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NOTES

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AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 11

MAY 31, 1974

The Structure of Sisomicin, a Novel Unsaturated Aminocyclitol Antibiotic from *Micromonospora inyoensis*

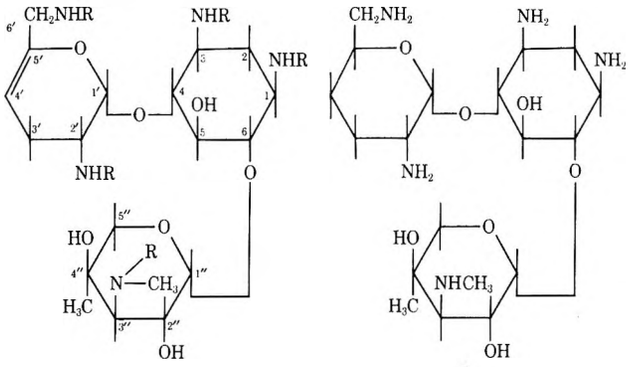
Hans Reimann,* David J. Cooper, Alan K. Mallams, Robert S. Jaret, Albert Yehaskel, Max Kugelman, H. Frederick Vernay, and Doris Schumacher

Research Division, Schering Corporation, Bloomfield, New Jersey 07003

Received December 19, 1973

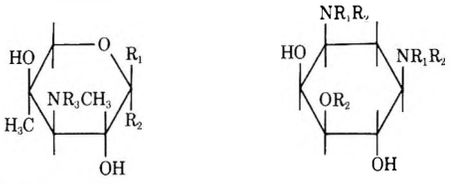
Sisomicin, the principal antibiotic produced in the fermentation of *Micromonospora inyoensis*, has been shown to be *O*-2,6-diamino-2,3,4,6-tetradeoxy-α-D-*glycero*-hex-4-enopyranosyl(1→4)-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl(1→6)]-2-deoxy-D-streptamine (**1**). Sisomicin contains a novel unsaturated sugar unit, not previously encountered in any aminocyclitol antibiotic.

Submerged fermentations of *Micromonospora inyoensis* (NRRL 3292) produce sisomicin,[1] a novel unsaturated aminocyclitol antibiotic[2,3] having broad spectrum antibacterial activity.[4] Sisomicin is the major component of the crude antibiotic complex, which was isolated from the fermentation broth by ion-exchange chromatography.[3] Column chromatography of the crude antibiotic on silica gel afforded pure sisomicin, which was crystallized from ethanol. Chemical and physical studies have established structure **1** for sisomicin.[5]



1, R = H
5, R = Ac
21, R = Cbz

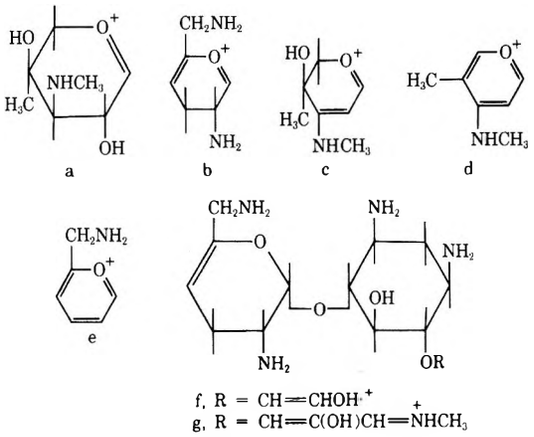
2



3, R_1, R_2 = H, OH; R_3 = H
11, R_1, R_2 = H, OH; R_3 = Ac
15, R_1 = OCH_3; R_2 = R_3 = H
16, R_1 = R_3 = H; R_2 = OCH_3

4, R_1 = R_2 = H
6, R_1 = Ac; R_2 = H
26, R_1 = Ac; R_2 = OCH_3

The molecular composition of sisomicin (**1**) was shown to be $C_{19}H_{37}N_5O_7$ by high-resolution mass spectrometry, and microanalyses were in agreement with a monohydrate of the above composition. The molecular weight and composition of sisomicin suggested that it was a dehydro derivative of gentamicin C_{1a} (**2**),[6-10] or an isomer thereof. The ir spectrum of sisomicin showed an absorption at 1690 cm^{-1} consistent with the presence of a vinylic ether group in the molecule. Further evidence for the presence of unsaturation in the molecule and for the location of the site of the unsaturation was obtained from a detailed study of the high-resolution mass spectrum. The latter exhibited prominent peaks at *m/e* 160 and 127 due to the ions[11] a and b formed by glycosidic cleavage of the sugar moieties in the molecule. Subsequent losses of water from the ion a gave rise to ions c and d at *m/e* 142 and 124, respectively. Loss of ammonia from the ion b gave rise to ion *e* at *m/e* 110. The formation of the ions f and g at *m/e*



a b c d e

f, R = $CH{=}CHOH^+$
g, R = $CH{=}C(OH)CH{=}\overset{+}{N}HCH_3$

330 and 372 due to cleavages adjacent to the 3″-amino group was consistent with structure **1** for sisomicin. Conclusive evidence for the location of the double bond at the 4′,5′ position in sisomicin was obtained by the presence of a prominent peak at *m/e* 362 for the ion h formed by retro-Diels–Alder cleavage of the enopyranoside moiety. The characteristic protonated formyl ions formed in the

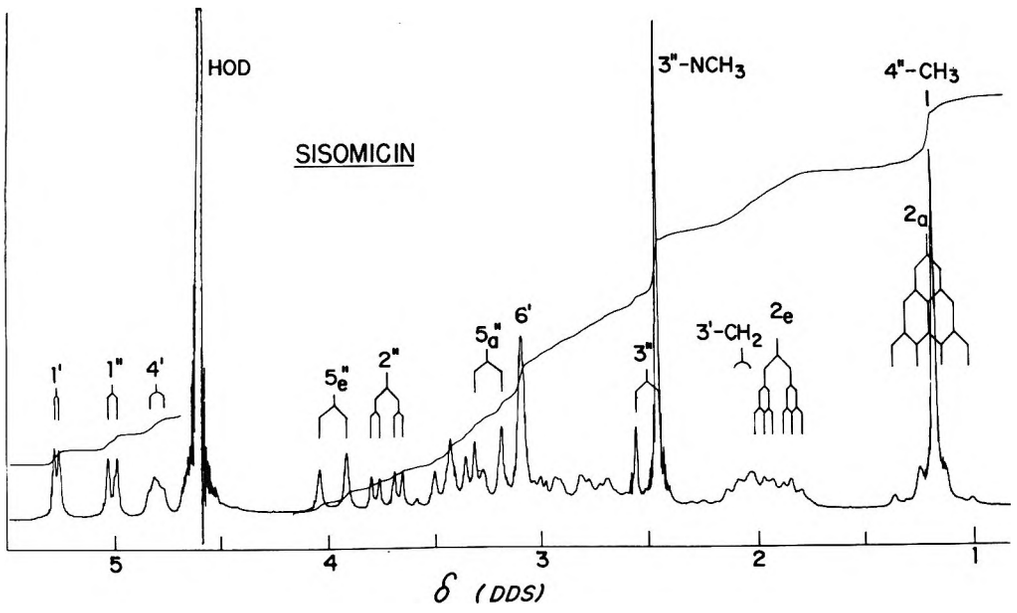
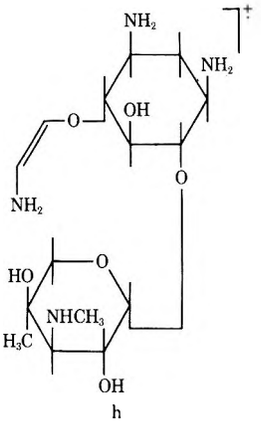


Figure 1.

mass spectra of aminoglycoside antibiotics[12] by initial cleavage of the C_1–C_2 bonds in the sugars followed by

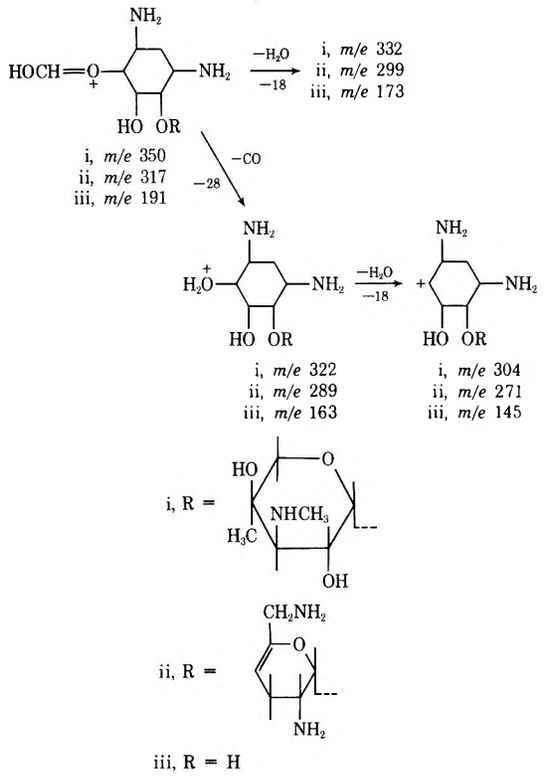


h

losses of carbon monoxide and water were also observed and are shown in Scheme I.

The 100-MHz nmr spectrum (Figure 1) of sisomicin (1) was consistent with the proposed structure and revealed the presence of one *C*-methyl group at δ 1.18 and one *N*-methyl group at δ 2.48. The anomeric proton of the saturated sugar moiety occurred as a doublet at δ 5.04 with $J_{1'',2''}$ = 4 Hz consistent with an axial glycosidic linkage for that sugar. Proton $H_{2''}$ gave rise to a doublet of doublets at δ 3.76 with $J_{2'',3''}$ = 10.0 Hz, while $H_{3''}$ occurred as a doublet at δ 2.53. These assignments confirmed the relative stereochemistry of C_1–C_3 of this unit. The $H_{5''a}$ and $H_{5''e}$ signals occurred as doublets at δ 3.28 and 4.00, respectively, with $J_{5''a,5''e}$ = 12.2 Hz. Irradiation of the $H_{5''e}$ signal caused the doublet at δ 3.28 to collapse to a singlet. The above assignments were consistent with the presence of garosamine (3)[7] as one of the sugar components of sisomicin. The anomeric proton of the enopyranoside moiety gave rise to a doublet at δ 5.30 having $J_{1',2'}$ = 2 Hz, consistent, with an axial glycosidic linkage. A multiplet at δ 3.13 due to $H_{2'}$ was in agreement with the presence of a 2′-equatorial amino group in the enopyranoside. Irradiation of this signal caused the signal due to $H_{1'}$ to collapse to a singlet. The 3′-methylene protons occurred as a complex multiplet at *ca.* δ 1.6. Irradiation of this signal caused the multiplet due to $H_{2'}$ to simplify and at the same time collapsed the multiplet at δ 4.83, due to

Scheme I



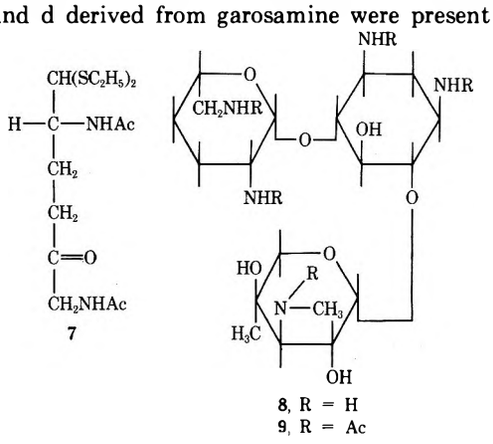
the vinylic 4′ proton, to a singlet. The 6′-methylene group appeared as a broad singlet at δ 3.12. Long-range coupling between the 6′-methylene group and the vinylic 4′ proton was demonstrated by irradiating the signal at δ 3.12, which sharpened the multiplet at δ 4.83. The above nmr observations established the essential structural features and relative stereochemistry of the novel enopyranoside unit of sisomicin. The presence of deoxystreptamine (4) was supported in the nmr spectrum by a doublet of a doublet of doublets at δ 1.19 having $J_{1a,2a} = J_{2a,3a} = J_{2a,2e}$ = 13 Hz due to H_{2a} and at δ 1.92 having $J_{2a,2e}$ = 13 and $J_{1a,2e} = J_{2e,3a}$ = 4 Hz due to H_{2e}.

The CD spectra of sisomicin (1) recorded in cuprammonium A and in TACu gave values for $[\theta]_{290}$ of −5890 and −8500, respectively. These were consistent with a 4,6 linkage of the sugar units, the 3-aminopentopyranoside

being in the β-L-arabino configuration, thus confirming that it is garosamine.

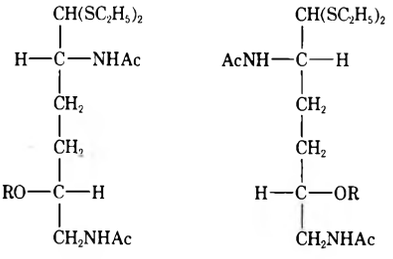
Acetylation of sisomicin (**1**) using acetic anhydride in methanol gave a penta-*N*-acetate (**5**). Mercaptolysis of the *N*-acetate **5** using ethanethiol and concentrated hydrochloric acid gave 1,3-di-*N*-acetyl-2-deoxystreptamine (**6**), which was identical with an authentic sample,[8] and (2*R*)-2,6-diacetamido-5-ketohexanal diethyl dithioacetal (**7**). The ir spectrum of the latter revealed the presence of keto and amide groups in the molecule. The nmr spectrum of **7** showed the presence of two ethyl groups and two *N*-acetyl groups. The chemical shifts of the 6- and 4-methylene groups were consistent with the location of the keto group at C_5 and of one of the amino groups at C_6. The occurrence of H_1 as a doublet and the chemical shift of the 2-methine proton at *ca.* δ 4.30 confirmed that the second amino group was situated at C_2. The mass spectrum of **7** showed the expected molecular ion at *m/e* 334 and a prominent ion at *m/e* 275 due to elimination of acetamide (M − 59) clearly supported the location of an amino group at C_2.[13] Subsequent cleavage of the C_3–C_4 bond to give an ion at *m/e* 161 confirmed the presence of a methylene group at C_3. These and other prominent ions are shown in Scheme II.

Hydrogenation of sisomicin (**1**) was expected to give gentamicin C_{1a} (**2**), thus affording a complete proof of structure, including stereochemistry and linkages to the 2-deoxystreptamine ring. However, when the catalytic reduction was carried out, an isomeric compound, dihydrosisomicin (**8**), was obtained and no gentamicin C_{1a} (**2**) could be demonstrated in the reduction product on careful chromatographic examination. The absence of a vinylic ether band in the ir spectrum of **8** and the presence of an $M^+ + 1$ peak at *m/e* 450 in the mass spectrum indicated that the double bond had been reduced. The expected ions a, c, and d derived from garosamine were present in the



7

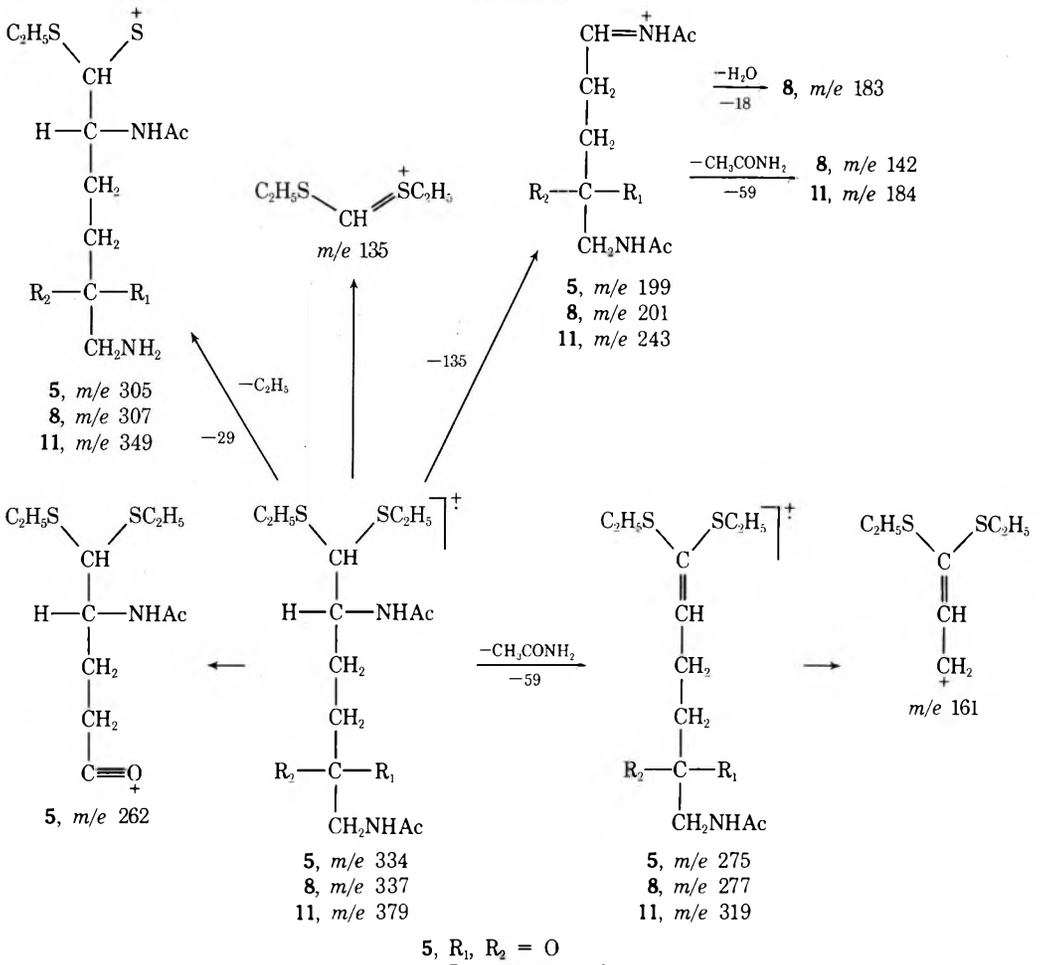
8, R = H
9, R = Ac



10, R = H
13, R = Ac

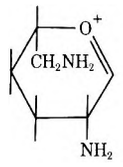
12, R = H
14, R = Ac

Scheme II

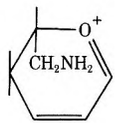


5, R$_1$, R$_2$ = O
8, R$_1$ = H; R$_2$ = OH
11, R$_1$ = H; R$_2$ = OAc

spectrum, while the new sugar moiety gave rise to the ions i and j at m/e 129 and 112, respectively. The prominent



i

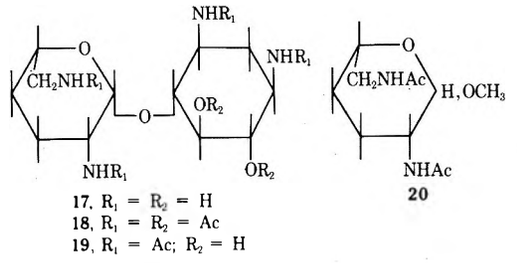


j

ion h formed by retro-Diels–Alder cleavage of the enopyranoside in sisomicin was absent in the spectrum of **8**. Ions corresponding to saturated derivatives of f and g were observed in the spectrum of **8**, at m/e 332 and 374, respectively. The characteristic ions in Scheme I for series i and iii were identical with those of sisomicin (**1**), while the series ii was shifted to higher mass by two mass units, corresponding to the saturated ions at m/e 319, 301, 291, and 273. The nmr spectrum of **8** showed the anomeric proton of garosamine as a doublet with J = 4 Hz at δ 5.10. The anomeric proton of the remaining sugar occurred as a doublet at δ 4.78 with J = 1.7 Hz. The chemical shift of the latter clearly indicated that $H_{1'}$ was not in an equatorial orientation, which would have resulted if reduction had occurred from the lower face of the enopyranoside to give gentamicin C_{1a}. Instead, reduction had taken place exclusively from the top face of the enopyranoside to give an L sugar having an axial CH_2NH_2 substituent at $C_{5'}$ and an axial glycosidic linkage at $C_{1'}$. The chemical shift of the anomeric proton may now be explained by a conformational inversion from the $^4C_1$ to the $^1C_4$ conformation, in order to relieve excessive 1,3-diaxial interaction. This resulted in an axial orientation for $H_{1'}$ causing an upfield shift for $H_{1'}$ relative to the corresponding proton in the isomeric gentamicin C_{1a} (**2**).[6] The signal due to $H_{1'}$ in the latter occurred as a doublet at *ca.* δ 5.10 with J = 4 Hz, consistent with an $H_{1'e}$, $H_{2'a}$ orientation in gentamicin C_{1a} (**2**).[6] The coupling constant of 1.7 Hz observed for $H_{1'a}$,$H_{2'e}$ in the spectrum of **8** was consistent with the above observations. Dihydrosisomicin (**8**) and gentamicin C_{1a} (**2**) could be distinguished by tlc on silica gel plates using chloroform–methanol–7% ammonium hydroxide (1:2:1) as the eluent. The compounds could also be distinguished by the color produced on spraying with ninhydrin.[3] Dihydrosisomicin (**8**) is inactive as an antibacterial agent.

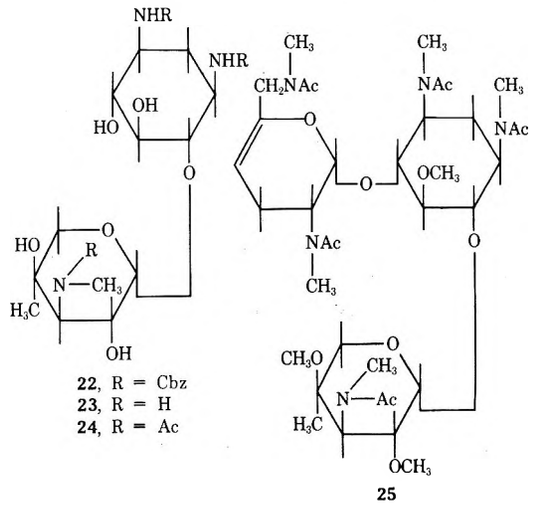
Acetylation of dihydrosisomicin (**8**) in methanol afforded the penta-*N*-acetyl derivative **9**. Mercaptolysis of the latter with ethanethiol and concentrated hydrochloric acid gave, after re-N-acetylation, 2,6-diacetamido-2,3,4,6-tetradeoxy-L-*threo*-hexose diethyl dithioacetal (**10**), 1,3-di-*N*-acetyl-2-deoxystreptamine (**6**), and 3-*N*-acetylgarosamine (anomeric mixture) (**11**). The nmr spectrum of the dithioacetal **10** supported the assigned structure and was identical with that of the D-threo enantiomer (**12**) which had been prepared by unambiguous synthesis.[14] The dithioacetals **10** and **12** were identical on tlc. The L-threo enantiomer (**10**) showed a rotation of +32° in methanol while the D-threo enantiomer (**12**) had a rotation of −30°.[14] Acetylation of **10** gave the *N,N,O*-triacetyl derivative (**13**) as a syrup having a rotation of +21.6° in methanol. The corresponding *N,N,O*-triacetyl-D-threo enantiomer (**14**)[14] had a rotation of −19° in the same solvent. The mass spectrometric fragmentation patterns of **10** and **13** supported the assigned structures and are given in Scheme II.

Methanolysis of dihydrosisomicin (**8**) gave methyl garosaminide (**15** and **16**)[7] and 5′-epigentamine C_{1a} (**17**), which was characterized as the hydrochloride salt. The spectroscopic and analytical data were in accord with the



17, $R_1 = R_2 = H$
18, $R_1 = R_2 = Ac$
19, $R_1 = Ac$; $R_2 = H$

20



22, R = Cbz
23, R = H
24, R = Ac

25

assigned structure. The free base **17**, obtained from the hydrochloride salt by passage over Amberlite IR 45 resin, was acetylated to give the *N,O*-peracetyl derivative (**18**), which on saponification with sodium methoxide in methanol gave the tetra-*N*-acetyl derivative (**19**). The CD spectrum of **19** run in cuprammonium A showed a negative extremum at 290 nm and a positive extremum at 575 nm consistent with a negative dihedral angle for the glycol system.[15,16] The above observation demonstrated that the sugar moiety is located at the 4 position of the deoxystreptamine ring in 5′-epigentamine C_{1a} (**17**). It follows that the enopyranoside moiety in sisomicin (**1**) is glycosidically linked to the 4-hydroxy group of deoxystreptamine.

Methanolysis of penta-*N*-acetyldihydrosisomicin (**9**) followed by re-N-acetylation gave 1,3-di-*N*-acetyl-2-deoxystreptamine (**6**), methyl 3-*N*-acetylgarosaminide, and methyl 2,6-di-*N*-acetyl-5-epipurpurosaminide C as an anomeric mixture (**20**). The two anomeric protons in **20** gave rise to doublets in the nmr spectrum at δ 4.50 with $J_{1e,2e}$ = 1.5 Hz due to the α-L anomer and at δ 4.40 with $J_{1a,2e}$ = 2 Hz due to the β-L anomer. Both signals were consistent with a $^1C_4$ configuration for this sugar, and with the assigned stereochemistry at C_2.

Sisomicin (**1**) was converted into the penta-*N*-carbobenzoxy derivative (**21**), which was found to be extremely labile to mildly acidic conditions. Thus hydrolysis of **21** with sulfuric acid in tetrahydrofuran, or with Amberlite IR 120 (H^+) resin in tetrahydrofuran at ambient temperature, gave 1,3,3′-tri-*N*-carbobenzoxygaramine (**22**), a novel pseudodisaccharide derivative, in high yield. Hydrogenolysis of tri-*N*-carbobenzoxygaramine (**22**) over 10% palladium on carbon gave the underivatized pseudo-disaccharide, garamine (**23**). The nmr and mass spectra were in accord with the assigned structure. Methanolysis of garamine (**23**) gave 2-deoxystreptamine (**4**) and methyl α- and β-garosaminides (**15** and **16**) which were identical with authentic samples obtained from the gentamicins.[7]

Garamine (**23**) was converted into the tri-*N*-acetyl derivative (**24**) in the usual manner. The CD spectrum of a cuprammonium A complex of **24** showed a positive extremum at 290 nm and a negative extremum at 560 nm con-

sistent with a positive dihedral angle for the 4,5-glycol.[15,16] The garosamine moiety is therefore located at the 6 position of deoxystreptamine in sisomicin (**1**).

