Even so, 4-chlorobiphenyl enhances the reactivity of 1-chloronaphthalene under these conditions, and we postulate that electron transfer to excited 1-chloronaphthalene is occurring (eq 1, X = $C_{12}H_9Cl$). Consistent with this view, 4-chlorobiphenyl quenches the fluorescence of 1-chloronaphthalene, despite its higher singlet energy. At high 4-chlorobiphenyl concentrations, the added substrate absorbs much of the light, and the photoreactivity of 1-chloronaphthalene drops again.

4. The binaphthyl fraction of the photolysis mixture is a complex mixture containing species with zero, one, and two chlorine atoms. This is consistent with arylation involving at least in part the radical cation (rather than the alternative hypothesis that the lack of arylation in the TEA-assisted reaction involves only scavenging by TEA) on the following grounds. Simple radical coupling leads only to unchlorinated binaphthyl, while arylation by a naphthyl radical affords biaryls containing zero or one chlorine, depending upon whether preformed naphthalene or unreacted 1-chloronaphthalene was substituted. Furthermore, in the reactions assisted by 4-chlorobiphenyl, biaryls containing both biphenylyl and naphthyl residues were observed. Although many other reactions besides attack on an arene are presumably open to the radical cation, we have no evidence for them. Electron transfer from some reaction component to restore chloronaphthalene is chemically undetectable, and while the observation of 1-naphthol and 1-methoxynaphthalene in solvents containing water or methanol might be construed as involving capture of a nucleophile by the radical cation, numerous other pathways can be devised to reach these products.

Table III. Effect of Added Substances on the Photoreactivity of 1-Chloronaphthalene

Added substance	(M)	$C_{10}H_7Cl$, M	Reactivity ratio[a]
TEA	(0.01)	1.0×10^{-3}	7.5[b]
TEA (0.01 M) and DMA	(0.02)	1.2×10^{-3}	1.1[b,c]
Acetonitrile and TEA	(0.01)	1.2×10^{-3}	2.2[d]
Acetonitrile		2.9×10^{-3}	2.5[d]
1,3-Cyclohexadiene	(0.07)	2.0×10^{-3}	23.0[e]
1,4-Cyclohexadiene	(0.59)	2.0×10^{-3}	2.2[e]
Cyclohexene	(1.0)	2.0×10^{-3}	1.2[e]

[a] Ratio of the rate of disappearance of 1-chloronaphthalene with the added substance compared with control reactions. [b] Solvent was isooctane. [c] Comparing solution with both addends with that containing neither. [d] In this experiment, the comparison was between acetonitrile containing 1 M cyclohexane and pure cyclohexane. [e] Solvent was hexane.

Table IV. Effect of Added Substances on the Fluorescence of 1-Chloronaphthalene[a]

Added substance	$k_q\tau$	k_q[b]	Exciplex
TEA	26	3.5×10^9	Yes[c]
DMA	59	7.9×10^9	No
TEA (10^{-2} M) + DMA[d]	52	6.9×10^9	
1,3-Cyclohexadiene	16	2.1×10^9	No
1,4-Cyclohexadiene	0.22	2.9×10^7	No
Cyclohexene	0.05	7×10^6	No
TMD[e]	400[f]	5×10^{10}	No
1,3-Pentadiene	1.3	1.7×10^8	No

[a] Solvent was isooctane. [b] τ_0 = 7.5 ns (ref 14). [c] λ_{max} 435 nm. [d] TEA concentration constant; DMA concentration varied. [e] Tetramethylazetine dioxide. [f] Based on only four data points in the Stern–Volmer plot.

The above observations and the self-quenching of 1-chloronaphthalene fluorescence suggest that, like the amine-assisted reaction, the direct photolysis involves electron transfer to a singlet excited state. It is not known whether the reaction is suppressed completely at very low concentration when bimolecular processes will be improbably slow, or whether another mechanism is possible. We had hoped to test this point using dilute solutions in the presence of tetramethylazetine *N,N*-dioxide, which is reported to quench triplet, but not singlet, excited states.[11] Unfortunately, the compound proved to be an efficient quencher of 1-chloronaphthalene fluorescence, so this was not possible.

Reactions in the Presence of Alkenes. We previously reported that 1,3-cyclohexadiene and 1,3-pentadiene enhanced the photoreactivity of 1-chloronaphthalene in methanolic solutions, and suggested that this involved some kind of complexation between the diene and the aryl halide.[1] Repetition of these experiments in alkane solvents produces a much more dramatic increase in reactivity. Like the amine-stimulated reactions, the diene-assisted photolyses lead predominantly to photoreduction, suggesting that aryl radicals are now the main intermediates derived from 1-chloronaphthalene. A reaction corresponding to eq 1, X = diene, is proposed on the basis of the following evidence.

1. The fluorescence of 1-chloronaphthalene is quenched by 1,3-cyclohexadiene at a rate similar to that reported for quenching naphthalene and 1-methylnaphthalene with the

same quencher.[12] However, no exciplex emission could be observed, even at low temperatures (cf. ref 13).

2. From photolyses of 1-chloronaphthalene assisted by 1,3-cyclohexadiene in methanolic solution, small quantities of the methanol adducts of cyclohexadiene are obtained. Such adducts can be rationalized as arising by attack of methanol on the radical cation of cyclohexadiene.

3. 1,4-Cyclohexadiene and cyclohexene are also effective at increasing the reactivity of 1-chloronaphthalene, but much less so than the conjugated diene. The order of effectiveness is 1,3-cyclohexadiene > 1,4-cyclohexadiene > cyclohexene, which is also the order of efficiency of quenching chloronaphthalene fluorescence.

Conclusions

The above observations are consistent with the operation of a mechanism such as that given in Scheme I. The photoreduction product naphthalene arises by expulsion of the chloride ion from the radical anion of 1-chloronaphthalene. Electron donor molecules such as cyclohexadiene or TEA increase the production of these radical anions and hence enhance photoreduction at the expense of arylation, which involves the radical cation of chloronaphthalene. These reactions take place from the singlet state of 1-chloronaphthalene as evidenced by the effect of the added substances in quenching the fluorescence and the parallel between the effectiveness of the compounds in enhancing reactivity and quenching fluorescence.

As mentioned in our previous paper, this study is part of an effort to determine whether photolysis is likely to be important as a mechanism for the natural degradation of halogenated aromatic pollutants. Further studies are planned into the mechanisms of photodegradation of chlorinated naphthalenes and biphenyls in aqueous, as well as organic, media.

Experimental Section

Procedures for photolysis and gas chromatographic analysis were described in detail previously.[1] Photolyses were normally carried out in sealed Pyrex glass ampules using illumination of maximum intensity at 300 nm, following evacuation of the ampules by freeze–pump–thaw cycles. For studying the effect of changing a reaction parameter, a merry-go-round was used to ensure equal illumination of the samples. In some cases noted in the tables, light of 254-nm wavelength was used, and quartz ampules were employed. Photochemical results are given in Tables I–III.

Product Analyses. Quantum yields for disappearance of 1-chloronaphthalene ($\approx 10^{-3}$ M) varied with solvent, but in alkanes were 0.001–0.002 at 300 nm based on ferrioxalate actinometry. Typical distributions of products were naphthalene 50–70% and binaphthyls 30–50% at these initial concentrations, with >95% material balance in the early stages of the reactions. In the presence of high (0.1 M) concentrations of TEA or 1,3-cyclohexadiene, naphthalene became the almost exclusive (90–98%) product.

Fluorescence experiments at room temperature were carried out using a Hitachi Perkin-Elmer Model MPF 2A fluorescence spectrophotometer. Isooctane (BDH spectroscopic grade) was used throughout as solvent. At least six data points covering at least a tenfold range in concentration were obtained for all the quenching studies, which are reported in Table IV. For work at low temperature, a Farrand Optical Co. Mark I spectrofluorometer was used; its low temperature cell holder was designed in our laboratory, and permitted temperature measurement by means of a thermocouple which protruded into the solution.

Photolysis of 1-Chloronaphthalene with 1,3-Cyclohexadiene in Methanolic Solution. A solution containing 1-chloronaphthalene (10^{-2} M) and 1,3-cyclohexadiene (10^{-2} M) in methanol was photolyzed at 300 nm for 20 days. Water was added, and the organic materials extracted into ether. The concentrated extract was analyzed by gas chromatography on columns of 3% SE-30 and 3% OV 225 each on Chromosorb W, and at two temperatures on each column. Small peaks corresponding in retention time to those of 3-methoxycyclohexene and 4-methoxycyclohexene were observed in each case. These amounted to only ~2% of the total product; however, no attempt was made to optimize their yield. The authentic materials were made by the action of methyl iodide upon the sodium salts of the corresponding alcohols, using dimethyl sulfoxide as solvent.

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Registry No.—1-Chloronaphthalene, 90-13-1; TEA, 121-44-8; DMA, 762-42-5; acetonitrile, 75-05-8; 1,3-cyclohexadiene, 592-57-4; 1,4-cyclohexadiene, 628-41-1; cyclohexene, 110-83-8; 1,3-pentadiene, 504-60-9.

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New Conditions for Controlled Claisen Rearrangements of Allyl Aryl Ethers

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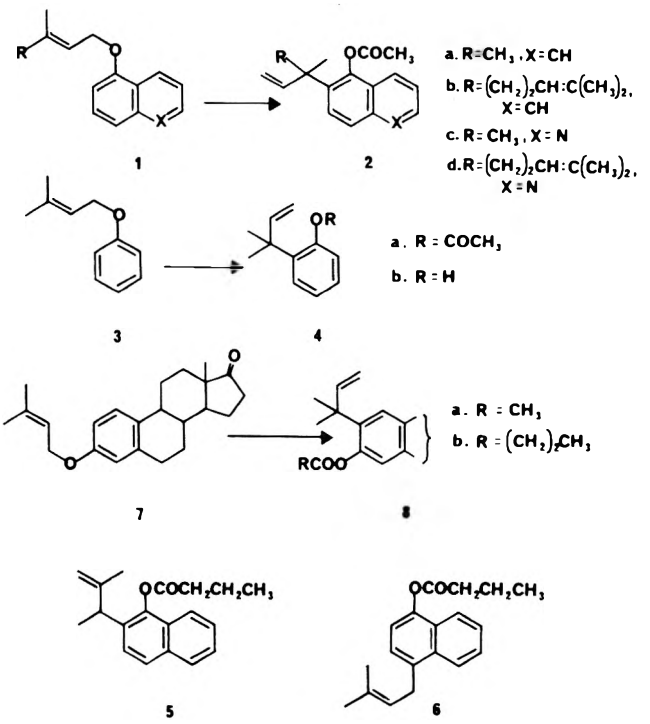
The Claisen rearrangement[1] of allyl aryl ethers is often complicated by the occurrence of abnormal rearrangements leading to structural isomerization of the migrating group, and in some cases by competitive ortho and para migrations. Although the ortho/para ratio can sometimes be effectively controlled by solvent polarity,[2,3] the abnormal rearrangement[4] becomes a serious problem in the rearrangement of ethers bearing γ-alkyl substituents on the allyl group. The occurrence of abnormal and para Claisen products has been attributed[3] to multiple sigmatropic rearrangements. Clearly, in order to obtain good yields of the thermodynamically unstable normal Claisen product, one needs to employ a base to ensure rapid enolization and an efficient trapping agent to prevent participation of the phenolic hydrogen in a (1,5) homosigmatropic hydrogen shift.[3]

In connection with synthetic studies on dihydroteleocidin B,[5] we sought to establish conditions which would afford only normal Claisen products from geranyl aryl ethers. Butyric anhydride in *N,N*-dimethylaniline has been reported[6,7] to be an effective trap of the normal Claisen product. However, this method is not general. Thus, when 3-methyl-2-butenyl 1-naphthyl ether (**1a**) was subjected to the above conditions,[8] the product mixture showed less than 7% of the normal Claisen product. The major products were the abnormal Claisen product (**5**) and the para Claisen product (**6**) in a ratio of 2.7:1, respectively.[9]

We wish to report that normal Claisen products can be obtained in good yields as the corresponding acetate by thermal rearrangement *in the presence of acetic anhydride and either sodium or potassium acetate* (Scheme I). Utilization of these conditions permitted the isolation in 76% yield of **2a**, the normal Claisen product of **1a**, in direct contrast to the results described above using the butyric anhydride/dimethylaniline conditions. Reaction conditions are given in Table I (see Experimental Section for details).

Scheme I



Claisen reported,[10] but without experimental details, that 3-methyl-2-butenyl phenyl ether (**3**) gave the expected normal product (**4b**) when heated in the presence of sodium carbonate. Attempts to repeat this work[3,11] failed to give o-(1,1-dimethylallyl)phenol (**4b**). Using our conditions we obtained a 3.5:1[9] mixture of **4a** and phenyl acetate along with minor amounts of unidentified compounds. After $LiAlH_4$ reduction of the crude mixture, **4b** was easily isolated in pure form (see Experimental Section) in an overall 44% yield.[12] Also, when our conditions were applied to the rearrangement of (3-methyl-2-butenyl)estrone ether (**7**), we obtained **8a** in a 41% yield, a substantial improvement over the reported[6] 14% yield using the butyric anhydride/dimethylaniline technique. The lower yields obtained with **3** and **7** are due, at least in part, to a competitive cleavage reaction of **3** and **7** to the corresponding phenols. This difficulty was not encountered with the naphthalene or quinoline derivatives.

Table I

Compd	Registry no.	Base	Reaction temp, °C	Reaction time, h	Product	Mp, °C	Yield,[a] %	Registry no.
1a	59671-60-2	NaOAc	170	3	**2a**	81.5–82.0	76	59671-64-6
1b	59671-61-3	KOAc	170	3	**2b**	130–132[g]	82	59671-65-7
1c	59671-62-4	NaOAc	160	4	**2c**	104–105	80	59671-66-8
1d	59671-63-5	KOAc	160	3.5	**2d**	73–75	76	59671-67-9
3	14309-15-0	NaOAc	200	21	**4a**	105–105.5[g]	44[b]	18272-61-2 (**4b**)
7	6562-03-4	NaOAc	190	15.5	**8a**	179–180	41 (53[e])	59671-68-0
1a[c]		$C_6H_5N(CH_3)_2$	170	3	**5** (2.7), **6** (1)		96[f]	59671-69-1 (**5**)
								59671-70-4 (**6**)
7[c,d]		$C_6H_5N(CH_3)_2$	Reflux	15	**8b**	140–141	14	6561-99-5

[a] Isolated yields of pure product. [b] Isolated yield of corresponding free phenol (**4b**) obtained by $LiAlH_4$ reduction of **4a**. [c] Using butyric anhydride as a trapping agent. [d] Reference 6. [e] Corrected for recovered starting material. [f] No attempt was made to separate these two compounds. [g] Melting point of corresponding phenylurethane.

Experimental Section

General. Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 727 spectrometer. NMR spectra were determined on a Varian HA-100 spectrometer using Me_4Si as an internal standard. Analytical gas chromatography was carried out on a Fisher Series 4800 gas chromatograph with a flame ionization detector, using a 6 ft × 0.125 in. column packed with 6% SE-30 in 90–100 mesh Chromosorb W. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Allyl aryl ethers were prepared by reaction of either 1-chloro-3-methyl-2-butene or geranyl bromide[13] with the corresponding phenols in the presence of K_2CO_3 in either acetone or DMF and purified by silica gel chromatography.

The following is a typical procedure for Claisen rearrangement.

Rearrangement of 5-Quinolinyl Geranyl Ether. A magnetically stirred mixture of 1.0 g of 5-quinolinyl geranyl ether (**1d**), 1.0 g of KOAc, and 15 ml of Ac_2O was heated at 160 °C (bath temperature) in a heavy-walled sealed tube for 3.5 h in an argon atmosphere. The cooled mixture was poured into 35 ml of distilled water and stirred vigorously for 0.5 h. The resulting aqueous solution was extracted with two 150-ml portions of ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution until the washings were basic. The resulting organic fraction was washed with 50 ml of saturated NaCl solution, dried over $MgSO_4$, and ether evaporated. After filtration through silica gel (15 g; EtOAc/hexane 1/2) the residue (1.098 g) was crystallized from pentane to give 814 mg of **2d** as tan crystals. Purification of the mother liquor by preparative layer chromatography (20 × 20 × 0.25 cm silica gel plate; EtOAc/hexane 1/1) yielded an additional 63 mg of **2d**. After one recrystallization from pentane **2d** was obtained as small plates: mp 73–75 °C; ir (CH_2Cl_2) 1760, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 3, CH_3), 1.50 (s, 3, CH_3), 1.62 (s, 3, CH_3), 2.34 (s, 3, $OCOCH_3$), 1.7–2.3 (m, 4, CH_2CH_2), ~5.1 (m, 3, C=CH_2, C=CH), 6.16 (dd, 1, J = 10, 18 Hz, C**H**=CH_2), 7.2–8.9 (m, 5, aromatic).

Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.91; H, 7.66; N, 4.37.

***o*-(1,1-Dimethylallyl)phenol (4b).** 3-Methyl-2-butenyl phenyl ether (**3**, 1.0 g), 1.0 g of anhydrous NaOAc, and 15 ml of Ac_2O was heated for 21 h under argon in a stainless steel bomb at 200 °C (bath temperature). The mixture was worked up exactly as described in the previous experiment. After evaporation of the ether, the crude residue was filtered through silica gel (15 g; CH_2Cl_2/petroleum ether 1/3) giving 0.976 g of a pale yellow oil. GLC analysis[14] showed *o*-(1,1-dimethylallyl)phenyl acetate (**4a**, 66.5%), phenyl acetate (19%), **3** (6.3%), and two unidentified compounds (total of 8.2%).

The crude mixture dissolved in 15 ml of dry ether was added dropwise to a suspension of 280 mg of $LiAlH_4$ in 50 ml of dry ether under argon. Once the addition was complete the mixture was refluxed for 15 min, cooled in an ice bath, and acidified to pH 1 with 3 N HCl. The organic layer was separated and the aqueous layer back-extracted with 35 ml of ether. The combined ether extracts were washed with two 50-ml portions of saturated NaCl solution, dried over Na_2SO_4, and ether evaporated. The residue was purified by column chromatography (35 g of silica gel; CH_2Cl_2/petroleum ether 1/6) to give 438 mg (44%) of *o*-(1,1-dimethylallyl)phenol (**4b**) as a colorless oil (homogeneous by TLC): ir (CH_2Cl_2) 3460, 1620, 1575, 1480, 1340, 1200, 925 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 6, CH_3), 5.27 (dd, 1, J = 10, 1 Hz, CH=C**H**$_2$), 5.31 (dd, 1, J = 18, 1 Hz, CH=C**H**$_2$), 6.20 (dd, 1, J = 18, 10 Hz, C**H**=CH_2), 6.76–7.32 (m, 5, aromatic).

A phenylurethane of **4b** gave mp 105–105.5 °C after one recrystallization from hexane.

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Registry No.—**4a**, 59671-72-6; **4b** phenylurethane, 59671-71-5; phenyl acetate, 122-79-2; 1-chloro-3-methyl-2-butene, 503-60-6; geranyl bromide, 5389-87-7; 1-naphthol, 90-15-3; 5-quinolinol, 578-67-6.

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(12) Yield was not optimized.
(13) Prepared by method of P. R. Oritz de Montellano, Thesis, Harvard University, 1968, p 75, using Aldrich gold label geraniol.
(14) Auto programmer: initial temperature 150 °C; final temperature 225 °C; initial delay 1 min; program rate: 20 °C/min; final delay 1 min.

Pyridopyrimidines. 5. N-Oxidations and Rearrangements in the Pyrido[2,3-*d*]pyrimidine Series

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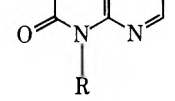
A number of pyrido[2,3-*d*]pyrimidine derivatives have been recently synthesized as potential antitumor,[1-3] carcinogenic,[4] or antibacterial[5] agents. Our interest in the antitumor properties of certain of these compounds has prompted a study of the synthesis and reactivity of the 8-*N*-oxides of 2,4-dioxopyrido[2,3-*d*]pyrimidine (1) and its 1,3-dimethyl derivative



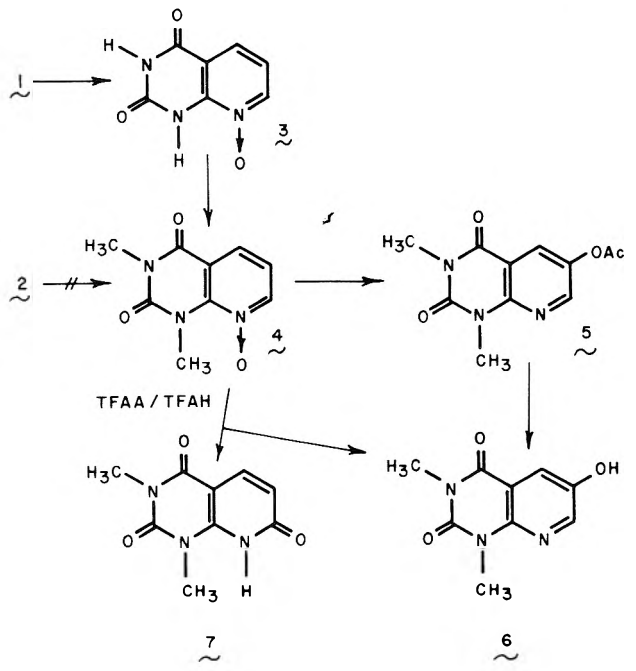
1, R = H
2, R = CH_3

2; these starting materials were prepared according to Robins and Hitchings[6] and McLean and Spring,[7] respectively.

The preparation of 2,4-dioxopyrido[2,3-*d*]pyrimidine 8-*N*-oxide (**3**) was carried out very simply in 80% yield by oxidation of **1** with *m*-chloroperbenzoic acid in glacial acetic acid (Scheme I). Because of the lactam structure of **1**, the only nitrogen atom available for N-oxidation should be N-8. Indeed, only one *N*-oxide was formed, which had similar physical properties to the same compound recently prepared[4] by an involved, much lower yield (42%) procedure. Additional support for the structural assignment was found in the uv spectrum; a very intense band (not previously reported[4]) at 237 nm, characteristic of *N*-oxide bonds in heteroaromatic systems,[8] was observed.

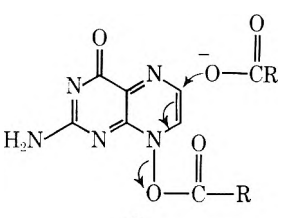
Oxidation of the 1,3-dimethyl derivative **2** could not be accomplished, presumably because of steric hindrance of the peri methyl group at N-1. Even trifluoroperacetic acid in refluxing trifluoroacetic acid failed to oxidize compound **2**. A study of the methylation of *N*-oxide **3** was therefore undertaken. The conditions usually used for the N-methylation of heteroaromatic lactam systems, e.g., dimethyl sulfate in aqueous base[7] or methyl iodide in an aprotic solvent in the presence of potassium carbonate,[9] failed to give a reasonable yield of the desired 1,3-dimethyl derivative. The use of diazomethane, which has the smallest steric requirements of all methylating agents, gave a good yield of a dimethylpyrido[2,3-

Scheme I



d]pyrimidine. Because diazomethane is known to give mixtures of *N*- and *O*-methyl derivatives in many cases,[10] it was necessary to establish that the reaction product was indeed **4**. Three lines of evidence firmly established the structure: the ^{1}H NMR spectrum in $(CD_3)_2SO$ revealed two sharp methyl singlets at δ 3.30 and 3.89, both of which are at higher field than would be the case for *O*-methyl signals; irradiation of **4** in aprotic media at 254 nm gave a product identical (TLC) with **2**; and, finally, the mass spectrum gave a relatively small molecular ion (M^+ 207) with the base peak at *m/e* 191 and all other peaks in the spectrum corresponding essentially identically to those of compound **2** as previously reported.[11]

N-Oxide rearrangements in heteroaromatic compounds are frequently induced by either photochemical or acid anhydride initiated processes, and usually involved formation of a C–O bond at the carbon α to the original *N*-oxide.[12] Two interesting exceptions to the latter generalization have been recently reported. The first of these was the observation by Taylor[13] that 2-amino-4-oxopteridine 8-*N*-oxide, although stable to prolonged refluxing in acetic anhydride–acetic acid mixtures, underwent a facile β-rearrangement in trifluoroacetic acid–trifluoroacetic anhydride (TFAH–TFAA) mixtures to give xanthopterin (2-amino-4,6-dioxopteridine) as the sole product. Taylor proposed that the reaction was facilitated by the rapid loss of a proton from N-1 to give an intermediate such as **8**, which was susceptible to direct attack at the β position



8

by trifluoroacetate as shown. He supported his argument with the observation that the 2,4-diamino derivative underwent the same reaction only under more vigorous conditions. The second recently reported exception was the $POCl_3$ induced rearrangement of 1-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine.[4] in which the newly formed leaving group was at N-1 and the product was 6-chloro-2,4-dioxopyrido[2,3-*d*]pyrimidine. These intriguing observations prompted us to study the rearrangements of *N*-oxides **3** and **4**.

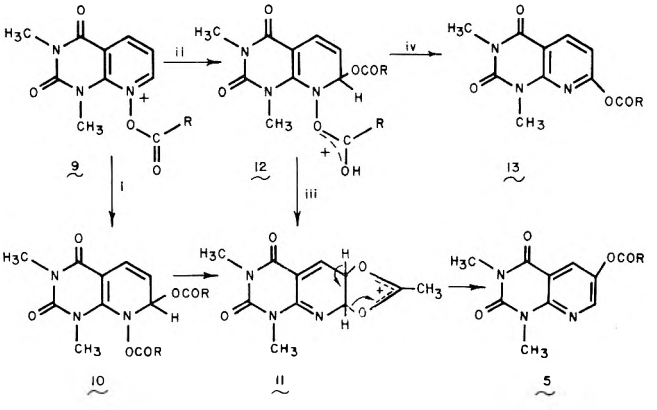
The reaction of **4** with a solution of acetic anhydride in acetic acid (1:1) at 90 °C gave only one product as judged by TLC. This new compound was readily characterized as the 6-acetoxy derivative **5** by elemental analysis and ^{1}H NMR spectroscopy. The signal at about δ 7.5 attributable to the proton at C-6 of **4** was missing and the remaining aromatic protons gave doublets having a coupling constant of 2.7 Hz, typcial of meta couplings of pyridine protons.[14] The acetyl methyl signal appeared as a sharp singlet at δ 2.40. Compound **5** underwent rapid deacylation with methanolic ammonia to give the 6-hydroxy derivative **6**. Similarly, treatment of **4** with neat trifluoroacetic anhydride at reflux followed by workup in aqueous base gave the 6-hydroxy derivative **6** as the *only* product in 97% isolated yield.

When the reaction was run at reflux in TFAH–TFAA a different rearrangement pattern emerged. As the reaction proceeded, two products were formed in nearly equal amounts; 46% isolated yields of each of the products were obtained. One was identical with the 6-hydroxy derivative **6**. The other was proved to be 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**7**) by establishing its identity (TLC, ^{1}H NMR, uv, ir, mass spectrum) with the authentic material which had been prepared by an unequivocal procedure and reported elsewhere.[1]

Thus, it is clear that the rearrangement of **4** induced by acetic anhydride in acetic acid or TFAA gave only the product of β-rearrangement whereas the strongly acidic system TFAH–TFAA led to the formation of equal amounts of both α and β rearrangement products. Because the pyridopyrimidine ring system is isoelectronic with the pteridine system, one might expect a marked facilitation of the β-rearrangement in the case of **3** by analogy with the previously noted ability of the pyridine ring to electronically enhance the rate of such a reaction.[13] It was therefore quite surprising to find that **3** is *completely resistant* to rearrangement; even under such forcing conditions as refluxing TFAH–TFAA for 30 h only starting material was present.

A mechanistic scheme has been developed (Scheme II)

Scheme II



which is consistent with these observations and which could be invoked to account for the β-rearrangement of 2,4-diaminopteridine 8-*N*-oxide under forcing conditions as described by Taylor.[13] The *N*-acyloxypyridinium cation (**9**) is the initial product of the reaction of an acid anhydride with *N*-oxide **4**. The course of subsequent reactions depends in part upon the presence or absence of a strong acid. In the absence of strong acid, i.e., in acetic anhydride–acetic acid or neat trifluoroacetic anhydride, addition of acetate to the α position must occur in the usual way to give **10** (Scheme II, i); this relatively stable (toward elimination) molecule then suffers intramolecular

attack by the acetate or trifluoroacetate carbonyl[15] with concomitant elimination of the N-8 acyloxy group to give **11**. The latter can undergo facile ring opening incident to loss of the more acidic allylic proton to give **5**. An alternative explanation involves addition of an additional acetate or trifluoroacetate moiety to carbon 6 of intermediate **10**, leading to a 6,7-dihydro-6,7-diacetoxy derivative which could undergo aromatization to give **5**. The former explanation is preferred because of the absence of trifluoroacetate ion in the neat TFAA reaction mixture (intermediate **10** incorporates all the elements of one TFAA molecule). In the strongly acidic medium containing TFAH, the intermediate trifluoroacetate adduct **12** may be protonated (ii), thereby enhancing the leaving ability of the trifluoroacetoxy group and enabling the simple β-elimination (iv) to compete effectively with the allylic nucleophilic displacement (iii). Although other parameters may be important in determining the details of the reaction mechanism (i.e., nucleophilicity vs. leaving ability), it is felt that the general features of the proposed mechanism are substantially correct in accounting for the rearrangements observed in this study and the β-rearrangement unfacilitated by rapid ionization of the pyrimidine ring proton in the pteridine series.[13] The strikingly enhanced reactivity of **4** relative to the unmethylated derivative **3** must arise from relief of the steric strain imposed upon **4** by the peri interaction of the 1-methyl and 8-*N*-oxide groups.

Experimental Section

Melting points were obtained on a Thomas-Hoover instrument and are uncorrected. ^{1}H NMR data were obtained using a JEOL C6OH NMR spectrometer at ambient temperature using $(CD_3)_2SO$ with 2,2-dimethyl-2-silapentanesulfonic acid sodium salt (DSS) as internal reference or in trifluoroacetic acid with tetramethylsilane as internal reference. Uv spectra were recorded by means of a Cary 15 spectrophotometer. Thin layer chromatography was carried out on SilicAR 7GF coated glass plates using ethyl acetate–water–1-propanol (4:2:1, upper phase) as developing solvent. Microanalyses were carried out by Heterocyclic Chemical Co., Harrisonville, Mo. Diazomethane solutions were prepared according to Noller.[16] Photolyses were carried out in a Rayonet photoreactor using GE "germicidal" (254 nm peak output) lamps.

2,4-Dioxopyrido[2,3-*d*]pyrimidine 8-*N*-Oxide (3). Compound **1**[6] (5 g, 30.6 mmol) was suspended in 60 ml of glacial acetic acid, 85% *m*-chloroperbenzoic acid (16.2 g, 80 mmol) was added, and the mixture heated at 55–60 °C for 3 h. 1,2-Dimethoxyethane (DME, 20 ml) was added to the mixture, followed by 40 ml of ethyl ether, and the mixture refrigerated for several hours. The white solid was collected, washed with DME and then ethyl ether, and dried to a fine powder: 4.4 g (80%); mp 332 °C dec; ^{1}H NMR (TFAH) δ 9.03 (d, C-5 H), 7.90 (t, C-6 H), 9.18 (d, C-7 H); uv max ($\epsilon_{max} \times 10^{-3}$) [pH] 237 nm (33.8), 336 (5.38) [1]; 237 (23.8), 257 (21.4), 363 (5.48) [7]; 257 (26.2), 280 (11.5), 368 (7.14) [11].

Anal. Calcd for $C_7H_5N_3O_3$: C, 46.93; H, 2.82; N, 23.46. Found: C, 46.91; H, 2.95; N, 23.49.

1,3-Dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine 8-*N*-Oxide (4). Compound **3** (3.0 g, 16.7 mmol) was suspended in 1,4-dioxane, and ethereal diazomethane (approximately 2.8 g, 67 mmol of diazomethane) was added in 20-ml portions over a 2-h period. The mixture was stirred at room temperature until solution was complete, and 5 ml of 50% aqueous acetic acid was added to decompose the excess diazomethane. The clear solution was evaporated to dryness and the solid residue was recrystallized from 80 ml of ethanol (after treatment with carbon) to yield 2.8 g (81%) of the desired compound: mp 174–175 °C; mass spectrum (70 eV) *m/e* (rel intensity) 207 (8), 191 (100), 163 (20), 134 (52), 106 (22); ^{1}H NMR ($(CD_3)_2SO$) δ 8.30 (s, CH_3), 3.89 (s, CH_3), 8.02 (d of d, C-5 H), 7.48 (q, C-6 H), 8.63 (d of d, C-7 H); uv max ($\epsilon_{max} \times 10^{-3}$) [pH] 243 nm (27.0), 342 (3.42) [1]; 243 (27.8), 344 (3.53) [7]; 247 (14.5) [11].

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.09; H, 4.40; N, 20.28.

1,3-Dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (2). Compound **4** (100 mg) was irradiated in deoxygenated DME for 3 h under 254-nm uv light. Thin layer chromatography in the solvents $CHCl_3$–MeOH (19:1) and concentrated NH_4OH–MeOH–DME (1.5:1.5:17) indicated that a significant amount of deoxygenation to 2 (prepared according to McLean and Spring[7]) occurred. No other photoproducts were observed.

1,3-Dimethyl-6-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (6) and 1,3-Dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (7). Compound **4** (900 mg, 4.35 mmol) was refluxed in 60 ml of 50% trifluoroacetic anhydride–trifluoroacetic acid (TFAA–TFAH) for 28 h. The clear solution was evaporated to a yellow oil, 15 ml of 2 N NaOH was added, and the mixture was heated on a steam bath for 5 min. The solution was cooled, adjusted to pH 5 with glacial acetic acid, and refrigerated. The solid weighing 850 mg was chromatographed on 30 g of deactivated silica gel. Elution with concentrated NH_4OH–MeOH–DME (1.5:1.5:22) afforded 415 mg (46%) of the 6-hydroxy compound **6**: mp 265 °C; ^{1}H NMR (TFAH) δ 3.76 (s, CH_3) 4.05 (s, CH_3), 8.67 (d, C-5 H), 9.06 (d, C-7 H), $J_{5,7}$ = 2.8 Hz; uv max ($\epsilon_{max} \times 10^{-3}$) [pH] 307 (13.1) [pH]; 273 (7.56), 308 (19.5), 321 (17.6) [7]; 273 (7.05), 308 (19.2), 321 (17.6) [11].

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.81; H, 4.60; N, 20.55.

Concentrated NH_4OH–MeOH–DME (1:3:16) eluted the 7-oxo compound **7**. The combined fractions were evaporated, and the residue remaining was dissolved in 25 ml of H_2O, adjusted to pH 5 with acetic acid, and refrigerated. The white solid was collected and dried to a weight of 412 mg: mp 282 °C (45.8%); ^{1}H NMR (TFAH) δ 3.74 (s, CH_3), 4.00 (s, CH_3), 8.74 (d, C-5 H), 6.97 (d, C-6 H), $J_{5,6}$ = 9.5 Hz; uv ($\epsilon_{max} \times 10^{-3}$) [pH] 248 nm (8.95), 338 (6.00) [1]; 340 (4.98) [7]; 268 (11.2) [11].

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.01; H, 4.45; N, 20.00.

6-Acetoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (5). Compound **4** (300 mg, 1.45 mmol) was heated at 90 °C in acetic anhydride–glacial acetic acid (2:1) for 24 h. The excess solvents were evaporated and the residue was dissolved in 15 ml of methanol, treated with carbon, filtered, and refrigerated. The crystals that separated were collected and dried to give 129 mg, mp 198–199 °C. Concentration of the filtrate produced a second crop of crystals weighing 50 mg, giving a total of 179 mg (50%): ^{1}H NMR ($(CD_3)_2SO$) δ 2.40 (s, CH_3), 3.53 (s, CH_3), 3.77 (s, CH_3), 8.31 (d, C-5 H), 8.47 (d, C-7 H), $J_{5,7}$ = 2.7 Hz; uv max ($\epsilon_{max} \times 10^{-3}$) [pH] 317 nm (6.38) [1]; 317 (6.50) [7]; 269 (11.6), 322 (3.05) [11].

Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.89; H, 4.68; N, 16.75.

1,3-Dimethyl-6-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (6). Method A. Compound **4** (700 mg, 3.4 mmol) was refluxed in 15 ml of TFAA (neat) for 1.5 h, and the excess solvents were evaporated. The white residue remaining was heated in 2 N NaOH for 5 min on a steam bath, neutralized with acetic acid, and refrigerated. The precipitate, 678 mg (97%), was collected and dried, mp 265 °C, and was chromatographically pure 6-hydroxy product **6**.

Method B. Compound **5** (50 mg) was dissolved in 10 ml of methanolic ammonia (saturated with NH_3 at 0 °C) and kept at room temperature for 0.5 h. Evaporation of the solvents afforded **6**, 40 mg (98%), mp 263–265 °C.

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Registry No.—**1**, 21038-66-4; **3**, 56783-86-9; **4**, 59588-16-8; **5**, 59588-17-9; **6**, 59588-20-4; **7**, 57821-20-2.