Further confirmation of the location of the enopyranoside at the 4 position and of garosamine at the 6 position in sisomicin was obtained chemically as follows. Permethylation of penta-*N*-acetylsisomicin (**5**) gave the permethylated derivative **25**, which on vigorous acidic hydrolysis gave the symmetrical 1,3-di-*N*-acetyl-1,3-di-*N*-methyl-5-*O*-methyl-2-deoxystreptamine (**26**), which was identical with an authentic sample.[8] The latter showed a prominent ion at *m/e* 270 due to loss of water from the molecular ion, which is characteristic[17] of a deoxystreptamine derivative containing hydroxyl groups at the 4 and/or 6 positions. If the *O*-methyl group had been at the 4 or 6 position a loss of methanol would also have been evident from the molecular ion, which was not the case. The CD spectrum of **26** in cuprammonium A showed only base-line absorption, indicating that the molecule contained no vicinal glycol system.

The total structure and absolute stereochemistry of sisomicin may therefore be represented by the structure **1**. The ^{13}C magnetic resonance spectrum of sisomicin obtained subsequently[18] was in full accord with this structure.

Experimental Section

Optical rotations were measured at c 0.3. Ir spectra were recorded either on a Perkin-Elmer Model 221 or on an Infracord 137 spectrometer. Nmr spectra were obtained at 60 or 100 MHz on a Varian A-60A or on an XL-100-15 spectrometer, respectively. Chemical shifts in D_2O solution are reported in parts per million downfield from internal or external DSS. All other chemical shifts are reported in parts per million downfield from internal TMS. CD spectra were run on a Cary 61 spectrometer. Mass spectra were recorded on a Perkin-Elmer RMU-6D instrument, a Varian MAT CH5 instrument, or on an AEI MS 902B spectrometer.

Isolation and Characterization of Sisomicin (1). Chromatography of the crude antibiotic complex produced by submerged fermentation of *Micromonospora inyoensis*[2] on silica gel using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide (1:1:1) system as the eluent gave sisomicin (**1**), which after passage over Amberlite IRA 401S (OH^-) resin, crystallized as needles from ethanol: mp 198–201°; $[\alpha]^{26}D$ +188.9° (H_2O); $[\theta]_{290}$ −8500 (TACu), −5800 (Cupra A); ν_{max} (KCl) 3370 (NH, OH), 1690 (CH=COC), 1065 cm^{-1} (COC); nmr (D_2O) δ 1.18 (s, 3, 4″-CH_3), 2.48 (s, 3, 3′-NCH_3), 2.53 (d, $J_{2'',3''}$ = 10.0 Hz, 1, $H_{3''}$), 3.12 (broad s, 2, 6′-CH_2), 3.28 (d, $J_{5''a,5''e}$ = 12.2 Hz, 1, $H_{5''a}$), 3.76 (dd, $J_{1'',2''}$ = 4, $J_{2'',3''}$ = 10 Hz, 1, $H_{2''}$), 4.00 (d, $J_{5''a,5''e}$ = 12.2 Hz, 1, $H_{5''e}$), 4.83 (broad t, 1, $H_{4'}$), 5.04 (d, $J_{1'',2''}$ = 4 Hz, 1, $H_{1''}$) and 5.30 (d, $J_{1',2'}$ = 2 Hz, 1, $H_{1'}$); *m/e* 447.262 ($M\cdot^+$) (calcd for $C_{19}H_{37}N_5O_7$, *m/e* 447.269).

Anal. Calcd for $C_{19}H_{37}N_5O_7\cdot H_2O$: C, 49.01; H, 8.46; N, 15.04. Found: C, 49.56; H, 8.26; N, 14.89.

1,3,2′,6′,3″-Penta-*N*-acetylsisomicin (5). Sisomicin (**1**, 500 mg) was dissolved in a mixture of methanol (25 ml) and acetone (25 ml) containing acetic anhydride (8 ml) and the solution was allowed to remain at 25° for 30 min. The solution was evaporated *in vacuo* and the residue, after azeotroping with toluene, was chromatographed on a silica gel column (110 × 2.5 cm) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide (1:1:1) system as the eluent to give the acetate **5**: 660 mg (90%); mp 188–198° dec; $[\alpha]^{26}D$ +194.6° (CH_3OH), +200° (H_2O); ν_{max} (Nujol) 3240 (OH, NH), 1650, 1550 ($NCOCH_3$), 1025 cm^{-1} (COC); nmr (CD_3OD)[19] δ 1.01, 1.10 (s, 3, 4″-CH_3), 1.90, 1.96, 1.99, 2.15 (s, 15, $NCOCH_3$), 3.01, 3.13 (s, 3, 3″-NCH_3), 5.19 (d, $J_{1'',2''}$ = 4 Hz, 1 $H_{1''}$), 5.54 (d, $J_{1',2'}$ = 2.5 Hz, 1, $H_{1'}$), δ (DMSO, at 140°) 0.97 (s, 3, 4″-CH_3), 1.76, 1.79, 1.82, 1.86, 1.99 (s, 15, $NCOCH_3$), 2.97 (s, 3, 3′-NCH_3), 5.09 (broad d, $J_{1'',2''}$ = 4 Hz, 1, $H_{1''}$), 5.32 (d, $J_{1',2'}$ = 2.5 Hz, 1, $H_{1'}$).

Anal. Calcd for $C_{29}H_{47}N_5O_{12}$: C, 52.95; H, 7.20; N, 10.65. Found: C, 52.45; H, 7.26; N, 10.44.

Mercaptolysis of 1,3,2′,6′,3″-Penta-*N*-acetylsisomicin (5). 1,3,2′,6′,3″-Penta-*N*-acetylsisomicin (**5**, 3 g) was added to a solution of ethanethiol (6 ml) and concentrated hydrochloric acid (6 ml) and the mixture was stirred at 7° for 24 hr. The solution was diluted with water (500 ml), neutralized with an excess of basic lead carbonate, filtered, and lyophilized. The solid was dissolved in methanol (100 ml), acetic anhydride (3 ml) was added, and the solution was allowed to remain at 25° for 1 hr. The solution was evaporated, the residue was triturated with chloroform (50 ml), and the insoluble 1,3-di-*N*-acetyl-2-deoxystreptamine (**6**), 1.07 g (96%), was filtered off. Trituration of the latter with chloroform gave colorless crystals which were identical (melting point and mixture melting point) with an authentic sample.[8] The filtrate was evaporated to dryness and the residue (1.75 g) was recrystallized repeatedly from benzene–methanol and then from ethanol to give (2*R*)-2,6-diacetamido-5-ketohexanal diethyl dithioacetal (**7**): 930 mg (61%); mp 153–154°; $[\alpha]^{26}D$ +33.7° ($CHCl_3$); ν_{max} ($CHCl_3$) 3380 (NH), 1740 (C=O), 1670, 1500 cm^{-1} ($NHCOCH_3$); nmr ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3, CH_3CH_2S), 1.30 (t, J = 7 Hz, 3, CH_3CH_2S), 1.98 (s, 3, NHAc), 2.02 (s, 3, NHAc), *ca.* 2.50 (m, 2, 4-CH_2), 2.69 (q, J = 7 Hz, 2, CH_3CH_2S), 2.70 (q, J = 7 Hz, 2, CH_3CH_2S), 3.92 (d, J = 4 Hz, 1, H_1), 4.11 (d, J = 5 Hz, 2, 6-CH_2), 6.00 (broad d, J = 9 Hz, 1, 2-NHAc), and 6.38 (broad m, $W_{1/2} \cong$ 9 Hz, 1, 6-NHAc; *m/e* 334 ($M\cdot^+$).

Dihydrosisomicin (8). Sisomicin (**1**, 1.79 g) in methanol (40 ml) was hydrogenated over 10% palladium on carbon (400 mg) at 25° (1 atm) for 23 hr. The catalyst was filtered off and washed with methanol and the combined filtrates were evaporated. The solid was chromatographed on a silica gel column (160 × 1 cm) using the lower phase of a chloroform–2-propanol–concentrated ammonium hydroxide (2:1:1) system as the eluent to give, after passage over Amberlite IRA 401S (OH^-) followed by lyophilization, the dihydrosisomicin (**8**), 1.05 g (58%), as a colorless solid: $[\alpha]^{26}D$ +145.0° (H_2O); ν_{max} ($CHCl_3$) 3550, 3200 cm^{-1} (NH, OH); nmr (D_2O) δ 1.21 (s, 3, 4″-CH_3), 2.52 (s, 3, 3″-NCH_3), 4.78 (d, $J_{1',2'}$ = 1.7 Hz, 1, $H_{1'}$) and 5.10 (d, $J_{1'',2''}$ = 4 Hz, 1, $H_{1''}$); *m/e* 450 [(M + 1)$^+$].

Anal. Calcd for $C_{19}H_{39}N_5O_7\cdot\frac{1}{2}CO_2$:[20] C, 49.67; H, 8.33; N, 14.85. Found: C, 50.12; H, 8.47; N, 14.32.

1,3,2′,6′,3″-Penta-*N*-acetyldihydrosisomicin (9). Dihydrosisomicin (**8**, 400 mg) was dissolved in methanol (10 ml), and acetic anhydride (1 ml) was added. After standing at 25° for 5 hr the mixture was poured into ether and the precipitate was filtered off and washed with ether to give the acetate **9** as a colorless, amorphous solid: 440 mg (75%); mp 192–200°; $[\alpha]^{26}D$ +98.0° (C_2H_5OH); ν_{max} (Nujol) 3250 (NH, OH), 1640, 1540 cm^{-1} ($NCOCH_3$).

Anal. Calcd for $C_{29}H_{49}N_5O_{12}\cdot H_2O$: C, 51.39; H, 7.59; N, 10.33. Found: C, 51.49; H, 7.43; N, 10.20.

Mercaptolysis of 1,3,2′,6′,3″-Penta-*N*-acetyldihydrosisomicin (9). 1,3,2′,6′,3″-Penta-*N*-acetyldihydrosisomicin (**9**, 600 mg) was dissolved in a mixture of 6 *N* hydrochloric acid (3 ml) and ethanethiol (3 ml) and the reaction mixture was stirred at 25° for 48 hr. The reaction mixture was worked up as before to give 1,3-di-*N*-acetyl-2-deoxystreptamine (**6**), 210 mg (94%), which was insoluble in chloroform. The chloroform-soluble material was chromatographed on a silica gel column (110 × 2.5 cm) using 15% methanol in benzene as the eluent to give 2,6-diacetamido-2,3,4,6-tetradeoxy-L-*threo*-hexose diethyl dithioacetal (**10**) as a low-melting crystalline solid: 235 mg (77%); mp 81–84°; $[\alpha]^{26}D$ +32.0° (CH_3OH); ν_{max} ($CHCl_3$) 3400, 3300 (OH, NH), 1650 cm^{-1} ($NCOCH_3$); nmr ([$^2H_5$]pyridine) δ 1.19 (t, J = 7.5 Hz, 3, CH_3CH_2S), 1.26 (t, J = 7.5 Hz, 3, CH_3CH_2S), 2.05 (s, 3, NAc), 2.12 (s, 3, NAc), 2.74 (q, J = 7.5 Hz, 2, CH_3CH_2S), 2.78 (q, J = 7.5 Hz, 2, CH_3CH_2S), 4.09 (m, 1, H_5), 4.40 (d, $J_{1,2}$ = 4 Hz, 1, H_1), and 4.70 (dt, $J_{1,2}$ = 4, $J_{2,3}$ = 9 Hz, 1, H_2); *m/e* 337 [(M + 1)$^+$].

Anal. Calcd for $C_{14}H_{28}N_2S_2O_3$: C, 49.97; H, 8.39; N, 8.33; S, 19.06. Found: C, 49.85; H, 8.44; N, 8.39; S, 18.22.

The more polar fractions from the column afforded 3-*N*-acetylgarosamine (**11**), which crystallized from methanol–benzene, 17 mg (9%), mp 183–185°, *m/e* 220 [(M + 1)$^+$] and was identical with an authentic sample.

5-*O*-Acetyl-2,6-diacetamido-2,3,4,6-tetradeoxy-L-*threo*-hexose Diethyl Dithioacetal (13). 2,6-Diacetamido-2,3,4,6-tetradeoxy-L-*threo*-hexose diethyl dithioacetal (**10**, 48 mg) was dissolved in dry pyridine (0.5 ml), and acetic anhydride (0.05 ml) was added. The mixture was allowed to remain at 25° for 16 hr. The solution was evaporated and the residue was chromatographed on a silica gel column (110 × 1 cm) using 15% methanol in chloroform as the eluent to give the acetate **13** as a colorless syrup: 32 mg (59%); $[\alpha]^{26}D$ +22.0° (CH_3OH); ν_{max} ($CHCl_3$) 3450 (NH), 1740, 1240 (CH_3COO), 1660 cm^{-1} ($NCOCH_3$); nmr ([$^2H_5$]pyridine) δ 1.20 (t, J = 7.5 Hz, 3, CH_3CH_2S), 1.25 (t, J = 7.5 Hz, 3, CH_3CH_2S), 1.88 (s, 3, OAc), 2.02 (s, 3, NAc), 2.11 (s, 3, NAc), 2.72 (q, J = 7.5 Hz, 2, CH_3CH_2S), 2.77 (q, J = 7.5 Hz, 2, CH_3CH_2S), 3.52 (dd, $J_{6,6'}$

= 14, $J_{5,6}$ = 6 Hz, 1, H_6), 3.73 (dd, $J_{6,6'}$ = 14 Hz, $J_{5,6'}$ = 5 Hz, 1, $H_{6'}$), 4.37 (d, $J_{1,2}$ = 4 Hz, 1, H_1), 4.70 (m, 1, H_2), and 5.30 (m, 1, H_5); *m/e* 379 [(M + 1)$^+$].

Methanolysis of Dihydrosisomicin (8). Dihydrosisomicin (**8,** 1.25 g) was heated under reflux with 6 *N* hydrogen chloride in methanol (125 ml) for 8 hr. The reaction mixture was cooled to 7° and the crystalline 5′-epigentamine C_{1a} (**17**) hydrochloride precipitate was filtered off, washed with cold methanol, and dried: 591 mg (49%); mp 270–275°; $[\alpha]^{26}D$ +24.5° (H_2O); ν_{max} (Nujol) 3350–3320 (OH, NH), 1975 cm^{-1} (NH^+Cl^-).

Anal. Calcd for $C_{12}H_{26}N_4O_4 \cdot 4HCl \cdot H_2O$: C, 31.72; H, 7.10; N, 12.33; Cl, 31.22. Found: C, 31.41; H, 7.11; N, 12.30; Cl, 30.82.

The hydrochloride (350 mg) was converted to the free base by passage over Amberlite IR 45 resin followed by lyophilization to give **17**: 255 mg; $[\alpha]^{26}D$ +31.0° (H_2O); nmr (D_2O) δ 4.87 (d, *J* = 1.5 Hz, 1, $H_{1'}$); *m/e* 291 [(M + 1)$^+$], 191, 173, 163, 145, 129.

The mother liquors after crystallization of 5′-epigentamine C_{1a} (**17**) hydrochloride on evaporation followed by chromatography on silica gel using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide (1:1:1) system as the eluent, gave additional 5′-epigentamine C_{1a} (**17**), 415 mg (51%), and methyl garosaminide (**15** and **16**) as a syrup, 400 mg (76%), which was identical with an authentic sample (tlc, ir, nmr, and mass spectrum).

1,3,2′,6′-Tetra-*N*-acetyl-5,6-di-*O*-acetyl-5′-epigentamine C_{1a} (18). 5′-Epigentamine C_{1a} (**17,** 90 mg) in pyridine (2 ml) was treated with acetic anhydride (0.5 ml) and the mixture was stirred at 25° for 24 hr. The solution was evaporated and the residue was dissolved in acetone and filtered. The hexaacetate **18** crystallized as a monohydrate, monoacetone solvate: 76 mg (45%); mp 161–164°; $[\alpha]^{26}D$ +8.1° (H_2O); ν_{max} (Nujol) 3440, 3290, 3100 (NH), 1755, 1720, 1690, 1240, 1225 (OAc), 1650 cm^{-1} (NAc); nmr (D_2O) δ 1.91 (s, 3, OAc), 1.97–2.00 (s, 12, NAc), 2.09 (s, 3, OAc) and 2.18 (s, 6, acetone); *m/e* 542 (M·$^+$), 483 (M − 59), 359, 313, 212.

Anal. Calcd for $C_{24}H_{38}N_4O_{10} \cdot H_2O \cdot C_3H_6O$: C, 52.41; H, 7.50; N, 9.06. Found: C, 52.68; H, 7.42; N, 9.41.

1,3,2′,6′-Tetra-*N*-acetyl-5′-epigentamine C_{1a} (19). 1,3,2′,6′-Tetra-*N*-acetyl-5,6-di-*O*-acetyl-5′-epigentamine C_{1a} (**18,** 40 mg) was dissolved in methanol (1.5 ml) and a catalytic amount of sodium metal was added to the stirred solution. After stirring at 25° for 1 hr, Dry Ice was added, the solution was concentrated, and the residue was triturated with ethanol. The sodium carbonate was filtered off and the filtrate was concentrated to give the crystalline tetra-*N*-acetate **19**: 21 mg (62%); mp 250–260° dec; ν_{max} (Nujol) 3500, 3450, 3300, 3100 (OH, NH), 1640, 1600 cm^{-1} (NAc); nmr (D_2O) δ 1.98–2.01 (s, 12, NAc) and 4.80 (d, *J* = 1.5 Hz, 1, $H_{1'}$); *m/e* 441 (M − 17), 399 (M − 59), 381 (M − 17 − 59), 275 (191 + $2CH_2CO$), 229 (145 + $2CH_2CO$), 257 (275 − 18), 239 (257 − 18), 211 (229 − 18), 213 (129 + $2CH_2CO$).

Methanolysis of 1,3,2′,6′,3″-Penta-*N*-acetyldihydrosisomicin (9). 1,3,2′,6′3″-Penta-*N*-acetyldihydrosisomicin (**9,** 2.5 g) was heated under reflux with 6 *N* hydrogen chloride in methanol (125 ml) for 7 hr and then allowed to remain at 25° for 16 hr. The reaction mixture was evaporated to dryness and the residue was chromatographed on a silica gel column (160 × 2.5 cm) using the lower phase of a chloroform–2-propanol–concentrated ammonium hydroxide (2:1:1) system as the eluent. The least polar component, methyl 3-*N*-acetylgarosaminide, was isolated as a crystalline solid, 190 mg (22%), mp 198–201°, $[\alpha]^{26}D$ +206.0° (H_2O), *m/e* 233 (M·$^+$), which was identical with an authentic sample.

The remaining fractions from the column were re-N-acetylated and then rechromatographed on a silica gel column (110 × 2.5 cm) using the same eluent as before to give additional methyl 3-*N*-acetylgarosaminide, 386 mg (44%), and methyl 2,6-di-*N*-acetyl-5′-epipurpurosaminide C (**20**) as a syrup: 628 mg (68%); $[\alpha]^{26}D$ −34.6° (H_2O); ν_{max} ($CHCl_3$) 3450 (NH), 1670 cm^{-1} (NAc); nmr ($CDCl_3$) δ 2.00 (s, 6, NAc), 3.35, 3.48 (s, 3, α- and β-1-OCH_3), 4.40 (d, $J_{1a,2e}$ = 2 Hz, 0.3, H_{1a}) and 4.50 (d, $J_{1e,2e}$ = 1.5 Hz, 0.7, H_{1e}); *m/e* 245 [(M + 1)$^+$], 213 (M − 31), 185 (M − 59, 184 (M − 60), 154 (M − 59 − 60), 153 (M − 60 − 31).

1,3,2′,6′,3″-Penta-*N*-carbobenzoxysisomicin (21). Sisomicin (**1,** 25 g) and sodium carbonate (13 g) were dissolved in distilled water (625 ml). Carbobenzoxy chloride (100 ml) was added to the stirred solution at 25° and the mixture was stirred for 16 hr. The solid was filtered off, washed thoroughly with water, dried *in vacuo*, and then washed with hexane to give **25,** 62 g (99%), as a colorless, amorphous solid. Preparative tlc on silica gel plates using 40% acetone in benzene as the eluent gave an analytically pure sample of **21**: mp 165–173° dec; $[\alpha]^{26}D$ +96.2° (CH_3OH); ν_{max} ($CHCl_3$) 3400 (OH, NH), 1720, 1515, 1215 (NHCOO), 1050 (COC), 695 cm^{-1} (C_6H_5); nmr ($CDCl_3$)[19] δ 1.03 (broad s, 3, 4″-CH_3), 3.02 (broad s, 3, 3″-NCH_3), 5.02 (broad s, 10, $-CH_2C_6H_5$), 3.28, 3.30 (broad s, 25, $-CH_2C_6H_5$).

Anal. Calcd for $C_{59}H_{67}N_5O_{17}$: C, 63.41; H, 5.99; N, 6.27. Found: C, 63.53; H, 6.23; N, 6.28.

1,3,3′-Tri-*N*-carbobenzoxygaramine (22). 1,3,2′,6′,3″-Penta-*N*-carbobenzoxysisomicin (**21,** 436 g) was dissolved in tetrahydrofuran (3 l.), and Amberlite IR 120 (H^+) resin (1 kg) was added. The mixture was allowed to stand at 25° for 3 days and was then filtered and the resin was washed with tetrahydrofuran. The combined filtrates were evaporated *in vacuo* in the presence of a few milliliters of water to give the crude product as a gum. Chromatography on a silica gel column (200 × 10 cm) using 10% methanol in chloroform as the eluent gave **22,** 200 g (71%), as a colorless, amorphous solid: mp 104–112°: $[\alpha]^{26}D$ + 69.6° (C_2H_5OH); λ_{max} (CH_3OH) 206 nm (ε 28,000) and 258 (538); ν_{max} ($CHCl_3$) 3350 (OH, NH), 1700, 1525 (NHCOO), 694 cm^{-1} (C_6H_5); nmr ($CDCl_3$)[19] δ 0.99 (broad s, 3, 4′-CH_3), 3.00 (broad s, 3, 3′-NCH_3), 5.00 (broad s, 6, $-CH_2C_6H_5$), 7.20 (m, 15, $-CH_2C_6H_5$), δ (DMSO, at 120°) 0.96 (s, 3, 4′-CH_3), 2.99 (s, 3, 3′-NCH_3), 5.02 (s, 2, $-CH_2C_6H_5$), 5.05 (s, 2, $-CH_2C_6H_5$), 5.11 (s, 2, $-CH_2C_6H_5$), 3.31 (s, 15, $-CH_2C_6H_5$).

Anal. Calcd for $C_{37}H_{45}N_3O_{12} \cdot H_2O$: C, 59.92; H, 6.34; N, 5.67. Found: C, 60.12; H, 5.83; N, 5.63.

Garamine (23). 1,3,3′-Tri-*N*-carbobenzoxygaramine (**22,** 2.02 g) was dissolved in methanol (100 ml) and hydrogenated over 10% palladium on carbon (1.0 g) at 25° (50 psi) for 16 hr. The catalyst was filtered off and rinsed with methanol and the combined filtrates were evaporated and chromatographed on a silica gel column (160 × 2.5 cm) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide (2:1:1) system as the eluent to give **23.** The latter, after passage over Amberlite IRA 401S (OH^-) resin followed by lyophilization, was obtained as a colorless amorphous solid: 750 mg (84%); mp 89–99°; $[\alpha]^{26}D$ +135.4° (H_2O); pK_a 8.5; $[\theta]_{290}$ −15,600 (TACu); ν_{max} (Nujol) 3300 (OH, NH), 1060 cm^{-1} (COC); nmr (D_2O) δ 1.19 (s, 3, 4′-CH_3), 2.51 (s, 3, 3′-NCH_3), 2.57 (d, $J_{2',3'}$ = 10.5 Hz, 1, $H_{3'}$), 3.30 (d, $J_{5'a,5'e}$ = 12.5 Hz, 1, $H_{5'a}$), 3.79 (dd, $J_{2',3'}$ = 10.5, $J_{1',2'}$ = 4 Hz, 1, $H_{2'}$), 4.03 (d, $J_{5'a,5'e}$ = 12.5 Hz, 1, $H_{5'e}$), 5.06 (d, $J_{1',2'}$ = 4 Hz, 1, $H_{1'}$); *m/e* 322 [(M + 1)$^+$], 246, 191, 173, 163, 145, 160.

Anal. Calcd for $C_{13}H_{27}N_3O_6$: C, 48.60; H, 8.41; N, 13.08. Found: C, 48.31; H, 8.54; N, 12.87.

Methanolysis of Garamine (23). Garamine (**23,** 484 mg) was dissolved in 6 *N* hydrogen chloride in methanol (30 ml) and the solution was heated on a steam bath for 6 hr. The insoluble 2-deoxystreptamine dihydrochloride, 223 mg (63%), mp 281–286° dec, was filtered off. The latter was dissolved in water and passed over Amberlite IR 45 resin and the eluate on evaporation gave 2-deoxystreptamine (**4**) which crystallized from ethanol, mp 220° dec, and which was identical (tlc, ir, nmr, melting point, analysis) with an authentic sample.

The filtrate after removal of **4** was passed over Amberlite IR 45 resin and the eluate was evaporated to give an oil. The latter was chromatographed on a silica gel column (110 × 1 cm) using the lower phase of a chloroform–methanol–17% ammonium hydroxide (2:1:1) system as the eluent to give a mixture of methyl α- and β-garosaminide (**15** and **16**), 225 mg (78%), as a colorless gum, which was identical (tlc, ir, nmr) with authentic samples.[7]

1,3,3′-Tri-*N*-acetylgaramine (24). Garamine (**23,** 500 mg) was dissolved in methanol (17 ml) containing acetic anhydride (2.5 ml) and the solution was allowed to remain at 25° for 20 min. The solution was evaporated to dryness and the resulting solid was chromatographed on preparative tlc plates using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide (1:1:1) system as the eluent. The acetate **24** was extracted from the silica gel with 25% methanol in chloroform, which on evaporation gave a colorless, amorphous solid, 450 mg (65%), which crystallized from ethyl acetate–methanol–acetone: mp 190–195°; $[\alpha]^{26}D$ +106.6° (C_2H_5OH), +108.2° (H_2O); $[\theta]_{290}$ +1970 (Cupra A); ν_{max} (Nujol) 3240 (OH, NH), 1650, 1550 ($NHCOCH_3$), 1050 cm^{-1} (COC); nmr (CD_3OD)[19] δ 1.02, 1.12 (s, 3, 4′-CH_3), 1.93, 1.98, 2.18 (s, 9, $NCOCH_3$), 3.05, 3.17 (s, 3, 3′-NCH_3), 5.22 (d, $J_{1',2'}$ = 4 Hz, 1, $H_{1'}$).

Anal. Calcd for $C_{19}H_{33}N_3O_9 \cdot H_2O$: C, 49.02; H, 7.58; N, 9.03. Found: C, 49.48; H, 7.51; N, 9.47.

Methylation and Acid Hydrolysis of 1,3,2′,6′,3″-Penta-*N*-acetylsisomicin (5). 1,3,2′,6′,3″-Penta-*N*-acetylsisomicin (**5,** 102 mg) was dissolved in dry DMF (5 ml) and sodium hydride (hexane washed, 214 mg) was added. The mixture was warmed to 50° and stirred for 1 hr. The mixture was cooled, methyl iodide (1.4 ml) was added, and the mixture was stirred at 25° for 24 hr. The

solids were filtered off and washed with tetrahydrofuran and the combined filtrates were evaporated to dryness. The residue was taken up in chloroform and washed with water. The chloroform extract was dried ($MgSO_4$) and evaporated to give 1,3,2′,6′,3″-penta-*N*-acetyl-1,3,2′,6′-tetra-*N*-methyl-5,2″,4″-tri-*O*-methylsisomicin (**25**) as a clear gum, *m/e* 755 ($M^{\cdot+}$), 614, 509, 500, 271, 239, 230.

The pseudotrisaccharide **25** was heated under reflux on a steam bath with 6 *N* hydrochloric acid (30 ml) for 2 hr. The solution was cooled and passed over Amberlite IR45 resin and the eluate was evaporated to dryness. The latter was taken up in methanol (5 ml), and acetic anhydride (1 ml) was added. After 25 min at 25° the mixture was evaporated to dryness and the residue was azeotroped with toluene and then chromatographed on a silica gel column (50 × 1 cm) using the lower phase of a chloroform–methanol–7% ammonium hydroxide (2:1:1) system as the eluent to give 1,3-di-*N*-acetyl-1,3-di-*N*-methyl-5-*O*-methyl-2-deoxystreptamine (**26**) as a colorless, amorphous solid, 11 mg (25%), *m/e* 288 ($M^{\cdot+}$), 270 ($M - H_2O$), which was identical (melting point, tlc, mass spectrum, ir) with an authentic sample.[9] The deoxystreptamine derivative (**26**) showed no CD in Cupra A solution.

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References and Notes

(1) Sisomicin was formerly known as antibiotic 66-40.
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Preparative Routes to 4-Amino-4-deoxy-D-galactose[1]

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The elaboration of two synthetic routes to methyl 4-acetamido-4-deoxy-α-D-galactopyranoside (**15**) is described, involving the displacement of the sulfonyloxy group by azide in methyl 4-*O*-methanesulfonyl-α-D-glucosides, in which the hydroxyl functions are blocked by benzoyl groups (**4**, route A) or by benzyl and trityl moieties (**6**, route B). With respect to yields and crystallinity of products, route A (**4** → **5** → **8** → **15**) proved to be the more efficient. Free 4-amino-4-deoxy-D-galactose, characterized in the form of its hydrochloride (**18**), its highly crystalline *N*-acetate (**20**), and its α- and β-pentaacetyl derivatives (**19**), was readily obtained by acetolysis of methyl tri-*O*-acetyl-4-azido-4-deoxy-α-D-galactoside **9** and subsequent hydrogenation. Nmr data and rotations unambiguously confirm the assigned structures and configurations, and are in excellent agreement with those of the respective 2-amino-2-deoxy and 3-amino-3-deoxy derivatives of D-galactose.

As a prelude to the synthesis of 4-aminogalactosyl nucleosides,[2] required for further assessing structure–activity relationships in the aminoacyl aminohexosyl cytosine group of antibiotics,[3,4] the elaboration of an adequate preparative sequence was considered essential, that not only would make 4-amino-4-deoxy-D-galactose accessible in a form suitable for subsequent nucleosidation, but also would be applicable to simple hexopyranosyl nucleosides without major modifications. We have, by consequence, initiated work on synthetic routes meeting these requirements,[1a] and herein report the details of these investigations. The preliminary published portions thereof[1c] already had sufficed to disprove an earlier structure of the nucleoside antibiotic gougerotin, the sugar part of which had erroneously been assigned the 4-aminogalacto configuration.[5]

Of the conceivable synthetic approaches to 4-aminogalactose or its derivatives, the oxidation of readily available methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[6] to its 4-hexuloside followed by oximation, reduction of the oxime, and removal of the protecting groups appeared to be the most propitious. Although this procedure has proved effective with hex-4-uloses carrying alkylidene protecting groups,[7-10] including a synthesis of 4-amino-4-deoxy-D-galactose from open-chain sugar derivatives,[10] its success appeared doubtful with an acylated glycopyranosid-4-ulose owing to extreme sensitivity toward β elimination under acidic and basic conditions.[11,12] Hence, another approach was deemed more promising, involving azide displacement of a 4-sulfonyl ester group in a suitable protected glucopyranoside. This route, which, at the outset of this work,[1] had been utilized in preparing 4-amino-4,6-dideoxy-[13] 4,6-diamino-4,6-dideoxy-,[14] and 2,3,4,6-tetramino-D-galactose derivatives,[15] was also used with two methyl 4-*O*-methylsulfonylglucopyranosides, in which the hydroxyl functions at C-2, C-3, and C-6 were

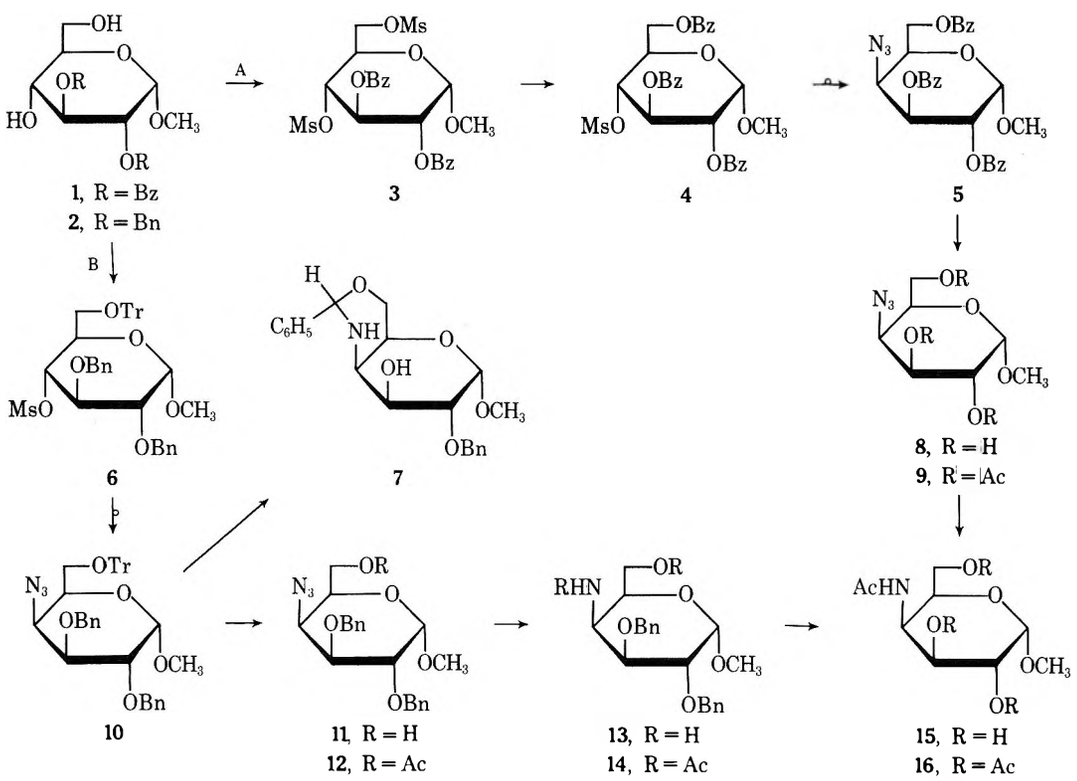
protected by benzoyl groups (**4**, route A) or by benzyl and trityl moieties (**6**, route B), respectively.

1,4-Amino-4-deoxy-α-D-galactosides. Route A. The more efficient synthetic sequence with respect to yields and crystallinity of products, proved to be route A. In the readily accessible methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-methylsulfonyl-α-D-galactopyranoside (**3**), the primary C-6 mesyloxy function can be displaced selectively by azide.[16] An analogous displacement on **3** with sodium benzoate in *N,N*-dimethylformamide (5 hr, 80°) gave methyl 2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-α-D-glucoside (**4**), which, under somewhat more forcing conditions (60 hr, 100° or 5 hr, 150°), was readily converted to the syrupy azido tribenzoate **5** in 85% yield. Deesterification afforded crystalline **8**, which in turn gave methyl 4-acetamido-4-deoxy-α-D-galactopyranoside (**15**) in 64% yield in the form of well-shaped needles. All attempts, however, by various methods of acetylation and purification, to obtain the tetraacetyl derivative **16** in crystalline form were unsuccessful. The product (**16**) was characterized as a syrup of $[\alpha]^{25}D$ +119°, which was sufficiently different from reported values of a gougerotin degradation product (mp 193°, $[\alpha]D$ +87°)[17] as to disprove[1c] structure **16** that had been assigned.[5]

Route B. The alternate procedure to the 4-aminogalactosides **15** and **16** started from methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**2**),[18] which by tritylation and subsequent mesylation was converted in 79% yield into the fully protected derivative **6**, suitable for an ensuing azidolysis. When heated with sodium azide in *N,N*-dimethylformamide for 30 hr at 100°, the 4-azido-galactoside **10** was readily obtained (93%). In **10**, the azido function as well as the trityl and benzyl protecting groups are sensitive toward hydrogenolysis conditions; yet its conversion into methyl 4-aminogalactoside could not be accomplished in one step. On hydrogenolysis of **10** over 10% palladium on carbon in methanol, only the azido function was reduced with partial detritylation, while methanolic hydrochloric acid—conditions that proved effective for the debenzylation of methyl 2,3-di-*O*-benzyl-4-amino-4,6-dideoxy-α-D-galactopyranoside[13]—removed only one of the benzyl groups, presumably the one located at C-3. The resulting product was characterized as its benzylidene derivative formed on treatment with benzaldehyde, which appeared to be the 4,6-*N,O*-benzylidene compound **7**[19] rather than the expected Schiff base. Owing to these difficulties, the conversion **10** → **16** was made stepwise: de-O-tritylation by acid afforded syrupy **11**, which was characterized as its crystalline 6-*O*-acetyl derivative **12**; subsequent treatment with lithium aluminum hydride gave the 2,3-dibenzyl-4-aminogalactoside **13**, similarly characterizable as its 4-*N*,6-*O*-diacetate (**14**); the removal of the benzyl groups was finally effected by sodium in liquid ammonia, giving on subsequent acetylation in 43% yield methyl tri-*O*-acetyl-4-acetamido-4-deoxy-α-D-galactoside (**16**), indistinguishable from a sample prepared by route A.

4-Amino-4-deoxy-D-galactose. Attempts to obtain reducing sugars from methyl 4-acetamido-4-deoxy-α-D-galactoside (**15**) or its tri-*O*-acetate **16** by hydrolysis were unsuccessful. Even short heating in 4 *N* hydrochloric acid at 80° resulted in extensive decomposition, as indicated by a black solution and the detection of at least four compounds by tlc. Less forcing acetolysis conditions,[20] which favor formation of acetyliminofuranose derivatives with 4-acetamido-4-deoxyaldosides,[21,22] were employed with the azido-tri-*O*-acetate **9** and gave tetraacetate **17** as a 10:1 α/β-anomeric mixture in 81% yield. De-O-acetylation of **17** with sodium methoxide in methanol followed by hydrogenolysis over 5% palladium on carbon in methanol containing hydrochloric acid gave the hydrochloride of 4-amino-4-deoxy-D-galactose (**18**) as an amorphous solid, exhibiting data, *e.g.*, $[\alpha]^{25}D$ +51°, that are practically identical with those observed for the same product from a different synthetic route.[10]

On conversion of the azido function in **17** into an acetamido group by hydrogenolysis and subsequent acetylation, a pentaacetyl derivative **19**, $[\alpha]^{25}D$ +82°, is obtained, comprising an approximate 10:1 anomeric mixture in

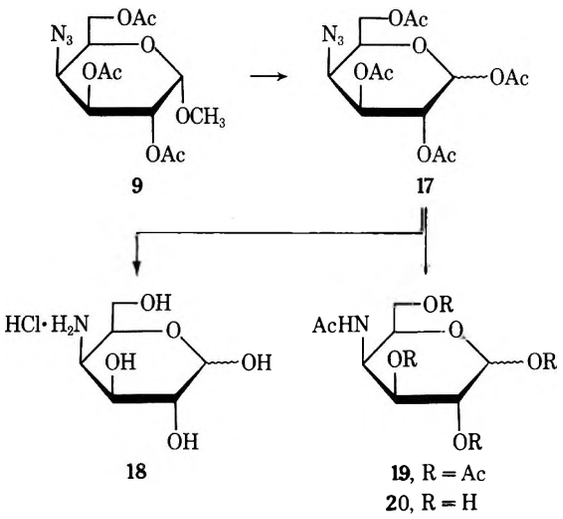


Bn = $C_6H_5CH_2$; Bz = C_6H_5CO; Tr = $(C_6H_5)_3C$

Table I
Nmr Data in $CDCl_3$ and Rotations of Peracetylated α-D-Galactopyranoses

Peracetyl derivative of α-D-hexopyranose	Registry no.	Chemical shifts[a] H-1	H-2	H-3	H-4	a-OAc	e-OAc a-NHAc 6-OAc	e-NHAc	$[\alpha]_D$ in $CHCl_3$, deg
α-D-Galactose	4163-59-1	3.64	4.65[d]	4.65[d]	4.48	7.85 (2)	7.97 7.99 8.00		+107[f]
2-Amino-2-deoxy-α-D-galactose[b]	10385-50-9	3.75	5.34	4.75	4.59	7.81 (2)	7.97 (2)	8.05	+102[g]
3-Amino-3-deoxy-α-D-galactose[c]	23743-53-5	3.72	4.80	5.36	4.56	7.83 (2)	7.96 (2)	8.03	+119
4-Amino-4-deoxy-α-D-galactose (**19**)		3.65	4.70[d]	4.70[d]	5.20	7.84	7.95 (2) 7.97 7.99		+89[h]
Methyl α-D-galactoside	5019-22-7	5.05[d]	5.05[d]	4.93	4.58	7.86	7.95 (2) 8.01		+133[i]
Methyl 3-amino-3-deoxy-α-D-galactoside	51015-64-6	5.07[d]	5.07[d]	5.31	4.49	7.87	7.93 7.95	8.09	+91[i]
Methyl 4-amino-4-deoxy-α-D-galactoside (**16**)		5.03[e]	5.05[e]	4.73	5.27		7.91 7.94 (2) 8.01		+119

[a] Coupling constants observed are $J_{1,2}$ = 2.0–3.8, $J_{2,3}$ = 10–11, $J_{3,4}$ = 3.0–4.1, $J_{4,5}$ = 1.0–1.5 Hz. [b] Nmr data from T. D. Inch, J. R. Plimmer, and H. G. Fletcher, *J. Org. Chem.*, **31**, 1825 (1966). [c] Data from F. W. Lichtenthaler, G. Bambach, and U. Scheidegger, *Chem. Ber.*, **102**, 986 (1969). [d] Unresolved 2 H multiplets. [e] Calculated values on the basis of an AB system with $J_{1,2}$ = 3.8 and $J_{2,3}$ = 10.5 Hz. [f] C. S. Hudson and P. O. Parker, *J. Amer. Chem. Soc.*, **37**, 1589 (1915). [g] M. Stacey, *J. Chem. Soc.*, 272 (1944). [h] Calculated value; *cf.* ref 23. [i] F. Micheel and O. Littmann, *Justus Liebigs Ann. Chem.*, **466**, 115 (1928). [j] H. H. Baer, *J. Amer. Chem. Soc.*, 84, 83 (1962).



favor of the α anomer on the basis of its rotation and nmr data (*cf.* Table I). The most suitable derivative for characterization appears to be the 4-acetamido-4-deoxy-D-galactopyranose, readily isolated in crystalline form from a de-O-acetylation of **19**. Expectedly, it shows mutarotation in water from +45 to +65°, which is interesting insofar as 4-acetamido-4-deoxy-D-glucose, although having a different initial rotation, features the same rotational value for the anomeric equilibrium ($[\alpha]^{20}D$ +91 → +66°, in water[10]). On treatment with pyridine–acetic anhydride, the 4-acetamido-4-deoxy-D-galactose **20** is converted to a syrupy pentaacetyl derivative **19**, in which now the β anomer preponderates by an approximate ratio of 9:1, as indicated by nmr data and its rotation of $[\alpha]^{25}D$ +15°.[23] It is interesting to note that no product corresponding to 1,2,3,5,6-penta-*O*-acetyl-4-acetamido-4-deoxy-D-galactofuranose[22] or to dimeric forms thereof[10] could be detected by either tlc or nmr in this tetra-*O*-acetyl-4-acetamido-4-deoxy-β-D-galactopyranose **19**, containing 10% of the α anomer.

Structural and Configurational Assignments. While the mode of preparation in itself is conclusive proof for the galacto configuration of compounds **5** and **7–20**, corroborative evidence is readily furnished by nmr data. In contrast to the respective gluco derivatives **3**, **4**, and **6**, in which coupling constants of 9–10 Hz ($J_{3,4}$ and $J_{4,5}$) are observed for the proton at C-4, in the galacto derivatives H-4 consistently appears as a quartet with $J_{3,4}$ = 3–4 and $J_{4,5}$ = 1–1.5 Hz. In the acetamido derivatives **14**, **16**, **19**, and **21**, this quartet is further split by coupling with the NH proton ($J_{4,NH}$ = 9 Hz), which, however, is eliminated on deuteration or on addition of trifluoroacetic acid.

These configurational assignments are further substantiated by the chemical shifts of the acetyl resonances of the peracetylated amino galacto derivatives **16** and **19**, which nicely comply with the empirical principles laid down in the "acetyl resonance rule" for cyclitols[24] and hexopyranoses,[25] as well as with the data for the other galactopyranose peracetates collected in Table I. Accordingly, **16** and the two anomers of **19** exhibit no acetyl resonances (in $CDCl_3$) attributable to an equatorial acetamido group (around τ 8.07), the signal at highest field appearing at τ 8.01. Similarly, a low-field resonance around τ 7.85 is only observed in the case of the α anomer of **19**, as expected for the C-1 acetoxy group.

Equally distinct configurational proof is provided by the nmr characteristics of the ring protons H-1–H-4 of **16** and **19**, particularly when juxtaposed with the corresponding derivatives of galactose, 2-aminogalactose, and 3-aminogalactose (Table I). In the pentaacetyl compounds the axially oriented anomeric proton appears within the narrow range of 3.64–3.75 ppm, while in the glycosides H-1a is shifted toward higher field by approximately 1.3 ppm. Another obvious relationship appears to be the consistent upfield shift of the ring protons by 0.7 ppm when replacing an acetoxy group at C-2, C-3, or C-4 in pentaacetyl-α-D-galactopyranose by an acetamido function.

Since replacement of an acetoxy by an acetamido group does not substantially affect rotational values,[26] their sign and magnitude should also be indicative of configuration. Indeed, all peracetylated α-D-galactopyranoses in Table I exhibit a high positive rotation in chloroform, the somewhat scattered values being within the limitations of this

type of comparisons. Thus, the $[\alpha]^{25}D$ of +119° observed for **16** compares well with those for other peracetylated α-D-galactosides (*cf.* Table I). For the respective β anomer of **16**, as yet unknown, a small negative or at best a small positive rotation must necessarily be predicted on the basis of $[\alpha]D$ −14° for methyl tetra-*O*-acetyl-β-D-galactopyranoside,[27] −17° for the 2-acetamido-2-deoxy,[28] and −5° for the 3-acetamido-3-deoxy compounds,[25] respectively. Nevertheless, Fox, *et al.*,[29] pretended that the tetraacetate of methyl 4-amino-4-deoxy-β-D-galactopyranoside could well have a rotation of +87°.

Experimental Section

Melting points were determined on a Bock Monoskop, and are uncorrected. Spectral measurement were effected with Perkin-Elmer 125 (ir), Perkin-Elmer 137 (uv), and Varian A-60A (nmr) instruments. Thin layer chromatography on Kieselgel F_{254} plastic sheets (Merck, Darmstadt) was used to monitor the reactions and to ascertain the purity of the reaction products; preparative tlc was done on 20 × 40 cm glass plates coated with a 1.5-mm layer of Merck Kieselgel HF. Developers employed (A) benzene–ethyl acetate (10:1); (B) chloroform–ethyl acetate (10:1); (C) ethyl acetate–ethanol–water (15:2:1). The spots were visualized by uv light, by iodine vapor, or by spraying with 80% aqueous sulfuric acid and charring at 110° for 5 min. Column chromatography was carried out on silica gel 70–230 mesh (Kieselgel 60, Merck, Darmstadt).

Route A. Methyl 2,3,6-Tri-*O*-benzoyl-4-*O*-methylsulfonyl-α-D-glucopyranoside (4). To a solution of methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-mesyl-α-D-glucopyranoside[16] (3, 9.3 g, 16.7 mmol) in *N,N*-dimethylformamide (50 ml) was added sodium benzoate (2.7 g, 18.5 mmol), and the mixture was heated for 5 hr at 80° with stirring, followed by evaporation to dryness *in vacuo*. A chloroform solution of the residue was washed with water, dried, and concentrated to a syrup, that was purified *via* elution from a silica gel column (2 × 50 cm) with solvent system B. An 8.7-g (89%) yield of a colorless, uniform (tlc in A) syrup was obtained: $[\alpha]^{25}D$ +139° (c 1, $CHCl_3$); nmr ($CDCl_3$) τ 1.9 and 2.5 (broad m, 6 and 9, 3 C_6H_5), 4.88 (t, 1, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 5.2–5.8 (m, 3, H-5 and 6-CH_2), 6.55 (s, 3, OCH_3), 7.10 (s, 3, OMs); H-1, H-2, and H-3 give an ABX spectrum, the AB part (seven lines centered around τ 4.7) and X portion (11 lines around τ 3.86) indicating $J_{1,2} = 3.5$ and $J_{2,3} = 9.5$ Hz as well as the chemical shifts for H-1 (4.75) and H-2 (4.71); a spectrum calculated on the basis of these data was in excellent agreement with the observed one.

Anal. Calcd for $C_{29}H_{28}O_{11}S$: C, 59.58; H, 4.83; S, 5.49. Found: C, 59.56; H, 4.80; S, 5.25.

Methyl 4-Azido-2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-galactopyranoside (5). A mixture of mesylate **4** (9.5 g, 16.3 mmol) and sodium azide (3.3 g, 3 molar equiv) in *N,N*-dimethylformamide (100 ml) was heated at 150° for 5 hr, followed by evaporation to dryness *in vacuo*. A chloroform solution of the residue was filtered, washed with water, and taken to dryness, leaving a syrup that was purified by elution from a silica gel column with solvent system A: 7.4 g (85%) of **5** as a chromatographically uniform syrup of $[\alpha]^{25}D$ +17° (c 1, $CHCl_3$).

Anal. Calcd for $C_{28}H_{25}N_3O_8$: C, 63.27; H, 4.74; N, 7.91. Found: C, 63.18; H, 4.78; N, 8.02.

Methyl 4-Azido-4-deoxy-α-D-galactopyranoside (8). De-*O*-benzoylation of tribenzoate **5** (7.0 g, 13.2 mmol) was effected by standing overnight in methanol (50 ml) containing 1 *N* sodium methoxide (2 ml), followed by deionization with an acidic resin (Merck IV, H^+ form) and evaporation to dryness. The residue was dissolved in water and extracted twice with ether for removal of methyl benzoate, to give, on evaporation of the aqueous phase to dryness, a residue that crystallized on gradual addition of benzene to a 2-propanol solution. Recrystallization from methanol–benzene afforded 1.99 g (69%) of azidogalactoside **8** as colorless crystals: mp 153–155°; $[\alpha]^{25}D$ +120° (c 0.5, CH_3OH); ir (KBr) 2130 cm^{-1} (N_3); nmr (D_2O) τ 5.18 (d, 1, $J_{1,2} = 3.5$ Hz, H-1), 6.61 (s, 3, OCH_3); CD_{max} 277 nm, θ in dioxane, +0.13, in methanol +0.09, in water +0.08.

Anal. Calcd for $C_7H_{13}N_3O_5$: C, 38.35; H, 5.98; N, 19.17. Found: C, 38.77; H, 6.03; N, 19.13.

Methyl 4-Azido-2,3,6-tri-*O*-acetyl-4-deoxy-α-D-galactopyranoside (9). A mixture of 2.5 g (11.4 mmol) of azidogalactoside **8** was kept in 2:1 pyridine–acetic anhydride (60 ml) for 24 hr at room temperature, followed by concentration to dryness and several reevaporations from water. The residue was purified by elution from a silica gel column with solvent system A, to give on evaporation and drying (50°, 0.1 mm) 2.8 g (72%) of a syrup, uniform by tlc (C): $[\alpha]^{25}D$ +93° (c 1, $CHCl_3$); nmr ($CDCl_3$) τ 4.56 (q, 1, $J_{2,3} = 10$ and $J_{3,4} = 3.5$ Hz, H-3), 4.84 (q, 1, $J_{1,2} = 3$ Hz, H-2), 5.05 (d, 1, H-1), 5.81 (m, 4, H-4, H-5, and 6-CH_2), 6.62 (s, 3, OCH_3), 7.88 (s, 3, 3-OAc), 7.92 (s, 6, 2- and 6-OAc).

Anal. Calcd for $C_{13}H_{19}N_3O_8$: C, 45.21; H, 5.55; N, 12.17. Found: C, 44.99; H, 5.57; N, 11.97.