References and Notes

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A New Pathway for Oxidation of Alcohols to Carbonyl Compounds[1]

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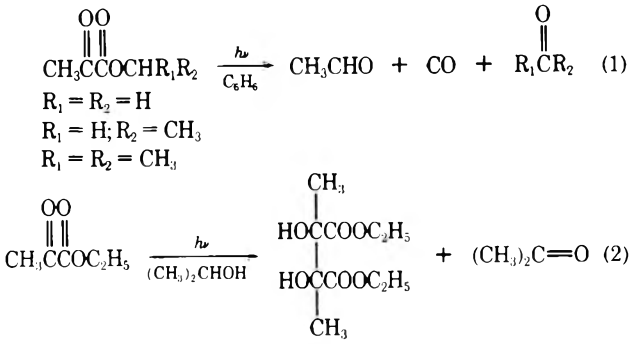
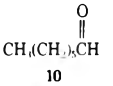
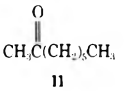
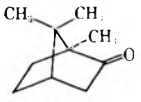
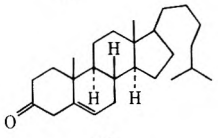
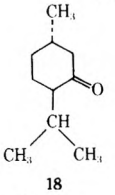
In the early 1960's several research groups studied the photochemistry of alkyl esters of pyruvic acid. Arising from these studies were the findings that in benzene pyruvates fragment photochemically as shown in eq 1[2,3] but they photoreduce when hydrogen donating solvents are used[4] (eq 2). Any interest in utilizing pyruvate photoreaction as a synthetic tool was tempered by the knowledge that the available syntheses of these compounds employed unacceptably forcing conditions for use with sensitive materials.[5] A recent report[6] of a new, simple synthesis of the acid chloride of pyruvic acid raised the possibility that esters of this acid easily could be formed under mild conditions and that synthetically useful photochemical reactions involving these compounds now could be considered. Specifically, the synthesis of pyruvates followed by their reaction as shown in eq 1 could represent an effective sequence for oxidation of alcohols to carbonyl compounds. Assuming that this oxidation sequence could be of general value, a variety of pyruvates were synthesized and irradiated. The results from study of these reactions suggest that the pyruvate oxidation sequence could be useful in solving problems of synthesis in a variety of areas.



In the opening phase of this investigation, the pyruvate esters of seven alcohols [1-phenylethanol (1), benzyl alcohol (2), 1-heptanol (3), 2-octanol (4), cyclohexanol (5), cyclopentanol (6), and borneol (7)] were prepared and irradiated. Alcohol esterification was quantitative. Photochemical reaction of the resulting esters, although not usually quantitative, produced good to excellent yields of the carbonyl compounds 8–14 (Table I). Analysis of the information in Table I reveals the following features for the pyruvate oxidation sequence: (a) the oxidation sequence works well for simple compounds of various structures; (b) primary alcohols are oxidized to aldehydes without further reaction; and (c) essentially complete photochemical reaction of pyruvates can be accomplished without noticeable secondary reaction.

The effect of five solvents on the photochemical reaction of 1-phenylethyl pyruvate is summarized in Table II. The photochemical process is quite solvent dependent. Benzene is an excellent choice and carbon tetrachloride appears to be equally good. Pentane and ethyl ether are poor reaction solvents since irradiation in either of these two results in considerable solvent incorporation.[4]

Table I. Alcohol Oxidation Products and Yields

Alcohol	Oxidation product	Yield, %	Unreacted alcohol, %
1	 8	100	None
	 9	95	4
3	 10	77	6
4	 11	85	None
5	 12	100	None
6	 13	84	None
7	 14	85	1
15	 16	80	None
17	 18	88	None
19	 20	76	2

Since the pyruvate synthesis–photoreaction combination was effective for oxidation of alcohols which are relatively easily oxidized, it was decided to test this combination in several situations where the oxidation products are known to be capable of facile, further reaction or where other reactions could intervene. Conditions for oxidation of cholesterol (15), for example, easily lead to isomerization of the carbon–carbon double bond into conjugation with the newly formed carbonyl.[7,8] In order to determine whether the pyruvate oxidation pathway would also lead to this isomerization, the pyruvate ester of cholesterol was synthesized and irradiated. No isomerization was observed; a good yield (Table I) of the nonconjugated enone (16) was obtained.

Oxidation of alcohols to aldehydes and ketones can be complicated by epimerization at the center next to the carbonyl. Conversion of menthol (17) to menthone (18), for example, is accompanied by formation of isomenthone, unless precautions are taken.[9] To test the possibility of epimerization in the pyruvate oxidation sequence, methyl pyruvate was

Table II. Irradiation of 1-Phenylethyl Pyruvate in Various Solvents

Solvent	Acetophenone yield, %
Benzene	100
Carbon tetrachloride	95
Acetone	86
Pentane	31
Ethyl ether	17

synthesized, irradiated, and found to produce methone (18) (Table I) with no detectable isomenthone present.

Oxidation of allylic alcohols can result in attack by the oxidizing agent on the double bond.[10] To investigate whether the pyruvate oxidation sequence avoids this competing pathway, 2-cyclohexen-1-ol (19) was studied. Oxidation of 19 proceeded in the normal manner to give 2-cyclohexen-1-one in good yield (Table I).

Pyruvate oxidation was unsuccessful in oxidation of *trans*-cinnamyl alcohol to *trans*-cinnamaldehyde. Although esterification occurred in the normal manner, irradiation of *trans*-cinnamyl pyruvate (21) resulted in isomerization to the cis isomer. This is not a surprising result when one considers that esters of pyruvic acid are believed to react via an excited triplet state[2,3] and the triplet state energy of the styrene chromophore should be lower in energy [E_t (styrene) = 61.7 kcal/mol[11]] than that of the keto ester portion [E_t (methyl pyruvate) = 65 kcal/mol[2,12]] of the molecule. Excitation absorbed by the keto ester chromophore would be transferred to the double bond and produce isomerization.

It would be desirable to conduct the pyruvate oxidation process without isolating the intermediate pyruvate ester. This possibility was investigated by irradiating directly the reaction mixture from esterification of 1-phenylethanol (1). The yield of acetophenone arising from this abbreviated procedure was good (90%); however, the reaction mixture had become quite dark during irradiation, a result of decomposition of pyridinium hydrochloride.

It is possible to oxidize alcohols to aldehydes and ketones using the pyruvate oxidation sequence described here without allowing the temperature of the reaction mixture to rise above room temperature. Further, no acids or inorganic oxidizing agents ever come in contact with the starting materials or products. Pyridine, the strongest base used, is involved only in the esterfication step. These reaction conditions must be among the mildest available for alcohol to carbonyl oxidations.

Experimental Section

General Procedures. The esterification, irradiation, and isolation procedure used for oxidation of each of the alcohols 1–7, 17, and 18 was identical. This procedure is described below.

A. Esterfication. The alcohol to be esterified (0.03 mol) and dry pyridine (0.033 mol) were dissolved in 100 ml of anhydrous benzene. Pyruvoyl chloride[6] (0.03 mol) in 50 ml of benzene was added in a dropwise manner with stirring. Precipitation of pyridinium hydrochloride was immediate. Cooling with cold water was necessary to keep the reaction mixture at 25 °C. After stirring for 15 min, the pyridinium hydrochloride was removed by filtration and the benzene distilled in vacuo to yield the pyruvate ester contaminated with pyridinium hydrochloride. The contaminant could be removed by dissolving the reaction mixture in 50 ml of carbon tetrachloride, allowing it to stand for a few hours, and filtering the insoluble material. When the carbon tetrachloride was evaporated from the filtrate, a quantitative yield of the appropriate ester remained.

The identity of each ester was established first by instrumental analysis [NMR (Varian T-60) and GC/MS (Finnigan 1015-D)] and then by saponification to the starting alcohol and sodium pyruvate. Stirring the ester for 12 h in a 1% solution of sodium hydroxide in methanol was sufficient for total saponification.

B. Irradiation and Isolation. The pyruvate ester (4.0 mmol) was dissolved in 350 ml of dry benzene and the solution purged with nitrogen for 1 h. The nitrogen purge was continued during Pyrex-filtered irradiation with a 450-W, medium-pressure Hanovia mercury lamp. After 1 h, the irradiation was stopped, the reaction mixture analyzed by GC/MS, the benzene removed by fractional distillation, and the residual liquid distilled in vacuo using a Buchi/Brinkmann microdistillation oven to give the products shown in Table I. Each product was compared by NMR and GC/MS with a known sample (Aldrich Chemical Co.). In several cases (Table I) small amounts of the starting alcohol were detected. For products 5, 6, 7, and 19, noticeable losses occurred during solvent removal; thus, the product yields as determined prior to solvent removal are given in Table I.

Oxidation of Cholesterol (15). Compound 15 was esterified and irradiated in the same manner as the other alcohols; however, the oxidation product 16 crystallized from the reaction mixture following benzene removal and was recrystallized from methanol rather than distilled. Compound 16 was identified by comparison with a known sample.[8]

Effect of Solvent on Pyruvate Oxidation. The effect of solvent change on the pyruvate oxidation process was tested by successively replacing benzene with carbon tetrachloride, acetone, ethyl ether, and pentane as an irradiation solvent in photolysis of 1-phenylethyl pyruvate. The results are shown in Table II. NMR spectra of crude reaction mixtures from irradiations in ethyl ether and pentane showed considerable solvent incorporation.

Acknowledgment. The author appreciates the helpful suggestions of A. H. Andrist, T. W. Flechtner, and J. I. Sarkisian.

Registry No.—1, 98-85-1; 2, 100-51-6; 3, 111-70-6; 4, 123-96-6; 5, 108-93-0; 6, 96-41-3; 7, 507-70-0; 8, 98-86-2; 9, 100-52-7; 10, 111-71-7; 11, 111-13-7; 12, 108-94-1; 13, 120-92-3; 14, 76-22-2; 15, 57-88-5; 16, 601-54-7; 17, 1490-04-6; 18, 89-80-5; 19, 822-67-3; 20, 930-68-7; pyruvoyl chloride, 5704-66-5.

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Stereochemistry of Hydroboration–Oxidation of Terminal Alkenes[1]

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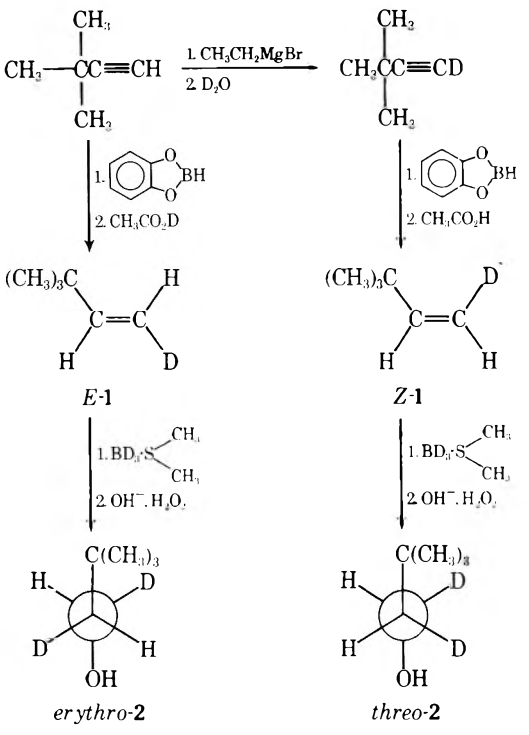
Hydroboration of alkenes followed by alkaline hydrogen peroxide oxidation of the resulting alkylboranes is the method of choice for the anti-Markownikoff hydration of carbon–carbon double bonds.[2] Although mechanistic studies have

been carried out with cyclic[3] and acyclic[4,5] secondary alkylboranes, the stereochemistry of hydroboration of a terminal alkene and the subsequent oxidation of the resulting primary alkylborane has never been determined.[6] The results described below show that these reactions are stereospecific and proceed with net cis addition of H and HO to terminal alkenes. The procedures described below also represent a general, stereospecific route to diastereomeric primary alcohols. Such primary diastereomeric alcohols are of proven utility in organometallic mechanistic studies,[7] and the procedures described below are a substantial improvement over currently available methods for the synthesis of such compounds.

Our results (Scheme I) show that hydroboration and subsequent alkaline hydrogen peroxide oxidation of (*Z*)- or (*E*)-3,3-dimethylbutene-*1*-d_1 (*Z*- or *E*-**1**) proceeds with >95% cis stereospecificity. Assuming cis hydroboration of the alkene, this means that alkaline hydrogen peroxide oxidation of primary alkylboranes occurs with retention of configuration at carbon. The stereochemistry of the products of these reactions, *erythro*- and *threo*-3,3-dimethylbutan-1-ol-*1,2*-d_2 (*erythro*- and *threo*-**2**), was determined by deuterium-decoupled ^{1}H NMR as has been previously described.[7] Non-deuterium-decoupled NMR does not permit a quantitative estimation of the diastereomeric purity of *erythro*- and *threo*-**2**, but approximate coupling constants can easily be obtained which can be used to identify the predominant diastereomer present. The approximate coupling constants obtained in this fashion for *erythro*- and *threo*-**2** are 10.5 and 5.5 Hz, respectively, and agree both with literature values and with those measured in the deuterium-decoupled spectra. The additional observation of a strong ir absorption at 1075 cm^{-1} for *threo*-**2** which is absent in the ir spectrum of *erythro*-**2** and corresponding absorptions at 1120 and 1100 cm^{-1} in the ir spectrum of *erythro*-**2** which are not present in the ir of *threo*-**2** provide further evidence for the purity of these diastereomers. Our experience with these and other similar compounds[8] suggests that in some cases the diastereomeric purity and which diastereomer is present can be determined by ir and ^{1}H NMR without the necessity of deuterium-decoupled ^{1}H NMR. However, deuterium-decoupled NMR is still the most general and best procedure available for determining the diastereomeric purity of 3,3-dimethylbutyl-*1,2*-d_2 derivatives.

Scheme I. Synthesis of *erythro*- and *threo*-3,3-Dimethylbutan-1-ol-*1,2*-d_2



The synthetic procedures leading to the diastereomers **2** are summarized in Scheme I. The straightforward reactions and the ready availability of the deuterated reagents used in this synthesis make these procedures the method of choice for the synthesis of these and similar diastereomeric primary alcohols. Such diastereomeric primary alcohols are of proven usefulness as precursors of ligands in organometallic mechanistic studies.[7,9-12] Synthetic reactions of known stereochemistry could also be used on diastereomeric primary alcohols prepared in this manner to synthesize compounds which would be useful as probes on conformation in simple acyclic systems.[13,14]

The results we have obtained support a concerted mechanism for hydroboration of alkenes. As proposed by Jones,[15] formation of a π complex between the alkene and boron followed by concerted rearrangement yields the alkylborane product. The stereochemical results we have obtained agree with this mechanism and demonstrate that alkylborane formation occurs without significant rotation of the developing carbon–carbon single bond. Although the stereochemistry of the intermediate alkylboranes was not determined in our studies, the paucity of examples of trans addition of metal hydrides to carbon–carbon double bonds and the stereospecificity of the oxidation reaction (vide infra) strongly suggest that hydroboration proceeds through cis addition of hydrogen and boron to the carbon–carbon double bond.

The stereospecificity observed in the alkaline hydrogen peroxide oxidation implies either complete retention or inversion of stereochemistry at the primary alkylborane in the oxidation reaction. Although there are some literature examples of free-radical intermediates in the alkaline hydrogen peroxide oxidation of alkylboronic acids[16] and in the neutral hydrogen peroxide oxidation of alkylboranes,[17] there is not evidence to support an inversion pathway in these oxidation reactions. Intermediate free-radical species would be expected to lead to epimerization which is not observed. We therefore conclude that alkaline hydrogen peroxide oxidation of primary alkylboranes occurs with complete retention of configuration at carbon in accord with Brown's original suggestions.[3]

Experimental Section

General Methods. All reactions of organometallic compounds were carried out in flame-dried glassware under prepurified nitrogen or argon using standard techniques.[2] Tetrahydrofuran and other ethereal solvents were distilled from a purple solution of benzophenone dianion prior to use. Methanol was purified by distillation from a methanol–sodium hypoiodate solution. Routine NMR spectra were recorded on a Varian T-60 NMR spectrometer; chemical shifts are reported in parts per million downfield from tetramethylsilane. Deuterium-decoupled NMR spectra were obtained using a Varian HA-100 spectrometer at the University of Texas at Austin.[18] Routine infrared spectra were obtained using 0.1 mm sodium chloride cells on a Beckman IR-8 spectrometer. Higher resolution infrared spectra were obtained on a Digilab FTS-20 vacuum infrared spectrometer. Raman spectra were recorded on a Cary 82 laser Raman spectrophotometer. A Perkin-Elmer 3920 gas chromatograph was used for GLC analyses. Solutions of deuterioborane–methyl sulfide complex in tetrahydrofuran were purchased from Aldrich Chemical Co. Other solvents and reagents were purchased from commercial sources in reagent quality.

3,3-Dimethylbutyne was prepared in 91% yield by the method of Collier and Macomber:[19] ir (neat) 3300, 2160, and 2110 cm^{-1}; Raman (neat) 2162 (w), 2130 (s), and 1933 cm^{-1} (w).

3,3-Dimethylbutyne-*1*-d_1 was prepared in 96% yield by the method of Zeil, Winnewisser, Bodenseh, and Buchert,[20] ir (neat) 2600 cm^{-1}. The isotopic purity of this compound was determined by the absence of an acetylenic proton in the NMR and by the disappearance of the carbon–carbon triple bond absorption in the ir spectrum (apparently because of coupling of the carbon–carbon triple bond ab-

sorption with the carbon-deuterium absorption). A strong carbon–carbon triple bond stretch was observed at 1982 cm^{-1} in the Raman with a corresponding weak absorption at 1980 cm^{-1} in the infrared.

(*Z*)-3,3-Dimethylbutene-*1*-d_1 (*Z*-1) was prepared in 85% yield from 3,3-dimethylbutyne-*1*-d_1 by the procedure of Brown and Gupta:[21] ir (neat) 2270, 802, 727 cm^{-1}; NMR (neat) δ 5.80 (m, 1, J_{H-H} = 12.0, J_{H-D} = 2.8 Hz), 4.73 (slightly broadened doublet, 1, J_{H-H} = 12.0 Hz), 1.03 (s, 9).

(*E*)-3,3-Dimethylbutene-*1*-d_1 (*E*-1) was prepared in 85% yield by hydroboration of 3,3-dimethylbutyne with 1,3,2-benzodioxaborole followed by deuterolysis of the intermediate at vinylborane with acetic acid-d_1 as has been previously described:[21] ir (neat) 2270, 980, 838 cm^{-1}; NMR (neat) δ 5.76 (m, 1, J_{H-H} = 18.0, J_{H-D} = 1.8 Hz), 4.78 (slightly broadened doublet, 1, J_{H-H} = 18 Hz), 1.01 (s, 9).

***threo*-3,3-Dimethylbutan-1-ol-*1,2*-d_2 (*threo*-2)** was prepared from *Z*-1 following the general procedure of Lane.[22] To a solution of 1.3 ml (10 mmol, 0.85 g) of *Z*-1 in 10 ml of THF in a three-necked, 100-ml, round-bottomed flask equipped with magnetic stirring bar, reflux condensor, and pressure equalized addition funnel was added 3.5 ml of a 0.95 M THF solution of deuterioborane–methyl sulfide at 0 °C dropwise with stirring. This reaction mixture was stirred for 1 h at 0 °C and 3 h at room temperature. Then 0.5 ml of absolute methanol was added by syringe and the reaction mixture cooled to 0 °C. The intermediate alkylborane was then oxidized by addition of 1.1 ml of 3 N aqueous sodium hydroxide followed by addition of 1.2 ml of a 30% hydrogen peroxide solution. After refluxing for 1 h, the reaction mixture was worked up by pouring it into a mixture of 40 ml of ice water and 20 ml of ether. The aqueous phase was separated and washed four times with 25-ml portions of ether. The combined ethereal phase was then washed twice with 10-ml portions of sodium thiosulfate. To ensure complete recovery of all the partially water soluble alcohol, these thiosulfate washes were in turn extracted with four 10-ml portions of ether. The combined ethereal phases were then dried (Na_2SO_4) and the ether was removed by fractional distillation. The resulting yellow oil was purified by a short-path distillation and isolated in 84% yield: bp 140–145 °C (lit.[7] bp 140–145 °C); ir (CS_2) 3350, 1294, 1128, 1075, 1045, 991, and 940 cm^{-1}; deuterium-decoupled NMR ($CDCl_3$) δ 3.65 (d, 1, J = 5.6 Hz), 3.47 (s, 1), 1.49 (d, 1, J = 5.6 Hz), 0.93 (s, 9).

***erythro*-3,3-Dimethylbutan-1-ol-*1,2*-d_2 (*erythro*-2)** was prepared from *E*-1 according to the procedure described for *threo*-2. The product alcohol was isolated in 85% yield by distillation: bp 140–145 °C (lit.[7] bp 140–145 °C); ir (CS_2) 3350, 1300, 1120, 1100, 1045, 1000, and 933 cm^{-1}; deuterium- decoupled NMR ($CDCl_3$) δ 3.65 (d, 1, J = 10.2 Hz), 3.52 (s, 1), 1.48 (d, 1, J = 10.2 Hz), 0.94 (s, 9). The infrared spectra for *erythro*- and *threo*-2 mainly differ in the 1000–1125-cm^{-1} region, *threo*-2 having a strong peak at 1075 cm^{-1} which is only present as a shoulder in *erythro*-2.

Acknowledgments. We are grateful to Drs. E. Kyba and B. Shoulders at the University of Texas at Austin for the deuterium-decoupled NMR measurements. The FTS-20 spectrophotometer was purchased with the aid of NSF Grant GP-37029 to Texas A&M University.

Registry No.—*Z*-1, 6833-43-8; *E*-1, 57002-05-8; *threo*-2, 52291-61-9; *erythro*-2, 23930-47-4; 3,3-dimethylbutyne, 917-92-0; 3,3-dimethylbutyne-*1*-d_1, 6833-44-9.

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Conformational Isomerism in *o*-Tolyldi-*tert*-butylcarbinol

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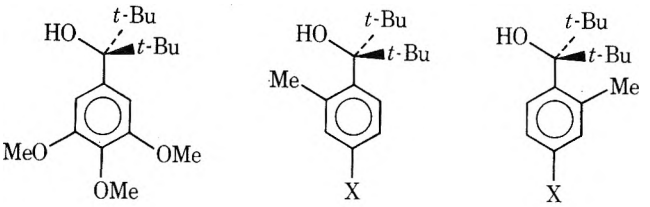
Barriers to rotation about sp^2–sp^3 and sp^3–sp^3 carbon to carbon bonds have been measured mainly by the NMR method[1] for a wide variety of compounds. Among the highest observed for nonbridged structures is the free energy of activation (18.7–21.4 kcal/mol) for rotation of the phenyl ring in 3,4,5-trimethoxyphenyldi-*tert*-butylcarbinol (**1**).[1c,2]

Our interest in the reactivity of congested tertiary carbinols and their derivatives[3] led us to synthesize *o*-tolyldi-*tert*-alkylcarbinols by condensation of *o*-tolyllithium with di-*tert*-alkyl ketones. GLC analysis of the crude product from the reaction with di-*tert*-butyl ketone revealed the presence of two components, denoted **2a** and **3a**, in the ratio 14:86,



1 2 3

a, X = H; b, X = OMe

whereas after distillation the product was exclusively **2a**. The unstable isomer, **3a** could, however, be isolated by chromatography on alumina in pentane and was found to differ significantly from **2a** in the ir absorption of the hydroxyl group and in the NMR of the aromatic and hydroxyl protons. A more dramatic difference in behavior was found when the dehydration rates were determined: **3a** reacts approximately 10 000 times faster than **2a**.

It is clear that **2a** and **3a** are conformational isomers, "atropisomers".[4] On the basis of kinetic[5] and spectral similarities it can be affirmed that isomer **2a** is of the same type as **2b** whose structure has been determined crystallographically.[7] In this molecule the distance between the carbon of the *o*-methyl group and the hydroxyl oxygen is very small (2.66 Å), this oxygen lying in a plane at 11.6° to the ring plane. Isomer **3a** therefore can only have a structure in which the *o*-methyl group is in the vicinity of the *tert*-butyl groups. The spectral data, as well as the relative amounts of **2a** and **3a** obtained in the synthesis and their relative dehydration rates, are consistent with this assignment. Thus, condensation of the aryllithium with di-*tert*-butyl ketone leads to the lithium

alkoxide ion pair. The preponderance of the less stable alcohol isomer can reasonably be attributed then to the steric requirements of the lithium ion and its solvation shell. In the same way, protonation of the hydroxyl group, the first step of the dehydration reaction, must in **2a** be hindered by the proximity of the *o*-methyl to such an extent that this step has a very small equilibrium constant or may even be rate determining.[8] This feature is absent in **3a** whose reactivity may be further enhanced by relief of steric strain between the *o*-methyl and *tert*-butyl groups in the normally rate-determining heterolytic bond cleavage step.[9]

Rate constants for the conversion of **3a** into **2a** in dodecane indicate that the activation enthalpy is 25.9 kcal/mol, that is, over 11 kcal/mol greater than that for rotation about the phenyl to sp^3 carbon bond of **1** in nonane.[2] This value is unusually high for rotation involving an sp^3 carbon; to date comparable values have only been reported for 9-arylfluorenes[10] and triarylmethanes.[11]

Experimental Section

Gas Chromatography. GLC was performed on a 25-cm column of 10% SE-30 on Chromosorb 80/100 at 120 °C with an inlet pressure of 1 atm. By this means the extent of **3a** → **2a** isomerization is limited to 5%; the data have been corrected appropriately.

Synthesis of o-Tolyldi-*tert*-butylcarbinol. Di-*tert*-butyl ketone was added to an equimolar quantity of o-tolyllithium in ether at ambient temperature (20 °C) under argon. After 1 h the reaction mixture was poured onto ice, washed with water, and dried over Na_2SO_4 before evaporation of the solvent at reduced pressure. GLC analysis of the crude reaction product revealed two compounds, **2a** and **3a**, in the ratio 14:86 and having retention times of 90 and 120 s, respectively. Distillation of this mixture gave **2a** in good yield [69%, bp 116 °C (2mm), mp 35 °C]. The unstable isomer **3a** was readily separated from the **2a**–**3a** mixture by chromatography on a column of alumina (Brockmann activity II–III) in pentane.

Alcohol **2a** has ir (CCl_4) 3644 cm^{-1} (free hydroxyl); NMR (Me_2SO) singlet (δ 1.11), 18 H of *tert*-butyl; singlet (δ 3.84), 1 H of hydroxyl; singlet (δ 2.60), 3 H of methyl; multiplet (δ 6.95), 3 aromatic H; multiplet (δ 7.42), 1 aromatic H.

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.78; H, 10.96.

Alcohol **3a** was obtained as a slightly impure oil with ir (CCl_4) 3613 and 3650 cm^{-1} (π-bonded[12] and free hydroxyl); NMR (Me_2SO) singlet (δ 1.13), 18 H of *tert*-butyl; singlet (δ 4.35), 1 H of hydroxyl; singlet (δ 2.62), 3 H of methyl; multiplet (δ 7.00), 3 aromatic H; multiplet (δ 8.01), 1 aromatic H.

Synthesis of p-Methoxy-o-tolyldi-*tert*-butylcarbinol. Addition of the aryllithium to di-*tert*-butyl ketone gave, after the usual workup, a product mixture which yielded pure **2b** upon standing for 4–5 weeks (4%, mp 96 °C). No attempt was made to isolate **3b**.

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.01; H, 10.63.

Alcohol **2b** has ir (CCl_4) 3643 cm^{-1} (free hydroxyl); NMR (Me_2SO) singlet (δ 1.09), 18 H of *tert*-butyl; singlet (δ 2.61), 3 H of methyl; singlet (δ 3.72), 3 H of methoxyl; singlet (δ 3.78), 1 H of hydroxyl; multiplet (δ 6.53), 2 aromatic H; multiplet (δ 7.38), 1 aromatic H.

Isomerization Kinetics. A thermostated solution of **3a** (0.02 M) and an internal standard, octadecane (0.01 M) in dodecane was sampled at convenient intervals and the reaction mixture analyzed by GLC as described above. First-order rate constants (±1–5%) were determined from the relative peak areas of **3a** and octadecane: 80 °C, 1.26×10^{-5}; 95 °C, 5.64×10^{-5}; 112 °C, 2.75×10^{-4}; 130 °C, 1.26×10^{-3} s^{-1}, whence $\Delta H^{\ddagger} = 25.9 \pm 0.4$ kcal/mol and $\Delta S^{\ddagger} = -8.2 \pm 0.9$ eu.

Dehydration Kinetics. Owing to the low solubility of octadecane a modification of the above method was employed. Samples (200 μl) of a solution of the alcohol (0.02 M) in H_2SO_4–acetic acid at 25 °C were quenched in 20% Na_2CO_3 solution (5 ml). After addition of 20 μl of a 0.1 M solution of octadecane in benzene the mixture was extracted with pentane (500 μl). Dehydration rates constants were as follows: **2a** (10% v/v H_2SO_4 in anhydrous acetic acid), 1.53×10^{-5}; **2b** (10% H_2SO_4), 3.02×10^{-4}; **3a** (2% H_2SO_4), 2.74×10^{-3} s^{-1}. For comparison *p*-tolyldi-*tert*-butylcarbinol has rate constants of 4.24×10^{-3} and 6.31×10^{-5} s^{-1} in 10% and 2% H_2SO_4, respectively. We estimate then that the **3a**:**2a** rate ratio is at least 10^4.

Registry No.—**2a**, 59434-44-5; **2b**, 59434-45-6; di-*tert*-butyl ketone, 815-24-7; *o*-tolyllithium, 6699-93-0.

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A Convenient Two-Step Synthesis of 2,6-Di-*tert*-butyl-4-methylpyridine, a Sterically Hindered Nonnucleophilic Base

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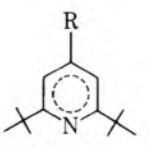
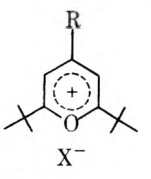
It is well known that pyridine rings containing the 2,6-di-*tert*-butyl functionality enable such bases to distinguish between Bronsted (protonic) and Lewis acids owing to steric crowding in the region of the nitrogen atom.[1a] In connection with some aspects of our work on vinyl triflate chemistry we had need of relatively large amounts of such a nonnucleophilic base. However, the usual synthesis of 2,6-di-*tert*-butylpyridine (**1**) from pyridine and *tert*-butyllithium requires anhydrous conditions, gives low yields, and results in a mixture of isomers that requires tedious separation.[1b] Hence, we decided to look for improved ways of preparing this or similar sterically hindered pyridine bases and wish to report the results in this note.

Pyridines substituted in the 2,6 positions are easily synthesized from the corresponding pyrylium salts[2] in nearly quantitative yields, i.e., conversion of **3** should yield **1**. Although pyrylium salt **3** is difficult to obtain, pyrylium salts substituted with an additional methyl group in the 4 position, **4**, are readily available in a single step. Compound **4** may then



1. R = H
2. R = CH_3

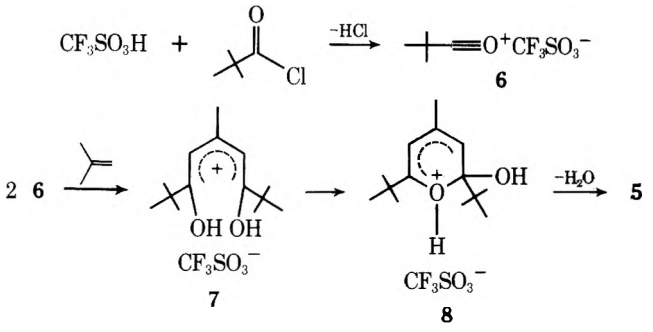


3. R = H
4. R = CH_3
5. R = CH_3; X = OTf

be converted into the title compound, **2**. Compound **4** has been prepared previously in yields of 4–40% starting with the chloride or anhydride of pivalic acid and employing various counterions such as ClO_4^-, $FeCl_4^-$, or $AlCl_4^-$.[3]

We have found that use of pivaloyl chloride and trifluoromethanesulfonic (triflic, –OTf) acid greatly simplifies the procedure for the preparation of **5** and results in improved yields of 54–60%. We assume that the reaction proceeds according to Scheme I;[4] the acylonium triflate, **6**, formed[5] from

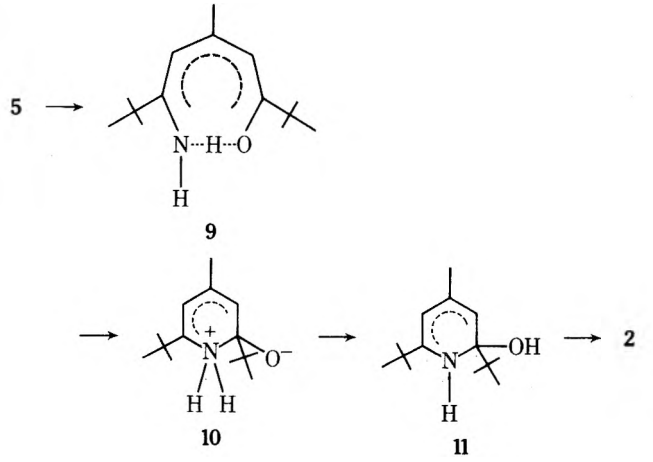
Scheme I



pivaloyl chloride and triflic acid adds twice to isobutylene, generated in situ from *tert*-butyl alcohol, to form **7**, which cyclizes to **8** and upon loss of water gives **5**. The reaction proceeds poorly unless the mixture is heated to 85 °C. Use of more than 1 mol of *tert*-butyl alcohol or less than 2 mol of triflic acid results in a lower yield. Use of anhydrous *p*-toluenesulfonic acid, polyphosphoric acid, sulfuric acid, or P_4O_{10} as a catalyst and counterion instead of triflic acid fails. Pyrylium salt **5** is nonhygroscopic and stable indefinitely at room temperature.

Crude **5** is readily converted into **2** by treatment with ethanolic ammonium hydroxide for 2 h at −40 °C. The reaction can be monitored by the formation and disappearance of a brilliant yellow intermediate[6] which is likely to be intramolecularly hydrogen bonded **9**[7] in Scheme II.

Scheme II



Upon subsequent reaction **9** is required to pass through a sterically crowded zwitterionic cyclic intermediate **10** which should transfer a proton to form **11** and by loss of water relieve crowding and aromatize to **2**. The final product, **2**, is isolated as a colorless, odorless, crystalline solid in 95% yield (55% overall) by extraction with pentane and is purified[8] by column chromatography on activated alumina.

Experimental Section

General. Melting points and boiling points are uncorrected. NMR spectra were recorded on a Varian 360A spectrometer and data are given in δ (ppm) relative to internal Me_4Si; ir spectra were recorded on a Beckman IR5A and are reported in wavenumbers (cm^{-1}) calibrated to the 1603-cm^{-1} line of polystyrene. Pentane (Phillips), pivaloyl chloride (Aldrich), trifluoromethanesulfonic acid (3M), and *tert*-butyl alcohol (Baker) were used directly without purification, as were reagent grade inorganic chemicals. Alumina (Fisher, neutral, 80–200 mesh) was activated by heating in an oven at 200 °C for 24 h.

2,6-Di-*tert*-butyl-4-methylpyrylium Triflate (5). Into a 100-ml three-necked round-bottom flask, equipped with a dry ice condenser capped with a drying tube, nitrogen inlet, constant-pressure addition funnel, and a magnetic stirrer was added 24.2 g (0.2 mol) of pivaloyl chloride and 3.7 g (0.05 mol) of *tert*-butyl alcohol. After the apparatus was flushed with a slow stream of nitrogen, the dry ice condenser was charged with dry ice/isopropyl alcohol and the reaction mixture was heated to 85 °C by means of an oil bath; then 15 g (0.1 mol)[9] of triflic acid was added over a period of 15 min. After addition was completed the mixture was stirred for an additional 10 min at 85 °C; the light brown reaction mixture was then cooled in an ice bath and poured into 100 ml of cold ether. The light tan precipitate was collected by filtration and air dried to give 9.6 g (54%) of pyrylium salt that was used without further purification in the next step. A sample twice recrystallized from $CHCl_3/CCl_4$ (3:1) gives colorless needles: mp 168–169 °C; NMR (CCl_4) δ 1.17 (s, 18 H), 2.07 (s, 3 H), 6.66 (s, 2 H); ir (KBr pellet) 3030, 2965, 1631, 1530, 1494, 1460, 1372, 1266, 1226, 1200, 1144, 1032, 973, 944, 921, 889, 776, 752, and 637 cm^{-1}.

2,6-Di-*tert*-butyl-4-methylpyridine (2). To a 1-l. round-bottom flask containing 100 ml of concentrated ammonium hydroxide cooled to −60 °C was added in one portion with stirring a slurry of 10 g (0.028 mol) of crude pyrylium salt **5** in 200 ml of 95% ethanol also cooled to −60 °C. The yellow reaction mixture was held at −60 °C for 30 min, then maintained at −40 °C for 2 h, during which time the slurry dissolved; the reaction mixture was then allowed to slowly warm up to room temperature. The reaction mixture was poured into 500 ml of a 2% NaOH solution and the resulting emulsion was extracted with four 100-ml portions of pentane; the combined extracts were washed with 25 ml of saturated NaCl and the pentane was removed on a rotary evaporator. The residual light yellow oil was chromatographed on a 50 × 0.5 cm activated alumina column using pentane as the eluent. All of the pyridine was obtained in the first 200 ml of eluent.[10] The pentane was removed on a rotary evaporator to yield 5.46 g (95%) of a colorless oil which solidifies on cooling or standing. Compound **2** sublimes slowly at room temperature and atmospheric pressure forming very thin 5 cm long needles: mp 31–32 °C; bp 148–153 °C (95 mm) [lit.[3a] 223 °C (760 mm)]; chloroplatinate salt mp 213–214 °C dec (lit.[3a] 212 °C); ir (melt) 3000, 1602, 1565, 1480, 1452, 1409, 1356, 1250, 1205, 1162, 1036, 925, 902, 851, and 769 cm^{-1}; NMR (CCl_4) δ 1.75 (s, 18 H), 2.72 (s, 3 H), 7.33 (s, 2 H).

Acknowledgments. This investigation was supported by Public Health Service Research Grant 1-RO-1CA16903-01 from the National Cancer Institute.

Registry No.—**2**, 38222-83-2; **5**, 59643-43-5; pivaloyl chloride, 3282-30-2; *tert*-butyl alcohol, 75-65-0; triflic acid, 1493-13-6.

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(7) However, other open-chain fully conjugated structures which could give rise to the yellow-colored intermediate might also be possible.
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(9) If desired, the excess triflic acid can be recovered as the solid monohydrate by pouring the ether solution remaining after the pyrylium salt is filtered

off into 50 ml of distilled water, separation of the two phases, extraction with 10 ml of pentane to remove pyvalic acid, and evaporation of the aqueous layer to dryness.

(10) The progress of the elution can be monitored by occasionally spotting a fluorescent TLC plate and examining the plate under short-wave uv light; the pyridine appears as a dark blue spot.

Carbon-13 Nuclear Magnetic Resonance Examination of Some [1-^{2}H]-4-*tert*-Butylcyclohexyl Derivatives

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Recently in this journal, one of us reported[2] the preparation of *cis*- and *trans*-4-*tert*-butylcyclohexane-*1*-d_1, and their characterization by infrared and ^{2}H nuclear magnetic resonance spectroscopy. These compounds, and their 1-oxy precursors, appeared attractive subjects for ^{13}C NMR examination, as considerable insight into the effects of ^{2}H substitution on ^{13}C spectra in a geometrically well-defined cycloalkyl system would result, and complement information available for other ^{2}H-substituted systems.[3-8] In addition, the 4-alkylcyclohexyl system frequently is employed in stereochemical and mechanistic studies, and with the growing use of ^{13}C NMR in this area, it is important to provide parameters for this system.

***trans*-4-*tert*-Butylcyclohexyl mesylate** provides a well-separated spectrum which is relatively straightforward to assign. C_1, bearing the mesyl ($-OSO_2CH_3$) function, resonates at lowest field (82.16 ppm) and C_4, $(CH_3)_3C$, and $(CH_3)_3C$ are assigned on the bases of chemical shifts and intensities. Differentiation between $C_{2,6}$ and $C_{3,5}$ is based on the expected greater shielding of $C_{3,5}$, as these carbons are located γ and anti-periplanar to the oxy function.[9] Examination of the spectrum of the 1-^{2}H isomer of this (trans) mesylate confirms the assignment of C_1 (signal now not visible under our pulse conditions) and of $C_{2,6}$ which has experienced a two-bond upfield (i.e., negative) ^{2}H isotope effect of -0.13 ppm, while the signal assigned to $C_{3,5}$ is unaffected within experimental error. This is consistent with other observations that three-bond ^{2}H isotope effects on chemical shifts are quite small.[3,4] We also anticipated that the $C_{3,5}$ signal should be perceptibly broader than that of $C_{2,6}$, because of the operation of significant vicinal ^{2}H–^{13}C coupling.[5,6] The signal of $C_{3,5}$ appears marginally broader, but a strong effect would not be expected for a dihedral angle of 60° (vide infra).

The spectrum of *trans*-4-*tert*-butylcyclohexyl tosylate is similar in many respects to that of the mesylate, and assigned with the same criteria. Another measure of the two-bond isotope effect (at $C_{2,6}$) is provided (-0.11 ppm).

***trans*- and *cis*-4-*tert*-Butylcyclohexane-*1*-d_1.** The spectrum of *tert*-butylcyclohexane was reported previously by Roberts,[10] but at the frequency employed several signals were not well separated, and assignments could not be definite. The cis isomer (i.e. axial ^{2}H) was examined initially as mass spectral examination showed it to be ~90% ^{2}H enriched, and hence the regular *tert*-butylcyclohexane (~10%) would serve as a useful internal standard for isotope shifts. One and two-bond isotope effects of -0.43 and -0.09 ppm (i.e., at C_1 and $C_{2,6}$, respectively) are measured, while any three-bond isotope effect must be less than 0.05 ppm.

The spectra of the above compounds are reproduced in Figure 1, and using the *tert*-butyl resonance as standard, it is clear that there are significant differences in the one- and two-bond isotope effects. This is not surprising as differences in other spectroscopic properties of equatorial and axial ^{2}H are well established.[11] The difference appears greater for the two-bond isotope effect.

Table I. Carbon-13 NMR Parameters[a] for 4-*tert*-Butylcyclohexyl Systems

Registry no.	Compd (X = Y = H; Y = D[b,c]; X = D; Y = H [corrected against $(CH_3)_3C$ as standard][b]; Y = H; X = OSO_2CH_3; Y = D; X = OSO_2CH_3[b]; Y = H; X = $OSO_2C_6H_4CH_3$; Y = D; X = $OSO_2C_6H_4CH_3$[b])	Carbon 1	2,6	3,5	4	$(CH_3)_3C$	$(CH_3)_3C$	Others
	X = Y = H	26.61	27.09	27.44	48.01	27.30	32.26	
	(reported[10])	27.2	27.8	28.2	48.9	27.7	32.7	
53042-76-5	X = H; Y = D[b,c]	26.18	27.00	27.44	48.01	27.30	32.26	
		(−0.43)	(−0.09)	~0[e]				
17553-36-5	X = D; Y = H	26.16	26.93	27.32	47.94	27.27	32.24	
	[corrected against $(CH_3)_3C$ as standard][b]	26.19	26.96	27.35	47.97	27.30	32.27	
		(−0.42)	(−0.13)	(−0.09)				
18508-90-2	Y = H; X = OSO_2CH_3	82.16	33.31	26.65	46.74	27.57	32.25	38.81
53111-68-5	Y = D; X = OSO_2CH_3[b]	n.o.	33.18	25.62	46.72	27.57	32.26	38.81
		[d]	(−0.13)	(~0)[e]				
7453-05-6	Y = H; X = $OSO_2C_6H_4CH_3$	81.78	32.58	25.30	46.12	27.24	31.88	21.39; 126.30; 128.44 133.53; 142.86
53042-75-4	Y = D; X = $OSO_2C_6H_4CH_3$[b]	n.o.	32.47	25.33	46.12	27.24	31.91	21.41; 126.33; 128.41 133.59; 142.86
		[d]	(−0.11)	(~0)[e]				

[a] Spectra recorded at 22.625 or 67.89 MHz (Bruker). Chemical shifts for dilute $CDCl_3$ solutions referenced to internal Me_4Si. [b] Values in parentheses are isotope shifts in parts per million. [c] $J_{^{13}C-^2H}$ = 19.2 Hz. [d] Signal not observable under our pulse conditions. [e] Not greater than experimental error.

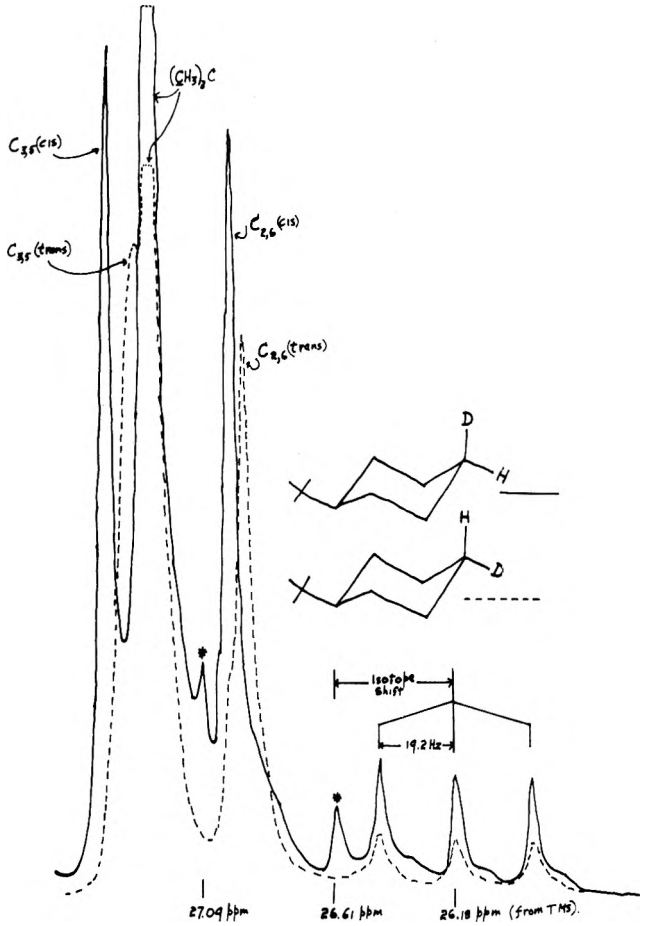

Figure 1. High-field part of the 67.89-MHz ^{13}C spectra (500-Hz expansion) of *trans*-4-*tert*-butylcyclohexane-*1*-d_1 (broken line) and *cis*-4-*tert*-butylcyclohexane-*1*-d_1 (full line). The signals marked with an asterisk correspond to C_1 (at 26.61 ppm) and $C_{2,6}$ (27.09 ppm) in regular (undeuterated) *tert*-butylcyclohexane, admixed (~10%) with the cis isomer. (The degree of deuteration was much higher in the trans case.) The C_1–D triplet ($J_{^{13}C-^2H}$ = 19.2 Hz) is indicated.

Comparison of the shape and position of the $C_{3,5}$ signals in the two isomers (Figure 1) reveals (a) that when ^2H is equatorial (i.e., trans isomer) $C_{3,5}$ is broader and at higher field than when ^2H is axial. The "broadness" was expected as vicinal ^2H coupling to ^{13}C in other systems is substantial for a dihedral angle of 180°,[5,6] which, of course, exists in the trans compound. In addition, it appears that the (γ)-antiperiplanar array of $C_{3,5}$ and ^2H promotes a greater three-bond isotope effect than when a (γ)-syn situation exists, as in the cis isomer.

Previously, Doddrell and Burfitt[8] had examined the effect of ^2H substitution on the ^{13}C spectra of some 1-^2H-1-substituted heptanes, and for the parent hydrocarbon, a one-bond effect (i.e., at C_1) of −0.28 ppm ($J_{^2H-^{13}C}$ = 19.2 Hz) was observed. These results are in line with the present data. More recently, Colli, Gold, and Pearson[7] reported ^2H isotope effects on the ^{13}C NMR spectra of a number of alkyl systems, but generally the compounds were polydeuterated, so that observed effects were combinations of nearest neighbor and more remote interactions. However, their reported (upfield) isotopic shift for perdeuteriocyclohexane of −1.33 ± 0.2 is quite consistent with the values noted here, i.e., (2 × ~0.4) + (4 × ~0.1) ≃ 1.2.

The spectral data are assembled in Table I.

The present results indicate that incorporation of ^2H in a defined way in a cycloalkyl system can be a substantial aid in assignment of carbon signals two and three bonds removed from the site of incorporation.[12] Alternatively, the effect ^2H might have on the spectra could provide insight into the stereochemical location of the ^2H label.

Experimental Section

The compounds examined have been described in detail elsewhere.[2]

Acknowledgments. The authors are grateful to Dr. Alan Jones, National NMR Centre, Canberra, Australia, for providing some detailed spectra and to the Australian Research Grants Committee for partially funding this research.

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The Effect of Substrate Micellization on the Hydrolysis of *n*-Decyl Phosphate[1]

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Catalysis and inhibition by micelles of added surfactant have been studied extensively,[3-6] but in only a few cases has the effect of substrate micellization been examined.[7-10] However, the rates of hydrolysis of monoalkyl sulfates are markedly affected by substrate micellization which speeds the acid-catalyzed hydrolysis but retards reaction with hydroxide ion.[7] Monoanions of monoalkyl phosphates decompose spontaneously in a reaction which almost certainly involves elimination of metaphosphate ion and proton transfer to the RO– moiety:[11-13]

$$RO{-}PO_3H^- \longrightarrow ROH + PO_3^- \xrightarrow[fast]{H_2O} Pi$$

At lower pH nucleophilic attack upon the alkyl and phosphoryl groups becomes important. For example, in the acid-catalyzed hydrolysis of a monoalkyl phosphate water can attack the protonated substrate on either the alkyl or phosphoryl group,[12,13] and halide ion can attack the alkyl group.[14]

$$ROPO_3H_2 \overset{H^+}{\rightleftharpoons} ROPO_3H_3^+ \xrightarrow{H_2O} ROH + H_3PO_4 + H^+$$
$$\searrow^{X^-}$$
$$RX + H_3PO_4 + H^+$$
$$(X = Cl, Br)$$

Our aim was to examine the hydrolysis of a hydrophobic monoalkyl phosphate by these various mechanisms at concentrations above and below the critical micelle concentration (cmc). We used *n*-decylphosphoric acid and its monoanion, because they are sufficiently water soluble that a wide concentration range can be used. (We will use the term "alkyl phosphate" without specifying its state of ionization, and refer to the acidic or anionic forms where necessary.)

Experimental Section

Materials. Decanol was converted into *n*-decylphosphoryl dichloride by $POCl_3$, followed by hydrolysis to *n*-decylphosphoric acid in ice water.[15] It was purified by solution in Et_2O and washing with water and after drying (P_2O_5) it had mol wt 236 (by titration) and mp 45.0 °C (lit.[16] 45.0 °C).

Kinetics. The hydrolysis at 100 °C was followed by determination of inorganic phosphate by Fiske and Subba Row's method,[17] or a variant of it, using extraction into 1-butanol, which gave much better results than the simple method, especially for solutions which contained much 1-decanol. Sealed Pyrex ampules were used and for the experiments in which micellized substrate was present only the initial part of the reaction was followed because the products, especially 1-decanol, could change the structure of the substrate micelles. For reaction at pH >4 the sodium salt was used.

Products. We detected no 1-chlorodecane in the products of hydrolysis of 3×10^{-3} M decyl phosphate in 3 M HCl at 100 °C. After ca. 60% reaction $Ba(OH)_2$ was added and the mixture was extracted with redistilled pentane. After drying ($MgSO_4$) the bulk of the pentane was distilled off. Decanol was detected by GLC (12 ft × 0.25 in. 15% Carbowax 20M in 60/80 Chromosorb W, 2% K_2CO_3 at 158 °C). Control tests showed that 5% chlorodecane could have been detected.

Critical Micelle Concentration. The cmc was determined by the surface tension method[18] at 23 °C. Plots of surface tension against log [decyl phosphate] gave sharp breaks at the cmc and there were no minima.

The values of the cmc in water at 23 °C are *n*-$C_{10}H_{21}OPO_3H_2$ (in 0.1 M HCl), 6.9×10^{-4} M; *n*-$C_{10}H_{21}OPO_3HNa$ (pH 4.5), 2.0×10^{-3} M; at pH 6.5, 4.2×10^{-3} M. As expected, the cmc of the undissociated acid is considerably lower than that of the monoanion and at pH 6.5 formation of the dianion further increases the cmc. (For monoalkyl phosphates $pK_2 \sim 6.5$.) Using *n*-decylphosphoric acid and with no control of pH cmc $\sim 2 \times 10^{-3}$ M, showing that under these conditions the acid is extensively dissociated into the monoanion.

Our rate experiments were at 100 °C, and we needed evidence that the values of the cmc at 23 °C would be indicative of micelle formation at higher temperatures. For most surfactants cmc increases slightly with increasing temperature above ca. 30 °C, but the standard compilation gives no values for temperatures >80 °C.[18] We therefore used the solubilization of sparingly soluble Orange OT to show that micelles were present in solutions of monosodium *n*-decyl phosphate at 100 °C. Aqueous solutions of 10^{-3} and 10^{-2} M decyl phosphate were saturated with the dye by shaking at room temperature for 3 days and the increased solubilization in 10^{-2} M decyl phosphate was visible. The solutions were then brought to 100 °C and then rapidly centrifuged, a sample 1 ml was diluted with MeCN (1 ml), and the absorbance was measured at 500 nm. The absorbances were in water, 0.131 (0.097); in 10^{-3} M decyl phosphate, 0.118 (0.100); in 10^{-2} M decyl phosphate, 0.338 (0.233). The values in parentheses were at room temperature.

These results show that the micelles of *n*-decyl phosphate monoanion are not disrupted at 100 °C.

Results and Discussion

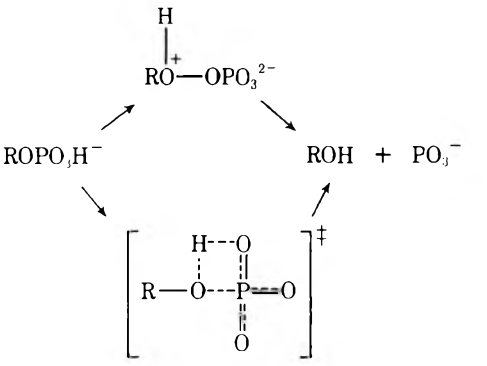
Hydrolysis of the Monoanion. The rate constant for hydrolysis of *n*-decyl phosphate monoanion at pH 4.5 is unaffected by micellization, and is only slightly lower than that for hydrolysis of methyl phosphate monoanion, which is 8.2×10^{-6} s^{-1} at 100 °C. Addition of decanol does not markedly affect the reaction rate (Table I) although it should promote micellization and stabilize a micelle. The dianion is unreactive as expected.[12,13]

Elimination of metaphosphate ion from a monoanion could be concerted with, or follow, the proton transfer.[11-14,19-21] Our observations are consistent with the insensitivity of rates of hydrolysis of monosubstituted phosphate monoanions to

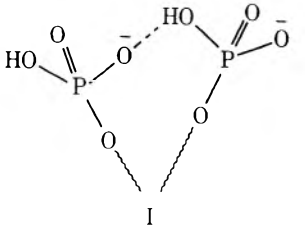
Table I. Hydrolysis of Monoanionic *n*-Decyl Phosphate[a]

10^3 [*n*-$C_{10}H_{21}OPO_3H^-$], M	$10^6 k_\psi$, s^{-1}	10^3 [*n*-$C_{10}H_{21}OPO_3H^-$], M	$10^6 k_\psi$, s^{-1}
0.6	4.14	15.0	5.70[b]
3.0	4.10	15.0	5.30[c]
4.0	4.13	25.0	5.06
10.0	4.33		

[a] At 100 °C; for hydrolysis of methyl phosphate $k_\psi = 8 \times 10^{-6}$ s^{-1}. [b] Taken to 60% reaction. [c] With 1.5×10^{-2} M 1-decanol.



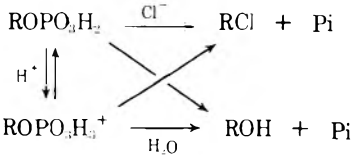
changes in solvent or incorporation into cationic micelles,[11,19-21] although we had expected that the necessity of proton transfer would cause this reaction to be sensitive to substrate micellization. The cmc of the monoanion of 2×10^{-3} M is considerably lower than that of sodium decyl sulfate (3.3×10^{-2} M at 25 °C[18]), and this low cmc of the phosphate monoanion suggests that its micelle is strongly stabilized by hydrogen bonding between adjacent head groups as in I. In this



I

event elimination of metaphosphate ion in the micelle will merely require rearrangement of existing hydrogen bonds.

Hydrolysis at Low pH. At substrate concentrations below the cmc, the rate constants for reaction of *n*-decyl phosphate are similar to those for methyl phosphate.[12,14] Both reactions are catalyzed by strong acid (Table II), and water can attack the methyl and phosphoryl groups of methyl phosphate. For reaction of methyl phosphate halide ion can attack the methyl group of undissociated methyl phosphoric acid or its conjugate acid, e.g.



and at concentrations below the cmc, the attack of chloride ion upon protonated *n*-decylphosphoric acid becomes very important as the hydrogen ion concentration is increased (Table II and Scheme I). (We cannot compare the two systems exactly, because the effect of chloride ion on the reaction of methyl phosphate was examined at constant ionic strength,[14] and we preferred not to use high salt concentrations wherever possible because they can alter micellar structure.)

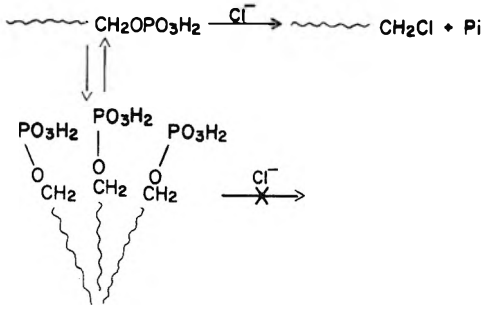
Micellization has a marked effect upon the hydrolysis of undissociated *n*-decylphosphoric acid, and it changes the

Table II. Reaction of *n*-Decyl Phosphate at Low pH[a]

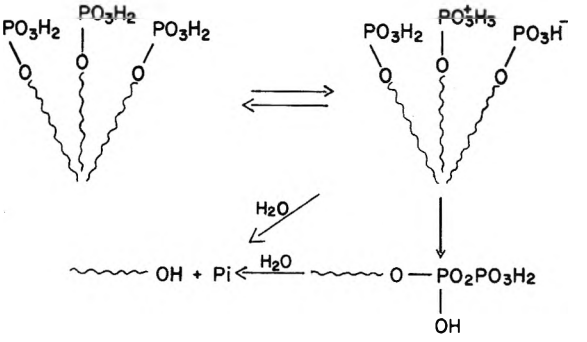
10^3 [n-$C_{10}H_{21}OPO_3H_2$], M	$HClO_4$			HCl		
	0.1 M	1 M	3 M	0.1 M	1 M	3 M
0.10				2.08		
0.53		2.61	8.24		2.67	67.2
2.44		21.5				
3.30	21.7	20.6	9.62	23.1	19.0	9.16

[a] Values of $10^6 k_\psi$, s^{-1} at 100 °C; for reaction of methyl phosphate $10^6 k_\psi$ = 3.45 in 0.1 M HCl; 5.08 in 1 M $HClO_4$ and 39.6 s^{-1} in 2.5 M $HClO_4$ + 1.5 M NaCl.

Scheme I



Scheme II



pattern of hydrogen and chloride ion catalysis. There are several effects at work and some of them can only be separated qualitatively, in part because there is always monomeric substrate in equilibrium with micellized substrate, and added solutes can affect this equilibrium. For monoalkyl phosphates (in the absence of micelles) pK_1 is typically ca. 1.5 and is not especially temperature sensitive,[12,22] so that in 0.1 M strong acid, ca. 80% of the substrate will be as undissociated acid. Thus any rate changes on micellization should not be caused by changes in the relative amounts of *n*-decylphosphoric acid and its monoanion.

Micellization markedly increases the rate of hydrolysis of undissociated *n*-decylphosphoric acid in dilute acid (Table II), but it eliminates the chloride ion promoted reaction and hydrogen ion catalysis of hydrolysis of *n*-decylphosphoric acid.

The absence of hydrogen ion catalysis is understandable, because the hydrogen ions should be almost wholly in the aqueous bulk solvent rather than at the surface of nonionic micelles of *n*-decylphosphoric acid, and formation of any appreciable amount of protonated substrate would create coulombic repulsions at the micellar surface. Attack of chloride ion upon *n*-decylphosphoric acid or its conjugate acid should also be inhibited by micellization, because the alkyl group will be shielded from the hydrophilic chloride ion by the phosphate moiety (Scheme I). We also found that when the concentration of *n*-decylphosphoric acid is well above the cmc the rate constants decrease in going from 1 M to 3 M strong acid, possible because of a change in the micellar structure or reduction in the cmc at high electrolyte concentration.

It is not obvious why micellization promotes hydrolysis of undissociated *n*-decylphosphoric acid. Probably one monomer can assist hydrolysis of its neighbor by partial or complete proton transfer, followed by attack of water (Scheme II), and the lowering of the cmc by interhead group hydrogen bonding was noted earlier. Alternatively a decyl phosphate monoanion could attack its neighbor to give *n*-decyl pyrophosphate which should then be hydrolyzed to alcohol and inorganic phosphate. Proton transfer to a phosphoryl group is shown in Scheme II, but it could be to an alkoxy group, because complete reaction requires loss of ROH. For reaction of methyl phosphate distinction between attack upon the methyl and phosphoryl groups was made isotopically,[12] but this approach is impracticable for the dilute solutions which we use in these experiments. There is considerable attack by water upon the methyl group of methylphosphoric acid, but shielding of the *n*-decyl group in a micelle should hinder attack on the decyl more than upon the phosphoryl group.

Comparison with Reactions of Other Micellized Substrates. There are considerable mechanistic similarities between the mechanisms of hydrolysis of monosubstituted phosphates and sulfates, and these similarities extend to the effects of added micelles on unimolecular reactions of phosphate dianions and sulfate monoanions.[21,23] But there are considerable differences for reactions of micellized monoalkyl phosphates and sulfates because it is the monoanionic alkyl phosphate and the undissociated alkylsulfuric acid which decompose spontaneously.[7,11]

It is difficult to find analogies for the effects of self-micellization of *n*-decyl phosphate at low pH, but the absence of attack of chloride ion upon *n*-decylphosphoric acid, even at relatively high acidities, is similar to the inhibition of attack of hydroxide ion upon *p*-nitrophenyl laurate by substrate micellization,[8] in that in both systems a hydrophilic reagent does not readily attack a micellized nonionic substrate.

Our micellar effects on nucleophilic attack illustrate the way in which substrate micellization can affect reactivity as, for example, in biologically important phosphates.

Registry No. —*n*-Decyl phosphate, 3921-30-0.

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Acid-Catalyzed Hydrolysis of 3-Isopropyloxatriazole

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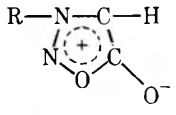
The mechanisms of the acid-catalyzed ring opening of mesoionic 3-aryl- and 3-alkylsydnones (**1**, R = alkyl or aryl) have been studied in some detail.[1,2] In contrast very little is known about the acid-catalyzed decomposition of the analogous (isosteric) oxatriazole system **2**. Boyer and Hernandez observed that cyclohexyloxatriazole (**2a**, R = C_6H_{11}) was re-



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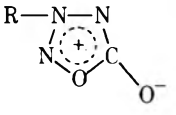


2a, b

sistant to dilute sulfuric acid but decomposed in strong acid to form cyclohexanol, carbon dioxide, and hydrogen azide,[3] whereas the products of hydrolysis of phenyloxatriazole have been reported to be phenyl azide and carbon dioxide.[4] The absence of cyclohexyl azide in the products of decomposition of **2a** reflects the instability of alkyl azides in strong acid.[5] The behavior of oxatriazoles in strong acid seems to be in sharp contrast to that of the sydnones which are converted to the corresponding alkyl and aryl hydrazines. We now report the first kinetic study of the acid-catalyzed ring opening of mesoionic oxatriazoles on 3-isopropyloxatriazole (**2b**, R = *i*-Pr).

The hydrolysis of **2b** only occurs at an appreciable rate at high acidity and high temperature. The first-order rate constants, k_ψ, for the hydrolysis of **2b** in aqueous solutions of mineral acids are shown in Table I.

In spite of the limited range of acidity over which the hydrolysis of **2b** could be studied, a plot of log k_ψ vs. $-H_0$ gives a slope of 1.3.[6] Analysis of the kinetic data in terms of Bunnett's approach[7] leads to a value of w (−0.74) which is in the range associated with reactions in which water does not participate in the rate-determining step. The value of ϕ (−0.30) obtained from the correlation of log k_ψ + H_0 with H_0 + log $[H^+]$[8] leads to a similar conclusion. The value of the entropy

Table I. Hydrolysis Rate, 10^3 k_ψ (min^{-1}), of 2b in Aqueous Mineral Acids

$HClO_4$ Concn, M, at 60 °C						
7.00	7.50	8.00	8.50	9.00	9.50	
1.84	4.69	12.7	38.2	106	460	
H_2SO_4 Concn, M, at 60 °C						
7.00	7.50	8.00	8.50	9.00	9.50	10.0
0.82	1.98	2.87	4.59	7.84	16.2	35.7
HCl Concn, M, at 60 °C						
	8.50	9.00	9.50	10.00		
	0.41	1.53	2.91	6.22		
$HClO_4$ (9.00 M) at Various Temp, °C						
	40.2	45.0	50.0	55.0	60.0	
	10.1	20.0	34.6	65.7	113	

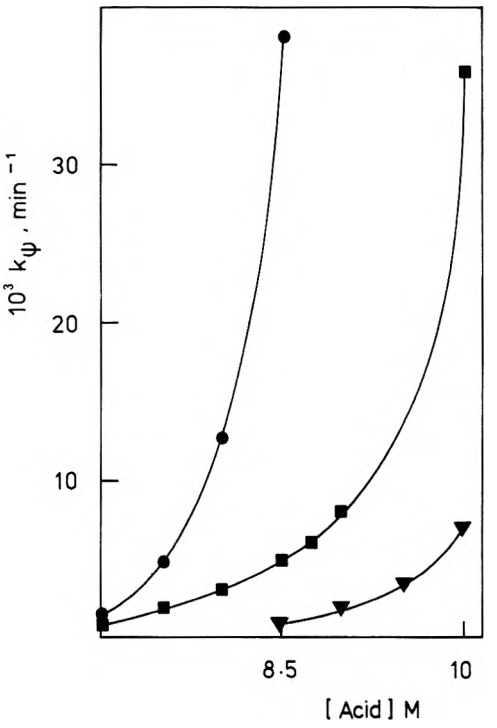
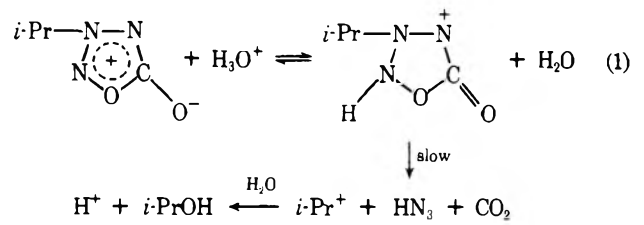


Figure 1. Hydrolysis of **2b** in water at 60 °C: ●, $HClO_4$; ■, H_2SO_4; ▼, HCl.

of activation calculated for 9 M $HClO_4$ ($\Delta S^\ddagger$ = +2.5 eu) is also consistent with an A-1 reaction.[9] The value obtained for the deuterium kinetic solvent isotope effect [$k_\psi(D_2O)/k_\psi(H_2O)$ = 1.42] for the perchloric acid catalyzed hydrolysis of **2b** is characteristic of reactions which proceed via specific hydrogen ion catalysis (although it is perhaps somewhat lower than usually observed for A-1 reactions[10]) and suggests that proton transfer occurs in a preequilibrium step.

The most striking feature of the effect of different acids on the hydrolysis of **2b** (Figure 1) is the order of effectiveness of the acids, viz., $HClO_4$ > H_2SO_4 > HCl. Bunton and his coworkers have suggested that such an order of reactivity is characteristic of A-1 reactions and that the transition states of such reactions are preferentially stabilized by anions of low charge density.[11] All the evidence presently available therefore suggests that the acid-catalyzed hydrolysis of isopropyloxatriazole follows an A-1 mechanism which can be represented as in eq 1. In the absence of any definitive evidence, protonation is assumed to occur on N-2 as has been assumed in the acid-catalyzed hydrolyses of 3-alkylsydnones.[12] Consistent with the proposed mechanism, the major products of hy-



drolysis in the presence of hydrochloric acid were found to be isopropyl chloride and hydrazoic acid.

Experimental Section

The isopropyloxatriazole **2b** prepared by the method of Boyer and Canter[13] had bp 63 °C (0.5 mm) [lit.[13] bp 60–61.5 °C (0.45–0.50 mm)]. Kinetics were followed spectrophotometrically at 255 nm in a Unicam Model S.P. 800 spectrometer using a constant temperature cell thermostated to ±0.1 °C.

Registry No.—**2b**, 7724-83-6; $HClO_4$, 7601-90-3; H_2SO_4, 7664-93-9; HCl, 7647-01-0.

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Reactions of Carbamylimidazoles with Nucleophiles—an Example of an Intramolecular Acyl Transfer Reaction

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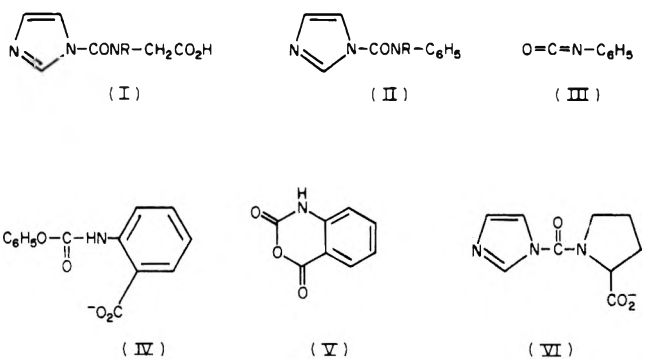
Glycine in an aqueous imidazole buffer has been shown[1] to react with carbonyldiimidazole to yield initially *N*-[imidazolyl-(1)-carbonyl]glycine (I), R = H. This intermediate



slowly polymerizes to yield oligoglycines. The suggested route for this polymerization is via a *N*-carboxyanhydride. The present report presents evidence that the cyclization of I proceeds via an addition–elimination, intramolecular acyl transfer reaction[2] involving a carbamylimidazole.[3,4] In general 1-substituted carbamylimidazoles react with nucleophiles via an intermolecular elimination–addition mechanism. Staab and Benz,[5] for example, showed that II, R = H, reacts with amines, while II, R = CH_3, does not. They concluded from this that II, R = H, reacts via its isocyanate (III). Kinetic evidence has been presented[3,4] to show that the hydrolysis of II, R = H, also proceeds via an intermolecular elimination–addition acyl transfer mechanism involving an isocyanate. In this case, II, R = CH_3, hydrolyzes much slower than II, R = H. *N*-Aryl carbamates, like the carbamylimidazoles, undergo hydrolysis[6] via the elimination–addition route. However, phenyl *N*-(*o*-carboxyphenyl)carbamate (IV) follows an addition–elimination route[7] via isatoic anhydride (V). This reaction is analogous to the one which we have discovered.

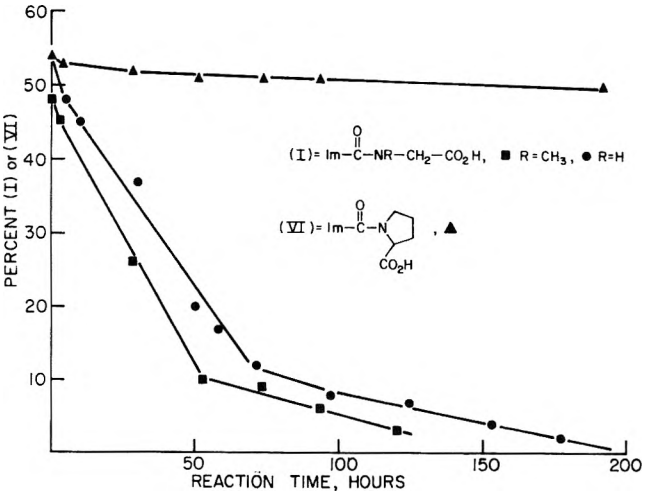


Figure 1. Plot of survival of I and VI as a function of time.

Carbonyldiimidazole (0.4 M) was added to 0.1 M [α-^{14}C]-glycine, [α-^{14}C]sarcosine, and [α-^{14}C]proline (specific activity in each case, 0.05 mCi/mmol) in imidazole buffer (0.5 M) at pH 7.0 and 0 °C. The carbamylimidazole intermediates I, R = H, I, R = CH_3, and VI were obtained in 84, 48, and 98% yield, respectively, from the three amino acids. The intermediates were identified by their electrophoretic behavior in systems II and III (unit negative charge[1,4,8]) and by their positive reaction with a sulfanilamide reagent.[1,9] As shown in Figure 1, the lifetime of I, R = CH_3, is strikingly similar to that of I, R = H, when the two are formed in approximately the same initial yield. By contrast, VI is extremely long lived.

To determine the rate of appearance of the sarcosine peptides, the origins of the system II electrophoreses papers were cut out, eluted with deionized water, and rerun in system I. The sarcosine peptides, which have almost the same mobility value as sarcosylglycine (see below), appeared at a rate similar to that found for glycine (see Figure 2). To further confirm this the previous experiment was modified as follows. Unlabeled amino acids were used to generate the initial intermediates, I and VI. Immediately after the dissolution of the carbonyldiimidazole at 0 °C, pH 7.0, [α-^{14}C]glycine (0.2 M glycine, 0.5 M imidazole, pH 6.85, specific activity 0.05 mCi/mmol) was added to each of the reaction mixtures in twofold molar excess. The appearance of aminoacylglycine with time is shown in Figure 3. Again, sarcosine behaves like glycine whereas proline is much less reactive. Cochromatography in solvent system IV and coelectrophoresis in solvent system I with authentic samples of sarcosylglycine and prolyglycine were used to establish the nature of the peptides generated in the above experiments.