Methyl 4-Acetamido-4-deoxy-α-D-galactopyranoside (15). A. From 4-Azidogalactoside 8 by Hydrogenation and N-Acetylation. A methanolic solution of **8** (1.0 g in 200 ml) was hydrogenated over 10% Pd/C for 6 hr, followed by removal of the catalyst and concentration of the filtrate to a volume of about 50 ml. Acetic anhydride (5 ml) was added, and, after being kept overnight at ambient temperature, the mixture was evaporated to dryness. Several reevaporations of the residue from benzene gave a product which slowly crystallized from a 2:1 ethanol–benzene solution on standing. Recrystallization from ethanol–acetone afforded 830 mg (76%) of **15** as needles: mp 203–205°; $[\alpha]^{25}D$ +182° (c 1, CH_3OH); nmr (DMSO-d_6) τ 2.40 (d, 1, $J_{4,NH} = 9$ Hz, NH), 6.70 (s, 3, OCH_3), 8.08 (s, 3, NHAc).

Anal. Calcd for $C_9H_{17}NO_6$: C, 45.95; H, 7.28; N, 5.96. Found: C, 45.86; H, 7.21; N, 6.00.

B. De-*O*-acetylation of Tetraacetate 16. A solution of **16** (2.5 g, 7 mmol) in methanolic ammonia (100 ml) was kept at room temperature overnight, followed by evaporation to dryness and trituration of the residue with methanol–benzene, which resulted in crystallization of 1.38 g (82%) of needles, indistinguishable from **15** prepared by method A.

Methyl 4-Acetamido-2,3,6-tri-*O*-acetyl-4-deoxy-α-D-galactopyranoside (16) by Acetylation of the *N*-Acetate (15). A solution of **15** (900 mg) in 2:1 pyridine–acetic anhydride (20 ml) was kept overnight at ambient temperature and subsequently evaporated to dryness followed by repeated coevaporations with water. The syrupy residue was applied to a silica gel column (2 × 30 cm) and eluted with solvent system C. The appropriate fraction was evaporated and dried (0.1 mm), affording **16** as a syrup: $[\alpha]^{25}D$ +119° (c 1, $CHCl_3$); 100-MHz nmr in $CDCl_3$, *cf.* Table I; in DMSO-d_6 τ 1.85 (d, 1, $J_{4,NH} = 10$ Hz, NH), 4.94 (m, 3, ABC system of H-1, H-2, and H-3), 5.44 (m, 1, H-4), 5.95 (m, 3, H-5 and 6-CH_2), 6.64 (s, 3, OCH_3), acetyl resonances at 7.96, 7.98, and 8,08 (2).

Anal. Calcd for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.42; N, 3.88. Found: C, 50.02; H, 6.58; N, 3.89.

Route B. Methyl 2,3-Di-*O*-benzyl-4-*O*-methylsulfonyl-6-*O*-trityl-α-D-glucopyranoside (6). To a solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[18] (**2**, 10.0 g, 27 mmol) in dry pyridine (125 ml) was added triphenylchloromethane (9.0 g, 32 mmol). The mixture was kept at ambient temperature overnight, followed by the addition of mesyl chloride (6 ml, 77 mmol) with cooling (0°), standing for 10 hr at room temperature, and evaporation to dryness *in vacuo*. The syrupy residue was dissolved in chloroform, which was washed with water and, after treatment with charcoal, dried ($MgSO_4$), followed by evaporation to dryness. Trituration of the residue with ethanol resulted in crystallization, amounting after recrystallization from the same solvent to 14.8 g (79%), as needles, mp 146–147°, $[\alpha]^{25}D$ +24° (c 0.5, $CHCl_3$). Two recrystallizations of this product, which was used for further experiments, from acetone–methanol raised the melting point to 152–153° without change in rotation.

Anal. Calcd for $C_{41}H_{42}O_8S$: C, 70.78; H, 6.09; S, 4.62. Found: C, 70.78; H, 6.12; S, 4.64.

Methyl 4-Azido-2,3-di-*O*-benzyl-4-deoxy-6-*O*-trityl-α-D-galactopyranoside (10). The mesyl glucoside **6** (6.0 g, 8.7 mmol) and sodium azide (2.3 g, 4 molar equiv) were heated with stirring for 30 hr at 100° in dry *N,N*-dimethylformamide (60 ml). After cooling, the mixture was poured into ice–water and the solid, separated, was filtered off and recrystallized from methanol to give 5.3 g (93%) of azide **10** as colorless crystals: mp 50–52°; $[\alpha]^{25}D$ +13° (c 2, $CHCl_3$);[30] ir (KBr) 2145 cm^{-1} (N_3).

Anal. Calcd for $C_{40}H_{39}N_3O_5$: C, 74.63; H, 6.13; N, 6.55. Found: C, 74.73; H, 6.10; N, 6.40.

Methyl 4-Amino-2-*O*-(3-*O*-)-benzyl-4-*N*,6-*O*-benzylidene-4-deoxy-α-D-galactopyranoside (7). To a prehydrogenated suspension of 10% Pd/C (500 mg) in methanol (75 ml) and 3.6 ml of concentrated hydrochloric acid was added 1.2 g (1.87 mmol) of azido galactoside **10** in 75 ml of methanol, and the hydrogenation was continued. After the uptake of H_2 had ceased (24 hr), the catalyst was filtered off and the filtrate was deionized by stirring with a

strongly basic ion-exchange resin (Merck III, OH^- form). On concentration of the solution, triphenylmethane crystallized and was removed (0.35 g, mp 87–89°). Evaporation to dryness *in vacuo* afforded a syrup, which, being not amenable to crystallization, was allowed to react with benzaldehyde (1.0 ml) for 2 hr at 80°. The excessive benzaldehyde was distilled off (0.1 mm) and the syrupy residue was dissolved in ethyl acetate and washed consecutively with saturated sodium bicarbonate solution and water. Evaporation of the solvent and trituration of the residue with methanol gave 0.31 g (44%) of **7** as needles: mp 204–206°; ir (KBr) OH and NH around 3530 cm^{-1}, no absorption in the 1690–1630-cm^{-1} region (C=N); nmr ($CDCl_3$) τ 2.3–2.7 (m, 10, 2 C_6H_5), 3.05 (s, 1, NH), 3.92 (s, 1, benzylidene CH), 4.64 (d, 1, $J_{1,2}$ = 2 Hz, H-1), 5.15 (m, 2, H-2 and H-3), 5.85 (broad m, 1, H-4), 6.25 (m, 5, H-5, 6-CH_2 and ArCH_2), 6.51 (s, 3, OCH_3), 7.18 (s, 1, OH); the signals at τ 3.05 and 7.18 disappear on treatment with D_2O.

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.01; H, 6.60; N, 3.86.

Methyl 4-Azido-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (11). The trityl derivative **10** (16.4 g, 25.6 mmol) was heated for 30 min at 100° in 100 ml of 4:1 acetic acid–water. On cooling, triphenylmethanol crystallized and was removed (5.7 g), and a second crop (0.7 g, total 95%) was obtained on concentration of the solution to a small volume. Evaporation to dryness *in vacuo*, followed by repeated coevaporations with water, afforded crude **11** as a syrup (9.1 g, 89%), which contained traces of triphenylcarbinol (tlc in B), yet was used for further experiments. For the analytical sample, 0.35 g was applied to a preparative tlc plate and developed with solvent system B. The zone containing **11** (R_f 0.3) was scratched off and thoroughly eluted with chloroform–ethanol (1:1), followed by evaporation of the extract to dryness *in vacuo* to give 230 mg of a chromatographically uniform (tlc in A and B) syrup, $[\alpha]^{25}D$ +3° (*c* 1, $CHCl_3$), ir (film) 2150 cm^{-1} (N_3).

Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 62.89; H, 6.26; N, 10.38.

Methyl 6-*O*-Acetyl-4-azido-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (12). The azido derivative **11** (140 mg) was kept in a mixture of pyridine (4 ml) and acetic anhydride (2 ml) overnight at ambient temperature. Concentration to dryness, several reevaporations from water to remove traces of solvents, treatment of an ethanolic solution with charcoal, and evaporation left a syrup, which crystallized on trituration with 2-propanol to give 72 mg (52%) of **12** as colorless needles: mp 76–78°; $[\alpha]^{25}D$ +8° (*c* 0.7, $CHCl_3$); nmr ($CDCl_3$) τ 6.65 (s, 3, OCH_3), 7.95 (s, 3, OAc).

Anal. Calcd for $C_{23}H_{27}N_3O_6$: C, 62.57; N, 6.16; N, 9.52. Found: C, 62.53; H, 6.15; N, 9.56.

Methyl 4-Amino-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (13). To a suspension of lithium aluminum hydride (2.5 g) in ether (100 ml) was added a solution of **11** (8.6 g, 21.5 mmol) in 200 ml of ether. After the reaction had ceased the mixture was refluxed for 1 hr. After cooling down, the excessive $LiAlH_4$ was destroyed by the addition of ethyl acetate, followed by evaporation to dryness. Suspension of the residue in ether (200 ml), gradual addition of water until coagulation occurred, decantation, and extraction of the residue with ether gave upon evaporation of the combined ether solutions a syrup (8.0 g), which was used for debenzylation although traces of triphenylcarbinol could be detected (tlc in B). For the analytical sample, 400 mg was applied to a preparative tlc plate and developed with solvent system B, followed by elution of the appropriate zone with ethyl acetate–methanol (1:1) and evaporation of the eluate to dryness *in vacuo* (finally 0.1 mm) to give 270 mg of a syrup, $[\alpha]^{25}D$ +54° (c 1, $CHCl_3$).

Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.32; H, 7.36; N, 3.68.

Methyl 4-Acetamido-6-*O*-acetyl-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (14). Acetylation of **13** (300 mg) in 2:1 pyridine–acetic anhydride (15 ml) overnight at room temperature and evaporation to dryness gave a syrup, which was dissolved in chloroform and thoroughly washed with water. The residue either as such or after preparative tlc (as described for **11**) was not amenable to crystallization, affording 250 mg (68%) of a colorless syrup: $[\alpha]^{25}D$ +51° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) τ 4.27 (d, 1, $J_{4,NH}$ = 10 Hz, NH), 6.62 (s, 3, OCH_3), 7.95 and 7.98 (two s, 3-, 6-OAc and 4-NHAc).

Anal. Calcd for $C_{25}H_{31}NO_7$: C, 65.62; H, 6.83; N, 3.06. Found: C, 65.67; H, 6.83; N, 2.98.

De-O-benzylation of 13 with Liquid Ammonia. To a stirred suspension of 2,3-di-*O*-benzylgalactoside **13** (6.5 g, 17.4 mml) in liquid ammonia was added, in small portions, 3.0 g of sodium. After 3 hr, the excessive sodium was decomposed by the addition of ammonium chloride and the ammonia was allowed to evaporate. The residue was dissolved in water, followed by washing with chloroform and evaporation to dryness, leaving a uniform (tlc in C), ninhydrin-active syrup that was subsequently acetylated by standing overnight in 2:1 pyridine–acetic anhydride (100 ml). The mixture was concentrated to a syrup, which was repeatedly coevaporated with water and purified by elution from a silica gel column (3 × 50 cm) with solvent system C. The appropriate eluate was evaporated to dryness and dried (0.1 mm), giving 4.4 g (70%) of the tetraacetyl-4-aminogalactoside **16** as a syrup, indistinguishable with respect to nmr and rotational data from a sample of the same compound prepared by route A (*cf.* above).

Derivatives of 4-Amino-4-deoxy-D-galactose. 1,2,3,6-Tetra-*O*-acetyl-4-azido-4-deoxy-α-D-galactopyranose (17). To a cooled (0°) solution of azido galactoside **16** (2.0 g, 5.8 mmol) in acetic anhydride (40 ml) was slowly added with stirring acetic acid (20 ml) containing 2 ml of concentrated sulfuric acid, and the mixture was kept at 6–10° overnight, followed by pouring into ice–water (300 ml). After decomposition of excess acetic anhydride (20 min) the solution was extracted with chloroform (3 × 100 ml) and the combined extracts were washed with water, treated with charcoal, and subsequently evaporated to dryness *in vacuo*. The residue was applied to a silica gel column (3 × 50 cm) and eluted with 1:1 benzene–ethyl acetate, to afford after evaporation of the appropriate fraction and drying at 55° (0.1 mm) 1.75 g (81%) of **17** as a colorless foam, uniform by tlc (C), which was used for further experiments, although analytical data were somewhat too low: $[\alpha]^{25}D$ +56° (c 1, $CHCl_3$); nmr ($CDCl_3$) τ 3.68 (narrow m, H-1), 7.88 s, 6, C-1 and C-3 OAc), 7.93 and 8.00 (two s, 3, C-2 and C-6 OAc); the content of the β anomer was below 10%.

4-Acetamido-1,2,3,6-tetra-*O*-acetyl-4-deoxy-D-galactopyranose (19). A. α Anomer (Containing 10% β). To a prehydrogenated suspension of 10% Pd/C in ethyl acetate (200 mg in 50 ml) was added 1.0 g (2.7 mmol) of syrupy azido tetraacetate **17**, and the hydrogenation was continued. After 6 hr the catalyst was removed, and the solution was evaporated to dryness followed by addition of 1:1 pyridine–acetic anhydride (10 ml). Standing overnight, concentration to a syrup with several coevaporations with water, and elution from a silica gel column (3 × 50 cm) with 1:1 benzene–ethyl acetate gave 0.68 g (65%) of a syrup, $[\alpha]^{25}D$ +82° (*c* 1, $CHCl_3$),[23] nmr ($CDCl_3$) *cf.* Table I.

Anal. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.35; H, 5.95; N, 3.60. Found: C, 49.22; H, 6.21; N, 3.61.

B. β Anomer (Containing 10% α). The *N*-acetate **20** (150 mg) was kept in 1:1 pyridine–acetic anhydride (6 ml) at room temperature overnight, followed by concentration to a syrup which was reevaporated repeatedly from water and methanol. Treatment of a methanol solution with charcoal, evaporation to dryness, and drying (55°, 0.1 mm) left 220 mg (86%) of a colorless syrup: $[\alpha]^{25}D$ +15°;[23] nmr ($CDCl_3$) τ 3.79 (d, 1, $J_{4,NH}$ = 9 Hz, NH), 4.34 (d, $J_{1,2}$ = 8 Hz, H-1); acetyl resonances at 7.90 (1-OAc), 7.95 (2-, 6-OAc and 4-NHAc), 8.01 (3-OAc); the intensity of the acetyl resonance at τ 7.84 (axial 1-OAc) indicated approximately 10% of the α anomer.

Anal. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.35; H, 5.95; N, 3.60. Found: C, 49.19; 5.90; N, 3.67.

4-Acetamino-4-deoxy-D-galactopyranose (20). To a methanol solution of pentaacetate **19** (450 mg in 20 ml) was added 1 *N* sodium methoxide (2 ml) and the mixture was kept at ambient temperature for 12 hr. Deionization by stirring with an acidic resin (Merck IV, H^+ form), evaporation to dryness *in vacuo*, and trituration of the residue with 2-propanol–benzene gave a solid mass that was recrystallized from ethanol to give 240 mg (47%) of **20** as colorless crystals: mp 193–195° dec; $[\alpha]^{25}D$ +45° (3 min) → +65° (2 days) (*c* 1, H_2O); nmr (100 MHz, in D_2O) τ 4.72 and 5.39 (two d of total integration 1, $J_{1e,2}$ = 3.8 and $J_{1a,2}$ = 7.5 Hz, H-1e and H-1a), 5.63 (q, 1, $J_{3,4}$ = 4.0 Hz, H-4), 7.94 (s, 3, NHAc).

Anal. Calcd for $C_8H_{15}NO_6$: C, 43.43; H, 6.84; N, 6.33. Found: C, 43.47; H, 7.03; N, 6.28.

4-Amino-4-deoxy-D-galactopyranose Hydrochloride (18). The 4-azido tetraacetate **17** (500 mg) was subjected to de-O-acetylation by 1 *N* sodium methoxide (1 ml) in 10 ml of methanol (3 hr, 25°), and after deionization with an acidic resin (Merck IV, H^+ form) was taken to dryness. The syrupy residue was dissolved in 10 ml of 0.1 *N* hydrochloric acid and hydrogenated over 5% Pd/C (50 mg) for 3 hr. Removal of the catalyst and evaporation to dryness *in vacuo* (bath temperature below 30°), followed by repeated reevaporations from water, afforded a syrup which was precipitated from a methanol–ether solution in an amorphous form to

give 185 mg (64%), melting gradually with decomposition from 110° on (after drying at 30°, 0.1 mm), $[\alpha]^{25}D$ +51° (c 1, H_2O) (lit.[10] $[\alpha]^{20}D$ +48.2°).

Anal. Calcd for $C_6H_{13}NO_5 \cdot HCl$: C, 33.41; H, 6.55; N, 6.50; Cl, 16.49. Found: C, 33.20; H, 6.70; N, 6.40; Cl, 16.04.

Registry No.—2, 17791-36-5; **3,** 22435-33-2; **4,** 19877-45-3; **5,** 51015-65-7; **6,** 19877-37-3; **7** 2-*O*-benzyl derivative, 51015-66-8; **7** 3-*O*-benzyl derivative, 51015-67-9; **8,** 21395-67-5; **9,** 51015-68-0; **10,** 19877-38-4; **11,** 19887-42-4; **12,** 19877-39-5; **13,** 19877-40-8; **14,** 19877-41-9; **15,** 19877-43-1; **16,** 19877-42-0; **17,** 51015-69-1; **18,** 24558-85-8; **18** hydrochloride, 51015-70-4; **19** α anomer, 51015-71-5; **19** β anomer, 51015-72-6; **20,** 51015-73-7.

References and Notes

(1) (a) Taken in part from the Doctoral Dissertation of P. H., Technische Hochschule Darmstadt, Feb 1969. (b) Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. (c) A preliminary account on part of this work has appeared: F. W. Lichtenthaler and P. Heidel, *Angew. Chem.*, **80**, 441 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 458 (1968).
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Sulfur-Containing Carbohydrates. Synthesis of 1,3,4,6-Tetrathio-D-mannitol[1,2]

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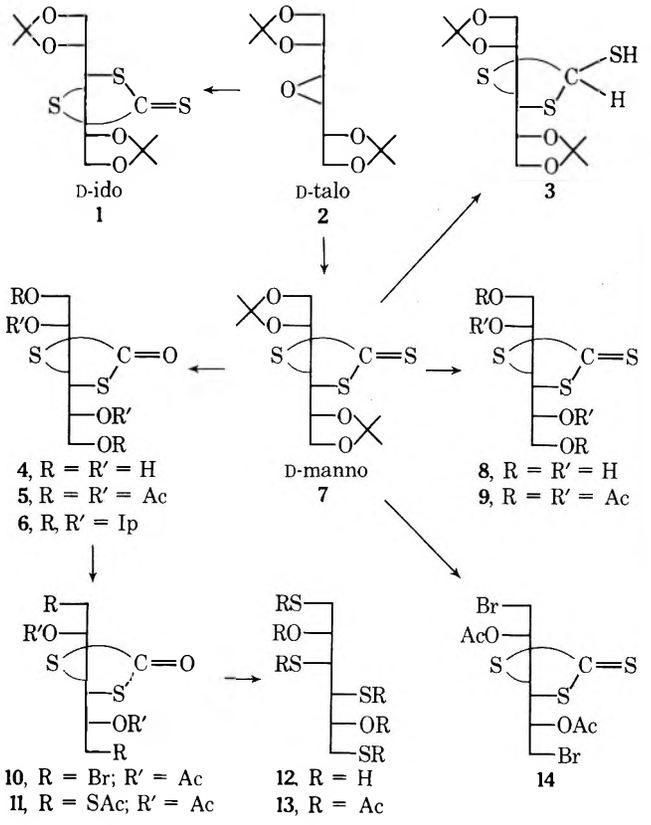
The di-*O*-isopropylidene derivative (**2**) of 3,4-anhydro-D-talitol on reaction with potassium methyl xanthate gave a mixture of two diastereomeric trithiocarbonates. One of these, mp 117°, was assigned the D-manno configuration (**7**), the other, mp 127°, the D-ido configuration (**1**), primarily on the basis of optical rotation studies. The yellow trithiocarbonate **7** was hydrolyzed to the tetrol **8**, which was converted to its tetraacetate **9**. The compound **7** was only partially reduced by lithium aluminum hydride, giving the mercaptodithiolane **3**. When oxidized, the trithiocarbonate **7** gave the corresponding dithiocarbonate **6**. The latter on hydrolysis gave the tetrol **4**, which was converted to its tetraacetate **5**. The dithiocarbonate **6** on reaction with hydrogen bromide in acetic acid gave the 1,6-dibromide dithiocarbonate diacetate **10**. The trithiocarbonate **7** similarly gave the 1,6-dibromide dithiocarbonate diacetate **14**. The compound **10** on reaction with potassium thiolacetate gave the 1,6-dithiol dithiocarbonate tetraacetate **11**. Reduction of the latter finally gave the desired 1,3,4,6-tetrathio-D-mannitol (**12**), mp 124° (hexaacetate mp 165°). Evidence for the constitution, configuration, and conformation of the various products was obtained by a variety of physical methods.

In the course of a project for synthesis of perthio carbohydrates (all oxygen atoms to be replaced by sulfur), we recently prepared a large number of hexitol and cyclitol analogs and their derivatives, in which from two to four of the oxygen atoms were replaced by sulfur.[2a]

Since it has, unfortunately, been necessary to discontinue the perthio carbohydrate project, we are now reporting on some of these partially thiolated products. A literature survey indicates that very few carbohydrates (or other organic compounds) containing three or more mercapto groups are known.[4,5] We are hopeful that some of the compounds now reported will have valuable physical, chemical, and especially biological properties.

The 3-benzoate-4-mesylate derivative[6,7] of 1,2;5,6-di-*O*-isopropylidene-D-mannitol was prepared by an improved method and converted to the di-*O*-isopropylidene derivative, **2** (Chart I), of 3,4-anhydro-D-talitol[7] (equally well named 3,4-anhydro-D-altritol). This epoxide on reac-

Chart I



tion with potassium methyl xanthate gave the expected mixture of diastereomeric trithiocarbonates, **1** and **7**, separated by crystallization.[8]

The reduction of a trithiocarbonate with lithium aluminum hydride usually produces a dithiol. However, reduction of **7** proceeded only to the mercaptodithiolane **3**, presumably because of steric hindrance.

We have encountered similar behavior with certain cyclitol trithiocarbonates.[9]

The trithiocarbonate diketal **7** was next hydrolyzed to the tetrol **8**, which was converted to its tetraacetate **9**. Both of these derivatives were also yellow and crystalline. It was hoped that the tetrol **8** could be converted *via* the 1,6-ditosyl derivative into the 1,2,:5,6-diepoxide, from which a hexathio (or at least a tetrathio) alditol should be obtainable. Since this approach was unsuccessful, we next prepared the trithiocarbonate 1,6-dibromide diacetate (**14**). The tetrol tetraacetate **9** was intended for use in this preparation; however, direct reaction of the trithiocarbonate **7** with hydrogen bromide in acetic acid was found more convenient.

Since the trithiocarbonate dibromide, **14**, was obtained only as an impure syrup, attention was shifted to the use of dithiocarbonate derivatives. Permanganate oxidation[10] of the trithiocarbonate **7** gave the expected product, **6**, which was converted to the corresponding tetrol and tetraacetate, **4** and **5**, both also crystalline. Compounds containing a trithiocarbonate ring have a pronounced yellow color; the dithiocarbonates are colorless.[11]

The dithiocarbonate diketal **6** on reaction with hydrogen bromide in acetic acid gave the dithiocarbonate dibromide diacetate **10**. This was a syrup, but on reaction with potassium thiolacetate it gave the crystalline tetraacetate, **11**, of the dithiocarbonate 1,6-dithiol-2,5-diol.

The latter intermediate on reduction gave the desired product, 1,3,4,6-tetrathio-D-mannitol (**12**) in the form of colorless needles, mp 123° (hexaacetate mp 165°). Even the analytically pure product has a slight odor (perhaps owing to traces of impurities). It is quite stable, at least in the crystalline state. The tetrathioldiol and its acetate were characterized by microanalysis, optical rotation, and infrared and nmr spectra.

Table I
Optical Rotations of Some Derivatives of D-Mannitol and D-Iditol

Derivative	Molecular rotation,[a] deg D-Manno	D-Ido
3,4-*O*-Isopropylidene	+52[b]	−93[c,d]
3,4-*O*-Isopropylidene-1,6-di-*O*-methyl	+65[e]	−33[c,e]
3,4-*O*-Isopropylidene-1,2,5,6-tetra-*O*-tosyl	+58[d]	−84[c,d]
1,2;3,4;5,6-Tri-*O*-isopropylidene	+38[f]	−37[c,d]
1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-thiocarbonyl-3,4-dithio	+1082[g]	−1105[h]
1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-carbonyl-3,4-dithio	+226[g]	−628[h]
1,6-Di-*S*-acetyl-2,5-di-*O*-acetyl-3,4-*S*-carbonyl-1,3,4,6-tetrathio	+800[g]	−460[h]

[a] (Specific rotation * molecular weight/100); sodium D line; for other conditions, see references. [b] J. C. Irvine and B. M. Paterson, *J. Chem. Soc.*, **105**, 988 (1914). [c] Negative of rotation reported for the L-iditol derivative. [d] E. J. Bourne, G. P. McSweeney, and L. F. Wiggins, *J. Chem. Soc.*, 1408 (1952). [e] L. Vargha and E. Kasztreiner, *Chem. Ber.*, **92**, 2506 (1959). [f] E. Fischer, *Ber.*, **28**, 1168 (1895). [g] This article. [h] G. E. McCasland, A. Zanlungo, and L. J. Durham, to be published.

Efforts to convert the dithiocarbonate dibromide diacetate **10** into a 1,2;5,6-diepoxide, from which hexathio-D-mannitol might be obtainable, have so far been unsuccessful.