There are three reasonable mechanisms for the formation of a *N*-carboxyanhydride from VII, R = H. By analogy with the behavior[7] of compound IV the addition–elimination route (2) involving direct closure of VII to the *N*-carboxyanhydride

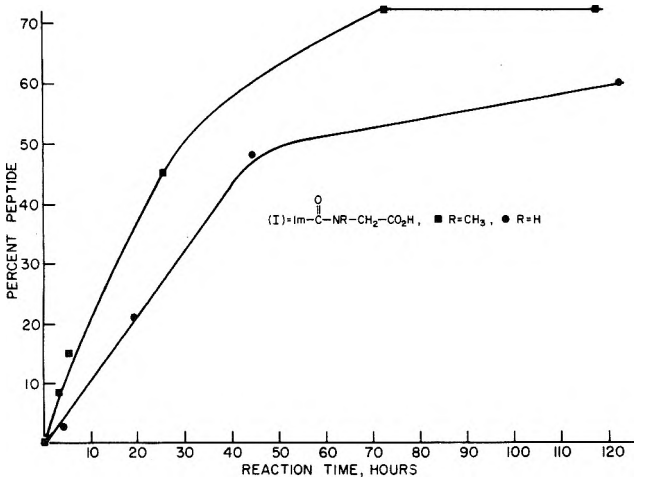
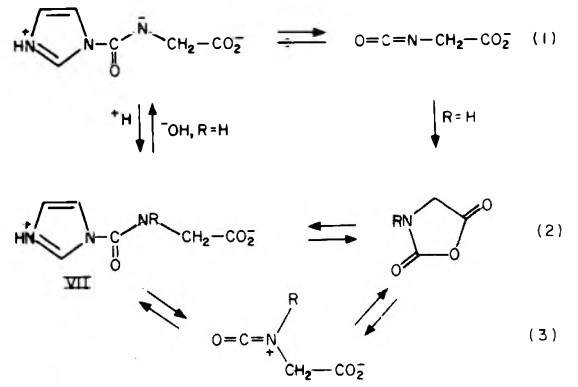


Figure 2. Plot of appearance of peptide as a function of time in the reaction of glycine and the reaction of sarcosine with carbonyldiimidazole in imidazole buffer.

seems the most probable route to the *N*-carboxyanhydride. The elimination–addition route (1) via the anionic zwitterion[4]



seems unlikely since glycine and sarcosine exhibit such similar behavior with respect to the disappearance of VII and to the appearance of peptide. Route 3, via the neutral zwitterionic isocyanate, seems unlikely on intuitive grounds and in light of the observation of Hegarty et al.[4] that the methyl analogue II, R = CH_3, hydrolyzes much slower than II, R = H. Again the similar behavior of glycine and sarcosine makes this route unlikely. The behavior of proline reflects the ring strain of its *N*-carboxyanhydride relative to that of most other amino acid *N*-carboxyanhydrides.[10]

This appears to be the first reported instance of an intramolecular acyl transfer reaction involving a carbamyl imidazole, and suggests that, despite Hegarty's work,[3,4] a careful study of the reaction of nucleophiles with carbamyl imidazoles at pH 7.0 is worthwhile.

Experimental Section

Sarcosine (98%, mp 208 °C) was purchased from Aldrich and purified by recrystallization from 3–4% aqueous ethanol. Glycine and proline were purchased from Calbiochem, *N,N'*-carbonyldiimidazole and imidazole from Sigma, and sarcosylglycine and prolylglycine from Vega-Fox-Biochemicals. Radioactive [α-^{14}C]glycine and [α-^{14}C]-proline were purchased from Schwarz. Radioactive [α-^{14}C]sarcosine was purchased from California Bionuclear Corp.

Paper electrophoresis was done on Whatman 3MM paper, using varsol as coolant, or using a Savant flat plate electrophoresis system. The buffers were I, 0.05 M formic acid adjusted to pH 2.7 with concentrated ammonium hydroxide; II, 0.03 M potassium phosphate, pH 7.1; III, 0.2 M lithium hydroxide adjusted to pH 4.5 with glacial acetic acid.

Paper chromatography was done in solvent system IV, isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2).

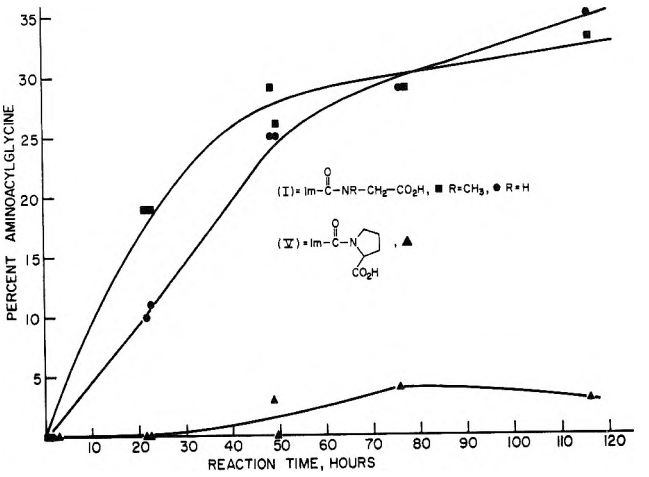


Figure 3. Plot of appearance of aminoacylglycine as a function of time in the reaction of glycine with I and VI.

Electrophoretograms of radioactive samples were treated as described earlier.

Acknowledgment. This work was supported by NSF Grant MPS 73-08792.

Registry No.—I (R = CH_3), 59643-40-2; I (R = H), 59643-41-3; VI, 59643-42-4; carbonyldiimidazole, 530-62-1; glycine, 56-40-6; sarcosine, 107-97-1; proline, 147-85-3.

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The Structures of Staphigine and Staphirine. Two Novel Bisditerpene Alkaloids from *Delphinium staphisagria*

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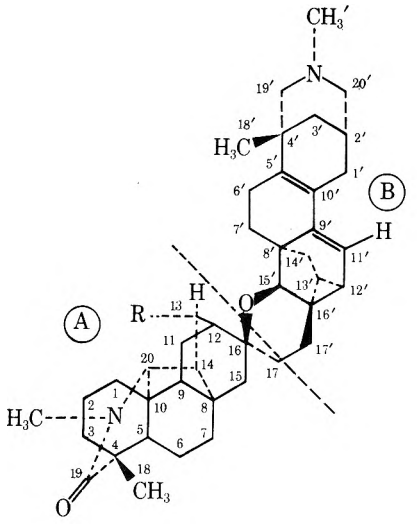
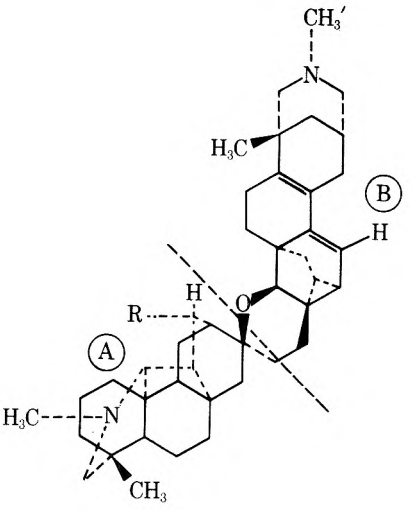
We wish to report the structures of staphigine (1) and staphirine (2), two new bisditerpene alkaloids isolated from the mother liquors of *Delphinium staphisagria*. ^{13}C and ^{1}H NMR spectroscopy played a major role in the determination of these structures. These alkaloids are unusual in containing a lactam moiety in addition to many of the uncommon features of the staphisine skeleton (3).[1]

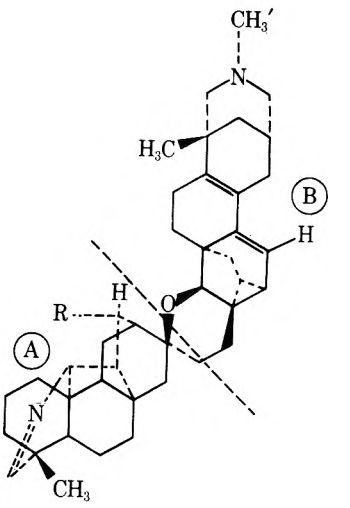
The mother liquors accumulated during the isolation of delphinine from the seeds of *D. staphisagria* were found to contain a relatively large amorphous fraction of alkaloids.[2] From these mother liquors, we have recently isolated three new bisditerpene alkaloids, staphidine (4), staphinine (5), and



1. R = OCH_3 staphigine
2. R = H staphirine



3. R = OCH_3 staphisine
4. R = H staphidine



5. R = OCH_3 staphinine
6. R = H staphimine

staphimine (6), and determined their structures by the successful application of ^{13}C and ^1H NMR spectroscopy.[3] In addition, we have isolated, by chromatography and crystallization, two new lactam-containing bisditerpene alkaloids designated as staphigine ($C_{43}H_{58}N_2O_3$) and staphirine ($C_{42}H_{56}N_2O_2$).[4]

Table I. ^1H NMR Chemical Shifts of Staphigine (1), Staphirine (2), Staphisine (3), Staphidine (4), Staphinine (5), and Staphimine (6)[a]

Carbon	1	2	3	4	5	6
-C-CH_3^{18}	1.12	1.12	0.91	0.91	1.00	1.00
-C-$CH_3^{18'}$	0.94	0.94	0.91	0.91	0.94	0.94
N-CH_3'	2.13	2.13	2.13	2.13	2.13	2.13
N-CH_3	2.98	2.92	2.27	2.21		
O-CH_3	3.30		3.30		3.30	
-C=CH-	5.85	5.85	5.85	5.85	5.85	5.85
-N=CH-					7.30	7.30

[a] ^1H NMR spectra were determined in $CDCl_3$ and shifts are given on the δ scale relative to Me_4Si.

Staphigine, mp 225–227 °C, $[\alpha]^{25}D$-116° (c 2.0, benzene), shows absorption at λ_{max} (EtOH) 267 nm (ϵ 17 200) in agreement with a transoid heteroannular conjugated diene system. The ir spectrum shows absorption at 1720 (conjugated diene), 1650 (lactam ring), 1101 and 1062 cm^{-1} (ether linkage). The mass spectrum exhibits a molecular ion peak at *m/e* 650 corresponding to the molecular formula $C_{43}H_{58}N_2O_3$.[4] The ^1H NMR spectrum reveals the presence of two angular methyl groups (δ 0.94 and 1.12), two *N*-methyl groups (δ 2.13 and 2.98), a methoxyl group (δ 3.30), and a vinyl proton (δ 5.85). Staphirine, mp 222–225 °C, $[\alpha]^{25}D$-126° (c 0.5, benzene), showed ir and uv spectra which are very similar to those of staphigine. The ^1H NMR spectrum was also identical in all respects with that of staphigine except for the absence of a methoxyl singlet at δ 3.30 (Table I). The above data indicate that staphigine (1) and staphirine (2) are similar to each other and are closely related to the known staphisine-type alkaloids staphisine (3), staphidine (4), staphinine (5), and staphimine (6).[3]

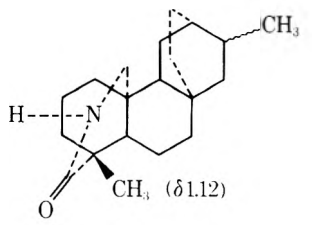
Further correlation of staphigine (1) and staphirine (2) with known alkaloids 3–6 and atisine derivative 7 was made

Table II. Carbon-13 Chemical Shifts of Staphigine (1), Staphirine (2), Staphisine (3), Staphidine (4), Staphinine (5), and Staphimine (6)

Carbon	1	2	3	4	5	6
C-4	44.6 (s)	44.7 (s)	34.2 (s)	34.2 (s)	41.5 (s)	41.5 (s)
C-8	38.4 (s)	38.7 (s)	37.4 (s)	37.6 (s)	38.1 (s)	38.3 (s)
C-10	44.6 (s)	44.3 (s)	46.0 (s)	45.5 (s)	44.3 (s)	43.7 (s)
C-13	90.3 (d)		89.4 (d)		91.2 (d)	
C-16	72.2 (s)	73.5 (s)	72.2 (s)	73.6 (s)	72.3 (s)	73.8 (s)
C-19	175.1 (s)	175.0 (s)	60.7 (t)	60.4 (t)	168.1 (d)	167.6 (d)
C-20	72.9 (d)	77.0 (d)	74.4 (d)	77.0 (d)	73.1 (d)	75.8 (d)
N-CH_3	46.9 (q)	46.9 (q)	43.9 (q)	43.5 (q)		
C-OCH_3	57.0 (q)		57.8 (q)		56.4 (q)	
C-4′	34.5 (s)	34.5 (s)	34.5 (s)	34.4 (s)	34.4 (s)	34.5 (s)
C-5′[a]	135.6 (s)	136.1 (s)	135.6 (s)	135.6 (s)	135.5 (s)	135.7 (s)
C-8′	41.8 (s)	41.9 (s)	41.8 (s)	41.6 (s)	41.6 (s)	41.6 (s)
C-9′[a]	128.2 (s)	128.1 (s)	127.6 (s)	127.7 (s)	127.7 (s)	127.9 (s)
C-10′[a]	136.1 (s)	136.4 (s)	135.6 (s)	135.8 (s)	135.5 (s)	135.7 (s)
C-11′	113.7 (d)	113.1 (d)	112.9 (d)	112.7 (d)	112.9 (d)	113.3 (d)
C-15′	78.5 (d)	78.1 (d)	78.1 (d)	77.6 (d)	78.5 (d)	77.9 (d)
C-16′	29.7 (s)	29.4 (s)	29.5 (s)	29.3 (s)	29.5 (s)	29.4 (s)
C-19′[b]	62.5 (t)	62.7 (t)	62.5 (t)	62.4 (t)	62.5 (t)	62.3 (t)
C-20′[b]	64.7 (t)	64.8 (t)	64.7 (t)	64.5 (t)	64.7 (t)	64.4 (t)
N-CH_3'	46.4 (q)	46.6 (q)	46.6 (q)	46.3 (q)	46.3 (q)	46.4 (q)

[a,b] These assignments may be interchanged.

through a study of their ^1H NMR spectra (Table I). The absorption at δ 2.13 in these alkaloids in comparison with that of compounds **3–6** is assigned to the *N*-methyl group in the B unit of the molecule. This result establishes the presence of a lactam ring in the A unit of the molecule. These data also indicate that the exceptionally low field absorptions at δ 2.98 and 2.92 in staphigine and staphirine, respectively, are accommodated by the *N*-methyl group of the lactam ring. The downfield methyl singlet at δ 1.12 is also in perfect agreement with the value for the methyl singlet of the atisine lactam derivative **7**.[5]



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The comparison of carbon-13 chemical shifts of these two new staphisine-type bisditerpene alkaloids was made with known alkaloids **3–6** to establish the presence of a lactam ring and their complete structures **1** and **2** (Table II). Assignment of the resonances to individual carbon atoms was achieved by using conventional techniques, chemical shift theory, and direct analysis of nonprotonated carbon centers.[6]

The pattern of carbon-13 chemical shifts in these new alkaloids is very similar to that of the known alkaloids **3–6**. The chemical shifts of C-4′, C-5′, C-8′, C-9′, C-10′, C-11′, C-15′, C-16′, C-19′, C-20′, and N-CH_3′ carbons in staphigine and staphirine are similar to those of compounds **3–6**, suggesting that the B unit is staphigine and staphirine is identical with that in compounds **3–6**.

The presence of the carbonyl group (singlets at 175.1 and 175.0 ppm),[7] and the lack of the *N*-methylene carbon resonance at 60.7 and 60.4 ppm in staphigine and staphirine when compared to **3** and **4**, indicate that the carbonyl carbon is present as a part of the lactam moiety in staphigine and staphirine. The downfield shifts (10.4 and 10.5 ppm) of the C-4 carbon and the upfield shift (1.5 ppm) of the C-20 carbon in **1** and **2** relative to **3** and **4**, respectively, are due to the presence of the lactam ring in the A unit. The lactam moiety in unit A was also confirmed on the basis of an *N*-methyl singlet at δ 2.13 in the ^1H NMR spectrum and the constant carbon-13 chemical shifts shown by C-19′, C-20′, and N-CH_3′ carbons of staphigine and staphirine in comparison with the known alkaloids **3–6** (Tables I and II). Based on the arguments presented here, we assign structures **1** and **2** for staphigine and staphirine, respectively.[8]

Staphigine and staphirine occur in extremely small amounts in the seeds of *D. staphisagria* in comparison with staphisine (**3**) and staphidine (**4**). These lactam alkaloids do not appear to be artifacts which arise by oxidation of compounds **3** and **4**, respectively, during isolation. All of these alkaloids (**1–6**) are closely related in structure and occur as methoxyl and demethoxyl pairs in *D. staphisagria*.

Experimental Section

Carbon-13 spectra were determined at 25.03 MHz in the Fourier mode using a JEOL-PFT-100 spectrometer in conjunction with an EC-100-20K memory computer. The spectrometer features a deuterium lock system, a JNM-SD-HC random noise (2500 Hz bandwidth) proton decoupler, and JNM-DP-1 digital pulse programmer. Spectra of the compounds were determined in deuteriochloroform solutions (which also provided the lock signal) with 5% Me_4Si added as internal reference. All samples were contained in precision ground 10-mm o.d. tubes. The spectrometer was used in the crosscoil configuration. On the average, a 12-μs pulse, corresponding to an approximate tilt angle of 45°, was employed. For the average spectral width of 5000 Hz the delay between pulses was 3 s. Acquisition times averaged 2–8 over 8K data points for concentrations of the order of 0.1–0.5 M. For of-resonance spectra this time was 8–32 h.

Acknowledgment. We thank Mr. Courtney Pape for providing the carbon-13 NMR spectra needed for this investigation. We acknowledge with pleasure a National Science Foundation matching grant to the department for purchase of the ^{13}C NMR spectrometer. We are grateful to the late Dr. Lyman C. Craig and to Dr. William C. Agosta of the Rockefeller University for generous supplies of the mother liquors of *D. staphisagria*.

Registry No.—**1**, 59588-13-5; **2**, 59588-14-6; **3**, 36575-56-4; **4**, 59588-15-7; **5**, 59588-19-1; **6**, 59588-18-0.

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(4) Elemental analyses for C, H, and N showed satisfactory agreement with the stated empirical formulas. The melting points are corrected and were taken on a hot-stage microscope equipped with a polarizer.
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(8) We were unable to carry out any transformation of compounds **1** and **2** to **3** and **4**, respectively, owing to the unstability of **1** and **2** toward various reagents (e.g., $LiAlH_4$, $NaBH_4$, etc.).

2*H*-Benzo[*b*]thiete 1,1-Dioxide

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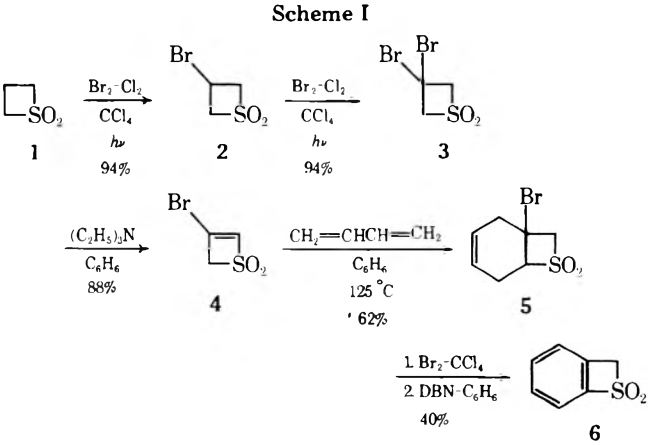
In 1967 the synthesis of 2*H*-benzo[*b*]thiete 1,1-dioxide (benzothiete sulfone) was reported in very low yield from 7-thiabicyclo[4.2.0]-1(6)-octene 7,7-dioxide.[1] Recently, the method described in our earlier report has been improved to provide benzothiete sulfone in a higher overall yield.[2] This report describes a different synthesis of the sulfone (in still higher yield) and some of its chemical properties. Scheme I illustrates this new synthesis.

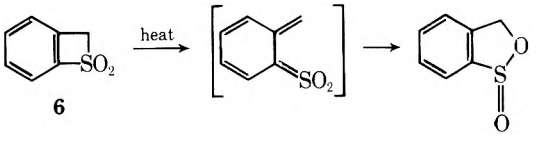
Scheme I



The yields in the bromination steps are generally good if a correction is made for the recovery of unreacted sulfone. Attempts to obtain the dibromide in one step were not successful. The bromination may involve chlorine bromide, and the selective halogenation of the 3 position may be a consequence of hydrogen atom abstraction by a chlorine atom produced by homolysis of chlorine bromide.[3] The abstraction of hydrogen atoms by chlorine atoms is influenced in other cases by electronic effects, hydrogen-atom abstraction occurring mainly at a site remote from an electron-withdrawing substituent.[4] A steric effect of the oxygen atoms of the sulfone group also could cause halogen atoms to attack the more remote 3 position. Bromination of diethyl sulfone with chlorine bromide gave the β-bromo derivative.[5] However, bromination of tetrahydrothiophene 1,1-dioxide by chlorine bromide is reported to yield the 2-bromosulfone although chlorination yields the 3-chlorosulfone.[6] Some chloride is produced as a by-product of the bromination, but its presence does not affect the synthesis of benzothiete sulfone. We have tried preformed chlorine bromide in the halogenation, but its use gave no better yield of the 3-bromosulfone, **2**.

The remaining steps are straightforward and require no comment except that the tribromide obtained from **5** is unstable and should be dehydrohalogenated at once.[7]

Thermolysis of benzothiete sulfone, either neat or dissolved in benzene, gave the sultine, 3*H*-2,1-benzoxathiole 1-oxide, in good yield. This sultine also has been obtained by thermolysis of 2*H*-1,2,3-benzothiadiazine 1,1-dioxide at 500 °C (1 mm), possibly via a vinyl sulfene intermediate.[8] Attempts to trap a vinyl sulfene intermediate with *N*-phenylmaleimide or maleic anhydride were unsuccessful, although *N*-phenylmaleimide was used to successfully trap an α,β-unsaturated thioketone intermediate in the photolysis of a thiolactone.[9] Thermolysis of a naphthothiete sulfone[10] or of thiete sulfone itself[11] yields cyclic sulfinate esters or sultines.[12] Possible intermediates are vinyl sulfenes. Vinyl sulfene, a presumed intermediate in the thermolysis of thiete sulfone, has been trapped by reaction with phenol[11] and by reaction with the strained, olefinic bond of norbornene.[13] Perhaps a more electron-rich dienophile would react better with the vinyl sulfene. A benzothiazete sulfone apparently decomposes via a nitrogen analogue of vinyl sulfene.[14]



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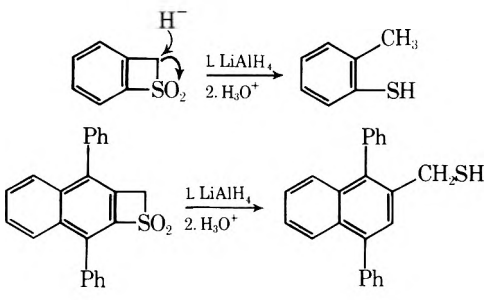
Reduction of benzothiete sulfone with lithium aluminum hydride gives o-toluenethiol. This result is surprising in view



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of the course of reduction of the naphthothiete sulfone, **7**, which yields a benzyl mercaptan.[15] Thiete sulfone, itself, is reduced to propanethiol.[16] Hydride attack at the methylene group in **7** may be hindered by the neighboring phenyl ring so that attack on the sulfone group occurs with cleavage of the aryl–sulfonyl bond. Cathodic cleavage of benzothiete sulfone also occurs principally at the aryl–sulfonyl bond and only to a minor extent between the sulfonyl group and the methylene group.[2]

Experimental Section[17]

3-Bromothietane 1,1-Dioxide (2). Thietane 1,1-dioxide[18] (**1**, 7.4 g, 70 mmol) was dissolved in 75 ml of warm carbon tetrachloride. The solution was brought to reflux and irradiated with a 250-W sun lamp. Bromine (6.4 g, 40 mmol) in 50 ml of carbon tetrachloride and chlorine (3.6 g, 50 mmol) in 100 ml of carbon tetrachloride were added dropwise and simultaneously to the stirring solution.[19] 3-Bromothietane 1,1-dioxide (12.2 g, 66 mmol, 94%) was removed by filtration: mp 153–155 °C (sealed capillary);[20] ir (KBr) 1300 (s), 1210 cm^{-1} (s); NMR (Me_2SO-d_6) δ 4.1–5.0 (complex m). Anal. Calcd for $C_3H_5BrO_2S$: C, 19.46; H, 2.70. Found: C, 19.70, H 3.02.

3,3-Dibromothietane 1,1-Dioxide (3). 3-Bromothietane 1,1-dioxide (9.2 g, 50 mmol) was dissolved in 250 ml of hot carbon tetrachloride and brominated as described above with a mixture of bromine (8.0 g, 50 mmol) and chlorine (3.6 g, 50 mmol). After the reaction mixture was cooled, 3,3-dibromothietane 1,1-dioxide was removed by filtration (12.4 g, 4.7 mmol, 94%): mp 165–166 °C (sublimes); ir (KBr) 1310 (s), 1210 (s), 1130 cm^{-1} (s); NMR (Me_2SO-d_6) δ 5.5 (s). An analytically pure sample, free of what is thought to be the bromo chloro compound, was obtained after three recrystallizations from carbon tetrachloride. Anal. Calcd for $C_3H_4Br_2O_2S$: C, 13.64; H, 1.52; S, 12.12. Found: C, 13.8; H, 1.41; S, 11.83.

3-Bromothiete 1,1-Dioxide (4). 3,3-Dibromothietane 1,1-dioxide (7.8 g, 29.5 mmol) was dissolved in warm benzene. To this was added triethylamine (5 ml) and the mixture was stirred for 2 h at 50 °C. The amine salt was removed by filtration and the solvent was removed in vacuo. The off-white solid residue was recrystallized from chloroform–hexane to give 3-bromothiete 1,1-dioxide (4.8 g, 26 mmol, 88%): mp 139–141 °C; ir (KBr) 1540 (s), 1310 (s), 1210 (s), 1120 cm^{-1} (s); NMR ($CDCl_3$) δ 7.05 (s, 1 H) 4.76 (s, 2 H). An analytically pure sample, free of what is thought to be the chloro compound, was obtained by five recrystallizations from chloroform–hexane. Anal. Calcd for $C_3H_3BrO_2S$: C, 19.67; H, 1.64; S, 17.49. Found: C, 19.43; H, 1.68; S, 17.80.

1-Bromo-7-thiabicyclo[4.2.0]-3-octene 7,7-Dioxide (5). 3-Bromothiete 1,1-dioxide (1.83 g, 10 mmol) was placed in a Carius tube, and butadiene (3 ml) was distilled into the tube. Benzene (5 ml) and hydroquinone (50 mg) were added and the tube sealed under vacuum at −196 °C. The tube was heated for 72 h at 125 °C and opened. The solvent was removed and the residue digested with methanol (50 ml). The methanol was removed in vacuo and the residue was recrystallized from chloroform–hexane to give the adduct (1.475 g, 6.2 mmol, 62%): mp 88–92 °C; ir (KBr) 1525 (w), 1340 (s), 1180 cm^{-1} (s); NMR ($CDCl_3$) δ 6.1 (m, 2 H), 5.0–4.15 (m, 3 H), 3.0–2.5 (m, 4 H); mass spectrum (70 eV) *m/e* 238, 236.

2*H*-Benzo[*b*]thiete 1,1-Dioxide (6). The adduct **5** (1.68 g, 7 mmol) was dissolved in carbon tetrachloride (25 ml). Bromine (1.6 g, 10 mmol) was added. The solution was refluxed for 1 h. The solvent and excess bromine were removed in vacuo. The resulting oil was then dissolved in benzene (50 ml) and 1,5-diazabicyclo[4.3.0]nonene (2.65 g, 21 mmol) was added. This mixture was refluxed for 1 h. The solution was washed twice with 10 ml of 10% HCl and dried over magnesium sulfate. The residue after removal of solvent was submitted to dry column chromatography (silica gel, chloroform eluent) and benzothiete 1,1-dioxide (0.44 g, 2.9 mmol, 41%) was obtained: mp 126–128 °C (lit.[1] mp 126–128 °C); ir 1300 (s), 1195 (s), 1120 (s), 720 (s), 710 cm^{-1} (s); NMR ($CDCl_3$) δ 7.55 (s, 4 H), 5.10 (s, 2 H). Admixture with an authentic sample[1] gave no melting point depression.

Thermolysis of Benzothiete 1,1-Dioxide in Solution. Benzothiete 1,1-dioxide (51 mg, 3 mmol) was dissolved in benzene (1 ml) and placed in a Carius tube. The tube was sealed under vacuum at −78 °C and then heated (sand bath) to 280 °C for 0.5 h. The tube was cooled and opened. The contents were rinsed into a flask with benzene and the solvent removed in vacuo. The residue was submitted to dry column chromatography (silica gel, chloroform eluent). Starting material (20 mg, 0.12 mmol, 40%) was recovered and 3*H*-2,1-benzoxathiole 1-oxide (20 mg 0.12 mmol, 40%) was also obtained as an oil which slowly crystallized on standing: mp 38–40 °C (lit.[21] mp 40–41 °C); ir (film) 1305 (m), 1120 (s), 945 cm^{-1} (s); NMR ($CDCl_3$) δ 7.8–7.4 (m, 4 H), 5.40, 5.76 (AB quartet, J = 13.5 Hz, 2 H).

Thermolysis of Benzothiete 1,1-Dioxide Neat. Benzothiete 1,1-dioxide (154 mg, 1 mmol) was placed in a test tube and heated to

210° (sand bath) under nitrogen for 2 h. At the end of this time an oil was observed above the sand level. The tube was cut below this level and the oil was washed into a flask with chloroform which was removed in vacuo leaving 3*H*-2,1-benzoxathiole 1-oxide (138 mg, 0.9 mmol, 90%) whose properties were identical with those reported above.

Reduction of Benzothiete 1,1-Dioxide with Lithium Aluminum Hydride. Benzothiete 1,1-dioxide (154 mg, 1 mmol) was dissolved in 10 ml of dry tetrahydrofuran (THF). This solution was added dropwise to a stirred suspension of lithium aluminum hydride (156 mg, 4 mmol) in THF (5 ml) at 0 °C. The mixture was quenched with H_2O (0.2 ml) and 3 N NaOH (0.2 ml). To this was added 3 N NaOH (3 ml) and diethyl ether (25 ml). The solid was removed by filtration and the layers were separated. The aqueous layer and solid were acidified with 10% hydrochloric acid and extracted twice with 10 ml of chloroform. The extracts were dried and the solvent removed in vacuo. The residue was submitted to dry column chromatography (silica gel, chloroform eluent). *o*-Toluenethiol (70 mg, 0.56 mmol, 56%) was obtained as a pale yellow oil: ir (film) 2600 (w), 1460 (s), 745 cm^{-1} (s); NMR ($CDCl_3$) δ 7.08 (m, 4 H), 3.32 (s, 1 H), 2.25 (s, 3 H). The ir and NMR spectra were identical with those reported for an authentic sample of *o*-toluenethiol.[22]

Acknowledgment. The authors are grateful to the National Cancer Institute (Grant CA 08250) for support of this work.

Registry No.—**1**, 5687-92-3; **2**, 59463-72-8; **3**, 59463-73-9; **4**, 59463-74-0; **5**, 59463-75-1; **6**, 16065-50-2; butadiene, 106-99-0; 3*H*-2,1-benzoxathiole 1-oxide, 31910-65-3; o-toluenethiol, 137-06-4.

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A Thiophene Analogue of 7,12-Dihydropleiadene

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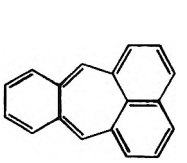
Replacement of the benzene ring in pleiadene (**1**) by a *b*-fused thiophene ring gives rise to the analogue naphtho[1,2-*b*]thiophene[1] (**2a**) as shown. Pleiadene itself has been gener-



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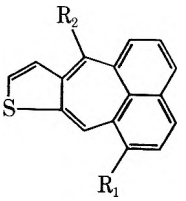
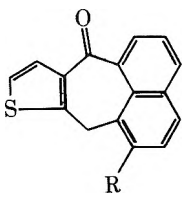
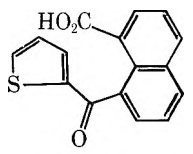


2a, $R_1 = R_2 = H$
b, $R_1 = OCH_3$; $R_2 = OCOCH_3$
c, $R_1 = OCH_3$; $R_2 = OK$



3a, R = H
b, $R = OCH_3$



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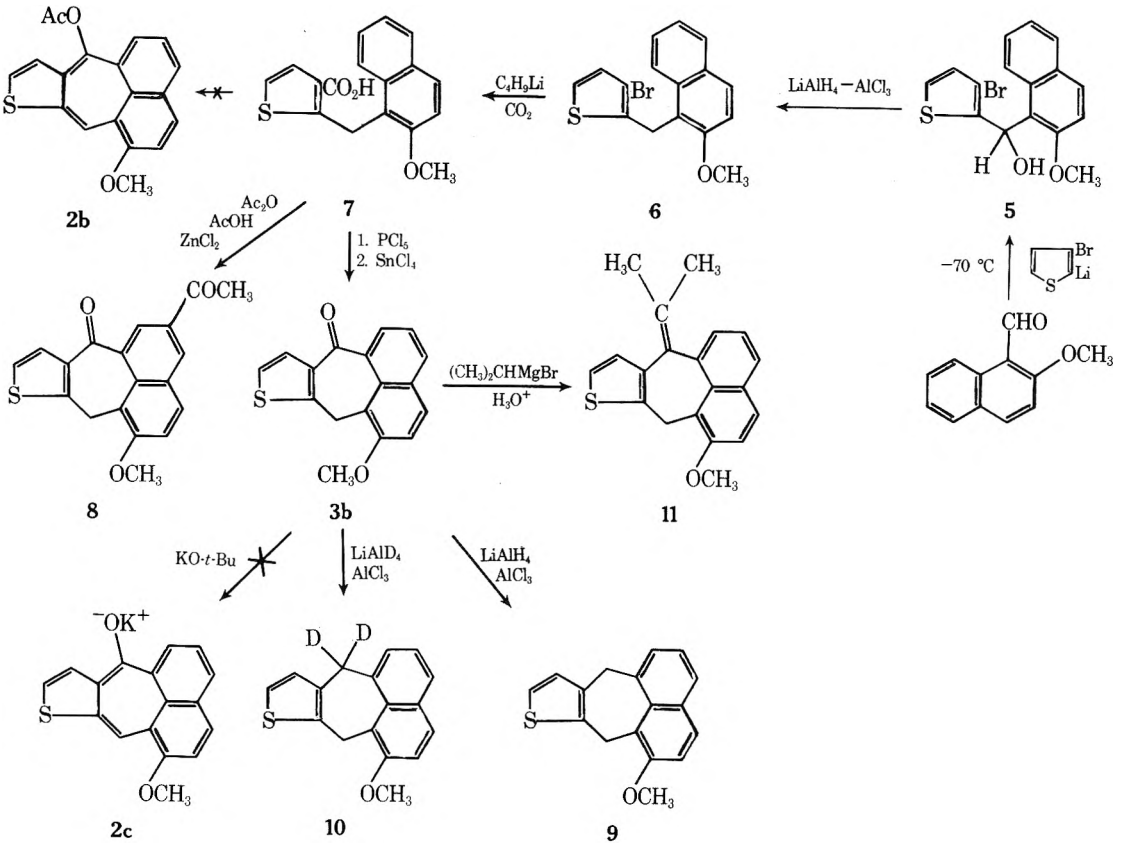
ated in solution by Cava and co-workers[2] and has been shown to undergo an addition reaction with *N*-phenylmaleimide and also to dimerize. The present work reports an attempt to ascertain if any quinodimethane character can be detected in a keto analogue of **2**, viz., **3b**. Attempts to utilize 8-(2-thenoyl)-1-naphthoic acid (**4**) (as a precursor for **3a**) were abandoned owing to difficulty in reducing the ketone group and the scheme outlined below was followed.

Reaction of 2-methoxy-1-naphthaldehyde with 3-bromo-2-thienyllithium at −70 °C afforded 1-(2-methoxynaphthyl)-3′-bromo-2-thienylmethanol (**5**) in 62% yield. Reduction of the alcohol function by means of lithium aluminum hydride–aluminum chloride[3] gave 1-(3′-bromo-2′-thenyl)-2-methoxynaphthalene (**6**) in 52% yield. The bromo derivative **6** was converted to the corresponding carboxylic acid **7** in 91% yield by treatment with *n*-butyllithium at −70 °C followed by carbonation. Cyclization of the resulting 1-(3′-carboxy-2′-thenyl)-2-methoxynaphthalene (**7**) by means of phosphorus pentachloride followed by stannic chloride gave the cyclic ketone 6-methoxynaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophen-11(7*H*)-one (**3b**) in 68% yield.

An attempt to form the pleiadene analogue 11-acetoxy-6-methoxynaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (**2b**) by treatment of the acid **7** with acetic anhydride and zinc chloride under conditions where acetoxyanthracenes were produced[4] afforded a product whose spectra and elemental analysis indicated it to be 2-(?)-acetylmethoxynaphtho-[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophen-11(7*H*)-one (**8**), together with unreacted starting material. When the above reaction was carried out in the presence of *N*-phenylmaleimide in an attempt to trap **2b**, only unchanged starting material was recovered.

An attempt was made to ascertain whether base-catalyzed enolization of **3b** could be induced by treatment of the ketone with freshly sublimed potassium *tert*-butoxide.[6] Upon mixing these reagents in THF solution no change in color was observed. Quenching of the mixture with deuterium oxide re-



sulted in a quantitative recovery of starting material with no deuterium incorporation as shown by NMR spectroscopy. This result indicates the absence of any species such as **2c.**

The ketone **3b** upon treatment with lithium aluminum hydride and aluminum chloride in refluxing ether gave 6-methoxy-7,11-dihydronaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (**9**) in 56% yield. A study of the NMR spectrum of **9** showed no evidence of coupling between the 7 and 11 hydrogen atoms at room temperature because of the rapid inversion of the seven-membered ring. At −74 °C the two signals for the nonequivalent methylene protons coalesced to a broad hump. Further cooling to −90 °C caused this broad hump to split into four signals: $J_{AA'}$ = 17 Hz, $J_{BB'}$ = 27 Hz; δ (measured from OCH_3) δ_A = 39 Hz, δ_B = 25 Hz at −90 °C; δ_A = 37 Hz, δ_B = 25 Hz at 25 °C. The 11,11-dideuterio compound **10,** prepared from **3b** by reduction with lithium aluminum deuteride–aluminum chloride, showed a splitting of the singlet into a clearly resolved doublet at −86 °C, J = 16 Hz, coalescence temperature −77 ± 1.5 °C.

Reaction of the ketone **3b** with isopropylmagnesium bromide followed by acid-catalyzed dehydration afforded 6-methoxy-11-isopropylidene-7,11-dihydronaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (**11**) which showed an AB quartet for the seven methylene protons with J_{AB} = 16 Hz and $\Delta\nu_{AB}$ = 34 Hz, which also paralleled the results found for 7-isopropylidene-7,12-dihydropleiadene.[5]

It is thus seen that the NMR spectral behavior of **9, 10,** and **11** is similiar to that of the analogous dihydropleiadene derivatives except that the coalescence temperatures for inversion of **9, 10,** and **11** are much lower than for 7,12-dihydropleiadene[5]—about −75 °C as compared to 8 °C. A more rapid inversion of the seven-membered ring in the thiophene series is indicated.

It has not been found possible to prepare derivatives of **2** analogous to **1.**

Experimental Section[7]

1-(2-Methoxynaphthyl)-3′-bromo-2′-thienylmethanol (5). To a solution of *n*-butyllithium in ether (110 ml, 1.76 M, 0.194 mol) cooled to −70 °C was added a solution of 2,3-dibromothiophene (46.8 g, 0.194 mol) in 30 ml of ether. After stirring for 30 min at −70 °C, 2-methoxynaphthaldehyde[8] (36.1 g, 0.22 mol) in 200 ml of 1:1 ether–benzene was added. The mixture was stirred for 5 h during which it was allowed to warm to 10 °C. Addition of ammonium chloride solution followed by extraction with ether, washing, and drying ($MgSO_4$) gave a deep green colored oil (64.7 g). Chromatography on alumina (900 g) with chloroform as eluent afforded a light yellow oil, 60 g (88%), which yielded colorless needles from cyclohexane: mp 74.5–75 °C; 40 g (62%); ir (CCl_4) 3450 cm^{-1}; NMR (CCl_4) δ 6.8–8.0 (m, 8 H, aromatic), 6.6 (s, H, CH), 4.0 (s, 1 H, OH), 3.8 (s, 3 H, OCH_3). Anal. Calcd for $C_{16}H_{13}BrO_2S$: C, 55.02; H, 3.75; S, 9.18. Found: C, 54.79; H, 3.90; S, 8.96.

1-(3′-Bromo-2′-thenyl)-2-methoxynaphthalene (6). To a suspension of lithium aluminum hydride (1.9 g, 0.05 mol) in anhydrous ether (50 ml) was added with cooling aluminum chloride (6.7 g, 0.05 mol) in anhydrous ether (2000 ml). To this mixture was added dropwise 9.7 g (0.028 mol) of 1-(2-methoxynaphthyl)-3-bromothienylmethanol (**5**) in 50 ml of ether over a period of 30 min. The mixture was heated under reflux for a further 30 min and was then decomposed by the cautious addition of 3 M H_2SO_4. Addition of water followed by extraction with ether, washing, and drying ($MgSO_4$) gave, upon removal of the ether, a yellow oil (8.8 g) which upon chromatography over alumina (170 g) with hexane as eluent gave a colorless oil which crystallized upon standing to white prisms. Recrystallization from hexane afforded large white cubes: 4.8 g (52%); mp 73–73.5 °C; ir (KBr) 3070, 2930 cm^{-1}; NMR (CCl_4) δ 6.8–8.0 (m, 8 H, aromatic), 4.5 (s, 2 H, CH_2), 3.9 (s, 3 H, OCH_3). Anal. Calcd for $C_{16}H_{13}BrOS$: C, 57.66; H, 3.93; S, 9.62. Found: C, 57.85; H, 4.03; S, 9.40.

1-(3′-Carboxy-2′-thenyl)-2-methoxynaphthalene (7). To a solution of ethereal *n*-butyllithium (8 ml, 0.013 mol) cooled to −70 °C under nitrogen was added 1-(3′-bromo-2-thenyl)-2-methoxynaphthalene (**6,** 3.3 g, 0.011 mol) in 50 ml of ether. The mixture was stirred for 30 min at −70 °C and was then poured onto an excess of dry ice (100 g) and allowed to come to room temperature. Addition of 1 M HCl (50 ml) followed by extraction with ether gave upon removal of the solvent a white solid which was recrystallized from 1:1 benzene–hexane to give the acid **7,** 2.7 g (83%), mp 175–177 °C. An additional recrystallization gave an analytical sample: mp 176.2–177 °C; ir (KBr) 3450, 1665 cm^{-1}; NMR (acetone-d_6) δ 6.6–7.6 (m, 8 H, aromatic), 4.6 (s, 2 H, CH_2), 3.5 (s, 3 H, OCH_3). Anal. Calcd for $C_{17}H_{14}O_3S$: C, 68.43; H, 4.73; S, 10.75. Found: C, 68.30; H, 4.77; S, 10.61.

6-Methoxynaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophen-11(7*H*)-one (3b). To a stirred suspension of the acid 7 (2.98 g, 10

mmol) in dry benzene (25 ml) at 5 °C was added phosphorus pentachloride (2.08 g, 10 mmol) over a 10-min period. When evolution of hydrogen chloride had ceased, the solution was cooled to 4 °C and a solution of stannic chloride (3.35 g, 13 mmol) in benzene (50 ml) was added dropwise with stirring over a 30-min period. The magenta colored mixture was allowed to warm up to room temperature and was stirred for 2 h. Decomposition of the complex with 0.1 M HCl and ice, followed by benzene extraction with washing and drying ($MgSO_4$), gave, upon removal of the solvent, a yellow oil. This was chromatographed on silica gel using 3:1 benzene–chloroform as eluent to give yellow crystals (1.9 g, 68%) mp 161–162 °C. An analytical sample (mp 162.5–163 °C) was obtained by recrystallization from benzene–hexane as bright yellow prisms with a brilliant green fluorescence: ir (KBr) 1625 cm^{-1}; NMR (Unisol-D) δ 7.0–8.3 (m, 8 H, aromatic), 4.6 (s, 2 H, CH_2), 4.0 (s, 3 H, OCH_3). Anal. Calcd for $C_{17}H_{12}O_2S$: C, 72.83; H, 4.32; S, 11.43. Found: C, 73.09; H, 4.25; S, 11.60.

Attempted Synthesis of 11-Acetoxy-6-methoxynaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (2b). A stirred mixture of 1-(3′-carboxy-2′-thenyl)-2-methoxynaphthalene (**7**, 1.0 g, 3.36 mmol), acetic anhydride (25 ml), acetic acid (20 ml), and freshly fused zinc chloride (1.2 g, 8.8 mmol) was heated under reflux for 0.5 h. To the hot solution was added water (25 ml) dropwise and the reaction mixture was cooled in ice. Yellow needles separated and were removed by filtration (0.8 g, 71%), mp 207–208.5 °C. This substance gave a positive iodoform test. Recrystallization from benzene–hexane followed by sublimation in vacuo gave **8** as pale yellow needles: mp 208–208.5 °C; ir (KBr) 1660 (C=O), 1645 cm^{-1} ($ArCOCH_3$); NMR (acetone-d_6) δ 7.5–6.9 (m, 7 H, aromatic), 4.55 (s, 2 H, CH_2); 4.0 (s, 3 H, OCH_3), 2.45 (s, 3 H, $COCH_3$). Anal. Calcd for $C_{19}H_{14}O_3S$: C, 70.79; H, 4.38; S, 9.95. Found: C, 70.59; H, 4.35; S, 10.06.

6-Methoxy-7,11-dihydronaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (9). To a cooled, stirred suspension of lithium aluminum hydride (0.23 g, 6.0 mmol) in ether (25 ml) was added, with cooling and stirring, a solution of aluminum chloride (0.80 g, 6 mmol) in 25 ml of anhydrous ether. To this was added a solution of 6-methoxynaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophen-11(7*H*)-one (1.0 g, 3.5 mmol) in ether (35 ml). The mixture was stirred under reflux for 16 h. Careful addition of 5% H_2SO_4 followed by extraction with ether, washing with $NaHCO_3$, and drying ($MgSO_4$) gave upon removal of the solvent a white solid (0.5 g, 54%), mp 130–132 °C. Sublimation gave an analytical sample: mp 129–130 °C; NMR ($CDCl_3$) δ 6.9–7.8 (m, 7 H, aromatic), 4.7 (s, 2 H, CH_2), 4.4 (s, 2 H, CH_2), 4.0 (s, 3 H, OCH_3). Anal. Calcd for $C_{17}H_{14}OS$: C, 76.66; H, 5.30; S, 12.04. Found: C, 76.41; H, 5.31; S, 12.13.

6-Methoxy-11,11-dideuterio-7,11-dihydronaphtho-[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (10). From the ketone **3b** (2.0 g), lithium aluminum deuteride (1.0 g), and aluminum chloride (32 g) there was obtained 1.85 g (98%) of **10**: mp 129.5–130 °C; NMR ($CDCl_3$) δ 6.8–7.7 (m, 7 H, aromatic), 4.6 (s, 2 H, CH_2), 3.9 (s, 3 H, OCH_3); mol wt by mass spectrum, 268 (calcd for $C_{17}H_{12}D_2OS$, 268).

6-Methoxy-11-isopropylidene-7,11-dihydronaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (11). To a filtered ethereal solution of isopropylmagnesium bromide from isopropyl bromide (12.37 g, 0.1 mmol) and magnesium (2.67 g, 0.11 g-atom) was added a solution of 1.0 g (3.5 mmol) of the ketone **3b** in 50 ml of 1:1 benzene–ether. The mixture was stirred under reflux for <1.5 hr. and was then hydrolyzed with 10% NH_4Cl solution (200 ml). The organic layer was separated, washed with water and Na_2CO_3, and dried ($MgSO_4$). Evaporation of the ether left a red oil which was taken up in methanol (30 ml) containing 2 drops of 12 M HCl and heated under reflux for 12 h. Removal of the methanol gave a yellow oil (2.0 g) which was freed from traces of acid and was then chromatographed on alumina (50 g) using hexane as the eluent. A colorless oil (0.2 g) was obtained which solidified after 5 days to white prisms (0.2 g, 19%), mp 119.5–120 °C. Recrystallization from hexane followed by sublimation gave an analytical sample: mp 119–120 °C; NMR ($CDCl_3$) δ 7.3–7.7 (m, 6 H, aromatic), 6.95 (s, 1 H, aromatic C_5H), 4.6 (2 H, quartet, 2 H), 4.0 (s, 3 H, OCH_3), 1.93 (s, 3 H, CH_3), 1.85 (s, 3 H, CH_3). The AB quartet centered at 4.6 has J_{AB} = 16 Hz and δ_{AB} = 34 Hz. Anal. Calcd for $C_{20}H_{18}OS$: C, 78.39; H, 5.92; S, 10.47. Found: C, 78.46; H, 6.06; S, 10.22.

Registry No.—**3b**, 59463-61-5; **5**, 59463-62-6; **6**, 59463-63-7; **7**, 59463-64-8; **8**, 59463-65-9; **9**, 59463-66-0; **10**, 59463-67-1; **11**, 59463-68-2; 2,3-dibromothiophene, 3140-93-0; 2-methoxynaphthaldehyde, 5392-12-1; isopropyl bromide, 75-26-3.

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A Reaction of Chlorosulfonyl Isocyanate and 6-Tritylaminopenicillanic Acid Leading to the Anhydropenicillin Rearrangement

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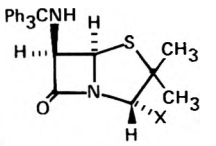
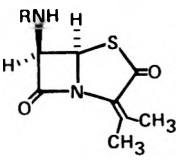
Since their initial preparation,[1] anhydropenicillins have continued to attract interest.[2] We now report a reaction of 6-tritylaminopenicillanic acid (**1**) with chlorosulfonyl isocyanate (CSI) that leads to the formation of anhydro-6-tritylaminopenicillanic acid (**5**).





1, X = COOH
2, X = CN
3, X = $CO_2CONHSO_2Cl$
4, X = $CONHSO_2Cl$

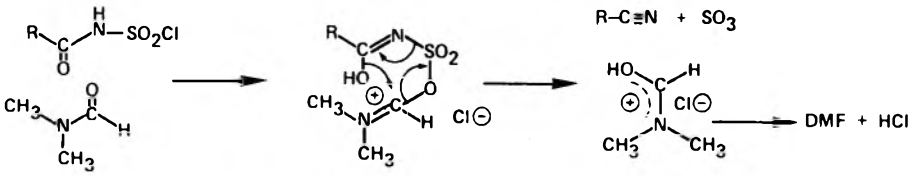
5, R = $-CPh_3$
6, R = $-H, CH_3(C_6H_4)SO_3H$

In connection with other work, we attempted a synthesis of the penicillin nitrile **2** from carboxylic acid **1** by application of the methods of Lohaus[3] and Vorbrüggen.[4] These involve, respectively, treatment of a chlorosulfonylamide with either an amide such as dimethylformamide (DMF, Scheme I) or a base such as triethylamine (Scheme II). In favorable cases, the chlorosulfonylamide is readily obtained by reacting a carboxylic acid with CSI.

When **1** was treated with a 5% molar excess of CSI in acetonitrile, followed by either DMF or triethylamine, no β-lactam containing materials were isolated with the neutral fraction. Various speculations may be proposed to account for the failure of these straightforward approaches patterened after the successful conditions of Lohaus and Vorbrüggen. The β-lactam moiety perhaps interacted with the chlorosulfonylamide **4**[3,5] or it reacted directly with the CSI.[5] The possibility of other undesirable reactions involving CSI and compounds **1**, **2**, **3**, or **4** may also be inferred.[5] Finally, the fact that penicillins are relatively strong acids[6] may have hampered the $CO_2H \rightarrow CN$ conversion because, according to results of both Lohaus and Vorbrüggen, the CSI reaction is sluggish with strong acids.

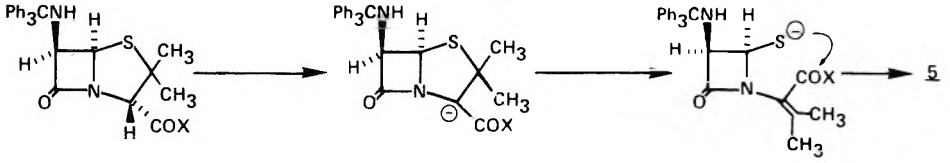
On the assumption that the β-lactam amide was the major cause of our difficulties, we treated **1** with CSI in the presence of either DMF or triethylamine. Neither small nor large amounts of DMF were useful, likely because the rate of CSI reaction with DMF[5] was faster than that with the penicillin carboxyl group. When, however, triethylamine was present during the CSI addition, we isolated[7] a fairly pure penicillin derivative contaminated by some triphenylcarbinol[8] according to ir, NMR, and TLC analysis. The presence of two vinylic methyl group resonances suggested that the anhydropenicillin rearrangement had occurred to afford anhydro-6-tritylami-

Scheme I



Scheme II

Scheme III



nopenicillanic acid (**5**). This was confirmed by comparison of the analytical data for **5** and for the detritylated derivative **6** with published data for these compounds[9] (see Experimental Section).

Our highest conversion from **1** to **5** was at least 45% without any attempt at optimization.[10] The isolated yields likely suffered because we routinely employed an isolation procedure that would have been satisfactory for our original synthetic goal, the nitrile **2**. This procedure included an aqueous extraction to which anhydropenicillins are reported to be sensitive.[11,12]

Although various speculations may be entertained about the reaction of **1** with CSI, the mechanism for the **1** to **5** conversion is likely analogous to that proposed by Wolfe,[1] which involves base abstraction of the C-3 proton of a suitably activated penicillin 3-carboxyl group (Scheme III) followed by elimination of thiolate and subsequent attack on the activated acid.

Experimental Section

Ir spectra were measured with a Perkin-Elmer Model 21 spectrometer. ^{1}H NMR spectra were recorded on a Varian Model T-60 spectrometer with a dilute solution in deuteriochloroform and tetramethylsilane as an internal standard.

Anhydro-6-tritylaminopenicillanic Acid (5). A solution of 9.16 g (20 mmol) of 6-tritylaminopenicillanic acid (**1**) and 13.9 ml (100 mmol) of triethylamine in 50 ml of acetonitrile was cooled to −35 °C under nitrogen. Then 1.84 ml (21 mmol) of chlorosulfonyl isocyanate (Aldrich Chemical Co., Milwaukee, Wis.) was added over a 5-min period.[13] The dry ice bath was removed and the mixture warmed to 22 °C over 35 min. Then the reaction mixture was heated at 40 °C. Evolution of CO_2 was monitored by sweeping the reaction surface with nitrogen and bubbling the effluent into an aqueous $Ba(OH)_2$ solution. After 20 h the reaction mixture was worked up; although the CO_2 evolution had not entirely ceased, it had greatly diminished. The reaction mixture was concentrated to half volume, diluted with 1:1 ether/saturated aqueous sodium bicarbonate, and partitioned between ether and water. The combined ethereal extracts were washed with a brine solution, dried over sodium sulfate, and concentrated, affording 5.7 g of a beige-colored foam. An ir spectrum showed the distinctive bands of **5** plus some triphenylcarbinol; by NMR analysis this material was about 69% pure **5** (corresponding to a corrected isolated yield of 45%) contaminated mainly by triphenylcarbinol plus a small amount of triethylamine and traces of other components.

The above crude product (2 g) was chromatographed on silica gel with a 7:3 hexane/chloroform solution. According to the ir and NMR spectra, **5** was not effectively separated from the triphenylcarbinol impurity. Adapting methodology suggested by Wolfe,[9] 394 mg from the early eluate were combined in chloroform and isopropyl alcohol and concentrated to a yellow, granular material. This was then triturated with cold acetic acid to afford an off-white solid which was filtered, washed with hexane, and dried to afford 194 mg of pure anhydro-6-tritylaminopenicillanic acid (**5**), mp 157–160 °C (lit.[9] 165–166 °C).

Anal. Calcd for $C_{27}H_{24}N_2O_2S$: C, 73.61; H, 5.49; N, 6.36; S, 7.27. Found: C, 73.71; H, 5.60; N, 6.15; S, 7.10.

The ir spectrum matched that published.[9] The NMR spectrum showed only resonances consistent with **5**: δ_{Me_4Si} ($CDCl_3$) 2.00 (3 H, s), 2.12 (3 H, s), 3.18 (NH, d, J = 11.8 Hz), 4.40 (C-7, 1 H, d, J = 4.0 Hz), 4.81 (C-6, 1 H, dd, J = 4.0, 11.8 Hz), and 7.1–7.7 ppm (Ph_3C, 15 H).

***p*-Toluenesulfonic Acid Salt of Anhydro-6-aminopenicillanic Acid (6).** **5** (50 mg) was dissolved in 0.25 ml of acetone and processed with *p*-toluenesulfonic acid hydrate according to Wolfe[9] to afford 30 mg of **6**, mp 155–157 °C dec (lit.[9] 153–154 °C dec). The ir spectrum matched that published.[9]

Acknowledgment. The expert technical assistance of Mr. Ralph Breitenbach is gratefully acknowledged.

Registry No.—**1**, 40124-92-3; **5**, 17276-71-0; chlorosulfonyl isocyanate, 1189-71-5.

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(5) R. Graf, *Angew. Chem., Int. Ed. Engl.*, **7**, 172 (1968).
(6) H. D. C. Rapson and A. E. Bird, *J. Pharm. Pharmacol., Suppl.*, **15**, 222T (1963).
(7) As judged by ir and NMR of the total reaction mixture, the anhydropenicillin **5** is already present before workup.
(8) Although secondary amines can react with CSI,[5] it was assumed that the trityl group would effectively block that of **1**. Isolation in good yield of **5** shows that this was largely the case. However, spectral and TLC identification of triphenylcarbinol in mixtures where solvolysis should not have occurred does indicate adverse behavior of the 6-tritylamino group under the reaction conditions.
(9) S. Wolfe, *Can. J. Chem.*, **46**, 459 (1968).
(10) Addition of CSI at 0 °C instead of at −35 °C led to a reduction in yield of **5** to 32% from 45%. Using 2 equiv of CSI (added at 0 °C) led to a yield of only 19% for **5** associated with the production of much more triphenylcarbinol.[8] Using pyridine in place of triethylamine led to an isolated mixture that contained only traces of **5** at best.
(11) H. Bundgaard and H. R. Angelo, *Tetrahedron Lett.*, 3001 (1974).
(12) S. Wolfe, J. C. Godfrey, C. T. Holdredge, and Y. G. Perron, *Can. J. Chem.*, **46**, 2549 (1968).
(13) Adding CSI to solutions of **1** in acetonitrile at 0 °C led to an exotherm, suggesting rapid formation of **3**; however CO_2 evolution (**3** → **4?**) continued for a long time although the reactions were heated at 40 or 60 °C.

Some Novel Reactions of Pyrrolecarboxylic Acid Chlorides

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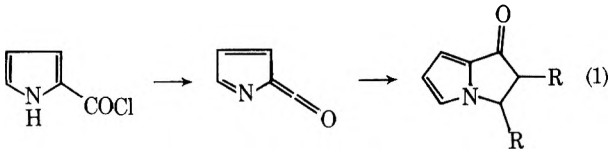
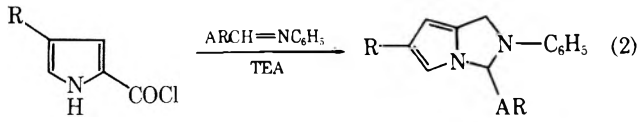
We have investigated the possibility of generating and trapping ketenes derived from pyrrole-2-carbonyl chloride and indole-2-carbonyl chloride as in eq 1. The reactivity of ketenes in cycloaddition reactions is well documented.[1-3]



(1)

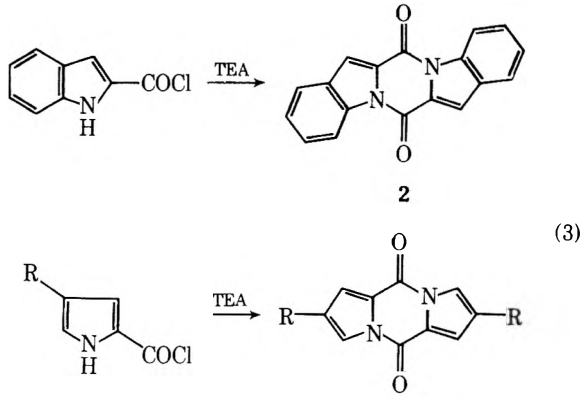
Pyrrole-2-carbonyl chloride[4] and 4-nitropyrrole-2-carbonyl chloride react with benzalaniline and *p*-methoxybenzalaniline in the presence of triethylamine (TEA) to afford the expected adducts (eq 2). In the case of indole-2-carbonyl chloride[5] no



(2)

1

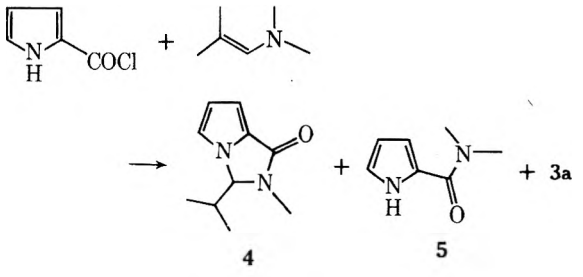
similar adducts could be isolated; rather the novel ketene dimer (**2**) was isolated.[10] Similar dimers were obtained from pyrrole-2-carbonyl chloride (**3a**) and 4-nitropyrrole-2-carbonyl chloride (**3b**) when treated with TEA in the absence of a trapping agent (eq 3).



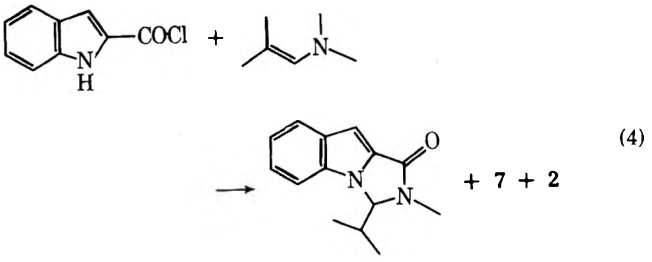
(3)

3a, R = H
b, R = NO_2

It was hoped that enamines could serve as traps of the presumably electrophilic ketenelike intermediates in this reaction. Reaction of pyrrole-2-carbonyl chloride with 2 equiv of isobutyraldehyde dimethyl enamine, however, gave **4** and **5** as major products[9] along with some dimer, **3a** (eq 4). Similar results were observed in the reaction of indole-2-carbonyl chloride with this enamine (eq 4). When these reactions were



4 5



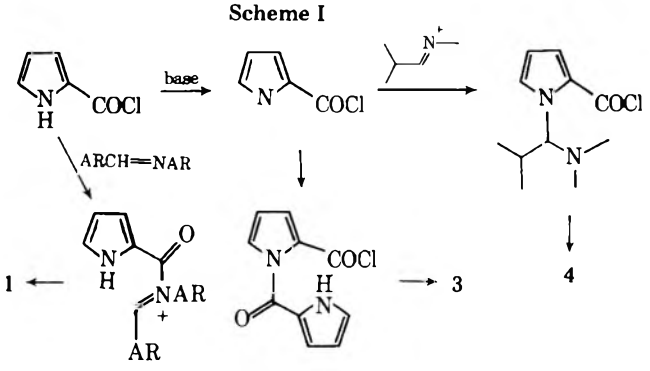
(4)

6

repeated in the presence of TEA neither **4** nor **6** were produced, the dimers **3a** and **2** and the *N,N*-dimethylamides (**5** and **7**) being isolated as the exclusive products. Attempted use of cyclohexanone pyrrolidine enamine, with or without added TEA, gave only dimers **3a** and **2** and the corresponding pyrrolidine amides.

While the above reactions could involve the intermediacy of the ketenes as in eq 1, these are not required by the data. An alternative simpler mechanism can be written as in Scheme I.[11]

Scheme I



Experimental Section[6]

Reagents. Acetone was dried over 4-Å molecular sieves and distilled fresh before use. Dimethoxyethane (DME) was distilled fresh from the sodium ketyl of benzophenone. Dichloromethane was dried over molecular sieves prior to use. Triethylamine (TEA) was distilled from molecular sieves.

Pyrrole-2-carbonyl Chloride. To a filtered solution of 3.0 g (27 mmol) of pyrrole-2-carboxylic acid in 100 ml of purified dimethoxyethane (DME) was added 5 ml of triethylamine. The solution was evaporated and dried at 0.5 mm for 4 h. The green, oily residue was then dissolved in 30 ml of DME and added dropwise, over a 10-min period, to a stirred, 0 °C solution of 30 ml of thionyl chloride in 50 ml of DME. The reaction mixture was then stirred at 0 °C for 30 min, filtered to remove a precipitate, and evaporated to afford 2.41 g of a light green solid: mp 74–83 °C; NMR (acetone-d_6) δ 6.43 (1 H, m), 7.22 (1 H, m), 7.41 (1 H, m), 11.5 (1.3 H, bs); ir ν_{KBr} 3373 and 1690 cm^{-1}; uv λ_{max} ($CHCl_3$) 288 nm (ϵ 17 000); mass spectrum *m/e* (peak match) 128.99806 (calcd for C_5H_4NOCl, 128.99814).

In a similar manner were prepared indole-2-carbonyl chloride,[5] mp 107–112 °C, *m/e* 179.01318 (calcd for C_9H_6NOCl, 179.01379), and 4-nitropyrrole-2-carbonyl chloride, mp 145–150 °C, δ 7.50 (1 H, d, J = 2.0 Hz) and 8.08 (1 H, d, J = 2.0 Hz).

Pyrrole-2-carbonyl Chloride and Benzalaniline. Adduct 1a. To a stirred solution of 0.27 g (2.1 mmol) of the above acid chloride and 0.61 g (3.4 mmol) of benzalaniline in 2 ml of dichloromethane was added at 0 °C 0.2 ml of triethylamine. After 5 min the reaction mixture was worked up to afford a gummy residue that was triturated with cold acetone. Sublimation (140 °C, 0.08 mm) afforded 0.35 g (62% yield) of adduct **1a** (Ar = C_6H_5): mp 207–208 °C; NMR (Me_2SO-d_6) δ 6.31 (1 H, dd, J = 3.7, 2.5 Hz), 6.53 (1 H, m), 6.81 (1 H, m), and 6.9–7.5 (1 H, m); ir ν_{KBr} 1695 cm^{-1}; uv λ_{max} (MeOH) 283 nm (ϵ 10 000) and 232 (7700); mass spectrum *m/e* 274.11069 (calcd for $C_{18}H_{14}N_2O$, 274.11061).

Anal. Calcd: C,78.80; H, 5.16; N, 10.22. Found: C, 78.84; H, 5.01; N, 10.33.

In a similar manner there was prepared from 4-nitropyrrole-2-carbonyl chloride and benzalaniline a 67% yield of adduct **1b** (Ar = C_6H_5): mp 209–212 °C; NMR δ 7.1–7.8 (14 H, m) and 8.37 (1 H, s); ν_{max}

(KBr) 1690 cm^{-1}; λ_{max} (MeOH) 303 nm (ϵ 11 000) and 256 (16 000); *m/e* 319.09549 (calcd for $C_{18}H_{13}N_3O_3$, 319.09568).

Anal. Calcd: C, 67.30; H, 4.06; N, 13.08. Found: C, 67.68; H, 3.99; N, 12.91.

Methanolysis of **1b** ($NaOCH_3$, MeOH) afforded benzalaniline and methyl 4-nitropyrrole-2-carboxylate.

Repetition of the above experiment with *p*-methoxybenzalaniline afforded **1a** (Ar = $CH_3OC_6H_4$): mp 143–145 °C; NMR δ 3.72 (3 H, s), 6.41 (1 H, dd, J = 5, 3 Hz), 6.63 (1 H, d, J = 5 Hz), and 6.80–7.93 (10 H, m); ν_{max} ($CHCl_3$) 1705 cm^{-1}; λ_{max} (MeOH) 230 nm (ϵ 1300) and 282 (12 000).

Anal. Calcd: C, 74.97; H, 5.31; N, 9.21. Found: C, 75.02; H, 5.24; N, 9.15.

Dimer of Pyrrole-2-carbonyl Chloride (3a). To a stirred solution of 0.21 g (1.6 mmol) of the above acid chloride in 2.0 ml of chloroform was added, with stirring, 0.5 ml of triethylamine. The resulting dark green solution was stirred for 30 min, the solvent evaporated, and the residue triturated with 10 ml of water. Recrystallization from a mixture of Me_2SoMe_2SO and CCl_4 (1:1 v/v) afforded 11 mg (4.7%) of the dimer **3a** (sublimes without melting above 250 °C): NMR (Me_2SO-d_6) δ 6.63 (2 H, dd, J = 4.2, 4.0 Hz), 7.43 (2 H, dd, J = 4.2, 2.0 Hz), and 7.85 (2 H, dd, J = 4.0, 2.0 Hz); ir ν_{max} (KBr) 1700, 1555, and 1460 cm^{-1}; uv λ_{max} (MeOH) 315 nm (ϵ 13 000), 303 (12 500), 273 (14 000), and 235 (22 000); mass spectrum *m/e* (rel intensity) 186 (32) and 86 (100); found, *m/e* 186.04291 (calcd for $C_{10}H_6N_2O_2$, 186.04293.)

Anal. Calcd: C, 64.52; H, 3.26; N, 15.05. Found: C, 63.19; H, 3.02; N, 14.82.

In a similar manner was prepared the dimer of 4-nitropyrrole-2-carbonyl chloride (**3b**) in 85% yield as light pink needles (from Me_2SO): mp > 340 °C; NMR (Me_2SO-d_6) δ 8.03 (2 H, d, J = 2 Hz) and 8.89 (2 H, d, J = 2 Hz); ν_{max} (KBr) 1735, 1560, and 1510 cm^{-1}; λ_{max} ($CHCl_3$) 288 nm (ϵ 28 300) and 266 (34 500); *m/e* 276.01297 (calcd for $C_{10}H_4N_4O_6$, 276.01308).

Anal. Calcd: C, 43.48; H, 1.46; N, 20.29. Found: C, 42.91; H, 1.78; N, 18.97.

Repetition of the above with indole-2-carbonyl chloride yielded the dimer, **2**, as an extremely insoluble orange solid: mp > 340 °C; ν_{max} (KBr) 1695 and 1560 cm^{-1}; λ_{max} ($CHCl_3$) 380 nm (ϵ 20 000), 263 (22 000), 308 (18 000), and 276 (35 000); *m/e* 286.07531 (calcd for $C_{18}H_{10}N_2O_2$, 286.07422).

Pyrrole-2-carbonyl Chloride and *N,N*-Dimethylisobutenylamine. Adduct 4. To a stirred solution of 0.43 g (3.2 mmol) of the above acid chloride in 2 ml of dry acetone was added a solution of 0.66 g (6.6 mmol) of the above enamine in 2 ml of acetone. The resulting solution was stirred for 30 min and solvent was evaporated, and the oily residue was subjected to thick layer chromatography (silica gel PF-254, 1.5 mm thick, 6% methanol in chloroform) to afford three fractions. (a) Pyrrole dimer **3a**: 11 mg. (b) Adduct **4**: 330 mg (58%), mp 79–81 °C (carbon tetrachloride); NMR (CCl_4) δ 0.62 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 2.25 (1 H, m), 2.95 (3 H, s), 5.08 (1 H, d, J = 1.5 Hz), 6.27 (1 H, m), 6.39 (1 H, m), and 6.76 (1 H, m); ν_{max} ($CHCl_3$) 1690 cm^{-1}; λ_{max} (MeOH) 278 nm (ϵ 8900), 242 (5500), and 235 (5800); *m/e* 178.11061 (calcd for $C_{10}H_{14}N_2O$, 178.11061).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 71.01; H, 8.36; N, 16.57. Found: C, 70.92; H, 8.21; N, 16.51.

(c) *N,N*-Dimethylpyrrole-2-carboxamide (**5**): 32 mg (8%) (sublimed at 55 °C 0.08 mm); mp 96–98 °C (lit.[7] 100–101 °C); NMR δ 3.18 (6 H, s), 6.13 (1 H, m), 6.58 (1 H, m), 6.93 (1 H, m), and 10.7 (1 H, bs); ν_{max} ($CHCl_3$)3450 and 1685 cm^{-1}; λ_{max} (MeOH) 263 nm (ϵ 12 000); *m/e* 138.07919 (calcd for $C_7H_{10}N_2$, 138.07931).

Repetition of the above experiment using 1 equiv each of the enamine and triethylamine afforded a 55% yield of the dimer (**3a**) and 18% yield of the dimethylamide (**5**).

If this experiment is repeated using the pyrrolidine enamine of cyclohexanone one obtains a 32% yield of the dimer and 24% yield of pyrrolidinopyrrole-2-carboxamide: mp 109–112 °C; δ NMR 1.97 (4 H, bs), 3.72 (4 H, bs), 6.28 (1 H, m), 6.62 (1 H, m), 6.97 (1 H, m), 6.97 (1 H, m), and 10.25 (1 H, bs); ν_{max} ($CHCl_3$) 3450 and 1590 cm^{-1}; λ_{max} (MeOH) 266 nm (ϵ 15 500) and 227 (7000).

Indole-2-carbonyl Chloride and *N,N*-Dimethylisobutenylamine. Adduct 6. To a stirred solution of 0.427 g (2.39 mmol) of the acid chloride in 2 ml of dry acetone was added a solution of 0.506 g (5.06 mmol) of *N,N*-dimethylisobutenylamine in 2 ml of acetone. The resulting solution was stirred for 4 h and evaporated, and the residue triturated with 25 ml of chloroform to afford 64 mg of the indole dimer (**2**) as an insoluble orange solid. The soluble material was subjected to thick layer chromatography (silica gel G, 6% MeOH in chloroform) to afford two components. (a) Adduct **6**: 399 mg, mp 139–131.5 °C (after sublimation); NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 8 Hz), 0.70 (3 H, d, J = 8 Hz), 2.6 (1 H, m), 3.14 (3 H, s), 3.38 (1 H, d, J = 1.5 Hz), and 6.8–7.8 (5 H, m); ν_{max} ($CHCl_3$) 1695 cm^{-1}; λ_{max} (MeOH) 312 nm (ϵ 9700), 298 (13 000), 290 (11 500), and 236 (11 700); *m/e* 228.1262 (calcd for $C_{14}H_{16}N_2O$, 228.1262).

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 73.65; H, 7.08; N, 12.28. Found: C, 73.64; H, 7.04; N, 12.21.