Previous work has shown that in the transformation of an epoxide to a trithiocarbonate, one but not both of the carbon–oxygen bonds undergoes inversion of configuration. The expected product from a "cis" or erythro epoxide is thus a mixture of two "trans" or threo trithiocarbonates (diastereomers).[12]

The expected product from the 3,4-anhydro-D-talitol derivative, **2**, would then be a mixture of the D-manno and D-ido trithiocarbonates, **7** and **1**, since positions 2 and 5 would be expected to retain their configurations.[13]

We have assigned the D-manno configuration to the trithiocarbonate of mp 117° (**7**) and to all of the related series of compounds here reported (**3**–**6** and **8**–**14**), because of striking regularities in their optical rotations. Such derivatives of D-mannitol and their sulfur analogs, and especially those derivatives having a heterocyclic ring attached at positions 3 and 4, have a strong tendency to be dextrorotatory (see Table I).

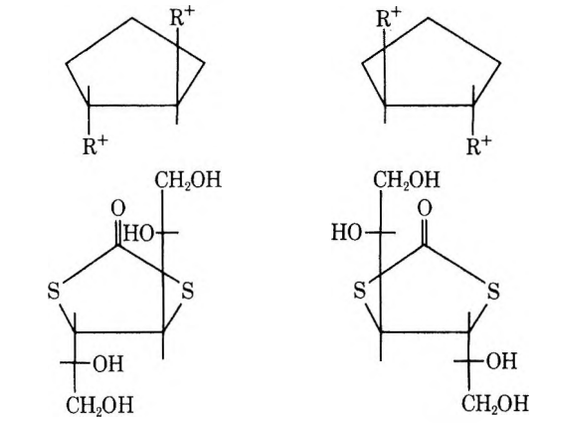
The other trithiocarbonate, **1**, mp 127°, and its numerous derivatives (to be described elsewhere)[14] have an equally strong tendency to be levorotatory, and thus we have assigned them the D-ido configuration.

Some theoretical support for these configurational assignments may be found in the optical rotation theories of Whiffen and of Brewster.[15] Derivatives of D-mannitol and D-iditol having a five-membered heterocyclic ring attached to positions 3 and 4 should be roughly comparable to the 1,2-trans disubstituted cyclopentanes shown in Chart II. Each substituent R^+ is assumed to be a *dissymmetric* group, *e.g.*, $-CHOHCH_2OH$. For this reason the two cyclopentane isomers shown in Chart II are *not* mirror images, because the mirror image of R^+ would be R^-. The two isomers in fact would be diastereomers, which should tend to have opposite signs of rotation, but not equal magnitudes of rotation.

According to the Whiffen and Brewster theories,[15] the left-hand cyclopentane diastereomer (Chart II) should be

Chart II

Optical Rotation Predictions[a]



D-ido (diketal −196°) D-manno (diketal 71°)

[a] See ref 15.

levorotatory, because of the (−)-synclinal conformation of its substituents. The right-hand isomer should be dextrorotatory because it is (+)-synclinal. Similar arguments should apply to the two dithiocarbonate diastereomers shown in Chart II.

It would have been very difficult to make the D-manno/D-ido configurational assignments on the basis of pmr spectra alone. However, after making these assignments on the basis of optical rotations, it was noted that our compounds of the D-manno series tend to have distinctly higher values of the coupling constants J_{23} (= J_{45}) than those of the D-ido series.[16]

When we inspected molecular models, each oriented in what appeared to be one of the most favored conformations, a tendency was noted for H-2 and H-3 (or H-4 and H-5) to be antiperiplanar in the D-manno series, but synclinal or gauche in the D-ido series. These findings are qualitatively consistent with the observed pmr data, but do not, of course, permit any precise predictions of the torsional angles or coupling constants. Details of the nmr spectra are given in the Experimental Section.[17]

It might be expected that the (as yet unknown) perthio- or hexathiohexitols will have considerably different properties from ordinary hexitols, because of nonpolar character and inability to form hydrogen bonds.

Our tetrathiohexitols, however, have properties which are not greatly different from ordinary hexitols. The D-manno and D-ido isomers, at least, are crystalline, and have melting points typical of ordinary hexitols. They have very little of the well-known "mercaptan" odor—perhaps none if completely pure. They are less soluble in water and more soluble in organic solvents than ordinary hexitols. For example, they are soluble in boiling (but not cold) isopropyl ether. They are stable in the solid state, but may need to be protected from oxygen in solution. The characteristically weak infrared S-H stretching absorption at about 2550 cm^{-1} is relatively strong in our products having four free -SH groups. Compounds containing the thiocarbonyl (C=S) group gave a characteristic strong stretching absorption at about 1080 cm^{-1}, as previously noted for other thiocarbonyl compounds by Haszeldine and Kidd.[18]

Experimental Section

All melting points (corrected) were measured on a Nalge-Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. Nmr spectra were recorded and integrated using Varian A-60D and/or HA-100 spectrometers; chemical shifts are expressed as parts per million (δ) unless otherise noted. Field sweep was used for 60-MHz and frequency sweep for 100-NHz nmr spectra. Infrared spectra using potassium bromide pellets were measured on a Perkin-Elmer Model 337 recording spectrometer.

3-*O*-Benzoyl-1,2;5,6-di-*O*-isopropylidene-D-mannitol. The following procedure was found much better than one previously reported.[6] A solution of 44.9 g of the mannitol diketal[19] (mp 120°) in 90 ml of dry pyridine was cooled to 0–5°, and 24.9 g of benzoyl chloride was added dropwise with stirring during 1 hr.

After 24 hr at 25°, the mixture was slowly poured into 900 ml of saturated sodium bicarbonate solution, with vigorous stirring. The syrup which separated was washed repeatedly with water by decantation, causing it to crystallize, dry weight 50.1 g.

By using isopropyl ether for recrystallization, we were able to omit the previously reported[6] column chromatography. The product was obtained as colorless crystals, 35.6 g (57%), mp 104–105° (reported[6] mp 104–107°, yield 46%).

3-*O*-Benzoyl-4-*O*-methanesulfonyl-1,2;5,6-di-*O*-isopropylidene-D-mannitol. This compound was prepared from the above 3-*O*-benzoate diketal (mp 105.5°) in the manner reported by Baker and Haines,[7] giving 47.3 g (96%) of a syrup, which was used directly in the next step (reported[7] yield 96%).

3,4-Anhydro-1,2;5,6-di-*O*-isopropylidene-D-talitol (2). The following procedure gave a much higher yield than one previously reported.[7] To a solution of 42.6 g of the 3-*O*-benzoyl-4-*O*-methanesulfonyl diketal of D-mannitol[7] in 100 ml of dry chloroform, a solution of 2.34 g of sodium in 140 ml of absolute methanol was added dropwise with stirring during 1 hr.

After stirring for 38 hr at 25°, the mixture was boiled under reflux for 2 hr. The cooled, filtered mixture was evaporated, and the residue was dissolved in 70 ml of chloroform. The solution was washed with water, dried, and evaporated, giving a syrup, from which methyl benzoate was removed by distillation (0.2 Torr, 90° bath).

The cooled residual syrup crystallized on seeding, giving 21.6 g (92%) of colorless crystalline product, mp 53–55° (reported[7] mp 53–55°), yield 59%. A sample was further purified by high-vacuum distillation: mp 56–57°; nmr ($CDCl_3$) δ 1.34, 1.39, 1.45, and 1.48 (each s, 3, isopropylidene methyl), 3.05 (m, 2, H-3 and H-4), 3.8–4.3 (m, 6, H-1. H-1′, H-2, H-5, H-6, H-6′); nmr (C_6F_6) δ 1.30 (s, 3), 1.36 (s, 6), 1.42 (s, 3), 3.87 (m, 2), 3.6–4.3 (m, 6).

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-thiocarbonyldithio-D-iditol (1). To a solution of 25.0 g of the above 3,4-anhydro-D-talitol diketal (mp 55°) in 50 ml of methanol was added a solution of 25.0 g of potassium hydroxide and 63.0 g of carbon disulfide in 300 ml of methanol, and the mixture was boiled under reflux for 18 hr.

The solution was evaporated, and the residual brown solid was crystallized from aqueous methanol, giving 11.1 g of a yellow solid. This material was extracted with 20 ml of boiling chloroform. The filtered extract was evaporated, and the crystalline residue was recrystallized from *n*-hexane, giving 4.50 g of crystals, mp 122–124°. A second crop, 1.0 g, mp 120–124°, was obtained.

The combined crops (5.50 g) were recrystallized again, giving 4.60 g (17%) of the pure D-ido stereoisomer, yellow plates, mp 126–127°. The further characterization and reactions of this stereoisomer will be described elsewhere.[14]

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-thiocarbonyldithio-D-mannitol (7). The combined mother liquors from the D-ido stereoisomer (see above) were evaporated to about half volume and cooled, causing separation of crystals, which were recrystallized from petroleum ether, giving 1.15 g of product, mp 113–115°.

This product was recrystallized, giving 650 mg (2.3%) of the D-manno stereoisomer, yellow plates, mp 116–117°. A portion was again recrystallized for analysis, giving yellow plates: mp 116–116.5°; $[\alpha]^{23}D$ 322° (c 2, $CHCl_3$); ir (KBr) 1080 (C=S), 1060, 1125, and 1145 cm^{-1} (dioxolane C-O); nmr ($CDCl_3$) δ 1.37, 1.48 (each s, 6, isopropylidene methyl), 3.80 (q, 2, J_{12} = J_{56} = 3.4, $J_{11'}$ = $J_{66'}$ = 9 Hz, H-1 and H-6), 4.22 (q, 2, $J_{1'2}$ = $J_{56'}$ = 5.5, $J_{11'}$ = $J_{66'}$ = 9 Hz, H-1′ and H-6′).

Anal. Calcd for $C_{13}H_{20}O_4S_3$: C, 46.40; H, 5.99; S, 28.59. Found: C, 46.30; H, 5.99; S, 28.40.

3,4-Thiocarbonyldithio-D-mannitol (8). A stirred mixture of 1.2 g of the above diisopropylidene derivative (mp 117°) with 160 ml of 95% ethanol and 5.2 ml of 6 *N* hydrochloric acid was boiled under reflux until complete dissolution (15 min), then for 3 hr more.

The solution was evaporated, giving a syrup. Portions of ethyl acetate were repeatedly added and evaporated. The final residue, still a syrup, was dissolved in boiling ethyl acetate. The solution

on cooling gave 400 mg of crystals, mp 112–115°. This product was recrystallized, giving 250 mg (27%) of crystals as yellow plates: mp 116–117.5°; $[\alpha]^{24}D$ 284° (c 0.7, $CHCl_3$); ir (KBr) 1065 (C=S) and 3400 cm^{-1} (broad, OH); nmr (100 MHz, D_2O with DSS) δ 4.48 (d, 2, J = 8.5 Hz, H-3 and H-4).

Anal. Calcd for $C_7H_{12}O_4S_3$: C, 32.80; H, 4.72; S, 37.52. Found: C, 32.90; H, 4.93; S, 37.16.

1,2,5,6-Tetra-*O*-acetyl-3,4-thiocarbonyldithio-D-mannitol (9). A solution of 70 mg of the tetrol in 0.5 ml of anhydrous pyridine and 0.5 ml of acetic anhydride was kept at 25° for 24 hr. The solution was then evaporated in a vacuum desiccator over sulfuric acid and sodium hydroxide. The residual solid (110 mg) was crystallized from isopropyl ether, giving 65 mg (56%) of crystals, mp 67.5–69°.

A portion recrystallized for analysis gave yellow plates: mp 67.5–68.5°; $[\alpha]^{24}D$ 271° (c 0.5, $CHCl_3$); ir (KBr) 1060 (C=S) and 1750 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.18 (s, 6, acetate methyl at 1 and 6, or 2 and 5), 2.24 (s, 6, acetate methyl at 2 and 5, or 1 and 6), 4.43 (q, 2 $J_{11'} + J_{66'}$ = 13, $J_{12} = J_{56}$ = 5 Hz, H-1 and H-6), 4.54 (d, 2, $J_{23} = J_{45}$ = 9 Hz, H-3 and H-4), 4.80 (q, 2, $J_{1'2} = J_{56'}$ = 3, $J_{11'} = J_{66'}$, H-1′ and H-6′), 5.67 (m, 2, H-2 and H-5).

Anal. Calcd for $C_{15}H_{20}O_8S_3$: C, 42.44; H, 4.75; S, 22.66. Found: C, 42.90; H, 4.77; S, 21.89.

1,6-Dibromo-1,6-dideoxy-2,5-di-*O*-acetyl-3,4-thiocarbonyldithio-D-mannitol (14). A 200-mg portion of the above trithiocarbonate diketal (mp 117°) was dissolved in 2.0 ml of a 30% solution of hydrogen bromide in anhydrous acetic acid. The solution was kept at 25° for 6 hr, then poured with stirring into 20 ml of saturated sodium bicarbonate solution. The resulting mixture was extracted with chloroform (two 50-ml portions) and the combined chloroform extracts were washed, dried, and evaporated.

The resulting syrup was purified by column chromatography on Woelm silica gel (20 × 1 cm), using benzene as solvent and eluent. The product was obtained as 150 mg (55%) of a yellow syrup, which could not be crystallized, but showed only one spot on thin layer chromatography, nmr ($CDCl_3$) δ 2.18 (s, 6, acetate methyl).

1,2;5,6-Di-*O*-isopropylidene-3,4-dithio-D-mannitol 3,4-Trithioorthoformate (Mercaptodithiolane Diketal) (3). A solution of 150 mg of the above trithiocarbonate diketal (mp 117°) in 25 ml of dry tetrahydrofuran was added dropwise to a slurry of 45 mg of lithium aluminum hydride in 2.5 ml of dry ether. After disappearance of yellow color, the mixture was stirred for 1 hr more.

Excess hydride was destroyed by careful addition of water at 0°, and the mixture was adjusted to pH 4 and immediately extracted with ether. The ether extract was immediately washed with sodium bicarbonate solution, and further processed in the usual manner.

The solid residue obtained by evaporation was crystallized from *n*-hexane, giving 50 mg of crystals, mp 86–92°. This product was recrystallized, giving 30 mg (20%) of material, mp 96–97°. A portion recrystallized for analysis gave colorless needles: mp 97–98°; $[\alpha]^{24}D$ 105° (c 0.6, $CHCl_3$); ir (KBr) 1040, 1060, and 1150 (dioxolane C–O), 2520 cm^{-1} (SH); nmr ($CDCl_3$) δ 1.33 (s, 3), 1.37 (s, 3), and 1.44 (s, 6), isopropylidene methyl groups, 2.93 (d, 1, –SH), 5.67 (d, 1, J = 7 Hz, –CHSH).

Anal. Calcd for $C_{13}H_{22}O_4S_3$: C, 46.13; H, 6.55; S, 28.42. Found: C, 46.16; H, 6.46; S, 28.30.

1,2;5,6-Di-*O*-isopropylidene-3,4-carbonyldithio-D-mannitol (6). To a cooled solution of 1.50 g of the above trithiocarbonate (mp 117°) in 50 ml of reagent-grade acetone, 3.7 g of powdered potassium permanganate was added in portions with stirring at 25° during 2 hr. After 1 hr more, the precipitate was collected and washed with acetone (three 10-ml portions).

The combined filtrates were evaporated, and the solid residue was extracted with boiling benzene (three 10-ml portions). The combined benzene extracts on evaporation gave 1.25 g (87%) of crystalline product, mp 73–74.5°.

A portion was recrystallized for analysis from methanol–water, giving colorless plates: mp 73–73.5°; $[\alpha]^{24}D$ 71° (c 0.6, $CHCl_3$); ir (KBr) 1025, 1070, and 1150 (dioxolane C–O), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.38 (s, 6) and 1.48 (s, 6), isopropylidene methyl groups, 3.34 (m, 2, H-3 and H-4).

Anal. Calcd for $C_{13}H_{20}O_5S_2$: C, 48.73; H, 6.29; S, 20.01. Found: C, 48.83; H, 6.20; S, 20.91.

3,4-Carbonyldithio-D-mannitol (4). A stirred solution of 400 mg of the above diisopropylidene derivative (mp 74°) in 8.0 ml of 40% aqueous acetic acid was heated at 100° for 11 hr. The solution was evaporated, and the residual syrup was vacuum dried (0.5 Torr, 70°). The dried syrup was crystallized from ethyl acetate, giving 110 mg of product, mp 121–124°. This material was recrystallized, giving 70 mg, mp 122–123.5°. A second crop of 100 mg, mp 122–124°, was obtained from the first crystallization filtrate, total yield 210 mg (70%).

A portion of the recrystallized first crop was again recrystallized for analyses, giving colorless needles: mp 122–123°; $[\alpha]^{23}D$ 62° (c 2.4, methanol); ir (KBr) 1650 (C=O) and 3400 cm^{-1} (broad, OH); nmr (D_2O with DSS) δ 4.38 (d, 2, $J_{23} = J_{45}$ = 8.5 Hz, H-3 and H-4).

Anal. Calcd for $C_7H_{12}O_5S_2$: C, 34.99; H, 5.03; S, 26.69. Found: C, 35.02; H, 4.95; S, 25.79.

1,2,5,6-Tetra-*O*-acetyl-3,4-carbonyldithio-D-mannitol (5). A solution of 150 mg of the above tetrol (mp 123°) in 0.5 ml of anhydrous pyridine and 0.5 ml of acetic anhydride was kept at 25° for 24 hr. The solution was evaporated in a vacuum desiccator over sulfuric acid and sodium hydroxide. The residual syrup was crystallized from a mixture of benzene and *n*-hexane, giving 220 mg (88%) of colorless needles: mp 84–85°; $[\alpha]^{23}D$ 132° (c 1.6, $CHCl_3$); ir (KBr) 1655 (carbonyldithio C=O) and 1750 cm^{-1} (acetate C=O); nmr ($CDCl_3$) δ 2.08 (s, 6) and 2.15 (s, 6), acetate methyl at 1,6 and 2,5, respectively.

Anal. Calcd for $C_{15}H_{20}O_9S_2$: C, 44.11; H, 4.94; S, 15.70. Found: C, 44.01; H, 4.90; S, 15.19.

1,6-Dibromo-1,6-dideoxy-2,5-di-*O*-acetyl-3,4-carbonyldithio-D-mannitol (10). An 800-mg portion of the above dithiocarbonate diketal (mp 74°) was dissolved in 7.0 ml of an anhydrous 32% solution of hydrogen bromide in acetic acid. After 4 hr at 25° the solution was poured with stirring into saturated sodium bicarbonate solution. The syrup which separated was washed repeatedly with water by decantation, then dissolved in chloroform. The dried solution on evaporation gave the product as a syrup which could not be crystallized, but had an appropriate spectrum: nmr ($CDCl_3$) δ 2.23 (s, 6, acetate methyl), 4.32 (d, 2, $J_{23} = J_{45}$ = 9 Hz, H-3 and H-4), 3.85 (m, 4) and 5.32 (m, 2), second-order pattern attributed to H-1, H-1′, and H-2, and to H-6, H-6′, and H-5.

1,6-Di-*S*-acetyl-2,5-di-*O*-acetyl-3,4-*S*-carbonyl-1,3,4,6-tetrathio-D-mannitol (11). A stirred mixture of 500 mg of the above dibromide diacetate (syrup), 600 mg of potassium thiolacetate, and 20 ml of reagent-grade acetone was boiled under reflux for 24 hr. The cooled, filtered mixture was evaporated, and the residual syrup was partitioned between chloroform and water. The suitably processed chloroform phase on evaporation gave a deep-brown syrup.

Since charcoal decolorization using ethyl acetate as solvent was ineffective, the decolorization was repeated using isopropyl ether. The latter solution on cooling gave 200 mg (42%) of colorless, crystalline product, mp 100–102.5°.

A portion was recrystallized for analysis, giving colorless needles: mp 102–103°; $[\alpha]^{23}D$ 182° (c 1.9, $CHCl_3$); ir (KBr) 1655 (dithiocarbonyl C=O), 1702 (thioacetate C=O), and 1745 cm^{-1} (acetate C=O); nmr ($CDCl_3$) δ 2.10 (s, 6) and 2.37 (s, 6), *O*- and *S*-acetate methyl, respectively.

Anal. Calcd for $C_{15}H_{20}O_7S_4$: C, 40.89; H, 4.58; S, 29.11. Found: C, 40.86; H, 4.61; S, 29.47.

1,3,4,6-Tetrathio-D-mannitol (12). A 250-mg portion of the above tetrathiomannitol dithiocarbonate tetraacetate (mp 103°) dissolved in 2.0 ml of anhydrous tetrahydrofuran was added dropwise to a slurry of 800 mg of lithium aluminum hydride in 10 ml of anhydrous ether. The reaction was conducted under dry nitrogen.

After 4 hr at 25°, excess hydride was destroyed with water in the usual manner, and the slightly acidified (pH 4) aqueous phase was extracted repeatedly with ether. The combined ethereal extract was washed with 5% sodium bicarbonate solution, dried, and evaporated.

The residual solid was crystallized from isopropyl ether, giving 32 mg (23%) of crystalline product, mp 118–120°. A portion was recrystallized for analysis, giving 9 mg of colorless needles: mp 122.5–123.5°; ir (KBr) 2520 (SH) and 3300 cm^{-1} (broad, OH); nmr ($CDCl_3$) δ 2.17 (s, 6) and 2.43 (s, 6), *O*- and *S*-acetate methyl, respectively, 3.28 (q, 2, $J_{12} = J_{56}$ = 6.5, $J_{11'} = J_{66'}$ = 15 Hz, H-1 and H-6), 3.65 (q, 2, $J_{1'2} = J_{56'}$ = 3.5, $J_{11'} = J_{66'}$ = 15 Hz, H-1′ and H-6′), 4.28 (d, 2, $J_{23} = J_{45}$ = 8 Hz, H-3 and H-4), 5.39 (m, 2, H-2 and H-5).

1,3,4,6-Tetra-*S*-acetyl-2,5-di-*O*-acetyl-1,3,4,6-tetrathio-D-mannitol (13). Attempted preparation of a second crop of tetrathiomannitol from the combined mother liquors (see above) gave only a syrup. This material (62 mg) was dissolved in a mixture of 0.5 ml of anhydrous pyridine and 0.5 ml of acetic anhydride. After 24 hr at 25°, the mixture was evaporated in a vacuum desiccator over sulfuric acid and sodium hydroxide.

The yellow, solid residue was purified by column chromatogra-

phy using Woelm silica gel (250 × 10 mm) and ethyl acetate as solvent. The column was eluted with 100 ml of *n*-hexane–isopropyl ether (2:1) and then with 50 ml of pure isopropyl ether. The latter eluate on evaporation give 40 mg (32%) of slightly yellow product, mp 162–164°. The chromatographic purification was repeated in the same manner, giving 30 mg of colorless crystals, mp 163–164°.

A portion was recrystallized for analysis from *n*-hexane, giving colorless needles: mp 163.5–164.5°; $[\alpha]^{23}D$ 94° (*c* 1.2, $CHCl_3$); ir (KBr) 1690 and 1705 (*S*-acetate C=O), 1750 cm^{-1} (*O*-acetate C=O); nmr ($CDCl_3$) δ 2.07 (s, 6) and 2.32 (s, 6), *O*-acetate methyl and *S*-acetate methyl, respectively.

Anal. Calcd for $C_{18}H_{26}O_8S_4$: C, 43.36; H, 5.26; S, 25.72. Found: C, 43.42; H, 5.20; S, 25.50.

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Registry No.—**1,** 51051-69-5; **2,** 24808-13-7; **3,** 51051-70-8; **4,** 51051-71-9; **5,** 51051-72-0; **6,** 51051-73-1; **7,** 51051-74-2; **8,** 51051-75-3; **9,** 51051-76-4; **10,** 51051-77-5; **11,** 51051-78-6; **12,** 51051-79-7; **13,** 51051-80-0; **14,** 51051-81-1; 3-*O*-benzoyl-1,2;5,6-di-*O*-isopropylidene-D-mannitol, 51051-82-2; 3-*O*-benzoyl-4-*O*-methanesulfonyl-1,2;5,6-di-*O*-isopropylidene-D-mannitol, 51051-83-3.

References and Notes

(1) Presented in part to the Division of Organic Chemistry at the 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 1970, and to the Division of Carbohydrate Chemistry at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(2) (a) For preceding publication on thio carbohydrates, see G. E. McCasland, A. K. M. Anisuzzaman, S. R. Naik, and L. J. Durham, *J. Org. Chem.*, **37**, 1201 (1972). (b) For preceding publication on alicyclic carbohydrates, see J. Shapira, T. Putkey, A. Furst, and G. E. McCasland, *Carbohyd. Res.*, **25**, 535 (1972); see also Y. Sanemitsu, N. Kurihara, M. Nakajima, G. E. McCasland, L. F. Johnson, and L. C. Carey, *Agr. Biol. Chem.*, **36**, 845 (1972).

(3) (a) To whom any communications should be addressed, at the University of San Francisco; (b) Stanford University.

(4) Reported preparations of compounds containing more than three mercapto groups include (a) 1,2,3,4-butanetetrathiol, see C. G. Overberger and A. Drucker, *J. Org. Chem.*, **29**, 360 (1964); (b) tetra(mercaptomethyl)methane, M. W. Farlow and F. K. Signaigo, *Chem. Abstr.*, **40**, 5763 (1946).

(5) (a) The preparation of a tetrathiohexitol was reported by S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, 1030 (1960). It had the L-ido configuration, and the sulfur groups were at positions 1, 2, 5, and 6 (isolated as hexaacetate, mp 133–135°). It should be noted that the tetrathiohexitols now reported by us have the D (ido or manno) configuration, and the sulfur groups are at positions 1, 3, 4, and 6.[5b] (b) This article describes a new series of stereoisomers (hexitol sulfur analogs). It is almost certain that the compounds in this series all have the *same* configuration (D-manno or D-ido), because the reactions employed would not invert position 2 or 5, and would retain or produce a threo configuration at positions 3 and 4.

Optical rotation studies further indicate, in the author's opinion, that the series configuration is D-manno (not D-ido), with a *very high probability.*

The reader is cautioned, however, that this rotation-based configurational assignment (like many similar assignments in the field of carbohydrates) cannot be regarded as absolutely certain. Accordingly (as suggested by a referee) we recommend that the D-manno assignments in this article be considered tentative until more rigorous evidence, *e.g.*, X-ray or neutron diffraction studies, is available. (Nmr spectra were recorded for these compounds, but could not be interpreted in terms of configuration.)

(6) J. M. Sugihara and G. U. Yuen, *J. Amer. Chem. Soc.*, **79**, 5780 (1957).

(7) (a) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 442 (1963); (b) *ibid.*, **28**, 438 (1963).