(b) *N,N*-Dimethylindole-2-carboxamide (**7**): 12 mg (3% yield); mp 183–185 °C (lit.[8] 180–182 °C); NMR (acetone-d_6) δ 3.32 (6 H, s), 6.80–7.70 (5 H, m), and 10.5 (1 H, bs); ν_{max} ($CHCl_3$) 3450 and 1610 cm^{-1}; λ_{max} (MeOH) 293 nm (ϵ 17 500); *m/e* 188.09480 (calcd for $C_{11}H_{12}N_2O$, 188.09496).

Repetition of the above experiment using 1 equiv each of the enamine and triethylamine afforded a 5% yield of the dimer (**2**) and a 9% yield of the amide (**7**).

If this experiment is repeated using the pyrrolidine enamine of cyclohexanone one obtains a 13% yield of the dimer (**2**) and a 15% yield of pyrrolidinopyrrole-2-carboxamide: mp 193–197 °C; NMR (Me_2SO-d_6) δ 1.98 (4 H, m), 3.67 (2 H, m), 3.87 (2 H, m), 7.0–7.8 (5 H, m), and 11.6 (1 H, bs); ν_{max} (KBr) 3240 and 1590 cm^{-1}; λ_{max} (MeOH) 293 nm (ϵ 17 000) and 225 (16 500).

Registry No.—**1a** (Ar = C_6H_5), 58881-38-2; **1a** (Ar = $CH_3OC_6H_4$), 58881-39-3; **1b** (Ar = C_6H_5), 58881-40-6; **2**, 58881-41-7; **3a**, 484-73-1; **3b**, 58881-42-8; **4**, 58881-43-9; **5**, 7126-47-8; **6**, 58881-44-0; **7**, 7511-14-0; pyrrole-2-carbonyl chloride, 5427-82-7; pyrrole-2-carboxylic acid, 634-97-9; indole-2-carbonyl chloride, 58881-45-1; 4-nitropyrrole-2-carbonyl chloride, 28494-49-7; benzalaniline, 538-51-2; *p*-methoxybenzalaniline, 836-41-9; *N,N*-dimethylisobutenylamine, 692-31-9; pyrrolidine enamine of cyclohexanone, 1125-99-1; pyrrolidinopyrrole-2-carboxamide, 58904-52-2.

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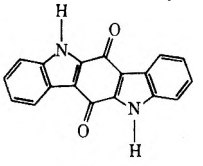
(10) A somewhat similar indole dimer has been prepared: J. Szmuskovicz, *J. Org. Chem.*, **28**, 2930 (1963). This structure for **2** was ruled out by comparison of uv data [**8**, λ_{max} 403 nm (ϵ 10 550)].



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(11) Support of this work by NIH is acknowledged.

^{15}N–^{13}C Coupling for Determination of the Site of N-Alkylation of Nitrogen Heterocycles. *linear*-Benzopurines

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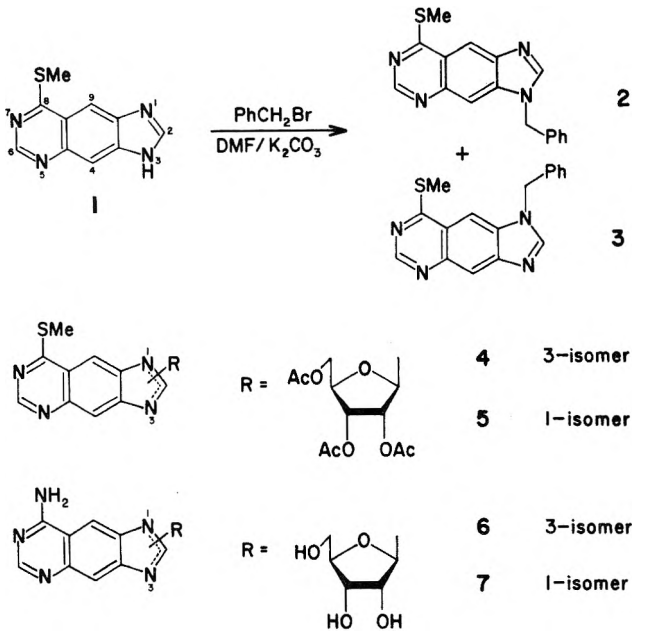
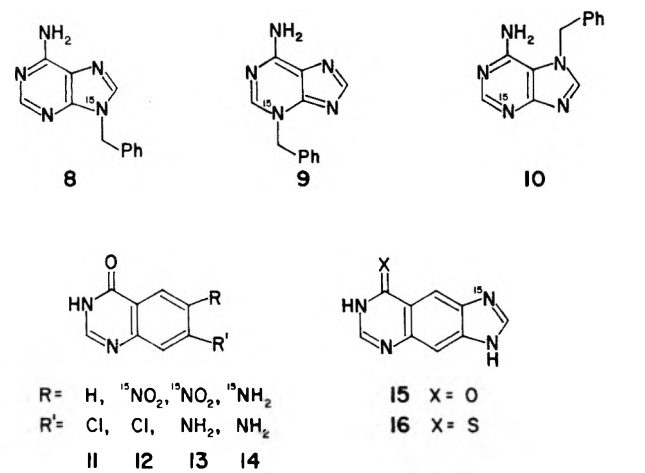
Observation of spin–spin coupling between ^{15}N and ^{13}C nuclei in ^{13}C NMR spectroscopy can be of considerable assistance in solving structural problems. For example, this technique has been used to advantage in the structure elucidation of the metabolites tenellin and bassianin,[1] and ^{13}C assignments have been determined from the magnitude of ^{15}N–^{13}C coupling constants.[2] In this paper we report the use of such coupling for determining the site of alkylation in a nitrogen heterocycle.

The benzylation products of 8-methylthioimidazo[4,5-*g*]quinazoline (1) have recently been assigned as 3-benzyl-



8-methylthioimidazo[4,5-*g*]quinazoline (**2**) and 1-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (**3**).[3] Since the 3-benzyl derivative **2** was prepared by an alternative unambiguous route its structure is certain, but that of the other isomer **3** was based on uv and NMR arguments[3,4] which, although compelling, were not definitive. The uv spectra of both **2** and **3** have been used as comparison models for the assignments of **4** and **5** as the products of ribosidation of 8-methylthioimidazo[4,5-*g*]quinazoline (**1**).[4] The ribosides **4** and **5** were subsequently converted to *linear*-benzoadenosine (**6**) and the 1 isomer **7**, respectively. In order to confirm the structure of the latter nucleoside isomer it becomes necessary to demonstrate that **3** is indeed the other product of benzylation of **1** and not an isomer derived from reaction at the 5 or 7 position.

NMR spectral studies of the benzylated products of 8-methylthioimidazo[4,5-*g*]quinazoline-*1*-^{15}N could lead to verification of the fact that benzylation of **1** occurs at the 1 position as well as the 3 position. Observation of ^{15}N–Cα–H coupling in the ^1H NMR spectrum would be indicative of the benzyl group being located at the 1 position, although ^{15}N–C–H couplings across an sp^3 carbon atom are generally small (0–1 Hz) and may not necessarily be detected.[5] In the ^{13}C NMR spectrum, observation of an ^{15}N–^{13}C coupling between $^{15}N^1$ and the benzylic carbon would unequivocally confirm the structural assignment **3** and thus place the earlier uv correlations on a firm basis. As suitable models for ^{15}N–^{13}C coupling between aromatic nitrogen and benzylic carbon we examined the proton-decoupled ^{13}C NMR spectra of the ^{15}N-labeled benzyladenine derivatives **8**,[6] **9**,[7b] and **10**[7a] which were available to us. ^{15}N–^{13}C coupling was observed for **8** (doublet at 48.2 ppm, $^1J_{(^{15}NC)}$ = 9.3 Hz) and for **9** (doublet at 54.0 ppm, $^1J_{(^{15}NC)}$ = 7.2 Hz). No long-range coupling between the benzylic carbon and $^{15}N^3$ of 7-benzyladenine-*3*-^{15}N was observed.



8-Methylthioimidazo[4,5-*g*]quinazoline-*1*-^{15}N was readily synthesized using the route previously described starting from 7-chloro-4-quinazolone (**11**).[3] The ^{15}N label was incorporated by nitration of **11** with nitric acid-^{15}N to give **12** under conditions somewhat modified from the earlier procedure (see Experimental Section). The remainder of the synthesis followed the sequence described in the earlier work through intermediates **13**, **14**, **15**, and **16**. Benzylation of **1**, using benzyl bromide and potassium carbonate in dimethylformamide, provided the two *N*-benzyl isomers, **2** and **3**, which were separated by column chromatography.

Definitive evidence for the sites of benzylation was obtained from the proton-decoupled ^{13}C NMR spectra of the two isomers. The benzylic carbon of 3-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline-*1*-^{15}N (**2**) resonates as a singlet at δ 52.3 ppm. That of the other isomer appears as a doublet ($^1J_{(^{15}NC)}$ = 8.6 Hz), due to ^{15}N–^{13}C coupling, at δ 50.6 ppm, thereby indicating direct attachment of the benzyl moiety to N-1. The magnitude of the ^{15}N–^{13}C coupling for this isomer is very similar to the values observed for the model systems 9-benzyladenine-*9*-^{15}N and 3-benzyladenine-*3*-^{15}N, **8** and **9**, respectively. The spectral data conclusively demonstrate the earlier structural assignment **3** to be correct for the second benzylation product of **1**. The ^1H NMR spectrum of each of the isomers was also examined, with irradiation at δ 7.30 to eliminate small long-range coupling with the protons on the phenyl ring. The signal for the benzylic protons of 3-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline-*1*-^{15}N was a singlet while the corresponding resonance for the other benzylation product appeared as a doublet ($^2J_{(^{15}NH)}$ = 1.2 Hz) due to ^{15}N–Cα–H coupling. This serves as further confirmation of our structural assignments although this approach may not be as widely useful because of the smaller $^2J_{(^{15}NH)}$ values across an sp^3 carbon atom. The positive assignment of structure **3** also confirms the assignment of N-1 as the site of ribosidation of compound **1**, along with the N-3 product.[4]

This method for determining the site of alkylation or ribosidation may well prove applicable in other heterocyclic systems where ^{15}N can be specifically incorporated. The variety of ^{15}N sources commercially available makes this possible in numerous systems.

Experimental Section

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Varian Associates HA-100 spectrometer using tetramethylsilane as an internal standard. The proton-decoupled ^{13}C NMR spectra were recorded on a Varian Associates XL-100-15A spectrometer interfaced with a Digilab NMR-3 data system (256 K disk) operating at 25.2 MHz. The ^{13}C NMR samples were run in $(CD_3)_2SO$/TFA solution (1:1 ratio) at a probe temperature of 35°C with an internal ^2H lock [$(CD_3)_2SO$]. Chemical shifts are given in parts per million downfield from internal tetramethylsilane as zero. Spectra were obtained in 24 h using the following typical conditions: bandwidth 5882 Hz, pulse width 10–20 μs, acquisition time 1–1.5 s, spin decoupler offset 45 800 Hz (corresponding to 5 ppm downfield from Me_4Si at 100 MHz), noise bandwidth 2.5 kHz, and a sampling of 16K data points. At 16K data points the system provides a frequency resolution of 0.7 Hz. Low-resolution mass spectra were obtained on a Varian MAT CH-5 spectrometer coupled with a 620i computer and STATOS recorder.

7-Chloro-6-nitro-4-quinazolone-6-^{15}N (12). 7-Chloro-4-quinazolone (1.0 g, 5.55 mmol) was added to an ice-cold solution of nitric acid-^{15}N (ICN, 1.0 g of 99 atom % nitric acid-^{15}N, purchased, as a 10 N solution) in concentrated sulfuric acid (8.5 ml). The mixture was allowed to warm to room temperature and was then heated at 100 °C for 2.0 h. The resulting solution was poured into ice water (150 ml) and the product was collected by filtration and air dried. Crystalli-

zation from acetic acid gave 12 (0.71 g, 57%) as yellow prisms, identical by TLC with an authentic sample: mp 300–302 °C (lit.[3] 300–303 °C); mass spectrum (70 eV) *m/e* (rel intensity) 228 (33, M^-), 226 (100, M^+), 225 (0.6, $C_8H_4ClN_3O_3$).

3- and 1-Benzyl-8-methylthioimidazo[4,5-*g*]quinazoline-*1*-^{15}N (2 and 3). These compounds were prepared from **12** via the sequence described in the text, using the experimental procedures which were reported previously.[3] Intermediates were characterized at each step by melting point, uv, and TLC comparison with authentic samples. The overall yield for the six-step sequence was ~19% for each isomer: **2**, ^1H NMR [$(CD_3)_2SO$/TFA] δ 5.84 (s, 2, CH_2), 9.66 d, 1, J = 6.5 Hz, 2-H); **3**, ^1H NMR [$(CD_3)_2SO$/TFA] δ 5.92 (d, 2, J = 1.2 Hz, CH_2), 9.69 (d, 1, J = 6.5 Hz, 2-H).

3-Benzyladenine-*3*-^{15}N (9) and 7-Benzyladenine-*3*-^{15}N (10). The ^{15}N label was incorporated via nitration of 4-bromoimidazole with nitric acid-^{15}N in the sequence previously described for the preparation of (unlabeled) 7-benzyladenine.[7a] Debenzylation of 7-benzyladenine-*3*-^{15}N with sodium/liquid ammonia[7b] provided adenine-*3*-^{15}N which was converted to **9** by the conventional procedure.[8] **10**: ^1H NMR [$(CD_3)_2SO$] δ 8.18 (d, 1, J = 15 Hz, 2-H).

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Registry No.—**1** ($^{15}N^1$), 59710-62-2; **2**, 59710-63-3; **3**, 59710-64-4; **9**, 59710-65-5; **10**, 59710-66-6; **11**, 31374-18-2; **12**, 59710-67-7; nitric acid-^{15}N, 43625-06-5; 4-bromoimidazole, 2302-25-2; benzyl bromide, 100-39-0.

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(8) (a) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 1914 (1962); (b) N. J. Leonard and T. Fujii, *ibid.*, **85**, 3719 (1963); (c) B. C. Pal, *Biochemistry*, **1**, 558 (1962).

Dihydro-1,4-dithiin Annelation

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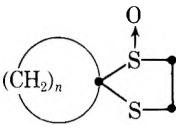
Synthetic methods available for the construction of rings fused to heterocyclic molecules are limited owing to the vulnerability of the heteroatom to the well-established conditions often employed in carbocyclic chemistry.[1] As part of our studies on the reactivity and synthetic uses of monosulfoxides of 1,3-dithiolane,[2] we now report a method for constructing carbocyclic fused dihydro-1,4-dithiins under mild conditions. This new heterocyclic annelation reaction is outlined in the following starting from the corresponding cyclic ketones **1**.

Dithiolation of **1** was accomplished in the usual manner.[3] Selective oxidation of the spiro-1,3-dithiolane **2** using *m*-chloroperbenzoic acid (MCPBA) in cold methylene chloride afforded the desired monosulfoxide **3** in good yields (Table I). Azeotropic distillation of the latter in benzene in the

Table I[5]



Registry no.	*n*	Bp (mp), °C	% yield
59796-89-3	3	59–60 (10–12 μ)	64[a]
59796-90-5	4	53.5 (8 μ)	64[b,c]
59796-91-7	5	(82.8)	75[a]
59796-92-8	6	(59.2)	64[a]
59796-93-9	11	(107.2)	88[a]
59796-94-0	14	(88.9)	87[b]

[a] Based on the corresponding ketone **1**. [b] Based on pure spiro-1,3-dithiolane **2**. [c] Prepared by $NaIO_4$ oxidation in methanol and water.

presence of a catalytic amount (ca. 10%) of *p*-toluenesulfonic acid (PTSA) smoothly transformed the spiro-1,3-dithiolane 1-oxide **3** by loss of H_2O to the dithiin **4** in essentially quantitative yield.

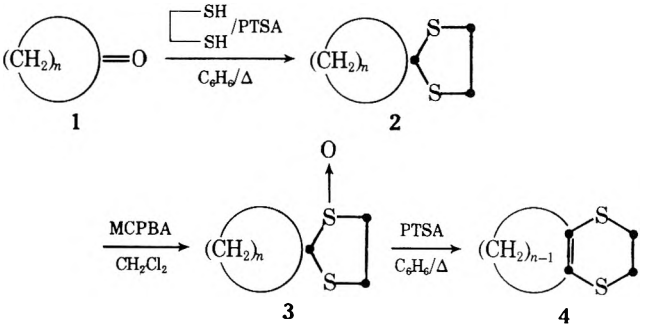
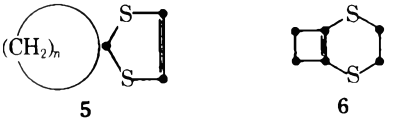
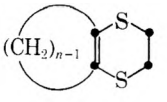


Table II lists yields of these ring expansion reaction products **4**. The absence of absorptions in the olefinic region of the NMR spectra of **4** and the appearance of a singlet at around δ 3.0 ppm for the ring protons of the dihydro-1,4-dithiin system[2] excludes the presence of isomeric 1,3-dithiole **5**, which would be expected to form under the normal Pummerer rearrangement conditions.[4] Attempts to prepare the cyclobutene derivative **6** were unsuccessful. While under the normal



experimental conditions (10% PTSA, PhH reflux, 30 h), the starting monosulfoxide **3** (n = 3) was found to be unreactive, under more strenuous conditions (e.g., 50% PTSA, PhH, re-

Table II[5]



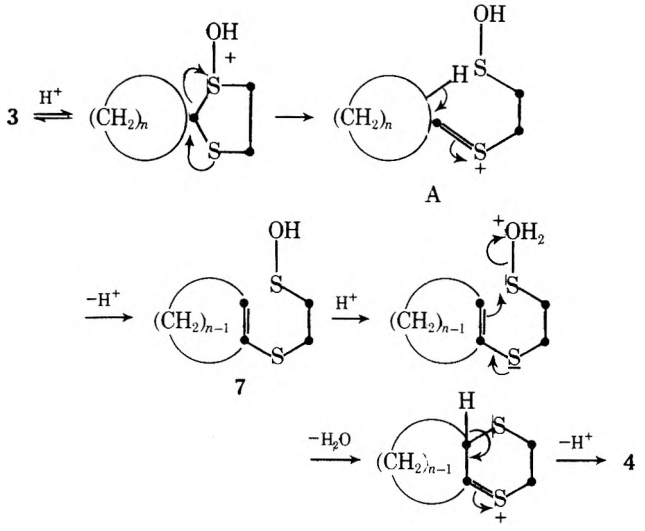
Registry no.	*n*	Bp, °C (mm)	% yield[a]
35756-14-0	4	71–72 (0.4)	96
23285-17-8	5	109–110 (1.4)[b]	93
59796-95-1	6	88–89 (0.3)	95
59796-96-2	11	169–170 (1.1)	96
59796-97-3	14	186–189 (0.8–0.9)	85

[a] Yield of pure product based on **3**. [b] Lit. bp 90–98 °C (1.0 mm): L. Levine and L. Jackson, U. S. Patent 3 439 051 (1969).

flux, 5 days), considerable tar formation prevailed and no **6** was detected. Isolation of the eight-membered monosulfoxide **3** (n = 7) has also been unsuccessful owing to its lability at room temperature such that even in the absence of acid catalyst, ring transformation occurred slowly giving usually a mixture of products including **4** (n = 7) as shown by mass spectrometric analysis[5] (m/e 200 M^+ for $C_{10}H_{16}S_2$) for the crude sulfoxide **3** (n = 7) (m/e 218 M^+ for $C_{10}H_{18}OS_2$).

A possible mechanism for this interesting ring expansion reaction of spiro-1,3-dithiolane 1-oxides **3** *under acid-catalyzed condition* is shown in Scheme I. Heterolytic cleavage

Scheme I



of the C(2)–S bond following initial protonation of the sulfoxide moiety would generate a sulfur stabilized carbonium ion A, which on loss of proton followed by acid-catalyzed ring closure of the sulfenic acid **7** affords the annelated 5,6-dihydro-1,4-dithiins **4** as shown. Similar intermediates of structure A have been proposed in the acid hydrolysis of 2,2-diphenyl-1,3-dithiolane 1-oxide,[6] and oxidative cleavage of 1,3-dithian[7,8] and dithiolane[9] derivatives in the synthesis of ketones.

Experimental Section[5]

The following experiments are illustrative of the general synthetic procedures.

2,2-Undecamethylene-1,3-dithiolane (2, n = 11). A mixture of 46.5 g of cyclododecanone, 24.1 g of 1,2-ethanedithiol, and 0.75 g of PTSA·H_2O in 200 ml of benzene was subjected to azeotropic distillation until the theoretical amount of water (4.5 ml) was collected. The benzene solution was concentrated in vacuo to give a solid, crude **2** (n = 11), which was suitable for use in subsequent reactions.

2,2-Undecamethylene-1,3-dithiolane 1-Oxide (3, n = 11). To an ice-cooled solution of 15 g of crude **2** in 100 ml of methylene chloride, a solution of 11.2 g of MCPBA (ca. 90% active) in 200 ml of methylene chloride was added dropwise over a 2-h period. The reaction mixture was quenched by addition of aqueous sodium carbonate and extracted twice with methylene chloride. The latter was dried ($MgSO_4$) and concentrated in vacuo to give a white solid which was recrystallized from hexanes to give 14 g (88%) of essentially pure **3** (n = 11). An analytical sample (mp 107.2 °C) was obtained by further recrystallization (Table I).

2,3-Decamethylene-5,6-dihydro-1,4-dithiin (4, n = 11). A mixture of 2 g of **3** (n = 11) and 0.2 g of PTSA·H_2O in 50 ml of benzene was subjected to azeotropic distillation via a Dean-Stark receiver for 18 h. The darkened benzene solution was taken up in ether and washed with sodium bicarbonate. The organic layer was separated, dried ($MgSO_4$), and concentrated to give a brown oil which was purified by short path distillation, affording 1.76 g (96%) of pure **4** (n = 11) (Table II): mass spectrum m/e 246 (M^+); NMR δ 1.0–2.0 (m, 16, carbocyclic ring protons), 2.2 (t, 4, allylic), and 3.0 ppm (s, 4, $-SCH_2CH_2S-$).

Registry No.—**2** (n = 3), 380-90-5; **2** (n = 4), 176-39-6; **2** (n = 5), 177-16-2; **2** (n = 6), 184-32-7; **2** (n = 11), 16775-67-0; **2** (n = 14), 59796-98-4.

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Preparation and Stereochemical Analysis of 5-Epibenzylpenicillin (*S*)- and (*R*)-Sulfoxide Esters

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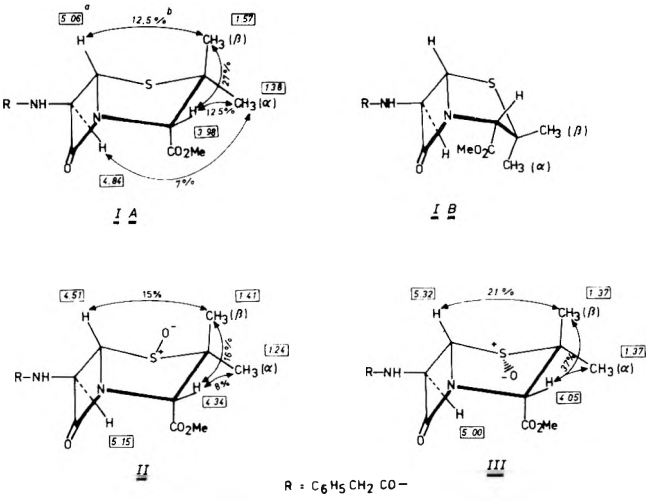
Oxidation of the 5 epimer of benzylpenicillin methyl ester[1] (I) with m-chloroperbenzoic acid yielded the (*S*)- and (*R*)-sulfoxide II and III in a ratio of 2:1. The isomers were isolated by column chromatography and crystallized from dry benzene. Apparently, steric control is the major directing influence in the oxidation of the 5 epimer, since neither sulfoxide configuration is likely to be stabilized by an internal hydrogen bond with the side chain amide proton,[2] as the two interacting atoms are manifestly too distant. It should be noted that natural or 6-epiphenoxymethyl- and benzylpenicillin esters yielded only the (*S*)-sulfoxide using this reagent.[2,3]

Thiazolidine ring conformation and sulfoxide configuration



[a] Chemical shifts in parts per million downfield from Me_4Si, for 5-H, 6-H, 3-H, 2 α-Me, and 2 β-Me, measured in dimethyl sulfoxide-d_6. [b] NOE values determined in dimethyl sulfoxide-d_6.

were defined using NMR techniques. Evidence for conformation A in the sulfide as well as in the sulfoxides was based on nuclear Overhauser effects, determined in dimethyl sulfoxide-d_6, a method which has been used on several occasions in studies of the penicillin series.[2-4] In 5-epibenzylpenicillin methyl ester a positive effect was observed between the low-field methyl signal and 3-H (27%) and 5-H (12.5%), whereas irradiation of the high-field methyl peak gave only 12.5% intensity increase of 3-H, a small increase of 6-H (5–10%), and no augmentation of the intensity of the 5-H signal. The (*S*)-sulfoxide (II) gave a positive effect between the low-field methyl signal and 3-H (16%) and 5-H (15%), and between the high-field methyl signal and 3-H (5–10%). In the (*R*)-sulfoxide (III) the chemical shift values of the two methyl groups are almost identical, excluding a selective irradiation. The NOE's observed for 3-H (37%) and for 5-H (21%) upon irradiation of this complex signal are thus composite values, and reflect the influence of both methyl groups, at least for 3-H. It should be noted that in neither sulfoxide a positive effect was observed between 6-H and one of the methyl groups.

From these NOE experiments, it may be concluded that the low-field methyl signal corresponds to the 2β-methyl protons, and that this group is in spatial proximity of 3-H and 5-H, a requirement inherent in conformation A, but not in B. They also indicate that the conformation of the thiazolidine ring of both sulfoxides is almost identical with that of the sulfide I. It has been shown for several penicillins and their 6 epimers that the conformation of the sulfoxide was different from that of the parent sulfide.[2,4,5]

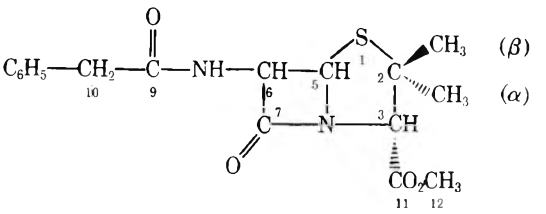
Assignments for sulfoxide configuration were made using ^{13}C NMR spectroscopy (Table I). In the 5-episulfide (I), as in penicillin methyl ester,[6] 2α-Me absorbs at higher field than 2β-Me, and this can be explained on the basis of the steric proximity of 2α-Me to the cis substituent at C-3 ($COOCH_3$).[7] Similarly, in the process sulfide → sulfoxide, it has been pointed out[6] that the upfield shifts observed for γ-situated carbons C-6, C-3, 2α-Me, and 2β-Me were best explained if a sizable steric effect was attributed to the S=O bond, causing thus larger upfield shifts for carbons in closer proximity to the sulfoxide oxygen.

In the process 5-episulfide → 5-episulfoxide-(*S*), 2β-Me is expected to undergo a larger upfield shift than 2α-Me, and the two Me carbons must from this fact display more similar δ values in this sulfoxide configuration than in the sulfide and in the (*R*)-sulfoxide. The *S* configuration has thus been assigned to the isomer II, having 2β-Me absorption at δ 18.25 ppm (upfield shift −11.8) and 2α-Me absorption at δ 18.9 ppm (upfield shift −5.8). In the other sulfoxide (III), the two Me carbons absorb at δ 23.25 (2β-Me, upfield shift −6.8) and 17.85 ppm (2α-Me, upfield shift −6.85). The 6.8 ppm upfield shift of 2β-Me carbon is difficult to rationalize on the basis of steric interaction with the sulfoxide oxygen, since the atoms are in a 1,2-trans diaxial arrangement. But from the strong NOE (21%), observed between 5-H and 2β-Me protons, it can be inferred that the 5-episulfoxide-(*R*) must be somewhat more puckered than the corresponding 5-episulfide, causing 1,3-diaxial interaction between 5-H and 2β-Me. Carbon C-6 in the azetidinone ring is also very sensitive to sulfoxide configuration, and the larger upfield shift (−8.45 ppm) measured in the (*R*)-sulfoxide (III), compared to the (*S*)-sulfoxide (II) (−4.6 ppm), is consistent with the pseudoaxial position of the exocyclic oxygen in the (*R*)-sulfoxide.

The downfield shifts observed for β-situated carbons C-2 and C-5 upon oxidation of the thiazolidine sulfur are in accord with previous observations.[6] They had been attributed to a reduction in electron density at these carbon nuclei as a result of the inductive effect of the sulfoxide group.

Oxidation of 5-epibenzylpenicillin benzyl ester with *m*-chloroperbenzoic acid also gave the two sulfoxides in a ratio of 2:1. However, the isomers were not obtained in a pure state, and were characterized only with ^1H NMR spectroscopy by comparison with the values of the corresponding methyl esters.

Table I. ^{13}C Chemical Shift Assignments[a] for 5-Epibenzylpenicillin Methyl Ester and Its Sulfoxides



	I	II	III
C_2	64.9	70.2	73.3
C_3	69.3	65.55	67.4
C_5	67.05	80.4	77.6
C_6	63.4	58.8	54.95
2β-CH_3	30.05[b]	18.25[b]	23.25
2α-CH_3	24.7[b]	18.9[b]	17.85
C_{12}	52.1	52.8	52.2
C_{10}	41.9	41.8	41.9
C_7	168.8	168.3	166.7
C_9	167.2	168.05	166
C_{11}	171	171.5	171.55

[a] 20% solution in dimethyl sulfoxide-d_6; chemical shifts in parts per million downfield from Me_4Si. [b] Assigned by selective decoupling of the corresponding protons.

Experimental Section

Melting points were determined in open capillaries with a Büchi-Tottoli apparatus. TLC was performed on silica gel F-254 plates (Merck) with benzene–acetone (80:20) as mobile phase. The optical rotation was measured in a Thorn-NPL photoelectric polarimeter type 243. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer, and mass spectra on an AEI MS-12 apparatus. ^1H NMR, NOE, and ^{13}C NMR spectra were recorded on a Varian XL 100-15 spectrometer equipped for CW (^1H) and FT (^{13}C) operation. NOE experiments were carried out with 10% solutions flushed out with nitrogen. For ^{13}C spectra the central peak of the solvent (Me_2SO-d_6) was used as internal reference, and was assumed to absorb at δ 39.6 ppm vs. Me_4Si.[8] The concentration was 20% w/v. Initially the ^{13}C spectra were recorded with complete proton (noise) decoupling. Assignments of the various ^{13}C resonances to methyl, methylene, methine, and quaternary carbons were made by single frequency off-resonance decoupling.

5-Epibenzylpenicillin (*S*)- and (*R*)-Sulfoxide Methyl Ester (II and III). 5-Epibenzylpenicillin methyl ester[1] (I, 2.0 g, 5.7 mmol) was dissolved in 50 ml of anhydrous methylene chloride. The solution was chilled to 0 °C, and a solution of *m*-chloroperbenzoic acid (80%, 1.23 g, 5.7 mmol) in anhydrous methylene chloride (30 ml) was added over a period of 30 min. The mixture was stirred for 1 h at 0 °C, extracted with $KHCO_3$ (0.5 M), washed twice with water, dried (Na_2SO_4), and chromatographed on silica gel (50 g) using a gradient of benzene–acetone changing from 93:7 to 85:15 as eluent. From the first fractions, 0.2 g (10%) of starting product I (TLC, R_f 0.52) was recovered, and from the rest of the eluate, two compounds with R_f value 0.12 and 0.07 were successively isolated and identified as (*S*)- and (*R*)-sulfoxide of 5-epibenzylpenicillin methyl ester (II and III). After crystallization from dry benzene, the yield of the isomers amounted to 0.770 g (37%) for II and to 0.400 g (19%) for III.

II: mp 158.5–159.5 °C; TLC R_f 0.12; $[\alpha]^{25}D$ −126.5° (*c* 1, acetone); *m/e* 364 (M^+); ir (KBr) 3340, 1685, 1520 (amide), 1795 (β-lactam), 1740, 1215 (ester), 1035 cm^{-1} (S=O); NMR ($CDCl_3$) δ 1.36 (s, CH_3), 1.53 (s, CH_3), 3.63 (s, CH_2), 3.82 (s, OCH_3), 4.11 (s, 3-H), 4.62 (d, *J* = 2 Hz, 5-H), 4.98 (dd, *J* = 2 and 7.5 Hz, 6-H), 6.45 (d, *J* = 7.5 Hz, CONH–), 7.28 (s, C_6H_5).

III: mp 160–161 °C; TLC R_f 0.07; $[\alpha]^{25}D$ −130° (*c* 0.2, acetone); *m/e* 364 (M^+); ir (KBr) 3260, 1650, 1560 (amide), 1790 (β-lactam), 1755, 1200 (ester), 1050 cm^{-1} (S=O); NMR ($CDCl_3$/Me_2SO-d_6) δ 1.38 (s, 6 protons, two CH_3), 3.50 (s, CH_2), 3.68 (s, OCH_3), 3.93 (s, 3-H), 5.00 (dd, *J* = 2 and 8 Hz, 6-H), 5.23 (d, *J* = 2 Hz, 5-H), 7.22 (s, C_6H_5), 8.78 (d, *J* = 8 Hz, CONH–).

5-Epibenzylpenicillin (*S*)- and (*R*)-Sulfoxide Benzyl Ester. 5-Epibenzylpenicillin benzyl ester[1] (1.272 g, 3 mmol) was oxidized with *m*-chloroperbenzoic acid as described for I. Owing to the instability of these sulfoxides when chromatographed on silica gel, they could not be isolated in a crystalline state, but they were obtained as a slightly impure oil, which was identified only by ^{1}H NMR spectroscopy.

(*S*)-Sulfoxide: TLC R_f 0.20; NMR ($CDCl_3$) δ 1.18 (s, CH_3), 1.39 (s, CH_3), 3.46 (s, $-CH_2CO-$), 4.03 (s, 3-H), 4.54 (d, J = 2 Hz, 5-H), 4.88 (dd, J = 2 and 7 Hz, 6-H), 5.13 (s, $-OCH_2-$), 7.19 (s, C_6H_5), 7.28 (s, C_6H_5), 7.40 (d, J = 7 Hz, CONH–).

(*R*)-Sulfoxide: TLC R_f 0.15; NMR ($CDCl_3$) δ 1.27 (s, CH_3), 1.34 (s, CH_3), 3.55 (s, $-CH_2CO-$), 3.89 (s, 3-H), 5.00 (dd, J = 2 and 7 Hz, 6-H), 5.11 (s, $-OCH_2-$), 5.20 (d, J = 2 Hz, 5-H), 7.26 (s, C_6H_5), 7.31 (s, C_6H_5), 7.41 (d, J = 7 Hz, –CONH–).

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Registry No.—I, 59034-27-4; II, 59751-74-5; III, 59751-75-6; *m*-chloroperbenzoic acid, 937-14-4; 5-epibenzylpenicillin benzyl ester 59034-28-5; 5-epibenzylpenicillin benzyl ester (*S*)-sulfoxide, 59751-76-7; 5-epibenzylpenicillin benzyl ester (*R*)-sulfoxide, 59751-77-8.

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Derivatives of 3,4-Dihydroxyphenylalanine for Peptide Synthesis

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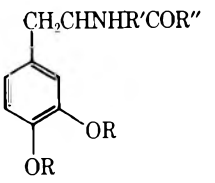
The current therapeutic use of levodopa (L-3,4-dihydroxyphenylalanine, Dopa, 1) in Parkinsonism[1] prompted us to consider a possible improved utilization of this amino acid when in peptide or other derivatized form. Moreover, when suitably incorporated as an analogue of tyrosine or phenylalanine into peptides, Dopa could furnish peptide hormone analogues of biological interest. This communication describes the synthesis of a number of protected derivatives of Dopa designed for use in solid-phase or conventional peptide synthesis: the *p*-nitrophenyl ester of *N-tert*-butyloxycarbonyl-*O,O'*-diacetyl-3,4-dihydroxyphenylalanine [Boc-Dopa-$(Ac)_2$-ONP, 2] and, in particular, the corresponding ester of *N-tert*-butyloxycarbonyl-*O,O'*-dibenzyl-3,4-dihydroxyphenylalanine [Boc-Dopa$(Bzl)_2$-ONP, 3]. The chief difficulty in working with Dopa is its well-known ease of oxidation,[2] probably to the quinone, and other products, and this formed the basis for protection of the phenolic groups.



	R	R'	R"
1	H	H	OH
2	$OCCH_3$	$COOC(CH_3)_3$	$OC_6H_4NO_2$
3	$CH_2C_6H_5$	$COOC(CH_3)_3$	$OC_6H_4NO_2$
4	H	H	$OCH_3 \cdot HCl$
5	H	$COOC(CH_3)_3$	OCH_3
6	H	$COOC(CH_3)_3$	OH
7	$OCCH_3$	$COOC(CH_3)_3$	OH
8	$CH_2C_6H_5$	$COOC(CH_3)_3$	OH

Prepared as intermediates for **2** and **3** were Dopa methyl ester hydrochloride (Dopa-OCH_3·HCl, **4**), *N-tert* butyloxycarbonyl-3,4-dihydroxyphenylalanine methyl ester (Boc-Dopa-OCH_3, **5**), *N-tert*-butyloxycarbonyl-3,4-dihydroxyphenylalanine (Boc-Dopa, **6**), and its diacetyl and dibenzyl derivatives, Boc-Dopa$(Ac)_2$ (**7**) and Boc-Dopa$(Bzl)_2$ (**8**). The diacetyl compounds belong to the DL series; all other compounds were of both the L and DL series.

At the inception of this work there were few known studies relating to the incorporation of Dopa into peptides. They involved the use of phthalyl and methyl ester to protect Dopa in N- and C-terminal position, respectively, without protection of the phenolic groups, as in the synthesis of a number of dipeptides of DL-Dopa.[3] After this work was essentially complete, a route to di- and tripeptides of L-Dopa was described in which Z-Dopa$(Z)_2$, Z-Dopa$(Z)_2$-ONP, and Dopa$(Z)_2$-OBzl served as the chief intermediates.[4] The nonselective removal of protecting groups by hydrogenolysis that was employed in general limits the utility of that route to the synthesis of small peptides for Dopa in endo position. Moreover, such intermediates are not designed for Merrifield solid-phase peptide synthesis, the *N*-benzyloxycarbonyl group being too stable for deprotection with the TFA reagent and the *O*-benzyloxycarbonyl group probably too labile to various hydrolytic conditions including exposure to triethylamine. The present work extends the synthetic scope of past studies by providing for stepwise introduction of L- and DL-Dopa in suitably protected form and for selective removal of the phenolic and amino protecting groups of Dopa, namely through utilization of derivatives **3** and **8**. In addition, it demonstrates that the ordinarily labile Dopa may be subjected safely to a variety of procedures frequently employed in conjunction with peptide synthesis including treatment with sodium in liquid ammonia. Addition of a small amount of hydrazine proved particularly effective in protecting against oxidation under alkaline conditions. The utility of derivative **3** in solid-phase synthesis has recently been demonstrated in the synthesis of a protected 2-Dopa-4-threonine nonapeptide analogue of oxytocin, Z-L-Cys(Bzl)-L-Dopa$(Bzl)_2$-L-Ile-L-Thr(Bzl)-L-Asn-L-Cys(Bzl)-L-Pro-L-Leu-Glyn.[5] The synthesis of the latter and the biological properties of [2-Dopa 4-Thr] oxytocin derived from it are to be communicated elsewhere.

Boc-L-Dopa (**6**) had been prepared previously by Kaiser et al.[6] by derivatization of Dopa with Boc azide in aqueous alkali under argon. In our hands this procedure generally gave dark, insoluble material unless most stringent anaerobiosis was attained. Moreover, the published elemental analyses for **6**, both calculated and obtained, were erroneous, especially the value for carbon which is high by 1.3%. These properties led us to examine an alternate route to **6** involving derivatization

of Dopa methyl ester in nonaqueous medium to give Boc-Dopa-OCH_3 followed by deesterification.

Dopa was esterified by the general procedure of Brenner and Huber.[7] L- and DL-Dopa-OCH_3·HCl agreed in melting point with these compounds prepared by the Fischer procedure.[8,9] A similar procedure was recently employed for the DL compound.[10] Treatment with Boc azide in pyridine converted the free base obtained from **4** to Boc-Dopa-OCH_3 (**5**). On standing in aqueous methanol containing 5.6 equiv of base and a trace of hydrazine, **5** was deesterified almost quantitatively. The resulting Boc-L-Dopa (**6**) agreed in optical rotation and melting point with a sample prepared by the procedure of Kaiser et al.[6] Moreover, discrepant values for carbon we attribute to solvation were obtained also for our preparations of L- and DL-**6** unless they were subjected to unusually prolonged, exhaustive drying.

When treated with 3 equiv of acetic anhydride in $NaHCO_3$ solution at room temperature **6** formed an *O,O'*-diacetyl derivative [Boc-Dopa(Ac)$_2$, **7**]. Refluxing with 2 equiv of benzyl chloride and K_2CO_3 in the presence of NaI, essentially as described for the preparation of 3,4-dibenzyloxybutyrophenone from the catechol compound,[11] converted **6** to *N*-Boc-*O,O'*-dibenzyl-L-Dopa (**8**). **7** and **8** were converted smoothly to their respective *p*-nitrophenyl esters by treatment with *N,N'*-dicyclohexylcarbodiimide and *p*-nitrophenol in the usual way. A reaction time of at least 24 h proved advantageous for **8**. Treatment of **8** with sodium in liquid ammonia[12] followed by TFA afforded Dopa in 93% yield as determined on the amino acid analyzer.[13] Optical rotation of the isolated material agreed well with that of starting L-Dopa. In addition, application of the Manning–Moore procedure[14] as employed by Felix et al.[4] confirmed that the route to **8** is free of significant racemization. Intermediates **3** and **8** are therefore expected to be compatible with routes to peptides of L-Dopa and cysteine to be introduced via *S*-benzylcysteine.

Experimental Section

Organic extracts were dried over $MgSO_4$. Evaporations were under reduced pressure. Boc azide was purchased from Aldrich Chemical Co., Milwaukee, Wis.; DL-Dopa from Schwarz/Mann, Orangeburg, N.Y. L- and D-Dopa were obtained by resolution of DL-Dopa as described.[15]

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were taken in a 2-dm cell in a Rudolph spectropolarimeter system, Model 80Q6-34402. Amino acid analyses were performed on a Beckman/Spinco amino acid analyzer, Model 120.[13] Dopa eluted at 70 ml on the 50-cm column, pH 4.26, at 30 °C; ninhydrin color constant 19.1 compared to 22.1 for leucine. Optical purity of L-Dopa was determined essentially as described by Felix et al.[4] except that analyses were in the 50-cm resin column of the analyzer[13] with sodium citrate buffer (pH 4.25, 0.2 M) at 50 °C. Elution volumes were 34 ml (Ala), 71 ml (Dopa), 154 ml (L-Ala-D-Dopa), and 183 ml (L-Ala-L-Dopa).

L- and DL-Dopa-OCH_3·HCl (4). Dopa (10 g, 50 mmol) was added portionwise to MeOH (120 ml) containing $SOCl_2$ (20 ml) held at 0 °C. The mixture was stirred at room temperature for 18 h, then evaporated to give DL-**4** (12.2 g, 98%), mp 182–183 °C (lit.[8] mp 180–181, 179–180 °C[10]); L-**4**, 87%, mp 172–174 °C (lit.[9] mp 170–171 °C).

Boc-L- and -DL-Dopa-OCH_3 (5). A solution of Dopa-OCH_3 (7.6 g, 36 mmol), obtained from **4** as described,[8] and Boc azide (7.6 g, 50 mmol) in pyridine (70 ml) was stirred for 2 days. The solvent was evaporated and the residue was taken up in EtOAc (100 ml). Some tar was filtered off. Dilution with hexane followed by recrystallization from MeOH–H_2O gave DL-**5** (8.6 g, 76%): mp 186–188 °C; ^{1}H NMR (MeOD) δ 1.36 [9 H, s, $C(CH_3)_3$], 2.84 (2 H, m, β-CH_2), 3.66 (3 H, s, OCH_3), 4.23 (1 H, m, α-CH), 6.6 (3 H, m, C_6H_3).

Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.9, H, 6.80, N, 4.50. Found: C, 57.8, H, 6.95, N, 4.52.

L-**5**: 71% yield, mp 133–135 °C, $[\alpha]^{26}$D 7.6° (c 1.2, MeOH).

Anal. Found: C, 57.8; H, 6.55; N, 4.46.

Boc-L- and -DL-Dopa (6). A solution of **5** (3.4 g, 10 mmol) in MeOH (30 ml) containing 2 N NaOH (28 ml, 56 mmol) and 2 drops of $N_2H_4·H_2O$ was allowed to stand at room temperature for 4 h. The mixture was taken to dryness, diluted with H_2O, and extracted with EtOAc. The aqueous solution was adjusted to pH 2 and extracted with EtOAc. The extract was dried and concentrated to give after recrystallization from EtOAc–benzene DL-**6** (3.2 g, 98%), mp 140–142 °C. For analysis DL-**6** like L-**6** was dried at 0.2 Torr at 100 °C for 5 days.

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6, H, 6.44, N, 4.71. Found: C, 56.4; H, 6.45; N, 4.83.

^{1}H NMR (MeOD), as for L-**6**. When a sample was dried instead at 0.2 Torr at 25 °C for 24 h, an additional ^{1}H NMR signal at 7.3 ppm was present attributed to occluded benzene. Anal. C, 58.1; H, 6.78; N, 4.62.

L-6, recrystallized from EtOAc–cyclohexane: 92% yield; mp 142–144 °C (very rate dependent); $[\alpha]$D +16.2° (c 1, MeOH) [lit.[6] mp 148 °C, $[\alpha]^{25}$D +16.4° (c 1, MeOH)]. A mixture melting point with a sample of L-**6**, mp 142–144 °C, prepared as described,[6] showed no depression: ^{1}H NMR (MeOD) δ 1.39 [9 H, s, $C(CH_3)_3$], 2.91 (2 H, m, β-CH_2), 4.27 (1 H, m, α-CH), 4.92 (4 H, s, exchangeable H), 6.67 (3 H, m, C_6H_3).

Anal. Found: C, 56.4; H, 6.42; N, 4.89.

Boc-DL-Dopa(Ac)$_2$ (7). Acetic anhydride (6 ml, 60 mmol) was added to a solution of **6** (6 g, 20 mmol) in aqueous $NaHCO_3$ (16 g, 20 mmol) and the mixture was stirred under N_2 for 30 min at room temperature. It was extracted with ether and then was cooled and adjusted to pH 2. The gum that separated was extracted with EtOAc, and the extract was dried and concentrated. The residue was recrystallized from benzene–hexane to give **7** (6.4 g, 83%): mp 132–134 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.3 [9 H, s, $C(CH_3)_3$], 2.24 (6 H, s, CH_3CO), 3.0 (2 H, m, β-CH_2), 4.15 (1 H, m, α-CH), 7.25 (3, m, aromatic).

Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.7; H, 6.08; N, 3.67. Found: C, 57.1; H, 6.04; N, 3.66.

Boc-Dopa(Ac)$_2$-ONP (2). A solution of **7** (3.8 g, 10 mmol) and *p*-nitrophenol (1.7 g, 12 mmol) in EtOAc (60 ml) was treated with DCCI (2.4 g, 12 mmol) for 2 h. The mixture was filtered and the solution was concentrated to give after recrystallization from benzene–hexane **2** (4.4 g, 88%), mp 109–112 °C.

Anal. Calcd for $C_{24}H_{26}N_2O_{10}$: C, 57.4; H, 5.22; N, 5.58. Found: C, 57.3; H, 5.20; N, 5.62.

Boc-Dopa(Bzl)$_2$ (8) and Its Deprotection. A solution of **6** (3.6 g, 13 mmol) and benzyl chloride (3.36 g, 26.4 mmol) in EtOH (60 ml) was refluxed with K_2CO_3 (3.69 g, 28.2 mmol) and NaI (156 mg, 1.1 mmol) for 3 h. Most of the solvent was evaporated and the residue was diluted with H_2O. The suspension at 0 °C was adjusted to pH 2. Extraction with EtOAc, drying, and concentration yielded a residue that was recrystallized from benzene–hexane to give DL-**8** (4 g, 69%), mp 140–142 °C.

Anal. Calcd for $C_{28}H_{31}NO_6$: C, 70.4; H, 6.54; N, 2.93. Found: C, 70.3; H, 6.62; N, 3.01.

L-**8** (65%): mp 105–107 °C, $[\alpha]^{25}$D +14.2° (c 1, MeOH).

Anal. Found: C, 70.1; H, 6.65; N, 2.96.

A solution of L-**8** (23.5 mg, 49.4 μmol) in 4 ml of liquid NH_3 was treated with sodium until a blue color throughout the solution lasting 40 s was obtained. NH_4Cl (20 mg) was added and the solution was evaporated in a stream of N_2. To the residue TFA (1 ml) was added. After 30 min at 25 °C under N_2 the mixture was taken to dryness. The residue was dissolved in water and it contained Dopa (45.8 μmol, 93%) on amino acid analysis. Treatment with 1 equiv of L-alanine *N*-carboxyanhydride[16] followed by amino acid analysis showed 0.09% L-Ala-D-Dopa.

The aqueous solution from treatment of 120 mg of L-**8** was adjusted to pH 5 with dilute NH_3 and it was then concentrated to incipient crystallization to give L-**1** (32 mg, 64%). One recrystallization from water (1 ml) gave 23 mg, $[\alpha]^{22}$D −32.9° (c 0.5, H_2O). Starting L-**1** had $[\alpha]^{22}$D −32.9° (c 0.4, H_2O).

Boc-L- and -DL-Dopa(Bzl)$_2$-ONP (3). Compound **8** (4 g, 10.6 mmol) was treated with *p*-nitrophenol (2.06 g, 148 mmol) and DCCI (2.62 g, 12.7 mmol) in EtOAc (105 ml) as described for **2**. Workup and crystallization from benzene–hexane furnished DL-**3** (1.9 g, 36%): mp 132–134 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.37 [9 H, s, $C(CH_3)_3$], 3.03 (2 H, m, β-CH_2), 4.4 (1 H, m, α-CH), 5.13 (4 H, s, OCH_2Ar), 6.75–7.73 (15 H, m, aromatic), 8.36 (2 H, d, aromatic ortho to NO_2).

Anal. Calcd for $C_{34}H_{34}N_2O_8$: C, 68.2; H, 5.72; N, 4.78. Found: C, 68.7; H, 5.77; N, 4.92.

A longer reaction time of 24 h gave L-**3** (56%), mp 142–144 °C, $[\alpha]^{25}$D −0.97° (c 1, EtOAc).

Anal. Found: C, 68.0; H, 5.79; N, 4.63.

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Registry No.—L-**1**, 59-92-7; DL-**1**, 63-84-5; DL-**2**, 59686-53-2; L-**3**, 59727-96-7; DL-**3**, 59727-97-8; L-**4**, 1421-65-4; DL-**4**, 40611-00-5; L-**5**, 37169-36-1; DL-**5**, 59686-54-3; L-**6**, 30033-24-0; DL-**6**, 59686-55-4; DL-**7**, 59686-56-5; L-**8**, 59727-98-9; DL-**8**, 59727-99-0; Boc azide, 1070-19-5; acetic anhyride, 108-24-7; *p*-nitrophenol, 100-02-7; benzyl chloride, 100-44-7.

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Stabilization of Substituted Cyclobutadienes

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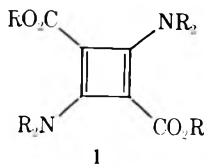
In the past several years there has been a renewed interest in the chemistry of cyclobutadiene and its derivatives.[1] Cyclobutadiene itself has been observed at low temperature;[2] but as was correctly predicted by theory,[3] is too reactive to be isolated at room temperature. A number of derivatives have been prepared which are isolable, though they generally have been found to be reactive. The stability of these derivatives has been ascribed either to the presence of bulky substituents which retard intermolecular reactions[4] or to the "push–pull" effect[5] when there are both electron-donating and electron-withdrawing groups attached to the cyclobutadiene ring.[6]

However, in the latter cases, there is a possibility that steric effects might be at least partially responsible for the increased stabilization. For example in **1**[6] the four substituents are not only of the "push–pull" type but also are relatively large groups in themselves. In order to determine to what degree the "push–pull" effect is responsible for the stabilization of substituted cyclobutadienes and also to search for other possible stable cyclobutadienes, we have carried out calculations with our successful adaptation of the Hückel method[3b,c,7] on the series **2**. The crucial feature of this modification is that



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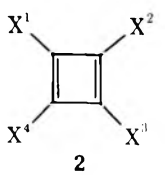


2

resonance energy is computed as the difference between the actual molecular energy and the energy the molecule would have, had it acted like a polyene. Following Dewar and de Llano,[8] the energy of the reference polyene is computed as the sum of bond energy terms. Results are summarized in Table I where it is seen that all compounds in which "push–pull" stabilization is possible (**2b–o**) show a decrease in antiaromaticity, thus giving support to the "push–pull" proposal. Furthermore, in all cases when electron-donating groups are placed between electron-withdrawing groups, a more stable compound is produced than when they are placed on adjacent carbons. This is in qualitative agreement with earlier calculations of Hoffmann,[9] but not with those of Weiss and Murrell,[10] who found that the position of donor and acceptor groups on the ring has little effect on stability.

Table I. Resonance Energies (RE) and Resonance Energies per π Electron (REPE) in Units of β for Substituted Cyclobutadienes

Compd	X^1	X^2	X^3	X^4	RE	REPE	REPE Aihara's method
2a	H	H	H	H	−1.07	−0.268	−0.307
2b	NH_2	NH_2	CHO	CHO	−0.65	−0.054	−0.057
2c	NH_2	CHO	NH_2	CHO	−0.33	−0.028	−0.037
2d	NH_2	NH_2	COOR	COOR	−0.64	−0.040	−0.043
2e	NH_2	COOR	NH_2	COOR	−0.32	−0.020	−0.028
2f	NH_2	NH_2	$CONH_2$	$CONH_2$	−0.66	−0.041	−0.046
2g	NH_2	$CONH_2$	NH_2	$CONH_2$	−0.32	−0.020	−0.030
2h	SH	SH	COOR	COOR	−0.64	−0.040	−0.045
2i	SH	COOR	SH	COOR	−0.36	−0.023	−0.030
2j	F[a]	F	CHO	CHO	−0.39	−0.033	−0.036
2k	F	CHO	F	CHO	−0.03	−0.002	−0.021
2l	F	F	COOR	COOR	−0.39	−0.024	−0.028
2m	F	COOR	F	COOR	−0.02	−0.001	−0.016
2n	F	F	$CONH_2$	$CONH_2$	−0.42	−0.026	−0.031
2o	F	$CONH_2$	F	$CONH_2$	−0.02	−0.001	−0.018
2p	F	F	NH_2	NH_2	−1.22	−0.101	−0.077
2q	F	NH_2	F	NH_2	−0.93	−0.078	−0.056
3a		H	H	H	−0.64	−0.160	−0.193
3b		NH_2	H	H	−0.40	−0.067	−0.093
3c		H	NH_2	H	−0.76	−0.127	−0.145
3d		NH_2	H	NH_2	−0.26	−0.032	−0.054
3e		NH_2	NH_2	NH_2	−0.46	−0.046	−0.049
3f		F	H	H	−0.18	−0.029	−0.069
3g		H	F	H	−0.69	−0.115	−0.130
3h		F	H	F	+0.05	+0.006	−0.033

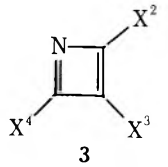
[a] For the fluoro-substituted compounds $h_F = 1.5$ and $k_{C-F} = 1.33$ were used. These were obtained using thermochemical data in the same manner as previously.[7] The carbon–fluorine bond energy terms used in the calculation of the reference energies are $E_{CH-F} = 0.74021\beta$ and $E_{C-F} = 0.66491\beta$.

It is of particular interest that the most stable of the "push–pull" cyclobutadienes synthesized to date[2b,2d] is a tetramethyl derivative of **2e**, one of the most aromatic compounds in Table I. The methyl groups will enhance the stability still further, both because of their bulk and their electron-donating ability. Our main conclusion about compounds such as **1** is that the "push–pull" effect does play a major role in stabilizing the cyclobutadiene system.

We also predict that the replacement of the amino group by fluorine should give cyclobutadienes even more stable than those already synthesized: the resonance energies per π electron of compounds **2k, 2m,** and **2o** are very close to zero. That is, the very substantial antiaromaticity of cyclobutadiene has been completely removed in these systems. These results are in accord with the known electron-donating ability of fluorine bonded to an electron-demanding site. The pronounced stabilizing effect of fluorine in carbene formation is an example of this.[11] Nevertheless, the stability of **2k, 2m,** and **2o** may not be due to the "push–pull" effect alone, and hence we cannot say that fluorine is necessarily a better electron donor than the amine group.

In addition, we have computed the resonance energies of

azacyclobutadiene (3) and several of its derivatives for which the "push–pull" effect has been proposed. The antiaromaticity of azacyclobutadiene (3a) is appreciably less than that of cyclobutadiene (2a); and electron-donating substituents in positions 2 and 4 stabilize the azacyclobutadienes, but destabilize in the 3 position. These results are in agreement with those of Wagner.[12] Only one substituted azacyclobutadiene (4) has been reported.[13] In Table I are several azacyclobutadienes that are predicted to be more stable than 4 and hence are good candidates for synthesis. However, possible reaction paths, here particularly those of dimerization, as well as inherent stability, determine whether or not a product can be isolated. The case of dimethylenecyclobutene, which can be isolated[14] in spite of its antiaromaticity,[15] illustrates this.



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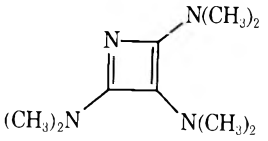

4

Very recently Aihara[16] has proposed an attractive alternative to our method of computing the reference polyene energy. The origin of his idea is a 1963 paper by Sachs[17] who showed how the characteristic polynomial of the adjacency matrix of a graph can be written down simply by counting certain of its subgraphs. This result was applied to molecular graphs (i.e., molecular structural formulas) by Gutman and Trinajstić with Wilcox, Mallion, and others.[18–21] Aihara then suggested that the energy of the polyene reference might be defined by summing the lower roots of a polynomial obtained from the Hückel matrix by Sachs' recipe, but neglecting all contributions of cyclic subgraphs. His results for hydrocarbons were similar to, but not identical with, ours and also to those of Herndon's[22,23] equally successful valence bond method.

We have applied Aihara's method to the substituted cyclobutadienes of Table I where these results are compared with ours. The numbers are parallel, but **2k, 2m, 2o,** and **3h,** which we predict to be olefin-like and hence relatively stable, are all calculated to have substantial antiaromatic character by Aihara's method. It must be admitted that few thermodynamic data were available for determining the heteroatom parameters used in both methods, and hence these predictions are not as sound as those for hydrocarbons, but still an experimental examination of these four molecules would be of considerable interest.

Registry No.—**2a,** 1120-53-2; **2b,** 59711-10-3; **2c,** 59711-11-4; **2f,** 59711-12-5; **2g,** 59711-13-6; **2j,** 59711-14-7; **2k,** 59711-15-8; **2n,** 59711-16-9; **2o,** 59711-17-0; **2p,** 59711-18-1; **2q,** 59711-19-2; **3a,** 287-24-1; **3b,** 59711-20-5; **3c,** 59711-21-6; **3d,** 59711-22-7; **3e,** 50870-40-1; **3f,** 59711-23-8; **3g,** 59711-24-9; **3h,** 59711-25-0.

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Tricyclic Dimers from Cyclic α Diketones

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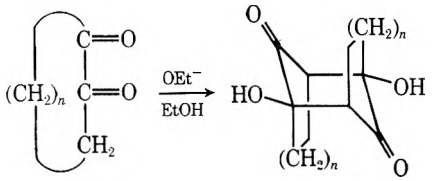
D. P. Bauer and R. S. Macomber*: Tricyclic Dimers from Cyclic α Diketones.

Page 3059. Professor George M. Whitesides (MIT) has called to our attention a publication by R. A. Raphael and A. I. Scott [*J. Chem. Soc.*, 4566 (1952)], where the preparation of the compounds we designated **2a** and **7-OH** was reported. The assigned structures and physical properties (mp, IR, UV) corresponded very closely to the data we reported. Professor Whitesides also described his group's related work in the area, which he intends to publish in another connection. We are grateful for his communication.

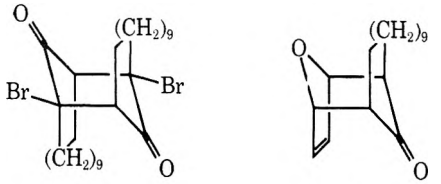
It was subsequently found that these side products could be directly prepared by simply treating the diketones with base. For example, when a solution of 1.96 g (10 mmol) of **1b** and 20 mmol of sodium ethoxide in 55 ml of absolute ethanol was stirred for 24 h at room temperature, 680 mg (after recrystallization from diglyme) of a colorless compound with mp 277–278 °C was isolated. The mass spectrum of this compound exhibited a parent ion at *m/e* 392 indicating a dimer of the starting diketone; the elemental analysis agreed with molecular formula $C_{24}H_{40}O_4$. Its infrared spectrum showed carbonyl (1702 cm^{-1}) and hydroxyl (3525 cm^{-1}) absorptions. NMR spectra for this compound could not be obtained owing to the extreme insolubility of the material (12 mg/ml diglyme at 161 °C). Attempts to increase its solubility by derivatizing the OH groups with acetic anhydride, acetyl chloride, methanesulfonyl chloride, and thionyl chloride all failed, indicating the extremely hindered nature of these groups. However, treatment with potassium *tert*-butoxide in glyme (70 °C, 2 h), or heating to 320 °C, regenerated yellow **1b.** These results, coupled with the observation that the re-

action with ethoxide could not be pushed to completion, suggest that this product is reversibly formed bisaldol dimer **2b**. Further confirmation could be adduced from the observation that **2b** affords 1,2-cyclododecanediol[1b] upon treatment with sodium borohydride in diglyme.



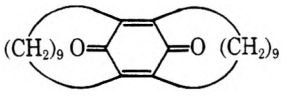
1a, $n = 7$ **2a**, $n = 7$
b, $n = 9$ **b**, $n = 9$
c, $n = 11$ **c**, $n = 11$

Compounds resembling **2** are known. Meier,[3] referencing unpublished work, reported that treatment of α,α'-dibromocyclododecanone (**3**) with potassium *tert*-butoxide led to tricyclic bromo ketone **4**. Similarly, treatment of **3** with zinc–copper couple in the presence of furan afforded **5** (ir 1703 cm^{-1}) along with several stereoisomers.[4]



4 **5**

Although **4** apparently resists further base-catalyzed dehydrobromination, we attempted to prepare benzoquinone **6** from **2b**. However, treatment with dicyclohexylcarbodiimide



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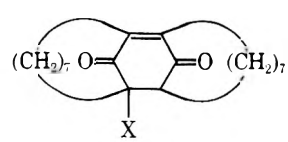
(DCC), *p*-toluenesulfonic acid in refluxing diglyme, and potassium permanganate left **2b** unchanged, further indication of its low reactivity.

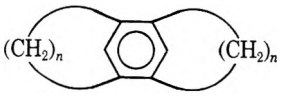
Diketone **1c** afforded dimer **2c** (mp 295–296 °C) in 38% yield, and its behavior matched that of **2b**. However, treatment of **1a** with ethoxide provided two products, the dimer **2a** (*m/e* 336, mp 247–248 °C) in 1% yield, and another product (*m/e* 318, mp 169–170 °C) in 35% yield. Absorptions for O–H (3450 cm^{-1}), C=O (1702), and C=C (1622) were apparent in its infrared spectrum, and its uv spectrum suggested conjugation with λ_{max} (ethanol) 247 nm (log ϵ 3.9).[5] Elemental analysis corroborated molecular formula $C_{20}H_{30}O_3$, corresponding to dehydration of **2a**. These data, together with the observation that a mesylate derivative could be prepared, tentatively suggest this compound to be enedione **7a**, another violation of Bredt's rule.[6] Both 7-OH and 7-OMs proved soluble enough to allow ^1H and ^{13}C NMR spectra to be obtained (Experimental Section). Although complex, these spectra were consistent with the proposed structures. But as with **2b** and **2c** no conditions were found that could induce 7-OH or 7-OMs to undergo further elimination. Thus, 7-OH could be reisolated after treatment with DCC, 9-BBN, $POCl_3$, or pyrolysis (passage through glass wool at 300 °C), and 7-OMs could be recovered after heating in pyridine (100 °C, 12 h).



7-X

Space-filling molecular models of **2b** show that the nine-carbon bridges are best accommodated when they are axially disposed and static, as was suggested by the C=O stretch (vide supra and ref 4). This requires the O–H groups to occupy equatorial positions which are hindered by the cyclic methylene chains toward electrophilic attack.

Why the ten-membered rings in **2a** better accommodate the flattening attending formation of 7-OH more than do the presumably[4] more flexible 12- and 14-membered rings in **2b** and **2c** is not clear. Models do suggest, however, that fully planar molecules such as **7** and **8** experience considerable



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buttressing of the one-carbon bridges with the *n*-carbon bridges, accounting for the low reactivity of the carbonyl groups. This type of dimerization may account for the fact that α diketones with α-methylene groups do not generally undergo the benzylic acid rearrangement in base.[7] Further work on the chemistry of these compounds is underway.[8,9]

Experimental Section

The following instruments were employed: Beckman IR-12 (calibrated with polystyrene); Varian A-60 [δ, parts per million downfield from internal $(CH_3)_4Si$]; Varian CFT 20 (^{13}C data are in parts per million downfield from Me_4Si); Hitachi RMU-7 (70eV); Cary 14. All starting materials, reagents, and solvents were obtained from Aldrich Chemical Co. or Fisher Scientific Co. Diglyme was distilled from $LiAlH_4$. Melting points are not corrected. The elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.

Dimerization of Cyclododecane-1,2-dione. To a cool (0 °C) stirred solution of cyclododecane-1,2-dione[1b] (1.96 g, 10 mmol) in 5 ml of absolute ethanol was added a cool (0 °C) solution of sodium metal (0.46 g, 20 mg-atoms) in 50 ml of absolute ethanol. After stirring for 24 h at room temperature, the reaction mixture was poured over ice, then neutralized with 1 N HCl. The yellowish solid was filtered and washed with 50 ml of diethyl ether. The remaining white solid was recrystallized from dry diglyme to yield 680 mg (35%) of **2b**: mp 277–278 °C; ir (Nujol) 3525, 1702, 1250, 1090, 1047, 1028, 741 cm^{-1}; mass spectrum *m/e* (rel abundance) 392 (M^+, 75), 374 (16), 364 (28), 346 (73), 197 (100).

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.58; H, 10.38.

Reaction of Compound 2b with Sodium Borohydride. Compound **2b** (392 mg, 1.0 mmol), sodium borohydride (75.6 mg, 2.0 mmol), water (1.0 ml), and 20 ml of diglyme were combined in a 50-ml round-bottom flask, then heated to 140 °C for 20 h. After cooling to room temperature, the reaction mixture was cautiously poured into 100 g of ice–water; then 10 ml of 10% NaOH was added to the solution. The white precipitate was filtered and recrystallized from ether–pentane to yield 360 mg (91%) of *cis*-cyclododecane-1,2-diol: mp 158–159 °C (lit.[1b] mp 159–160 °C); R_f (EtOAc) 0.43; ir (KBr) 3312 cm^{-1}, no C=O; ^1H NMR (pyridine-d_5) δ 1.31 (s, $\Delta\nu_{1/2}$ = 8 Hz, 16 H), 1.80 (br m, 4 H), 4.20 (t, J = 6 Hz, 2 H), 5.51 (s, 2 H); mass spectrum *m/e* (rel abundance) 200 (M^+, 2), 94 (100).

Dimerization of Cyclotetradecane-1,2-dione. Cyclotetradecane-1,2-dione[1c] (2.24 g, 10 mmol) in 5 ml of absolute ethanol and sodium metal (0.46 g, 20 mg-atoms) in 50 ml of absolute ethanol were allowed to react as described in the preparation of compound **2b**. After the usual aqueous workup and recrystallization from dry diglyme, compound **2c** was isolated in 38% yield (850 mg): mp 295–296 °C; ir (KBr) 3530, 2940, 2860, 1709, 1445, 1370, 1250, 1230, 1080, 1055, 1037, 1004 cm^{-1}; mass spectrum *m/e* (rel abundance) 448 (M^+, 28), 430 (20), 420 (16), 402 (34), 225 (100).

Anal. Calcd for $C_{28}H_{48}O_4$: C, 74.95; H, 10.78. Found: C, 74.89; H, 10.48.

Dimerization of Cyclodecane-1,2-dione. A 10-mmol sample of cyclodecane-1,2-dione[1a] in 5 ml of absolute ethanol was reacted with 20 mg-atoms of sodium metal in 50 ml of absolute ethanol. After the usual aqueous workup, the precipitate was filtered and washed with

pentane. Fractional recrystallization from diethyl ether yielded 15 mg (1%) of compound **2a** at 15 °C and 620 mg (37%) of compound 7-OH at −20 °C.

Compound **2a:** mp 247–248 °C; ir (KBr) 3535, 2950, 2865, 1699, 1468, 1450, 1258, 1229, 1141, 1000, 983, 965 cm^{-1}; mass spectrum *m/e* (rel abundance) 336 (M^+, 45), 318 (7), 308 (7), 290 (45), 169 (100). Compound 7-OH: mp 169–170 °C; ir (KBr) 3450, 2950, 2870, 1702, 1622, 1470, 1220, 1191, 1140, 1080, 1043 cm^{-1}; ^1H NMR (pyridine-d_5) δ 1.10–2.90 (m, 28 H), 3.22 (br m, 1 H) 7.05 (s, 1 H); uv (ethanol) λ_{max} 247 nm (log ϵ 3.9); ^{13}C NMR ($CDCl_3$) 20.4, 20.9, 21.8, 22.5, 23.2, 24.2, 24.7, 25.6, 25.8, 26.7, 37.4, 41.8, 51.1, 85.6, 138.2, 161.0, 164.8, 169.3 ppm; mass spectrum *m/e* (rel abundance) 318 (M^+, 100), 300 (12), 290 (18), 151 (16).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.29; H, 9.56.

Preparation of 7-OMs. To a frozen solution of compound 7-OH (318 mg, 1.0 mmol) in pyridine (3.0 ml) was added a cool (−5 °C) solution of methanesulfonyl chloride (228 mg, 2.0 mmol) in pyridine (2.0 ml). The mixture was immediately frozen, then slowly allowed to warm to −20 °C. After storing at −20 °C for 2 days the reaction mixture was poured over 15 g of ice, then extracted with two 15-ml portions of diethyl ether. The ethereal layer was separated and washed with water, 1 N HCl, 5% $NaHCO_3$, and brine, then dried, filtered, and concentrated in vacuo. Preparative layer chromatography (benzene elution) of the white residue resulted in the isolation of 322 mg (81%) of compound 7-OMs: mp 138–139 °C; R_f (Bz) 0.46; ir ($CHCl_3$) 2940, 2879, 1719, 1700 (sh), 1620, 1470, 1350, 1330, 1173, 960, 932, 852 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–2.30 (m, 24 H), 2.38 (m, 4 H), 3.30 (s, 3 H), 3.89 (m, 1 H); mass spectrum *m/e* (rel abundance) 396 (M^+, 0.4), 317 (25), 300 (100).

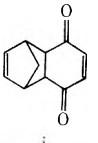
Anal. Calcd for $C_{21}H_{32}O_5S$: C, 63.60; H, 8.13. Found: C, 63.51; H, 8.14.

Acknowledgment. This work was generously supported by USPHS-NIH Grant 5 R01 AI 11690. The technical assistance of Rodney Erkes is also gratefully acknowledged. The ^{13}C spectra were obtained with the help of Dr. David Behnke, U. C. School of Medicine.

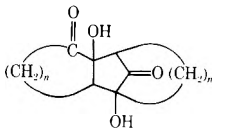
Registry No.—**1a,** 96-01-5; **1b,** 3008-41-1; **1c,** 23427-68-1; **2a,** 59654-89-6; **2b,** 59654-90-9; **2c,** 59654-91-0; 7-OH, 59654-92-1; 7-OMs, 59654-93-2; *cis*-cyclododecane-1,2-diol, 4422-05-3; methanesulfonyl chloride, 124-63-0.

References and Notes

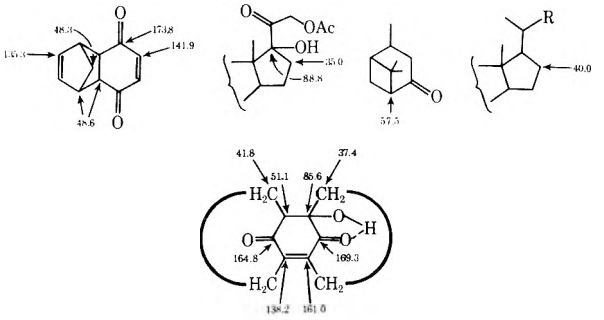
(1) (a) n = 7: A. T. Blomquist, R. E. Burge, Jr., and A. C. Sucsy, *J. Am. Chem. Soc.*, 74, 3636 (1952). (b) n = 9: V. Prelog and M. Speck, *Helv. Chim. Acta*, **38,** 1786 (1955). (c) n = 11: T. Mori, T. Nakahara, and H. Nozaki, *Can. J. Chem.*, **47,** 3266 (1969).
(2) D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, **40,** 1990 (1975).
(3) H. Meier, *Synthesis*, 235 (1972).
(4) J. G. Vinter and H. M. R. Hoffmann, *J. Am. Chem. Soc.*, **95,** 3051 (1973). Compound **5** is stereochemically rigid, giving a single C=O ir stretch. Its cis,syn,cis isomer is fluxional and shows two C=O bands in solution.
(5) A. Wasserman [*J. Chem. Soc.*, 1511 (1935)] lists the λ_{max} (ethanol) for the enedione below as 225 nm (log ϵ 4.11). Using Woodward's rules, two



substituents (one α + one β) would add 22 nm: calcd 247 nm; observed 247 nm. The position and intensity of this band further argue for the near-planarity of the enedione moiety in **7-X**.
(6) For a leading reference, see H. O. Krabbenhoft, J. R. Wiseman, and C. B. Quinn, *J. Am. Chem. Soc.*, **96,** 258 (1974).
(7) W. Huckel, "Theoretical Principles of Organic Chemistry", Vol. I, American Elsevier, New York, N.Y., 1955, p 461.
(8) The systematic names for these dimers follow: **2a,** 1,10-dihydroxytricyclo[9.7.1^{2,10}]eicos-19,20-dione; **2b,** 1,12-dihydroxytricyclo[11.9.1.1^{2,12}]-tetracos-23,24-dione; **2c,** 1,14-dihydroxytricyclo[13.11.1.1^{2,14}]octacos-27,28-dione; **7-OH,** 1-hydroxytricyclo[9.7.1.1^{2,10}]eicos-10-ene-19,20-dione.
(9) One referee has suggested the structure below as an alternate of **2.** We



had considered this possibility, but eliminated it on the basis of the compounds' ir spectra. The structure below would show two carbonyl bands, one at ca. 1745 cm^{-1}. None of the compounds in this study exhibited a second C=O stretch, and none came above 1709 cm^{-1}.
(10) Analogues for the ^{13}C chemical shifts can be found in L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley, New York, N.Y., 1972, and the spectrum of i in footnote 5 (determined in this work). The substantial difference in chemical shift between the olefinic carbons in 7-OH may be caused by internal hydrogen bonding in the neighboring carbonyl:

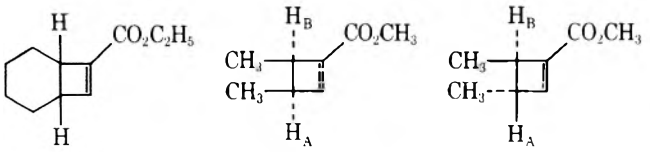


Communications

The Stereospecific Aluminum Chloride Catalyzed [2 + 2] Cycloaddition of Propiolate Esters with Unactivated Alkenes

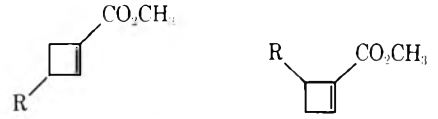
Summary: The aluminum chloride catalyzed reaction of alkenes with propiolate esters at 25 °C produces either ene adducts and/or stereospecific [2 + 2] cycloadducts depending on the substitution pattern of the alkene.