(8) In 1960 L. N. Owen and S. M. Iqbal by a similar reaction of 3,4-anhydro-1,2;5,6-di-*O*-isopropylidene-D-talitol obtained a trithiocarbonate (reported mp 108–110°) and reduced it to a dithiol. We now believe that each of these products was a mixture of the D-ido and D-manno diastereomers. See *J. Chem. Soc.*, 1030 (1960).

(9) For an example of the formation of a mercaptodithiolane diketal in the cyclitol series, see G. E. McCasland, S. Furuta, A. Furst, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **28**, 459, 462 (1963).

(10) F. Runge, Z. El-Hewehi, H. J. Renner, and E. Taeger, *J. Prakt. Chem.*, **11**, 284 (1960).

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Scission of the Sulfur–Sulfur Bond in Dipurinyl and Dipyrimidinyl Disulfides by Cyanide[1,2]

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Bis(1-β-D-ribofuranosyl-4-thiouracil) disulfide, its methyl analog, and bis(9-methyl-6-thiopurine) disulfide are decomposed quantitatively into the corresponding thiocyanato and thio derivatives by CN^- buffered at pH 7. 4-Thiocyanatouridine and its methyl analog decompose quantitatively in alkali to the corresponding thio and oxo compounds in 2:7 and 1:1 ratio, respectively. 9-Methyl-6-thiocyanatopurine decomposes in alkali to 9-methyl-6-thiopurine. The reaction of the three above-mentioned disulfides in unbuffered CN^- apparently proceeds through the intermediate formation of the thio and thiocyanato derivatives, the latter decomposing *in situ* under alkaline conditions in the same manner. Synthesis and properties of 4-thiocyanatouridine, its methyl analog, 9-methyl-6-thiocyanatopurine, and bis(1-methyl-4-thiouracil) disulfide are described.

The extreme susceptibility of the disulfide bond in bis(1-β-D-ribofuranosyl-4-thiouracil) disulfide and its methyl analog to nucleophilic attack by OH^- reported earlier from this laboratory[3] led us to extend this study to the

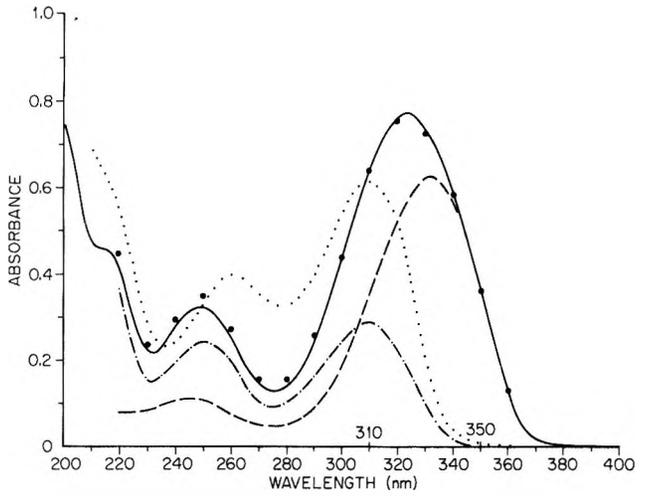


Figure 2. Decomposition of bis(1-β-D-ribofuranosyl-4-thiouracil) disulfide (Ir) by NaCN at pH 7. The uv absorption spectra of Ir at pH 7 (· · ·), Ir after treatment with NaCN at pH 7 (——), IIr at pH 7 normalized at 350 nm (- - -), and IIIr at pH 7 normalized at 310 nm (- · -). Addition spectrum of IIr and IIIr (●).

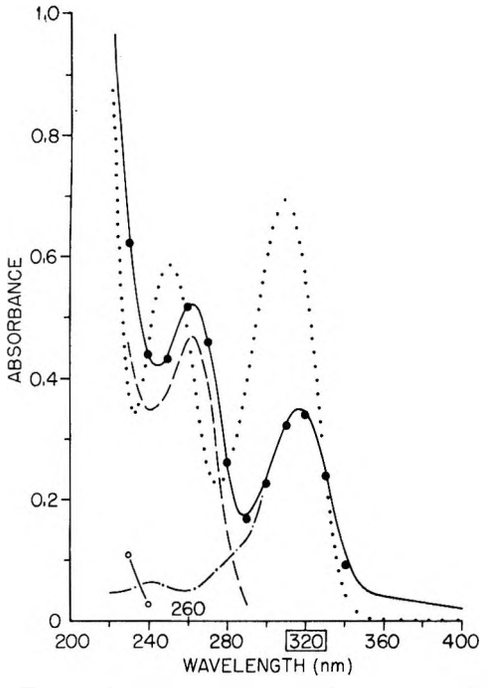


Figure 5. The uv absorption spectra of 4-thiocyanatouridine (IIIr) at pH's 2 and 7 (· · ·) and 12 (——) (decomposes), and spectral correlation of its hydrolysis products at pH 12. The uv absorption spectra of IIr at pH 12 normalized at 320 nm (- · -), IVr at pH 12 normalized at 260 nm (- - -), and thiocyanate at pH 12 normalized at 230 nm (O - O). Addition spectrum of the last three (IIr + IVr + SCN^-) (●).

cleavage of the disulfide bond in these compounds and bis(9-methyl-6-thiopurine) disulfide by CN^-. The first step in the reaction of all three purine and pyrimidine disulfides with CN^- was very similar. All three quantitatively decomposed into the thiocyanato and thio derivatives when the reaction was carried out with NaCN buffered at pH 7. In each case, the spectra of the disulfides treated with CN^- can be shown to be the addition spectra of the two products formed in stoichiometric amounts (Figures 1-3).[4] In unbuffered CN^-, however, the intermediate thiocyanato derivatives were degraded owing to alkaline conditions.

In order to demonstrate that the reaction with unbuffered CN^- proceeded through the intermediate formation of the thiocyanato derivatives, we synthesized all three of them (IIIr, IIIm, and VII) independently and studied their spectral properties and decomposition in alkali (Table I, Figures 4-6). The spectra of all three thiocyanates are essentially the same at pH 2 and pH 7. Compounds IIIm and IIIr decomposed in alkali to IIm and IVm, and IIr and IVr, in 1:1 and 2:7 ratio, respectively (Figures 4 and 5). The decomposition of the thiocyanates IIIm and IIIr takes place according to the following equations.

Table I
Spectral Properties

Compd	pH or solvent	Spectral characteristics, λ, nm (ε × 10^{-3}) Maxima	Minima
Ir	7[a]	309 (19.60)	279 (10.50)
		261 (11.70)	236 (7.70)
	Ethanol[b]	311 (18.15)	280 (9.46)
		262 (12.38)	237.5 (7.70)
Im	7	307.5 (18.12)	277 (8.70)
		257 (12.10)	236 (8.30)
V	7	290 (26.10)	287 (25.48)
		283 (25.69)	239 (5.94)
		215 (28.60)	208 (28.13)
IIr[c]	6.5	331 (21.00)	274 (1.65)
		245 (4.00)	225 (2.60)
	11.8	316 (19.70)	268 (2.40)
IIm	2, 6	334 (20.19)	278 (0.90)
		242.5 (4.04)	225 (2.31)
	12	315 (17.05)	257 (2.65)
VI[d]	0	326 (18.5)	
	5.1	321 (26.1)	
		229 (12.7)	
	11.1	309 (21.4)	
		234 (13.0)	
IIIr[e]	2, 6	309 (8.41)	275 (2.74)
		251 (6.83)	233 (4.15)
IIIm	2, 6	307 (7.79)	271.5 (1.99)
		245 (6.35)	232 (4.56)
		217.5 (12.72)	
	Ethanol[f]	312 (6.5)	
		245.5 (5.4)	
VII	2, 6	277 (12.73)	237.5 (2.40)
IVm	2, 6	267 (9.48)	232 (1.32)
	12	264 (6.74)	241 (3.43)
NaCNS	2	ϵ_{240} 250, ϵ_{230} 1500, ϵ_{220} 2950, ϵ_{210} 3350	
	12	ϵ_{240} 250, ϵ_{230} 1500, ϵ_{220} 4000	

[a] Reported max 309, 261; min 278, 236 (ref 12). [b] Reported max 320 (29.75), 260 (6.50); min 280 (5.40) (ref 7). [c] Data from N. K. Kochetkov, E. I. Budowsky, V. N. Shibaev, and M. A. Grachev, *Biochim. Biophys. Acta*, **59**, 749 (1962). [d] Data from J. H. Lister in "Fused Pyrimidines," Part II, D. J. Brown, Ed., Wiley-Interscience, New York, N. Y., 1971, p 485. [e] Reported max 310 (8.00), 250 (7.80); min 280 (4.00) in ethanol (ref 7). [f] Reported, in ethanol, max 318.5 (7.78), 256 (6.7) (ref 6).

(IIIm) $2R'SCN + 4OH^- =$
$R'O^- + R'S^- + SCN^- + OCN^- + 2H_2O$

(IIIr) $9R'SCN + 18OH^- =$
$7R'O^- + 2R'S^- + 7SCN^- + 2OCN^- + 9H_2O$

Titration of IIIm with alkali to pH 11 indicated the consumption of 2 equiv of alkali per mole of IIIm. The amounts of $R'O^-$, $R'S^-$, and SCN^- formed were calculated from the spectra; the spectral correlation is shown in Figures 4 and 5. We were unable to obtain any direct evidence for the formation of CNO^-; its extinction in the ultraviolet range is negligible at the concentrations used in these experiments. The compound VII, on the other hand, was transformed in alkali to VI to the extent[5] of 85% with no evidence for the formation of any oxo compound, for VI could be recovered completely by treatment of the reaction mixture with Na_2S. This indicates that the stability

Table II[a]
Cleavage of the Thiocyanates and Disulfides by H^+, OH^-, HS^-, and CN^-

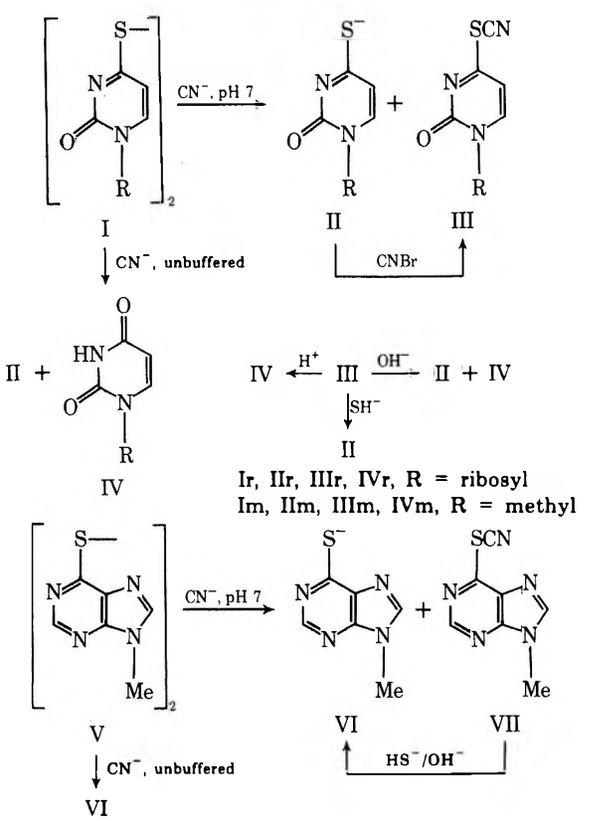
Compd	Reaction conditions	Reagent	Products
Ir (31.4)	1 hr	CN^- (pH 7)	IIIr (34), IIr (29.7)
Ir (35.7)	2 hr	CN^- (unbuffered)	IVr (26.2), IIr (43.3), CNS^- (26.2)
Im (33.7)	3 hr	CN^- (pH 7)	IIIm (33), IIm (36)
Im (33.9)	2 hr	CN^- (unbuffered)	IVm (18.1), IIm (51.8), CNS^- (18.1)
V (33.3)	3.5 hr	CN^- (pH 7)	VI (32.6), VII (31.4)
V (32)	72 hr	CN^- (unbuffered)	VI (61.8)
IIIr (82)	Immediate	OH^-	IIr (18), IVr (64), CNS^- (64)
	48 hr	H^+	IVr (81)
	Immediate	HS^-	IIr (82)
IIIm (59)	Immediate	OH^-	IIm (29), IVm (29), CNS^- (29)
	48 hr	H^+	IVm (59)
	Immediate	HS^-	IIm (59)
VII (71.6)	5 days	OH^-	VI (60.8)
	1 day	H^+	No reaction
	Immediate	HS^-	VI (71)

[a] Numbers in parentheses indicate one-third the number of nanomoles of the compounds in a 3-ml cuvette. All reactions were carried out at 25°.

of the ring-S bond in these compounds decreases in the order VII > IIIm > IIIr. Compounds IIIm and IIIr are converted into IVm and IVr quantitatively in acid, while VII is unaffected in acid. All three thiocyanato derivatives are readily reduced to thio compounds by SH^-. The decomposition of the thiocyanato derivatives in alkali is parallel to the decomposition of the thiocyanato derivatives formed *in situ* as a result of the nucleophilic attack of the unbuffered CN^- (pH 10.2) on the disulfides. The amounts of products formed were in exactly the same ratio as predicted on the basis of the formation of the thiocyanates as intermediates (Table II, Figures 7–9).

The compounds IIIm and VII were prepared, in good yield, by the action of CNBr on the solution of IIm and VI in equivalent amounts of alkali. We were unable to prepare IIIm by the published method.[6] The spectral properties of the compound prepared by us also do not agree with the data reported earlier[6] (*cf.* Table I). The preparation of IIIr, however, was difficult owing to its lability. Although reports on the preparation of this compound have appeared in the literature,[6,7] it has not been characterized rigorously. We found that the best way to prepare this compound is to use the cyanide cleavage reaction of the disulfide Ir. In the first step, the disulfide Ir was treated with NaCN buffered at pH 7. When completion of the reaction was indicated by the uv absorption spectrum of the reaction mixture, the solution was treated with CNBr to convert the thiol IIr to the thiocyanato derivative IIIr (Scheme I). This method was also successful with the methyl analog (Figures 10 and 11).

Scheme I



Degani and Patchornik[8] used a similar method for the synthesis of 2-nitro-5-thiocyanatobenzoic acid from 5,5′-dithiobis(2-nitrobenzoic acid). Cyanogen bromide has previously been shown to oxidize thiols to disulfides when 0.5 mol of reagent is used per mole of the thiol.[9] Compound IIr has also been reported to form a disulfide when treated with 0.5 mol of CNBr per mole of reactant. In addition, we found that IIm, on treatment with even 1.1 mol of CNBr in ethanol containing 1 mol of triethylamine, forms the disulfide Im instead of the expected thiocyanato derivative IIIm. Paralleling the experience of Degani and Patchornik,[8] we found that, to obtain a quantitative yield of the thiocyanate from the disulfide by cyanide cleavage (step 1) followed by cyanogen bromide treatment (step 2), the presence of cyanide is necessary in the second step to decompose any disulfide that may be formed in this step. The disulfide formation from the thiouridine by cyanogen bromide probably proceeds *via* the intermediate sulfenyl bromide.[7] We have examined and eliminated the alternate possibility involving the intermediate formation of thiocyanate, since attempts to prepare Im by reaction of IIIm with IIm were not successful. The thiocyanate IIIr was characterized by its quantitative conversion to IVr in acid and to IIr in sodium bisulfide (Figure 12). Moreover, the similarity of its uv absorption spectrum with that of its methyl analog characterizes IIIr to be 4-thiocyanatouridine (Figures 4 and 5).

Contrary to earlier observation,[7] we found that the spectra of Ir and IIIr are very similar (Figures 2 and 5). Both of them have their higher absorbancy peak at 309 nm, although the lower absorption peak position of IIIr shows a comparative blue shift of about 10 nm. However, the two can be distinguished by their spectra in alkali. In alkali, Ir forms sulfenic acid[3] which shows an absorption maximum at 360 nm, whereas IIIr in alkali does not show appreciable absorbance at 360 nm (Figure 5). The previously reported spectral data of Ir do not agree with our

results[7] (Table I). The use of commercial preparations without purification might have led to this anomaly.

We have thus established that the disulfides Ir, Im, and V are initially cleaved by the cyanide to form the thiocyanato and thio derivatives quantitatively in 1:1 ratio, the former undergoing further degradation under alkaline conditions. Thiocyanatopyrimidines IIIr and IIIm form IIr and IVr, and IIm and IVm, in 2:7 and 1:1 ratio, respectively. Thiocyanatopurine VII, however, is quantitatively converted into VI resembling the behavior of 6-thiopurine itself.[11] Our results support the findings of Walker and RajBhandary[10] that 4-thiocyanatouridine, like its methyl analog, is degraded under alkaline conditions partly to thiouridine and partly to uridine, instead of its complete degradation to uridine as earlier reported.[6]

Experimental Section

Melting points were observed in a Thomas-Hoover apparatus and are uncorrected. Thin layer chromatography was carried out by use of E. Merck tlc plates and Cellulose F and with the following solvent systems: A, 1-butanol–water, 86:14 (v/v); B, isobutyric acid–ammonia–water, 66:1:33 (v/v/v); and C, 0.1 *M* phosphate buffer (pH 6.8)–ammonium sulfate–1-propanol, 100:60:2 (v/w/v). Bis(1-β-D-ribofuranosyl-4-thiouracil) disulfide,[12] its methyl analog,[3] and 1-methyl-4-thiouracil[12] were synthesized by published methods. 9-Methyl-6-thiopurine was obtained from Cyclo Chemical Corp., Los Angeles, Calif. All other chemicals were reagent-grade commercial products. The uv absorption spectra at different pH's were recorded on a Cary recording spectrophotometer Model 14 PM on the same solution in the same cuvette using small amounts of acid, alkali, or buffer solutions to alter the pH. The ir spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer with KBr disks. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn.

Bis(9-methyl-6-thiopurine) Disulfide (V). 9-Methyl-6-thiopurine (VI), 166.2 mg (1 mmol), was brought into solution in 25 ml of water by adding 1 *N* NaOH to a pH of 10.5. The solution was cooled in ice water and treated with 1 ml of 1 *N* iodine solution. The pH fell to 9.5. The precipitate was filtered and washed with water, crude yield 136 mg. It was washed with dilute ammonia in the cold to remove traces of starting material, and recrystallized from 50% ethanol. Yield of chromatographically homogeneous material was 90 mg (27% of theory), mp 232–233°.

Anal. Calcd for $C_{12}H_{10}N_8S_2$: C, 43.62; H, 3.05; N, 33.92. Found: C, 43.41; H, 3.09; N, 33.78.

Bis(1-methyl-4-thiouracil) Disulfide (Im). A suspension of 1-methyl-4-thiouracil, 142.2 mg (1 mmol), in 10 ml of ethanol was treated with triethylamine (1 mmol) and cyanogen bromide (1.1 mmol) at 25° with stirring. A white precipitate was formed in about 10 min. The reaction mixture was chilled in ice and filtered, yield, 100 mg (71% of theory). It was identified as the disulfide by comparing its melting point, uv spectra, and tlc in solvents A and B with those of an authentic specimen.

9-Methyl-6-thiocyanatopurine (VII). A solution of 9-methyl-6-thiopurine, 83.1 mg (0.5 mmol), in a mixture of 0.5 ml of 1 *N* NaOH and 2.5 ml of water was treated with 1 *M* ethanolic CNBr, 0.55 ml, at 25°. A white precipitate appeared almost immediately. The reaction mixture was allowed to stand at room temperature for 30 min, then cooled in ice, filtered, washed with ice-cold water, and dried *in vacuo* over P_2O_5: yield 81 mg (85% of theory); mp 181.5–182°; ir 2180 cm^{-1} (-SCN).

Anal. Calcd for $C_7H_5N_5S$: C, 43.97; H, 2.64; N, 36.63. Found: C, 43.72; H, 2.48; N, 36.45.

1-Methyl-4-thiocyanatouracil (IIIm). A solution of 1-methyl-4-thiouracil, 142 mg (1 mmol), in 5 ml of 0.2 *N* NaOH was treated at once with 1.1 ml of 1 *M* ethanolic CNBr while stirring at room temperature. The reaction mixture was allowed to stand for 1 hr, cooled in ice, filtered, and washed with a little ice-cold water: yield 110 mg (66% of theory); white, glistening plates; mp 145–146° dec; chromatographically homogeneous (solvents A. C).

Anal. Calcd for $C_6H_5N_3OS$: C, 43.10; H, 3.10; N, 25.13. Found: C, 43.19; H, 2.93; N, 25.22.

4-Thiocyanatouridine (IIIr). One milliliter of freshly prepared 1 *M* NaCN was added dropwise to a suspension of bis(1-β-D-ribofuranosyl-4-thiouracil) disulfide (Ir), 5.2 mg (0.01 mmol), in 5 ml of 0.05 *M* phosphate buffer (pH 7). The pH of the reaction mixture was maintained by simultaneous addition of 0.5 *M* KH_2PO_4 in a pH stat. The disulfide gradually went into solution. After standing for 1.5 hr, the A_{325}/A_{275} was found to be 5.9. It is necessary to attain this ratio to ensure complete conversion of the disulfide. One milliliter of 1 *M* ethanolic solution of CNBr was added and the reaction mixture was allowed to stand for 10 min. It was then run through a column of Sephadex G-10 (25 × 2 cm), eluting with oxygen-free water and collecting 5-ml fractions. The appropriate fractions were combined and evaporated in a rotary evaporator under high vacuum at room temperature to half the original volume. The yield of chromatographically homogeneous 4-thiocyanatouridine was practically quantitative. The aqueous solution deteriorated slowly on standing, as judged by its uv spectrum.

The above preparation has been spectrophotometrically duplicated (Figure 10). Three milliliters of an aqueous solution of Ir containing 50 μl of 0.5 *M* phosphate buffer, pH 6, was treated with 10 μl of 1 *M* freshly prepared NaCN. The spectra were recorded before, and 2 hr after, addition of NaCN. Then 10 μl of 1 *M* ethanolic CNBr was added and the spectrum of the thiocyanate IIIr formed was recorded. For characterization of the thiocyanate IIIr, the solution was transferred from the cuvette to a flask and weighed. The solution was then evaporated at room temperature in a rotary evaporator under high vacuum to about half its volume to remove excess CNBr. It was then reconstituted by adding water to compensate for the loss in weight, after which it was treated with 10 μl of 1 *M* Na_2S and the spectrum was recorded after addition of 25 μl of 10 *N* NaOH. Another sample of thiocyanate IIIr, prepared in identical manner, was treated with 50 μl of 10 *N* HCl and the spectrum was recorded. The results are shown in Table II and Figure 12. The spectral properties are recorded in Table I. The molar extinction of 4-thiocyanatouridine was calculated on the basis of its quantitative conversion to 4-thiouridine in sodium sulfide.

Action of Acid, Alkali, and Sodium Sulfide on 4-Thiocyanatouridine (IIIr), Its Methyl Analog (IIIm), and 9-Methyl-6-thiocyanatopurine (VII). Three milliliters of a solution of each thiocyanate in oxygen-free water was treated separately with 25 μl of 10 *N* HCl, 25 μl 10 *N* NaOH, and 10 μl of 1 *M* Na_2S at 25°. The results are shown in Table II and Figures 4–6 and 12.

Reaction of Bis(1-β-D-ribofuranosyl-4-thiouracil) Disulfide (Ir), Its Methyl Analog (Im), and Bis(9-methyl-6-thiopurine) Disulfide (V) with Cyanide. Three milliliters of a solution of each disulfide in oxygen-free water was treated with 50 μl of 0.5 *M* phosphate buffer followed by 10 μl of 1 *M* freshly prepared NaCN at 25°. For studying the reactions of unbuffered NaCN, the phosphate buffer was omitted. The results are shown in Table II and Figures 1–3 and 7–9.

Attempted Preparation of Bis(1-methyl-4-thiouracil) Disulfide (Im) from the Thio (IIm) and Thiocyanato (IIIm) Derivatives. A mixture of 1-methyl-4-thiouracil, 2.84 mg (0.02 mmol), 1-methyl-4-thiocyanatouracil, 3.34 mg (0.02 mmol), ethanol, 0.5 ml, and triethylamine (0.02 mmol) was stirred at room temperature for 1 hr. It was centrifuged and, after removal of the supernatant, the residue was taken up in water and the uv absorption spectrum in alkali was recorded. Absence of any appreciable absorbance at 360 nm indicates absence of formation of any disulfide. In alkali, the uv absorption spectrum of Im shows a peak at 360 nm due to the formation of sulfenic acid.[3]

Titration of 1-Methyl-4-thiocyanatouracil (IIIm) with Alkali. Compound IIIm, 11.55 mg, was suspended in 5 ml of water containing 2 drops of thymolphthalein indicator solution [0.04 g/100 ml of ethanol–water (1:1)] and titrated with 0.1 *N* NaOH solution. The amount of alkali consumed was 1.35 ml or 1.95 mol/mol of IIIm.

Acknowledgment. Thanks are due to Dr. W. E. Cohn for his interest and encouragement.

Registry No.—Im, 23193-01-3; Ir, 18427-02-6; IIm, 35455-86-8; IIr, 13957-31-8; IIIm, 29401-10-3; IIIr, 51056-62-3; IVm, 615-77-0; V, 51056-63-4; VI, 1006-20-8; VII, 51056-64-5; NaCN, 143-33-9; NaCNS, 540-72-7.

Supplementary Material Available. Figures 1, 3, 4, and 6–12 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for

photocopy or $2.00 for microfiche, referring to code number JOC-74-1466.

References and Notes

(1) Research supported by the U. S. Atomic Energy Commission under contract with the Union Carbide Corp.
(2) Presented at the 24th Southeastern Regional Meeting of the American Chemical Society, Birmingham, Ala., Nov. 2–4, 1972.
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(4) See paragraph at end of paper regarding supplementary material.
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Ultraviolet- and γ-Ray-Induced Reactions of Nucleic Acid Constituents. Reactions of Purines with Ethers and Dioxolane

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Ultraviolet- and γ-ray-induced reactions of caffeine, adenine, and guanosine with tetrahydrofuran, tetrahydropyran, dioxane, tetrahydrofurfuryl alcohol, and dioxolane are described. The reactions lead to the appropriate 8-substituted purines in yields of up to 90% when performed in the presence of photoinitiators. A free-radical mechanism is proposed for these reactions.

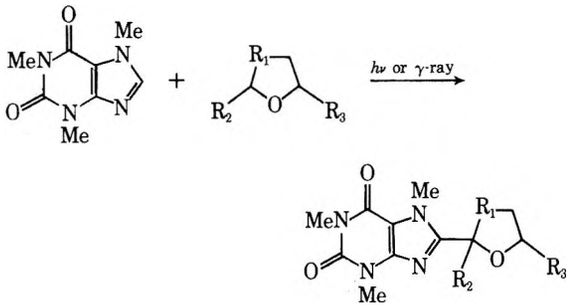
Ultraviolet and γ-ray-induced reactions of purines with alcohols or amines have been described recently.[1] These reactions resulted in the substitution of the appropriate moiety for the 6- or 8-hydrogen atom in the purine system. Thus, in reactions of purines with alcohols the substituent was usually the α-hydroxyalkyl group, while with amines it was the α-aminoalkyl group. The reactions could be induced directly with ultraviolet light (λ >260 nm) or by the use of photosensitizers (with light of λ >290 nm), which increased the yields of the photoproducts.

The aim of the present study is the investigation of the photochemical reactions of purines with a variety of substrates, mainly with those present in living systems. This will contribute to a better understanding of the photochemical reactions of purines, and subsequently to the development of selective photochemical reactions for these moieties in nucleic acids. In addition, it is anticipated that this study will shed further light on the interaction under irradiation of nucleic acids with their environment. The photoreactions of purines with ethers[2] and acetals serve as models for the interaction of purines with sugars and might lead to the discovery of new, so far unknown, irradiation-induced modifications in nucleic acids. The present publication includes full details of the photochemical and γ-ray-induced reactions of purines and purine nucleosides with a variety of ethers, hydroxy ethers, and dioxolane. An attempt was made to carry out the reactions under conditions in which purine moieties in nucleic acids would react selectively; therefore, photosensitizers which have been shown previously to induce selective reactions of purines,[3] *e.g.*, peroxides, were employed.

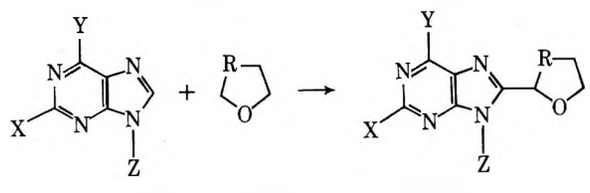
Results and Discussion

Irradiation with ultraviolet light or exposure to γ rays of caffeine, adenine, or guanosine with ethers, hydroxy ethers, or dioxolane led to the substitution of the appropriate moiety for the hydrogen atom at the 8 position of the purine. The site of binding to the purine in the ether moiety is at the carbon atom α to the ether oxygen,[2] whereas with dioxolane it is at the acetalic carbon. The reactions studied can be presented as shown in Scheme I.

Scheme I



1, $R_1 = CH_2$; $R_2 = R_3 = H$
2, $R_1 = O$; $R_2 = R_3 = H$
3a, $R_1 = CH_2$; $R_2 = H$; $R_3 = CH_2OH$
3b, $R_1 = CH_2$; $R_2 = CH_2OH$; $R_3 = H$
4a, $R_1 = CH_2$; $R_2 = H$; $R_3 = CH_2OCOCH_3$
4b, $R_1 = CH_2$; $R_2 = CH_2OCOCH_3$; $R_3 = H$
5, $R_1 = CH_2O$; $R_2 = R_3 = H$
6, $R_1 = (CH_2)_2$; $R_2 = R_3 = H$



X = H; Y = NH_2; Z = H (adenine)
X = NH_2; Y = OH; Z = ribose (guanosine)

7, R = CH_2
8, R = O
9, R = CH_2O
10, R = $(CH_2)_2$
11, R = CH_2
12, R = $(CH_2)_2$

The reactions could be either induced directly by ultraviolet light (λ >260 nm) or through photochemical initiation with peroxides (with light of λ >290 nm) with higher yields of the photoproducts. Products were isolated by column chromatography using a modified "dry column" technique[4] followed by elution with acetone–petroleum ether mixtures for the caffeine derivatives, and methanol–

Table I
Photochemical and γ-Ray-Induced Reactions of Caffeine, Adenine, and Guanosine with Ethers, Hydroxy Ethers, and Dioxolane

Purine	Substrate	Reaction conditions	Product	Product mp, °C	Yield, %[a]
Caffeine	THF[b]	Caffeine (0.5 g), water (10 ml), THF (140 ml), DBP[c] (6 ml); 6 hr	1	128–129	90
	THF[d]	Caffeine (0.5 g), water (10 ml), THF (200 ml), DBP (8 ml); 8 days	1		50
	THF[e]	Caffeine (1 g), water (20 ml), THF (120 ml); 48 hr	1		50
	Tetrahydropyran[b]	Caffeine (3 g), water (10 ml), tetrahydropyran (110 ml), *tert*-butyl alcohol (30 ml), DBP (8 ml); 21 hr	6	160–161	74
	Dioxane[f]	Caffeine (1 g), water (10 ml), dioxane (140 ml); 168 hr	5	201–202	43
	Dioxane[b]	Caffeine (2 g), water (15 ml), dioxane (120 ml), DBP (8 ml); 24 hr	5		73
	Dioxane[e]	Caffeine (1 g), water (20 ml), dioxane (120 ml); 48 hr	5		50
	Tetrahydrofurfuryl alcohol[b]	Caffeine (2 g), water (20 ml), tetrahydrofurfuryl alcohol (120 ml), DBP (6 ml); 24 hr	3a	90–91	58
			3b	191–192	23
	Tetrahydrofurfuryl acetate[b]	Caffeine (3.2 g), water (15 ml), tetrahydrofurfuryl acetate (120 ml), DBP (10 ml); 24 hr	4a	89–90	60
			4b	187–180	22
	Dioxolane[b]	Caffeine (0.4 g), water (10 ml), dioxolane (50 ml), DBP (6 ml); 4 hr	2	215–216	55
	Dioxolane[d]	Caffeine (0.5 g), water (10 ml), dioxolane (100 ml), DCP[g] (6 g); 8 days	2		67
Adenine	THF[f]	Adenine (1 g), water (30 ml), THF (120 ml); 48 hr	7	290–291	40
	THF[b]	Adenine (1 g), water (30 ml), THF (120 ml), DBP (6 ml); 20 hr	7		90
	THF[i]	Adenine (0.5 g), water (20 ml), THF (200 ml), DCP (6 g); 16 days	7		80
	THF[e]	Adenine (2.03 g), water (50 ml), THF (360 ml); 64 hr	7		60
	Tetrahydropyran[b]	Adenine (1 g) water (30 ml), tetrahydropyran (70 ml), *tert*-butyl alcohol (50 ml), DBP (8 ml); 28 hr	10	305–306	44
	Dioxane[b]	Adenine (2 g), water (100 ml), dioxane (600 ml), DBP (10 ml); 60 hr	9	328–329	58
	Dioxolane[b]	Adenine (1 g), water (30 ml), dioxolane (120 ml), DBP (8 ml); 14 hr	8	267–268	90
Guanosine	THF[b]	Guanosine (1.5 g), water (100 ml), THF (650 ml), DBP (15 ml); 52 hr	11	190–191 dec	67
	Tetrahydropyran	Guanosine (1.3 g), water (90 ml), tetrahydropyran (500 ml), *tert*-butyl alcohol (150 ml), DBP (10 ml); 168 hr	12	264–265 dec	60

[a] Based on reacted purines (conversions usually ranged from 50 to 90%). [b] Hanovia 450-W high-pressure mercury vapor lamp (Pyrex filter). [c] DBP, di-*tert*-butyl peroxide. [d] In sunlight. [e] With γ rays. ^{60}Co source Gammacell 220 (Atomic Energy of Canada Ltd., Ottawa, Canada); dose rate 12,000 rads/min. [f] Corex filter. [g] DCP, dicumyl peroxide.

chloroform for the other purine derivatives. Progress of the reactions was followed by thin-layer chromatography and more quantitatively by nmr measurements. In the latter, the disappearance of the H-8 absorption band of the purine with the simultaneous appearance of the absorption of the protons of the substituent at C-8 could be followed. Our results are summarized in Tables I and II.

All new photoproducts gave correct analytical data for the proposed structures and were characterized by their uv, nmr, and mass spectra. The nmr spectra of the caffeine photoproducts exhibited the three characteristic singlets of the *N*-methyl groups at the τ 6–7 region. The substitution at the C-8 position of the caffeine was indicated by the absence of the H-8 absorption in the photoproducts. Determination of the site of attachment in the ether or acetal moieties to the C-8 position of caffeine was also made through the nmr spectra of the products. The absorption at lowest field (τ 4.82 for the hydroxy ether or its acetate, and τ 3.95 for dioxolane) is attributed to the proton attached to the carbon atom of the ether or the acetal moiety which is bound to the C-8 position of caffeine. It appears as a multiplet in the hydroxy ethers and as a singlet in the dioxolane photoproduct, which is in agreement with the proposed structures. The absorption bands of the other protons in the ether or acetal moiety are similar to those of the starting ether or acetal. Substitution in adenine also occurred at the C-8 position, as the photoproducts possessed only one band (singlet) at the τ 2 region, which was not changed by treatment with D_2O at 105°.[5] The site of binding in the ether or acetal moiety was also determined by nmr spectra as described above and was shown to be the carbon atom α to the ether oxygen or at the acetalic carbon, respectively. All guanosine photoproducts do not possess the absorption band of the H-8 proton in the nmr, thus indicating that the hydrogen atom at C-8 was substituted. The absorption of the sugar moiety in the photoproduct is very similar to that of the starting nucleotide, except for the anomeric proton.[1b] The

Table II
Analytical and Nmr Data of 8-Substituted Purines

Compound	Elemental analysis[a]	Solvent[b]	Nmr spectrum τ values
2	Calcd for $C_{11}H_4N_4O_4$: C, 49.62; H, 5.31; N, 20.25; mol wt, 266. Found: C, 49.62; H, 5.30; N, 21.04; mol wt, 266	A	3.95 (s, 1 H, O–CH–O), 5.82 (m, 4 H, $-CH_2CH_2-$), 5.95 (s, 3 H, N-7 CH_3), 6.45 (s, 3 H, N-3 CH_3), 6.64 (s, 3 H, N-1 CH_3)
3a	Calcd for $C_{13}H_{18}N_4O_4 \cdot H_2O$: C, 50.0; H, 6.40; N, 17.93; mol wt, 294 + 18. Found: C, 50.15; H, 6.47; N, 17.93; mol wt, 294	A	4.82 (m, 1 H, caffeine CH–O), 5.7 (m, 1 H, $-CHCH_2OH$) 6 (d, 3 H, N-7 CH_3; J = 3.6 Hz), 6.28 (m, 2 H, $-CH_2OH$), 6.46 (s, 3 H, N-3 CH_3), 6.64 (s, 3 H, N-1 CH_3), 7.68 (br m, 4 H, $-CH_2CH_2-$)
3b	Calcd for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04; mol wt, 294. Found: C, 53.06; H, 6.28; N, 18.81; mol wt, 294	A	5.8 (s, 3 H, N-7 CH_3), 6.02 (m, 2 H, CH_2O), 6.2 (s, 2 H, CH_2OH), 6.47 (s, 3 H, N-3 CH_3), 6.63 (s, 3 H, N-1 CH_3), 7.75 (br m, 4 H, CH_2CH_2-)
4a	Calcd for $C_{15}H_{20}N_4O_5$: C, 53.56; H, 5.99; N, 16.66. Found: C, 53.80; H, 6.12; N, 16.82	A	4.83 (m, 1 H, –CHO), 5.78 (m, 3 H, –CHO + CH_2CO-), 5.94 (s, 3 H, N-7 CH_3), 6.42 (s, 3 H, N-1 CH_3), 7.47 (br m, 7 H, $-COCH_3$ + $-CH_2CH_2-$)
4b	Calcd for $C_{15}H_{20}N_4O_5$: C, 53.56; H, 5.99; N, 16.66. Found: C, 53.43; H, 6.16; N, 16.43	A	5.84 (s, 3 H, H-7 CH_3), 6.02 (m, 2 H, $-CH_2O$), 6.21 (m, 2 H, $-CH_2OCO-$), 6.5 (s, 3 H, N-3 CH_3), 6.67 (s, 3 H, N-1 CH_3), 8 (br m, 7 H, $-COCH_3$ + $-CH_2CH_2-$)
7	Calcd for $C_9H_{11}N_5O$: C, 52.47; H, 5.56; N, 34.03; mol wt, 205. Found: C, 52.67; H, 5.40; N, 34.13; mol wt, 205	B	1.73 (s, 1 H, C-2 H), 2.73 (s, 2 H, $-NH_2$), 4.1 (t, 1 H, OCH, J = 6.5 Hz), 6.02 (m, 2 H, CH_2O), 7.92 (br m, 4 H, $-CH_2CH_2-$)
8	Calcd for $C_8H_9N_5O_2 \cdot H_2O$: C, 42.66; H, 4.92; N, 31.1; mol wt, 207 + 18. Found: C, 42.37; H, 5.05; N, 31.34; mol wt, 207	B	1.77 (s, 1 H, C-2 H), 2.69 2 H, $-NH_2$), 4.0 (s, 1 H, –CHO), 5.87 (d, 4 H, $-CH_2CH_2-$)
9	Calcd for $C_9H_{11}N_5O_2$: C, 48.70; H, 4.99; N, 31.46; mol wt, 221. Found: C, 48.86; H, 5.01; N, 31.66; mol wt, 221	B	1.82 (s, 1 H, C-2 H), 2.86 (s, 2 H, $-NH_2$), 5.12 (m, 1 H, –CHO), 6.15 (m, 6 H, $-CH_2O$)
10	Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.93; N, 31.95; mol wt, 219. Found: C, 55.02; H, 5.80; N, 32.2; mol wt, 219	B	1.85 (s, 1 H, C-2 H), 2.95 (s, 2 H, $-NH_2$), 5.4 (m, 1 H, CHO), 6.07 (m, 2 H, CH_2O), 8.3 (br m, 6 H, $-CH_2CH_2CH_2-$)
11	Calcd for $C_{14}H_{19}N_5O_6 \cdot H_2O$: C, 45.28; H, 5.70; N, 18.86. Found: C, 45.42; H, 5.67; N, 18.95	B	3.58 (s, 2 H, $-NH_2$), 4.11 (apparent d, 1 H, H-1′), 4.83 (br m, 4 H, OH-3′, OH-2′, OH-5′, –CHO), 5.82 (m, 2 H, CH_2O), 6.2 (m, 4 H, H-3′, H-4′, 2 H-5′), 8 (br m, 4 H, $-CH_2CH_2-$)
12	Calcd for $C_{15}H_{21}N_5O_6$: C, 49.04; H, 5.76; N, 19.07. Found: C, 48.82; H, 5.92; N, 18.97	B	3.65 (s, 2 H, $-NH_2$), 4.12 (apparent d, 1 H, H-1′), 4.73 (m, 1 H, OH-3′), 5.05 (m, 2 H, OH-2′, OH-5′), 5.45 (m, 1 H, CHO), 5.78 (m, 2 H, CH_2O), 6.32 (m, 5 H, H-2′, H-3′, H-4′, 2H-5′), 8.26 [broad m, 6 H, $(CH_2)_3$]

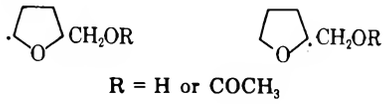
[a] Molecular weights were determined by mass spectrum. [b] A is $CDCl_3$; B is $(CD_3)_2SO$.

presence of an absorption of a single proton in the tetrahydropyranyl derivative at τ 5.54 indicates that substitution in tetrahydropyran occurred at the carbon atom α to the ether oxygen. In the tetrahydrofuranyl side chain the absorption of the methine proton was hidden by that of the hydroxylic protons of the sugar moiety (at τ 4.83). All other tetrahydropyranyl and tetrahydrofuranyl protons exhibited absorption bands similar to those of the parent ethers.

All caffeine photoproducts exhibited a strong molecular peak in their mass spectra, except **4a** and **4b**. In these compounds the ester was decomposed to the appropriate alcohol and to ketene.[6] Their mass spectra are similar, therefore, to those of **3a** and **3b**, respectively. A fragment common to all caffeine photoproducts is that of *m/e* 194, which is the fragment of the caffeine moiety. Other typical fragments of ether or acetal entities attached to the C-8 position, and of other caffeine moieties, were also observed.[2,7] Adenine photoproducts exhibited the appropriate molecular peaks and a common fragment of the adenine moiety at *m/e* 135. Other fragments are typical of ether or acetal and of adenine fragmentations.[5] The guanosine photoproducts did not exhibit molecular peaks in their spectra. It is interesting to note that guanosine itself does not show a molecular peak under the same conditions of recording. A typical fragmentation pattern of ribose nucleosides was observed in these spectra, *i.e.*, peaks of B + H, B + 24, B + 30, and M + 89 (B represents the mass of the free base with the ether or the acetal moiety attached at the C-8 position minus one).[8]

The reported reactions could be induced by light of λ >260 nm (Corex filter) or λ >290 nm (Pyrex filter) in the presence of photosensitizers. In the former case, the purine serves as the light absorbing system and the excited purine abstracts a hydrogen atom from the hydrogen donor forming a free radical of the latter. This radical is scavenged by a neighbor purine molecule which subsequently yields the appropriate photoproduct. In the peroxide-initiated reactions, most of the incident light (λ >290 nm) is absorbed by the photoinitiator[1e] which decomposes to oxy radicals which subsequently abstract a hydrogen atom from the α position of the ether or the acetal. The resultant free radicals are

X = $(CH_2)_n$ (n = 0 or 1)



R = H or $COCH_3$

The next step involves the attack of an ether or acetal free radical on the carbon end of the C-8=N-7 bond of a ground state purine molecule leading to a radical which by further hydrogen atom abstraction yields the N-7, C-8 adducts ("dihydro" type). These are then oxidized to yield the appropriate C-8 substituted purine.[1b] The free radical nature of the reactions is indicated by the possible induction of the reactions with peroxides, either photochemically or thermally. Further evidence for such a mechanism is derived from the formation of dehydro dimers, of the ethers, such as dioxanyl-dioxane in the reaction mixture. The quantum yields of the peroxide-induced reactions of caffeine were measured by the ferrioxalate method[9] and were found to be *ca.* 5×10^{-2}.

The reactions described in this publication can serve as models for the interaction of purines and sugars in photochemical reactions. They also have an implication on the possible cross linking of nucleic acids and sugars through the purine moieties. In addition, the reactions of the acetal can serve as a means for the introduction of an aldehydic group at the C-8 position of the purines in nucleic acids. The resulting aldehyde may be useful for the cross linking with other functional groups (*e.g.*, amino groups) in the nucleic acid chain or in proteins.

Experimental Section

Caffeine (Schuchardt, München) was recrystallized from water prior to use. Other purines (Fluka, CHR grade) were used without further purification. Ethers (Frutarom), tetrahydrofurfuryl alcohol (Fluka), and dioxolane (Fluka) were freshly distilled before use. Kieselgel (0.063-0.2 mm Merck) was used for column chromatography. Progress of the reactions were followed by ascending tlc on aluminum plates (Riedel-de-Haen, Kieselgel SIF). Acetone-petroleum ether mixtures were used as eluents for the caffeine derivatives, and methanol-chloroform for the adenine and guanosine derivatives. Spots were detected by mineralight lamp. Column chromatography was performed on silica gel (Kieselgel 60, Merck) using a modified "dry column" technique.[4] Nmr spectra were determined with a Varian A-60 instrument in the appropriate organic solvent using TMS as internal standard. Mass spectra were recorded with a MAT Atlas CH4. Uv spectra were recorded on a Cary 14 spectrophotometer.

Irradiations were carried out in an immersion apparatus with internal water cooling using Hanovia 450-W high-pressure mercury vapor lamps as the light source. The irradiation vessel was flushed with oxygen-free nitrogen for 15 min prior to irradiation, and nitrogen bubbling, as well as mechanical stirring, were sustained throughout the irradiation. Quantum yields were measured by ferrioxalate actinometry.[9] γ-Ray irradiation was conducted in a Gammacell 220 apparatus (Atomic Energy of Canada Ltd. Ottawa, Canada), with an internal air cooling device, and at a dose rate of 12,000 rads/min. Oxygen-free nitrogen was bubbled through the solution.

Typical experiments are described. Other experiments were conducted under similar conditions and are summarized in Tables I and II. Unless otherwise stated, Pyrex filters were employed.

Reaction of Caffeine and 1,3-Dioxolane (with DBP). A mixture of caffeine (0.4 g), dioxolane (50 ml), and water (10 ml) was irradiated for 4 hr, while DBP (total amount 6 ml) was added periodically in small portions. Excess reagent was removed under reduced pressure, and the residue was chromatographed on silica gel (100 g). Acetone-petroleum ether (3:17) eluted **2** (0.25 g), mp 215-216° (from acetone-petroleum ether).

Reaction of Adenine and THF (with DBP). A mixture of adenine (1 g), water (30 ml), and THF (120 ml) was irradiated for 20 hr, while DBP (6 ml) was added in small portions. The usual work-up and chromatography led to **7** [0.56 g; eluted with methanol-chloroform (1:9)], mp 290-291° (from chloroform-methanol).

Reaction of Guanosine and THF (with DBP). A solution of guanosine (1.5 g), water (100 ml), and THF (650 ml) was irradiated for 52 hr. DBP (15 ml) was added periodically in small amounts. The usual work-up led to **11** [0.91 g; eluted with methanol-chloroform (1:9)], mp 190-191° dec (from methanol-chloroform).

Registry No.—**1**, 27077-61-8; **2**, 51015-44-2; **3a**, 51015-45-3; **3b**, 51015-56-6; **12**, 51015-57-7; caffeine, 58-08-2; adenine, 73-24-5; guanosine, 118-00-3; 1,3-dioxolane, 646-06-0; tetrahydrofuran, 109-51015-56-6; **12**, 51015-57-7; caffeine, 58-08-2; adenine, 73-24-5; guanosine, 118-00-3; 1,3-dioxolane, 646-06-0; tetrahydrofuran, 109-99-9; tetrahydropyran, 142-68-7; dioxane, 123-91-1; tetrahydrofurfuryl alcohol, 97-99-4; tetrahydrofurfuryl acetate, 637-64-9.

References and Notes

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Hemiacetal Mediated Reactions. Directed Synthesis of Diols and Acetals

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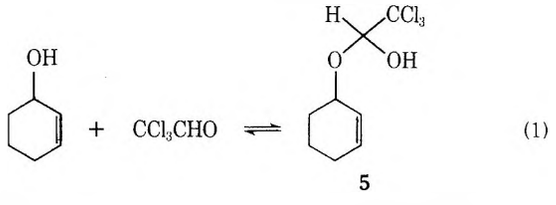
The mercuric trifluoroacetate promoted intramolecular addition of trichloroacetaldehyde (chloral) hemiacetal derivatives of unsaturated alcohols to carbon-carbon double bonds is reported. This process results in the intramolecular delivery of an oxygen nucleophile by the hydroxyl group. The chloral acetal products are converted to the corresponding diols by reduction. In several cases this overall process results in a highly specific conversion of a cyclic or acyclic unsaturated alcohol into a single diol product. For example, the equatorial allylic cyclohexenols **1a**, **1b**, and **10** are transformed in overall yields of 60–80%, and >99% isomeric purity, into the corresponding *cis*-1,2-diols **3a**, **3b**, and **12**, respectively. The scope and limitations of this process for the directed hydration of cyclic and acyclic unsaturated alcohols is described.

The importance of the alcohol function as a handle for directing the stereospecific establishment of new asymmetric centers and for controlling regiochemistry in stereorational organic synthesis is well recognized.[1] The secondary alcohol group is particularly useful in this sense since its stereospecific introduction by reduction is one of the best studied of all organic synthetic reactions.[2] We began a few years ago studies aimed at using the alcohol functionality as a handle to direct the addition of "complexed" nucleophiles to neighboring electrophilic centers.[3] We wish at this time to report our studies of the addition of hemiacetal derivatives of unsaturated alcohols to neighboring carbon-carbon double bonds, a process which results in the intramolecular delivery of an oxygen nucleophile (a "water equivalent") by the hydroxyl group. In several cases this process results in a highly specific conversion of a cyclic or acyclic unsaturated alcohol into a single diol product.

Results

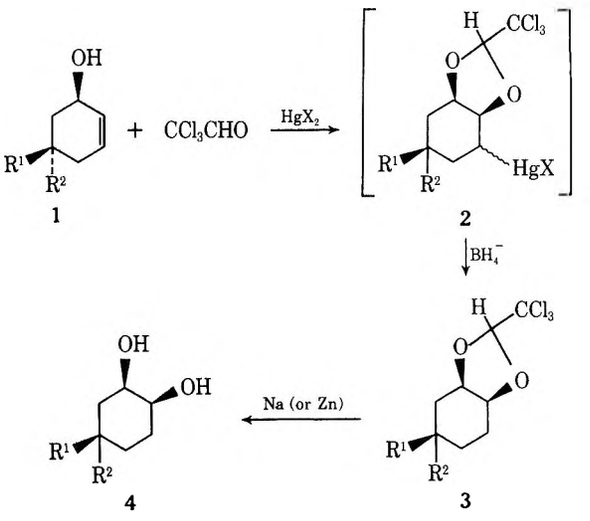
Owing to its high propensity for forming hemiacetals,[4] trichloroacetaldehyde (chloral) was chosen for our preliminary work. The addition of 2 equiv of chloral to a solution of a primary or secondary alcohol in an aprotic solvent such as tetrahydrofuran (THF) resulted in quantitative formation of the hemiacetal derivative, *e.g.*, eq 1. Hemiacetal formation was easily monitored by observing the appearance of the characteristic singlet, in the nmr spectrum, near τ 5 for the methine hydrogen attached to the trichloromethyl-bearing carbon (see Table I).[5] To promote addition of the hemiacetal hydroxyl group to the neighboring double bond, mercuric trifluoroacetate was chosen, since it is both soluble in the aprotic solvents necessary for hemiacetal formation and is known to promote the addition of a variety of nucleophiles to carbon-carbon double bonds.[6,7] Treatment at room temperature of a THF solution of 2-cyclohexen-1-ol (**1a**, 0.5 *M*) and chloral (1.0 *M*) with mercuric trifluoroacetate (0.5 *M*) for 48 hr followed by demercuration[8] with alkaline sodium borohydride afforded the known[9] cyclic chloral adduct **3a** in 62% distilled yield (see Scheme I). The observation of two singlets (total of one hydrogen) in the nmr spectrum at τ 4.59 and 4.76 indicated that **3a** was a 92:8 mixture of epimers at the trichloromethyl-bearing carbon. The alternate possibility, that a mixture of cis-trans or positional isomers was formed, was ruled out by removal of the $CCl_3CH<$ group.