Sir: We have previously shown that aluminum chloride catalyzes the reaction of methyl acrylate with 1,1-disubstituted olefins at 25 °C, giving good yields of ene adducts.[1,2] Since acetylenes are known to be more reactive than the corresponding alkene as enophiles,[1] we decided to examine Lewis acid catalyzed reactions of propiolate esters with alkenes. With 1,2-disubstituted olefins or monosubstituted double bonds an unexpected reaction occurs. With cyclohexene two products are obtained on treatment with ethyl propiolate and 0.5 equiv of aluminum chloride in benzene for 7 days at 25 °C. The expected ene adduct **17** is isolated in 15% yield.[3,4] The major product isolated in 72% yield is assigned structure **1** based on ir, NMR, and mass spectral considerations. The cis fusion is assigned based on steric considerations and the nature of the cycloaddition (vide infra). This type of cycloaddition has precedent in the cycloaddition of propiolate esters with enamines.[6] It has not been observed previously in nonphotochemical reactions of propiolates with unactivated olefins. In order to test the specificity of the addition, methyl propiolate was treated with excess *cis*- or *trans*-2 butene in the presence of 0.5 equiv of aluminum chloride for 2 days. In neither case is any ene adduct detected. The *cis*- and *trans*-3,4-dimethylcyclobutenecarboxylates, **2** and **3,** are obtained stereospe-



1 2 3

cifically with retention in 35 and 31% yields,[7] respectively and are >98% isomerically pure based on GC analysis. The stereochemistry is assigned by analysis of NMR coupling constants.[8] These compounds are identical by spectral comparison with those prepared by an alternate synthesis.[9] With propene the 1:1 adducts are obtained in 64% yield.[7] The ene adduct **13** is obtained as 24% of these adducts. Two other products are obtained as 43 and 33% of the mixture. These are isolated by gas chromatography and are assigned the structures **4** and **5**, respectively. Similarly, 1-butene gives a 74%



4, R = CH_3
6, R = C_2H_5

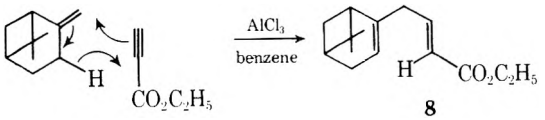
5, R = CH_3
7, R = C_2H_5

yield of 1:1 adducts[7] which consists of 14.7% ene adduct **14** and 31 and 25% cyclobutene adducts **6** and **7**, respectively.[10]

The mechanism of these cycloaddition reactions is open to question. The two mechanistic extremes are a concerted [$2_s + 2_a$] cycloaddition or a polar two-step sequence. It is possible for these cycloadditions to go by the [$2_s + 2_a$] route since one of the addends is an acetylene.[11] On the other hand, a variety of polar two-step cycloadditions are known to proceed stereospecifically.[12] From the mixtures of cyclic products obtained with monosubstituted olefins it is clear that the dominant feature is the great stabilization of at least a partial negative charge on the carbon α to the complexed ester in either a transition state or intermediate. On the other hand, if there is an intermediate, it must collapse very rapidly since no isomerization is observed. It should be noted that in similar uncatalyzed thermal reactions no cycloadducts are observed.[13]

With olefins containing two substituents on one end of the double bond no cycloaddition product can be detected. Addition of a slight excess of β-pinene to a solution of ethyl propiolate in benzene containing 0.2 equiv of aluminum chloride gives after 2 days the expected ene adduct **8** in 82% yield (Scheme I). As one would expect with a six-membered-

Scheme I



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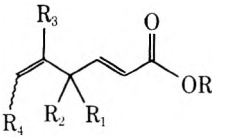
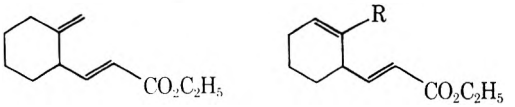
ring transition state the α,β-unsaturated ester is formed stereospecifically trans. Furthermore, NMR spectra of the crude product indicates that no conjugation of the δ,ϵ double bond, has occurred. This is somewhat surprising given the length of time and very acidic conditions of the reaction. Similarly, isobutylene gives the corresponding ene adduct **9**[14] in 61% yield after 5 days with 0.5 equiv of aluminum chloride and 2-ethyl-1-butene gives a 60:40 mixture of olefin isomers **10** in 56% yield after 6 days[7] with 0.33 equiv of $AlCl_3$. 3-Methyl-2-butene and ethyl propiolate containing 0.85 equiv of $AlCl_3$ gives rise to the ene adduct **11** in 74% yield. Similarly 1-methylcyclohexene gives a 70:30 mixture of adducts **15** and **16** in 90% yield while 2,3-dimethyl-2-butene gives only the expected ene adduct **12** in 92% yield.

The reactions described here provide ready access to a variety of 2,5-dienoates and cyclobutenecarboxylates which were previously difficult to prepare. We are investigating the use of these compounds in synthesis, intramolecular versions of these reactions, and the extension of this reaction to acetylenes with other electron-withdrawing substituents.



9, R_1, R_2, R_4 = H; R_3 = CH_3
10, R_1, R_2 = H; R_3 = C_2H_5; R_4 = CH_3
11, R_1, R_3 = CH_3; R_2, R_4 = H
12, R_1, R_2, R_3 = CH_3; R_4 = H
13, R_1, R_2, R_3, R_4 = H
14, R_1, R_2, R_3 = H; R_4 = CH_3



15

16, R = CH_3
17, R = H

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to Princeton University for support of this research.

References and Notes

(1) For a review of the ene reaction, see H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).
(2) B. B. Snider, *J. Org. Chem.*, **39**, 255 (1974).
(3) All new compounds were characterized by NMR, ir, and mass spectra and exact mass determination.
(4) Typically the reactions are run at 25 °C in benzene (1.5 ml/mmol of acetylene) with excess olefin present. The amount of aluminum chloride used varies from 0.2 to 0.85 equiv depending on the reactivity of the olefin. If more than 1 equiv of $AlCl_3$ is used, facile Friedel–Crafts reactions take place. The reaction time varies from 2 to 7 days and is determined by chromatographic analysis of reaction mixtures. The choice of benzene as solvent and aluminum chloride as catalyst is important.[5] Reactions are worked up by quenching with bicarbonate solution, filtration through Celite, and extraction with ether.
(5) T. Inuki and M. Kasai, *J. Org. Chem.*, **30**, 3567 (1965), describe the use of this system for Diels–Alder reactions. We have found that solvents like methylene chloride give rise to extensive double-bond isomerization while other aromatic solvents like chlorobenzene or toluene give results similar to those obtained in benzene. Aromatic solvents form weak complexes with aluminum chloride which presumably deactivate it sufficiently to allow these reactions to take place cleanly. Strongly complexing solvents like ether give only traces of product.
(6) R. Fuks, and H. G. Viehe in H. G. Viehe, "Chemistry of Acetylenes", Marcel Dekker, New York, N.Y., 1969, pp 435–440.
(7) The other products in these reactions are traces (~5%) of telomerized olefin and Friedel–Crafts reaction of the olefin on benzene. Most of the remaining material is unreacted starting material. Aluminum chloride also catalyzes the isomerization of olefins at a rate competitive with ene reaction so that in the case of 2-ethyl-1-butene one obtains an 8% yield of ene adducts of methyl propiolate with 3-methyl-2-pentene.
(8) For the cis isomer **2**, J_{AB} = 4.5 Hz. For the trans isomer **3**, J_{AB} = 1.4 Hz. This is consistent with predictions based on the Karplus equation: I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967); E. A. Hill and J. D. Roberts, *J. Am. Chem. Soc.*, **89**, 2047 (1967).
(9) The author thanks Maitland Jones, Jr., and R. Galucci for communicating these results prior to publication.
(10) The remaining 30% consisted of 15% *sec*-butylbenzene, (from Friedel–Crafts reaction), 4.9% methyl *trans*-3,4-dimethyl-1-cyclobutenecarboxylate and ~10% methyl *cis*-3,4-dimethylcyclobutenecarboxylate (from isomerization of 1-butene followed by the normal reaction expected for 2-butenes).
(11) R. B. Woodward and R. Hoffmann, *Ang. Chem., Int. Ed. Engl.*, **8**, 781,841 (1969).
(12) N. D. Epiotis et al., *J. Am. Chem. Soc.*, **98**, 453 (1976).
(13) K. Alder and H. v. Brachel, *Justus Liebigs Ann. Chem.*, **651**, 141 (1962).
(14) This material was identical by ir spectra with an authentic sample: G. P. Chuisoli et al., *Chim. Ind. Milan*, **46**, 21 (1964).

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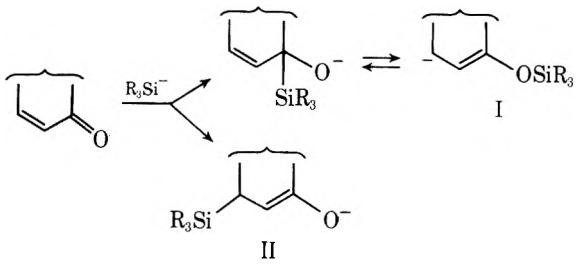
Received July 15, 1976

Conjugate Addition of Trimethylsilyllithium. A Preparation of 3-Silyl Ketones

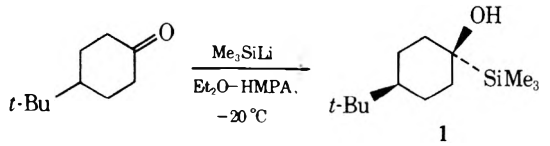
Summary: Trimethylsilyllithium is readily prepared by adding methyllithium to hexamethyldisilane in hexamethylphosphoramide (HMPA); this reagent undergoes rapid 1,4 addition to cyclohexenones at low temperature to give enolates of 3-silyl ketones (II).

Sir: Since the late 1950's, it has been known that silyl anions[1] undergo smooth addition to a variety of organic electrophiles[2] including ketones, epoxides, and halides. However, we know of no report of the reaction of these reagents with simple α,β-unsaturated carbonyl compounds.[3] The result of such a reaction is of special interest since it could lead via 1,2 addition to an allyloxy carbanion[4] (I) or via 1,4 addition to a regiospecific enolate of a 3-silyl ketone[5] (II). In this communication,



we report an extremely convenient preparation of trimethylsilyllithium and a study of its addition to representative α,β-unsaturated ketones.

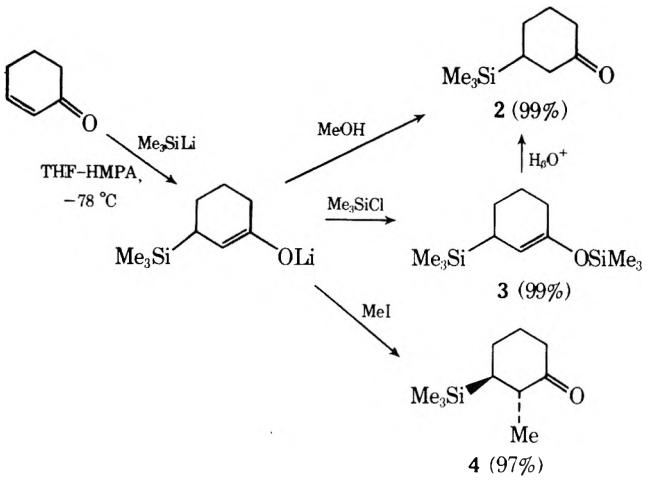
Trimethylsilyl alkali metal compounds have been prepared traditionally by a metal exchange reaction between an alkali metal and bis(trimethylsilyl)mercury.[6] However, the lengthy preparation[7] required for the latter compound and the inherent danger of handling volatile mercury compounds make this route to trimethylsilyl anions unattractive. More recently, cleavage of hexamethyldisilane by sodium or potassium methoxide has been used to prepare trimethylsilylsodium or -potassium.[2d,e] However, the sodium and potassium reagents have been reported[8] to be less effective in addition reactions with carbonyl compounds than the corresponding lithium compounds. We therefore sought a convenient preparation of trimethylsilyllithium. We have found that 1.25 equiv of hexamethyldisilane[9] react rapidly with an equivalent of methyllithium in HMPA (0 °C, 15 min) to produce a deep red solution of trimethylsilyllithium and inert tetramethylsilane (TMS). Utilization of methyllithium appears complete since addition of excess 4-*tert*-butylcyclohexanone to the reagent in ether yields no methylcarbinol. Instead, a single product, the crystalline alcohol **1** (mp 90.5–91.5 °C), is produced. The stereochemistry of **1** is assumed to be that which would result



1

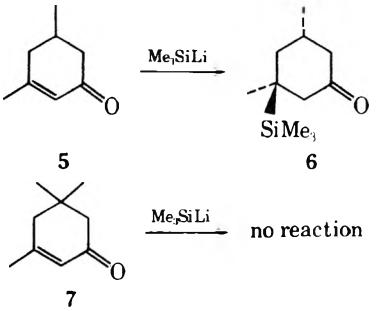
from less hindered equatorial attack by a trimethylsilyl anion.[10] It should be mentioned here that the latter reaction is very sensitive to the nature of the solvent. Replacing ether by tetrahydrofuran, for example, resulted in significant byproduct formation.

Addition of 2-cyclohexenone to trimethylsilyllithium in THF–HMPA (5:1) at −78 °C results in immediate disappearance of the red color of the reagent. Quenching with methanol and workup yields the known compound, 3-(trimethylsilyl)cyclohexanone[5d,e] (**2**) as the only product. Alternatively, quenching with trimethylchlorosilane produces the corresponding enol silyl ether[5e] **3**. The intermediate enolate



can also be alkylated cleanly by reactive alkyl halides without equilibration. For example, addition of excess methyl iodide to the reaction mixture yields a methylated silyl ketone (spectral data given in experimental procedure) in 97% yield after bulb-to-bulb distillation. TLC, VPC, and NMR indicate this compound to be a single isomer to which the structure **4**[11] has been assigned. The regiochemistry of the alkylation follows from mechanistic considerations and from the observation of a 12% NOE enhancement of the trimethylsilyl grouping (relative to tetramethylsilane) on irradiation of the 2-methyl signal in the NMR.[12] The equatorial nature of the methyl group (and therefore the trans disposition of the two substituents) is indicated by the stability of **4** to epimerizing conditions (NaOMe, MeOH, 1 hr, 25 °C) and by a half-height peak width for each member of the methyl doublet which is only 0.3 hertz broader than tetramethylsilane.[13] Reaction of the intermediate enolate with less reactive halides (e.g., *n*-propyl iodide) gives rise to complex mixtures.

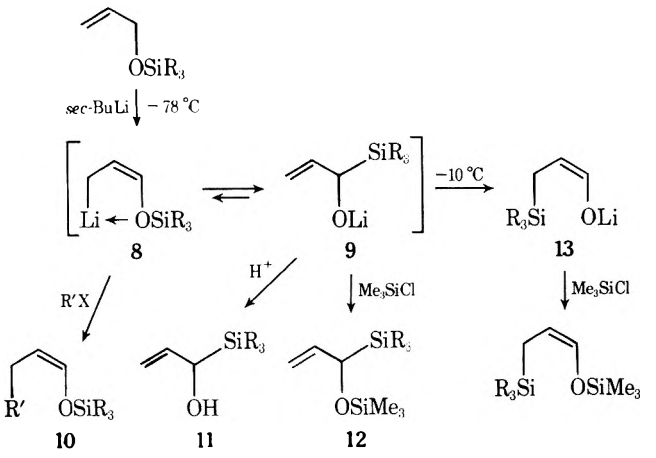
Our results with other enones indicate that the reagent has a strong preference for axial addition. For example, 3,5-dimethyl-2-cyclohexenone (**5**) leads to the silyl ketone **6** [ir (neat) 1712, 1250, 840 (br) cm^{-1}; NMR δ^{CDCl_3} 0.99 (3 H, d, J = 6 Hz), 0.97 (3 H, s), −0.02 (9 H, s); MS (70 eV) 183 (parent − CH_3)] in 78% yield after column chromatography. The assignment of *cis*-dimethyl stereochemistry is based on the chemical shifts of the two methyl signals in the NMR. While 3-methylcyclohexanone and *cis*-3,5-dimethylcyclohexanone exhibit methyl resonances at δ 1.00, cyclohexanones with β-methyl groups constrained to be axial show signals shifted to higher field (δ 0.75–0.90).[14] Since the methyls in **6** have similar chemical shifts (δ 0.99, 0.97) which are clearly outside the high field range, these substituents have been assigned as cis diequatorial.[15] More support for the axial mode of attack is found in the reaction of trimethylsilyllithium with isophorone (**7**). Unlike the previously described reactions, the addition



of isophorone to the silyllithium reagent does not result in disappearance of the red color. Instead, the reaction is incomplete even after 30 min at −78 °C. Quenching and workup as before returns a pale yellow oil which is 90–95% starting material. This result is not unexpected. Although steric effects

for equatorial attack on **5** and **7** are very similar, a severe 1,3-diaxial methyl–trimethylsilyl interaction would be expected to destabilize the transition state for axial addition to isophorone.

Unlike most other conjugate additions, the 1,4 addition of trimethylsilyllithium to enones appears to be a kinetic process since 1,2 adducts like **9** are stable to the reaction conditions reported above (−78 °C). As we reported previously, allyloxy carbanions (**8**) derived from allyl silyl ethers are in rapid equilibrium with the corresponding silyl alkoxide **9**.[4] Such species may be alkylated on carbon to give **10** or they may be protonated or silylated on oxygen to give **11** or **12**. If, however,



R = Me, Et

the allyloxy carbanion reagent is allowed to warm to approximately −10 °C, it undergoes irreversible rearrangement to the silyl enolate **13**.

The marked preference for a kinetic 1,4 addition with axial attack is most compatible with an electron-transfer mechanism. Other reagents (R_2CuLi and Li/NH_3) believed to react with enones by electron-transfer processes show similar regiochemistry and stereochemistry.[16,17] Further support for this mechanism is given by a number of reports which indicate that silyl anions are potent one-electron reducing agents.[18] For example, trimethylsilylsodium has been reported to reduce benzophenone and naphthalene to the corresponding radical anions and to effect reductive coupling of alkyl halides.

The following procedure for synthesis of **4** illustrates the preparation and use of the trimethylsilyllithium reagent. A solution of 0.50 ml (2.5 mmol) hexamethyldisilane[9] in 2 ml of anhydrous HMPA was cooled to 0 °C under nitrogen. Ethereal methyllithium (2 mmol) was added via syringe and the resulting deep red solution was stirred for 15 min to complete the preparation of trimethylsilyllithium. Anhydrous THF (10 ml) was added and the solution was immediately chilled to −78 °C. A solution of 144 mg (1.5 mmol) of 2-cyclohexenone in 1 ml of THF was then added dropwise. After stirring an additional 5 min, 0.5 ml of methyl iodide was injected and the mixture was allowed to warm slowly to 0 °C. The reaction mixture was poured into 50 ml of pentane and thoroughly washed with water (2 × 25 ml) to remove HMPA. Drying ($MgSO_4$) and solvent removal gave a colorless oil (308 mg). Kugelrohr distillation (1 mm, oven 80 °C) gave 268 mg (97%) of *trans*-3-trimethylsilyl-2-methylcyclohexanone (**4**): ir (neat) 1710, 1250, 853, 838 cm^{-1}; NMR δ^{CDCl_3} 1.10–2.44 (8 H, m), 1.03 (3 H, d, J = 6.5 Hz), 0.6 (9 H, s); MS (70 eV) 184 (15) (parent), 179 (53), 156 (9), 155 (12), 141 (19), 75 (75), 74 (22), 73 (100), 67 (20), 59 (45), 58 (32), 53 (25), 45 (90), 44 (20), 43 (78), 42 (22), 42 (62).

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References and Notes

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Facile Reduction of Alkyl Tosylates with Lithium Triethylborohydride. An Advantageous Procedure for Deoxygenation of Cyclic and Acyclic Alcohols

Summary: Lithium triethylborohydride rapidly reduces *p*-toluenesulfonate esters of both cyclic and acyclic alcohols to the corresponding alkanes in excellent yields and is applicable even to tosylates derived from hindered alcohols.

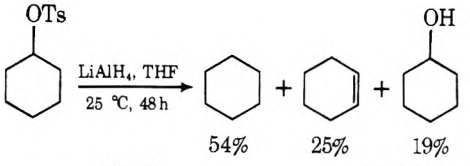
Sir: Deoxygenation of alcohols to the corresponding alkanes, a frequently encountered transformation in synthetic organic chemistry, is usually achieved by the reduction of *p*-toluenesulfonate ester of the alcohol with lithium aluminum hydride.[1] Although this procedure works satisfactorily with relatively unhindered primary alcohols, the results are less favorable for the more hindered alcohols as well as for certain cycloalkanols. In such cases, the yield of the desired alkane

Table I. Reduction of Representative Alkyl Tosylates with Lithium Triethylborohydride in Tetrahydrofuran (THF)[a]

Compound	Time, hr	Products[b,c]	%
n-Octyl tosylate	0.25	*n*-Octane	96
2-Methyl-1-pentyl tosylate	0.25	2-Methylpentane	98
2-Octyl tosylate	0.25	*n*-Octane	99
Cyclopentyl tosylate	0.25	Cyclopentane	100
Cyclohexyl tosylate	12.0	Cyclohexane	80
		Cyclohexene	20
Cycloheptyl tosylate	0.5	Cycloheptane	100
Cyclooctyl tosylate[d]	0.5	Cyclooctane	97.5
		Cyclooctene	2.5
2,2-Dimethyl-1-hexyl tosylate[e]	3.0	2,2-Dimethylhexane	81
		2,2-Dimethyl-1-hexanol	9

[a] In all cases solutions were 0.25 M in tosylate and 0.5 M in $LiEt_3BH$ at 25 °C. [b] The yields reported were determined by GLC using a suitable internal standard and authentic synthetic mixtures. [c] Except where indicated, no olefins or alcohols were detected. [d] Isolated in 81% yield. [e] At 65 °C.

is often reduced as a result of two significant side reactions: (a) elimination to form olefins, and (b) attack at the sulfur–oxygen bond to form the parent alcohol (eq 1 and 2).[2]



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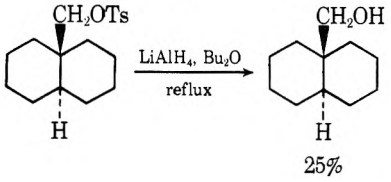
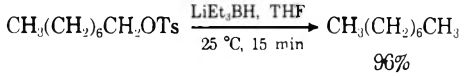


(2)

Recently, lithium triethylborohydride (Super Hydride) has emerged as an exceptionally powerful nucleophilic reducing agent capable of reducing hindered alkyl halides, epoxides, and quaternary ammonium salts rapidly and cleanly to the desired products.[3-6] It appeared possible that lithium triethylborohydride might overcome these difficulties. Accordingly, we tested the effectiveness of this reagent for the reduction of representative alkyl tosylates to the corresponding alkanes[7] (Table I).

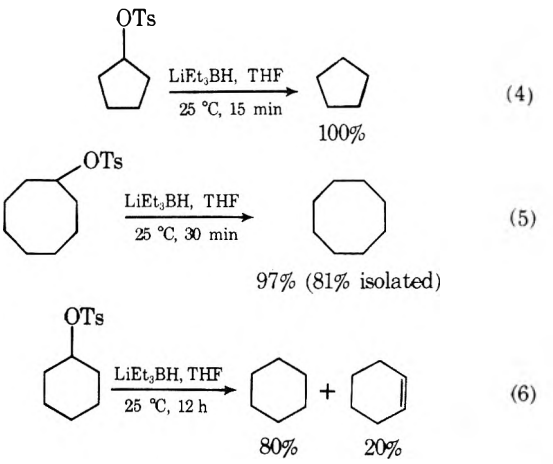
Tosylates of primary alcohols such as *n*-octyl tosylate and 2-methyl-1-pentyl tosylate are rapidly converted into *n*-octane and 2-methylpentane in yields of 96 and 98%, respectively (eq 3).



(3)

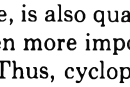
The secondary tosylate, 2-octyl tosylate, is also quantitatively reduced to *n*-octane in 15 min. Even more important is the reduction of cycloalkyl tosylates. Thus, cyclopentyl, cycloheptyl, and cyclooctyl tosylates are rapidly reduced to their corresponding alkanes in excellent yields (eq 4 and 5).

The reduction of cyclohexyl tosylate is comparatively sluggish requiring 12 h for completion, producing 80% cyclohexane, 20% cyclohexene, and only traces of cyclohexanol (eq 6). This represents a major improvement over the results realizable with lithium aluminum hydride.[2a] Further, the cyclohexyl moiety is prevalent in many naturally occurring molecules of biological interest, such as steroids, terpenes, etc. Consequently, we undertook to examine the reaction of cyclohexyl tosylate, the model compound, with various hydridic



reducing agents; other parameters, such as the influence of solvent, metal ion, steric bulk of the reagent, etc. were also briefly examined (Table II). The conventional reagent, lithium aluminum hydride, yields a mixture of cyclohexane, cyclohexene, and cyclohexanol. The alkoxy derivatives of lithium aluminum hydride and aluminum hydride are essentially ineffective for this reduction. Further, the tosylate is essentially inert to borane–THF, disiamylborane, thexylborane, 9-BBN, and lithium borohydride. It is quite evident that the less hindered trialkylborohydrides, such as lithium *B*-methyl-9-borabicyclo[3.3.1]nonyl hydride and lithium triethylborohydride, are preferred over the more hindered reagents. The metal ion does not seem to alter the course of the reaction significantly. However, solvent does exert a major role; THF is preferred over ether and benzene. Lowering the temperature increases the substitution/elimination ratio only slightly. Sulfur–oxygen bond cleavage is unimportant in all of the reductions examined utilizing trialkylborohydride. In short, the results of the comparative study clearly indicates the advantages of lithium *B*-methyl-9-borabicyclo[3.3.1]nonyl hydride and lithium triethylborohydride over the conventional re-

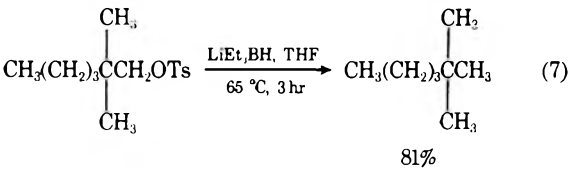
Table II. Reduction of Cyclohexyl Tosylate with Various Hydride Reducing Agents

Reagent	Temp, °C	Product composition,[a] %		
				
$LiAlH_4$, THF[b]	25	54	25	19.5
$LiAlH_4$, Et_2O[c]	25	38	55	7
$LiAlH(O\text{-}tert\text{-}Bu)_3$, THF[d]	0	0	0	0
$LiAlH(OCH_3)_3$, THF[e]	25	0	0	0
AlH_3, THF[f]	0	0	0	0
BH_3–THF[g]	0	0	0	0
9-BBN, THF[c]	25	0	0	0
$LiBH_4$, THF[c]	25	Trace	0	Trace
	25	84	16	0
	0	88	12	0
$LiEt_3BH$, THF[c]	25	80	20	0
	0	84	16	0
$LiEt_3BH$, DG[c]	25	79	21	0
$NaEt_3BH$, THF[c]	25	83	17	0
$NaEt_3BH$, C_6H_6[c]	25	18	82	0
Li-*sec*-Bu_3BH, THF[c]	25	52	48	0

[a] Analysis by GLC. Normalized yields. [b] Reference 2a. [c] Present study. [d] H. C. Brown and P. M. Weissman, *Israel J. Chem.*, 1, 430 (1963). [e] H. C. Brown and P. M. Weissman, *J. Am. Chem. Soc.*, 87, 5614 (1965). [f] H. C. Brown and N. M. Yoon, *ibid.*, 88, 1464 (1966). [g] H. C. Brown, P. Heim, and N. M. Yoon, *ibid.*, 92, 1637 (1970).

agents for the reduction of the tosylates of related structures.

Finally, the hindered tosylate, 2,2-dimethyl-1-hexyl tosylate, is reduced at a rate even slower than that exhibited by cyclohexyl tosylate. However, the reaction is reasonably rapid at 65 °C (refluxing THF), providing a satisfactory yield of the



(7)

desired product, 2,2-dimethylhexane, free of isomeric alkanes (eq 7).

The following procedure for the reduction of cyclooctyl tosylate is representative. An oven-dried, 300-ml flask equipped with a side arm fitted with a silicone rubber stopple, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was cooled to room temperature under a dry stream of nitrogen. THF (20 ml) was introduced, followed by 7.1 g (25 mmol) of cyclooctyl tosylate. The mixture was cooled to 0 °C (ice bath). To this stirred solution, lithium triethylborohydride,[8] 33.3 ml (50 mmol), of a 1.5 *M* solution in THF was added and the ice bath removed. The mixture was stirred for 2 h (~25 °C). Excess hydride was decomposed with water. The organoborane was oxidized with 20 ml of 3 N NaOH and 20 ml of 30% H_2O_2. Then the THF layer was separated. The aqueous layer was extracted with 2 × 20-ml portions of *n*-pentane. The combined organic extracts were washed with 4 × 15-ml portions of water to remove ethanol produced in the oxidation. Organic extract was dried ($MgSO_4$) and the volatile solvents were removed by distillation. Distillation of the residue yields 2.27 g (81%) of cyclooctane as colorless liquid, bp 142–146 °C, $n^{20}D$ 1.4630. GLC analysis indicated 97% cyclooctane and 3% cyclooctene.

In conclusion, it is evident that lithium triethylborohydride possesses certain major advantages over the conventional reagents for the deoxygenation of certain cycloalkyl and hindered alcohols, with attack at the sulfur–oxygen bond and the elimination curtailed considerably.

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(9) 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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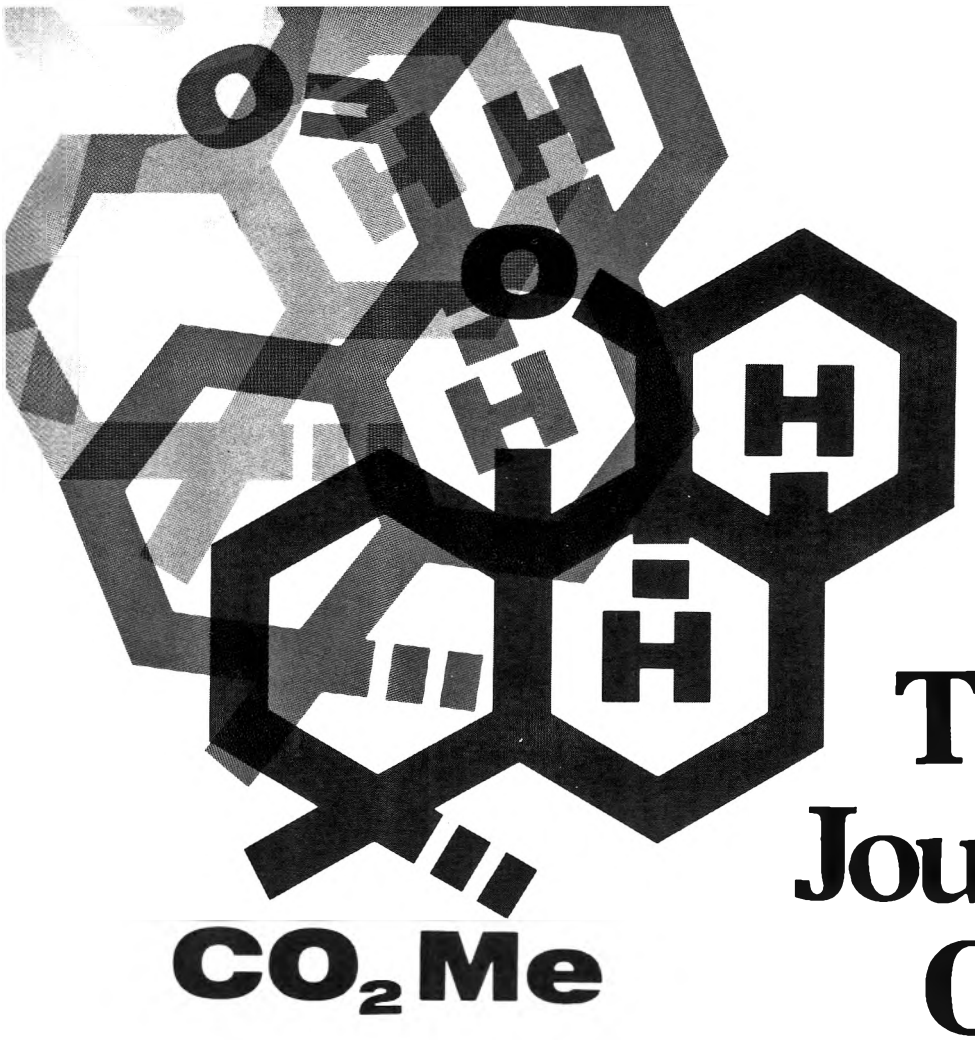

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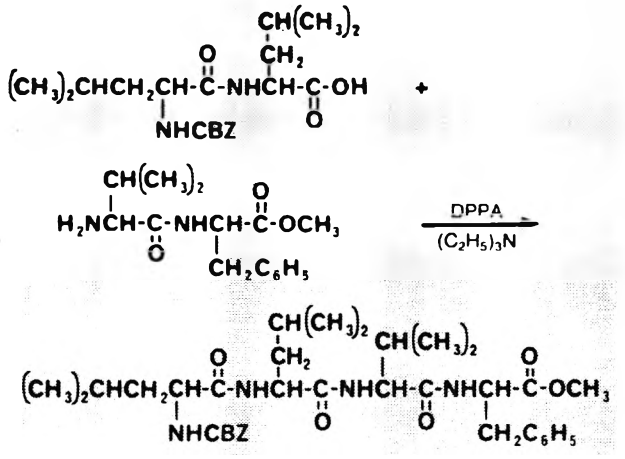
Diphenylphosphoryl azide {DPPA}

Diphenylphosphoryl azide (DPPA), reportedly a stable and nonexplosive liquid,[1] has a variety of interesting applications in synthetic organic chemistry.[2,3]

I. Peptide Synthesis

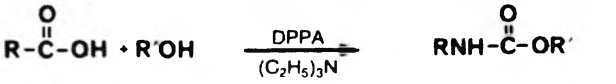
DPPA is an efficient and selective coupling agent in peptide synthesis. In the presence of base, **DPPA** allows coupling of acylamino acids or peptides with esters of other amino acids or peptides. This utility of **DPPA** in peptide synthesis is enhanced by the fact that no racemization products are observed. Thus, **DPPA** couples *N*-carbobenzyloxy-L-leucyl-L-leucine and L-valyl-L-phenylalanine methyl ester in DMF and triethylamine below 0° in 87% yield with no racemization.[4]



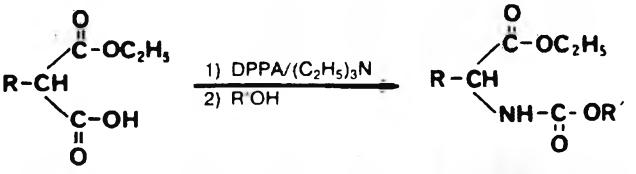
The selective synthesis of peptides using **DPPA** has been extensively reviewed.[5,6]

II. Urethanes, α-amino acids

Urethanes are obtained by refluxing an equimolar mixture of a carboxylic acid, triethylamine, an alcohol and **DPPA** for 5-25hr. This modified Curtius reaction is preferred to the tedious classical method.



Malonic acid monoethyl ester undergoes the Curtius reaction when refluxed in benzene with an equimolar mixture of **DPPA,** triethylamine and an alcohol.[7,8]



When benzyl alcohol is used in the above reaction, *N*-carbobenzyloxy-α-amino acid ethyl esters are obtained.[9]

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