(1)

5

Scheme I



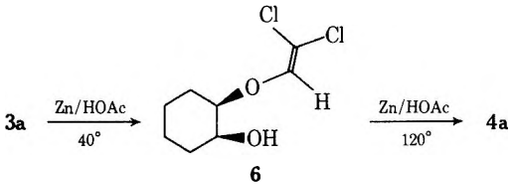
X = $OCOCF_3$

a, $R^1 = R^2 = H$

b, $R^1 = t$-Bu; $R^2 = H$

c, $R^1 = H$; $R^2 = t$-Bu

Although acetal **3a** was extremely resistant to cleavage by acids,[10] it could be cleaved in nearly quantitative yield by either of two reductive methods: (a) treatment for 24 hr with excess zinc dust in refluxing acetic acid (the diacetate is isolated)[11] or (b) treatment for 12 hr with excess sodium dispersion in ether.[12] The two reductive steps have quite different rates, since treatment of **3a** with zinc for 2 hr at 40° afforded cleanly vinyl ether **6** characterized



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by OH stretching absorption in the ir at 3400 cm^{-1} and a one-hydrogen singlet for the olefinic hydrogen at τ 3.33 in the nmr. The diol (or diacetate) formed by either reductive method was shown to be the *cis*-1,2-diol **4a**, uncontaminated (gc) by other isomers.

The time course of cyclic acetal formation was studied in detail for **1a**. Build-up of **2a** (characterized after demercuration to **3a**) occurred slowly and reached a maximum only after 50 hr (see Figure 1). On the other hand, hemiacetal **5** disappeared rapidly and was present to the extent of only 22% 15 min after the addition of mercuric trifluo-

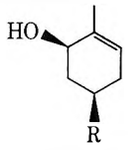
Table I
^{1}H Nmr Chemical Shifts of Hemiacetals

Hemiacetal	Solvent	τ $CHCCl_3$[a]	τ $CH_2OCHCCl_3$[b] OH
15	CCl_4	5.14	5.77
22	C_6H_6	5.23	6.25
23	C_6H_6	5.27	6.42
5	CCl_4	5.11	5.97
1-Hexanol[c]	C_6H_6	5.34	6.33
1-Hexanol[d]	CCl_4	4.53	6.47

[a] Singlet. [b] Center of multiplet. [c] Chloral hemiacetal. [d] Benzaldehyde hemiacetal.

roacetate. Change of the solvent to a mixture of THF and cyclohexane (1:1)[13] or the use of mercuric acetate in dimethylformamide did not improve the rate or yield of **3a** formation.

Our studies of the scope of the chloral cyclization reaction are summarized in Table II. For cyclic alcohols adduct formation occurs readily with equatorial allylic alcohols **1a, 1b,** and **10,** and fails completely for the axial allylic alcohol **1c,** the homoallylic alcohol 3-cyclohexen-1-ol, and 2-cycloocten-1-ol. A serious limitation is that the double bond cannot be trisubstituted, since a competing oxidation reaction predominates.[7] For example, treatment of the cyclic enols (−)-carvotanacetol (**13**), (−)-carveol (**14**),



13, R = $CH(CH_3)_2$
14, R = $C(CH_3)=CH_2$

or cholest-4-en-3β-ol with chloral and mercuric trifluoroacetate resulted within 4–8 hr in the formation of a gray precipitate [presumed to be $Hg_2(OCOCF_3)_2$].[8c] The occurrence of an oxidation reaction is well documented in solvomercuration of tri- and tetrasubstituted olefins.[7,8c,15,16] As with **3a** the structure of the chloral adducts **3b, 8,** and **11** was confirmed by reductive cleavage to afford the corresponding 1,2-diols (Table II).

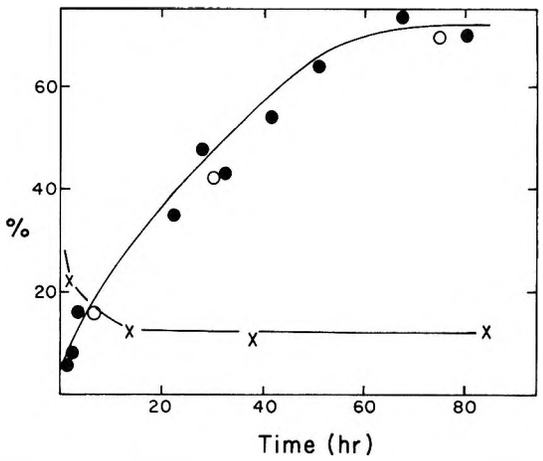
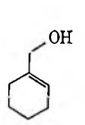
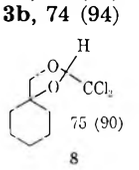
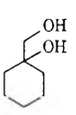
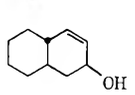
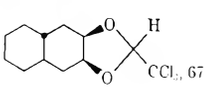
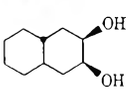


Figure 1. Rate of formation of cyclic acetal **3a** in THF (●) and in 1:1 THF–cyclohexane (○) as determined by gc, and the rate of disappearance of hemiacetal **5** in THF (X) as determined by the disappearance of the olefinic hydrogens in the nmr. Initial conditions were [**5**] = $Hg(OCOCF_3)_2$ = 0.5 *M*.

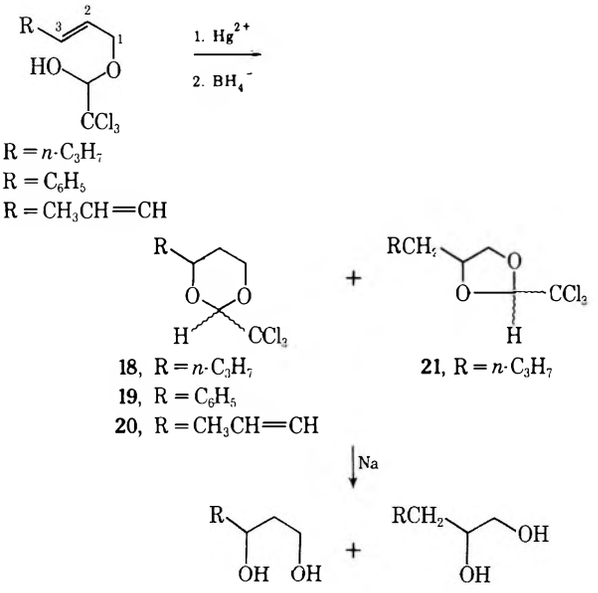
Formally cyclization of the hemiacetal derivatives of unsaturated acyclic alcohols can occur to afford products of two ring sizes. Mercuric trifluoroacetate treatment of the hemiacetal derivative of (*E*)-2-hexen-1-ol (**15**) in THF followed by demercuration affords a mixture of cyclic acetals **18** and **21** (Scheme II). The nmr spectrum of this mixture shows three singlets at τ 5.29, 4.79, and 4.72 (total of one hydrogen) for the >$CHCCl_3$ methine hydro-

Table II
Chloral Mediated Conversion of Unsaturated Alcohols into Cyclic Trichloroacetals and Diols

Unsaturated alcohol	Mercuration[a] Time, hr	Mercuration[a] Solvent	Cyclic trichloroacetal, % yield[b]	Diol products[c,d]
1a	60	THF	**3a**, 62 (80)	**4a**
1b	48	THF	**3b**, 74 (94)	**4b**
 7	28	THF	 75 (90) 8	 9
 10	66	THF	 11	 12
(*E*)-2-Hexen-1-ol	23	THF	**18** and **21**, 79 (94)	1,3-Hexanediol (56%), 1,2-hexanediol (44%)
	24	Benzene	**18**, 72	1,3-Hexanediol (83%), 1,2-hexanediol (17%)
(*E*)-Cinnamyl alcohol	60	THF	**19**, 63	$C_6H_5CHCH_2CH_2OH$ | OH
(*E*)-3-Hexen-1-ol	60	THF	**25** and **27**, 32 (44)[e]	1,3-Hexanediol (45%), 1,4-hexanediol (55%)
		Benzene	**25** and **27**, 32[e]	1,3-Hexanediol (92%), 1,4-hexanediol (8%)
(*Z*)-3-Hexen-1-ol	48	THF	**25** and **27**, 72 (92)	1,3-Hexanediol (65%), 1,4-hexanediol (35%)
		Benzene	**25** and **27**, 75	1,3-Hexanediol (91%), 1,4-hexanediol (9%)
(*E*)-3-Hepten-1-ol	48	THF	**26** and **28**, 55 (68)[f]	1,3-Heptanediol (40%), 1,4-heptanediol (60%)
2,4-Hexadien-1-ol[g]	36	THF	**20**, 43	1,2-Hexanediol (13%), 1,3-hexanediol (87%)[h]

[a] In THF at 25°, [enol], $Hg(OCOCF_3)_2$ = 0.5 *M*, [CCl_3CHO] = 1.0 *M*. [b] Distilled yield. Yields in parentheses were determined by gc analysis using internal standards. [c] For reactions in THF this is the kinetic product ratio while in benzene equilibration occurs (see Experimental Section). [d] Prepared in >85% yield by reduction method b and analyzed as the diacetates by gc. [e] 50% unreacted alcohol by nmr analysis. [f] 32% unreacted alcohol by nmr analysis. [g] A mixture of isomers. [h] Analyzed after hydrogenation.

Scheme II



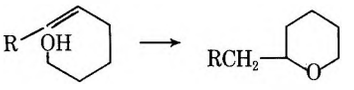
15, R = n-C_3H_7
16, R = C_6H_5
17, R = $CH_3CH{=}CH$

18, R = n-C_3H_7
19, R = C_6H_5
20, R = $CH_3CH{=}CH$

21, R = n-C_3H_7

gens of three of the four possible isomers of **18** and **21**. The composition of this isomer mixture remains constant up to 24 hr, but changes thereafter. As a result the kinetic product ratios for this and other cyclic acetal mixtures were determined at short reaction times (see Experimental Section). Confirmation of the gross structure of this isomer mixture was achieved by reductive removal of the $CCl_3CH<$ group to afford a 44:56 mixture of 1,2-hexanediol and 1,3-hexanediol, implying a similar ratio for the 1,3-dioxolane isomer **21** and the 1,3-dioxane isomer **18** respectively. Equilibration to afford the more stable cyclic adduct is apparently more rapid in benzene, as acetal **18** is the predominant product formed after 24 hr in this solvent. Related work in the literature on mercurative cyclization of unsaturated alcohols (4-en-1-ols) indicates a kinetic preference for cyclization to afford the five-membered ring (tetrahydrofuran) rather than the six-membered (tetrahydropyran) product.[17]

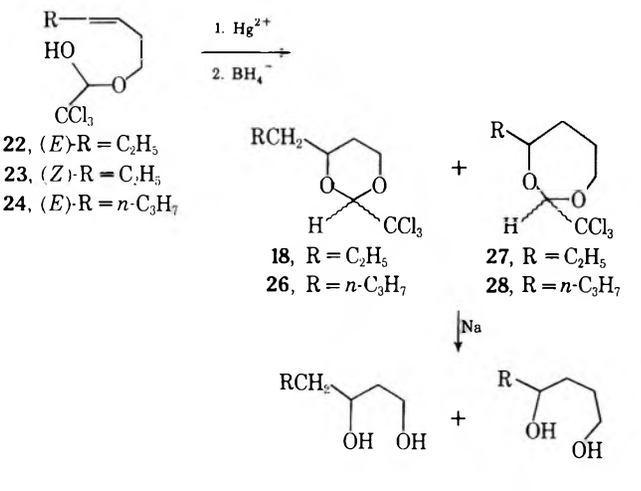
Mercuration–demercuration of the homoallylic alcohol hemiacetals **22–24** also affords a mixture of cyclic acetals (Scheme III). Again the gross structure was confirmed by reduction to afford a mixture of 1,3- and 1,4-diols (Scheme III and Table I). Surprising is the large amount of the seven-membered ring 1,3-dioxepane isomer (**27** or **28**) which is formed in the kinetic product mixture. In fact, for the trans isomers **22** and **24** there is an apparent kinetic preference for formation of the dioxepane isomers. This kinetic preference for formation of the seven-membered ring adducts is unprecedented. For example, the E and Z isomers of octadec-5-en-1-ol (**29**) are reported to afford only the tetrahydropyran derivative **30** upon treatment in dimethylformamide with mercuric acetate.[17] A small amount (1–4%) of a seven-membered ring product, 2,7-dimethyloxepane, has, however, been reported by Brown from mercuration–demercuration of 1,7-octadiene with mercuric acetate in THF–H_2O.[6c]



29 **30** 100%

R = $C_{12}H_{25}$

Scheme III

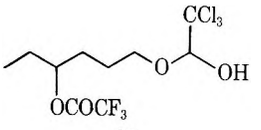


22, (E)-R = C_2H_5
23, (Z)-R = C_2H_5
24, (E)-R = n-C_3H_7

18, R = C_2H_5
26, R = n-C_3H_7

27, R = C_2H_5
28, R = n-C_3H_7

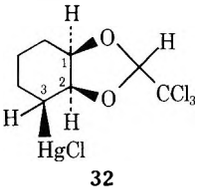
Several control experiments were performed to confirm that the seven-membered ring acetals were formed during mercuration and not during the alkaline demercuration step. (1) Treatment of 1,4-hexanediol for 24 hr with chloral (2 equiv) and mercuric trifluoroacetate (1 equiv) followed by alkaline borohydride treatment afforded no cyclic acetal and resulted in near-quantitative recovery of the diol. (2) Similar treatment of a 1:1 mixture of (E)-3-hexen-1-ol and 1,4-hexanediol resulted in formation of no more **27** than is formed in the absence of the diol. (3) Treatment of 1,4-hexanediol sequentially with chloral (1 equiv) and trifluoroacetic anhydride (1 equiv), to prepare *in situ* **31** (40% by nmr), followed by alkaline borohydride



31

treatment, afforded no cyclic acetal **27**. As in the allylic case, change of the solvent to benzene resulted in a cleaner product mixture, and both **22** and **23** afforded after 24 hr an acetal mixture rich in the 1,3-dioxane isomer.

The stereochemical relationship between the trifluoroacetoxymercuri group and the chloral-derived oxygen atom is of interest. Most often a trans relationship, resulting from the usual anti addition mechanism, is observed between HgX and X of the kinetically formed olefin–HgX_2 adduct;[7,18] however, examples of the kinetic formation of cis adducts are known.[19] Several examples also exist in the cyclohexane series of thermodynamically controlled isomerization of the initially formed trans-diaxial adduct.[20] The nmr spectrum of the chloromercuri adduct **32** allows the assignment of a cis relationship between the HgCl group and the oxygen atom at C-2. The chloromercuri adduct was isolated (crude yield 46%) by quenching the mercuration of **1a** with sodium chloride, rather than sodium borohydride, and was purified by recrystallization from benzene. The hydrogen bonded to the chloromercuri-bearing carbon appeared as a multiplet centered at τ 7.23 with a half-height bandwidth of 19 Hz. This hydrogen is therefore clearly axial[21] and thus the two possible chair cyclohexane structures (ignoring for the moment the $>CHCCl_3$ group) are **33** and **34** (Scheme IV). Although H_1 and H_2 appear as overlapping multiplets in deuteriochloroform, they are clearly resolved in pyridine.[19d,22] In pyridine H_2 appears as the four-line X portion of an AMX system centered at τ 4.92 and H_1 as a complex multiplet



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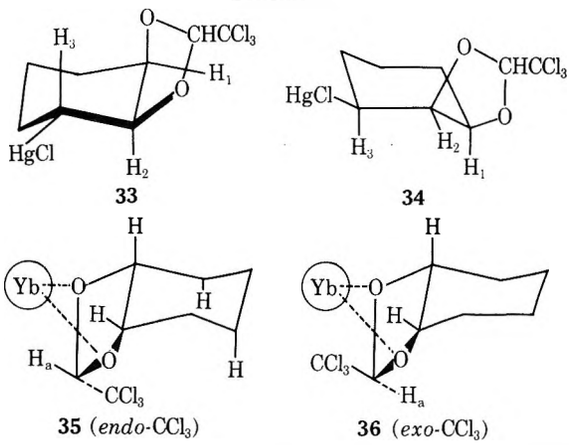
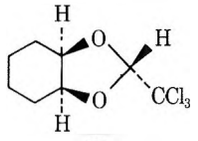
Scheme IV



centered at τ 5.38. The observed coupling constants for H_2 ($J_{1,2}$ and $J_{2,3}$) of 4.6 and 5.8 Hz are most consistent with the two axial–equatorial coupling expected for the cis isomer **34**, and, except for the possibility that there are major distortions caused by the fused five-membered ring, are inconsistent with structure **33** and its expected axial–axial coupling.[21]

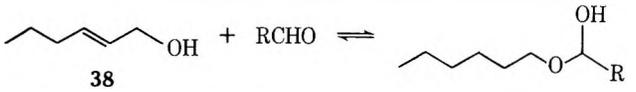
Stereochemical assignments for the $>CHCCl_3$ group of the **3a** and **3b** epimer mixture were tentatively made by assuming that the major isomer would have the bulky CCl_3 group oriented exo, isomer **37**. This assignment has



37

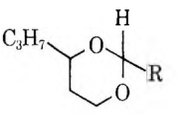
been confirmed by lanthanide-induced nmr shift experiments. If one makes the reasonable assumption that the shift reagent will complex with the acetal oxygens only from the less hindered exo side[23] (see **35** and **36** of Scheme IV), then one predicts that a major effect expected upon adding the lanthanide is a pronounced shift for the methine hydrogen H_a of isomer **35** and a correspondingly small shift for isomer **36**. Such behavior was observed when the **3a** epimer mixture was treated with $Yb(dpm)_3$; H_a of the minor isomer experienced a downfield shift of 4 ppm mol^{-1} mol^{-1}, while the corresponding shift for the major isomer was only 0.1 ppm mol^{-1} mol^{-1} (see Figure 2).

Changes in the aldehyde portion of the hemiacetal intermediate were briefly studied. The trifluoroacetaldehyde (fluoral) hemiacetal of (*E*)-2-hexen-1-ol (**38**) could be pre-



38

39, R = CF_3
40, R = C_6H_5



41, R = CF_3
42, R = C_6H_5

pared *in situ* by adding 1 equiv of **38** to a 1 *M* solution of fluoral (2 equiv) in diethyl ether at −78°. Ether solutions of hemiacetal **39** were stable at 25° for at least 24 hr, although excess fluoral rapidly degassed from solution at this temperature. Mercuration with mercuric trifluoroacetate for 90 hr followed by demercuration afforded in 52% yield the 1,3-dioxane fluoral adduct **41**, contaminated with 4% of the isomeric 1,3-dioxolane adduct.[24] As with

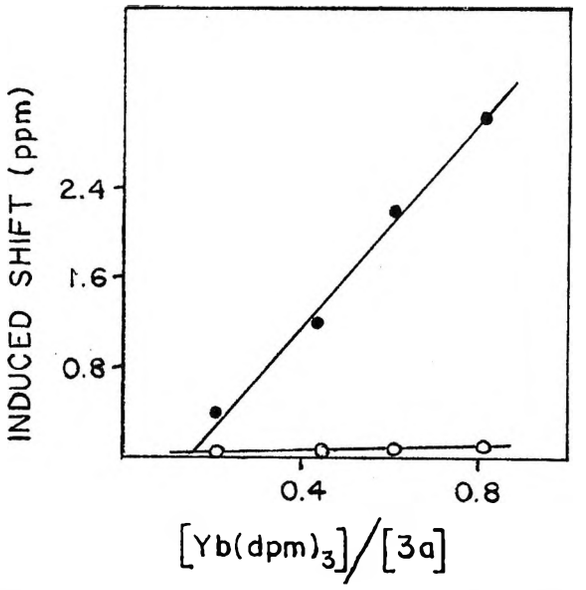


Figure 2. Ytterbium tris(2,2,6,6-tetramethylheptanedionate) induced shifts for the $CHCCl_3$ methine hydrogen of the major (○) and minor (●) epimers of acetal **3a**, in CCl_4 with [**3a**] = 0.4 *M*.

the corresponding chloral adducts, **41** was characterized by removal of the $CF_3CH<$ group with sodium in ether. Similar treatment of fluoral hemiacetals of secondary alcohols proved unsuccessful since, owing to the lower hemiacetal formation constants, fluoral was lost by degassing more rapidly than cyclization occurred.[25] For this reason and the difficulty we experienced (see Experimental Section) in storing and handling fluoral, no further work with fluoral hemiacetals was attempted.

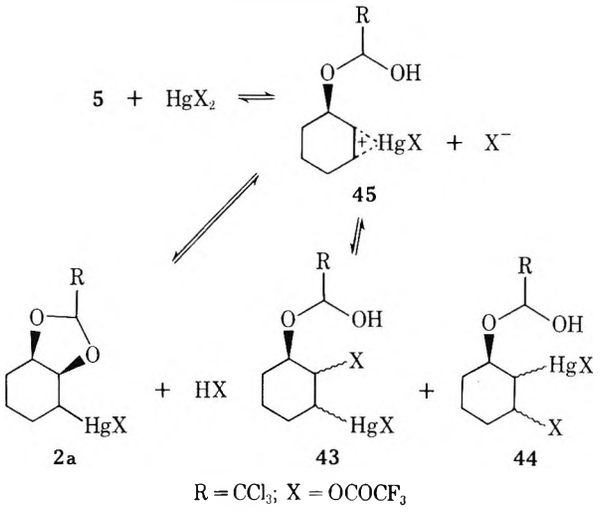
Although benzaldehyde does not readily form hemiacetal intermediates,[4] treatment of a benzaldehyde solution of **38** with mercuric trifluoroacetate for 140 hr, followed by reductive demercuration and purification by distillation and chromatography, afforded the cyclic 1,3-dioxane benzaldehyde adduct **42**[24] in 18% yield (crude yield 35%). Nmr experiments indicated that 40% of the starting alcohol **38** was bound as hemiacetal **40** under these conditions and this fact is undoubtedly responsible for the modest yield of adduct which was formed.

Discussion

Although the intermediacy of reversibly formed carbonyl addition intermediates (*e.g.*, hemiacetals) is well known in a variety of hydrolytic reactions,[26] this report constitutes one of few examples of their participation in stereospecific reactions of synthetic interest.[27] The two-step hemiacetal mediated hydration reaction described here is most useful for converting equatorial allylic cyclohexenols into the corresponding *cis*-1,2-diols. By this procedure **1a**, **1b**, and **10** are transformed in overall yields of 60–80%, and >99% isomeric purity, into the corresponding *cis*-1,2-diols **3a**, **3b**, and **12**, respectively. No alternate hydration method exhibits this high degree of regio- and stereospecificity. For example, the conventional oxymercuration–demercuration sequence is reported for **1a** to afford a mixture of all four possible diols with the major isomer (80%) being *trans*-1,3-cyclohexanediol and with the *cis*-1,2 isomer **4a** comprising only 1% of the isomer mixture.[28] Similarly, the corresponding *trans*-1,3-diol is reported to be the major product formed when **1b** is treated with mercuric acetate in $THF-H_2O$.[29]

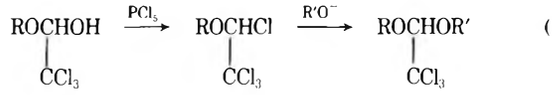
For acyclic unsaturated alcohols the hemiacetal mediated hydration reaction shows little regiospecificity in THF. The reaction in benzene, however, is much more regiospecific. Even so the reaction appears of little synthetic use,

Scheme V



since the conventional oxymercuration–demercuration reaction is reported to afford equally high yields of the corresponding 1,3-diol. For example, Brown reports that 2-buten-1-ol is converted in 84% yield into a diol mixture containing 95% 1,3-butanediol by treatment with mercuric acetate in THF–H_2O.[30] The hemiacetal mediated reaction does, however, appear useful for hydration of homoallylic alcohols, since conventional oxymercuration–demercuration affords mainly cyclized tetrahydrofuran products.[17,30] In contrast, by the method reported here (*Z*)-3-hexen-1-ol is converted in 70% overall yield into a mixture of diols containing 91% 1,3-hexanediol.

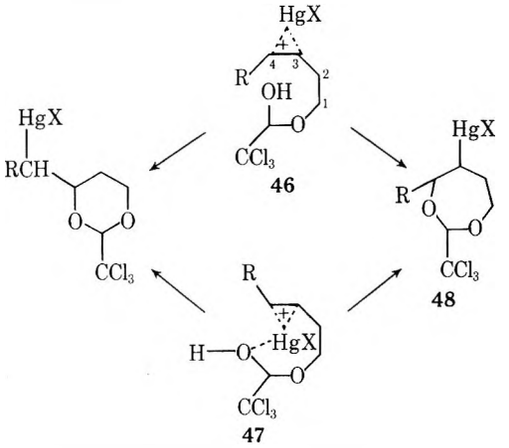
The mercuration–demercuration of chloral hemiacetals will in some cases be a useful route for preparing chloral acetals themselves. Acetals of chloral are not easy to prepare and have generally been synthesized by either the two-step route of eq 2[31] or in some cases from the direct



acid-catalyzed condensation of alcohols with chloral.[32] The later method is most successful for 1,2- and 1,3-diols.[32] For example, **3a** was prepared in 43% yield from diol **4a** by this route.[9] Previous to this report no seven-membered ring chloral acetal, a 2-trichloromethyl-1,3-dioxepane, had been reported. Chloral acetals are useful intermediates for the preparation of dichloroketene acetals.[31c,32b]

The mechanism for the hemiacetal cyclization reaction which we prefer is illustrated for the case of 2-cyclohexen-1-ol in Scheme V. Addition of mercuric trifluoroacetate to hemiacetal **5** is postulated to form initially adducts **43** and **44** of which the kinetically preferred isomer should be **44** with X axial (trans to the oxygen atom at C-1).[28] These adducts are, however, formed reversibly and, if thermodynamically favored, capture at C-2 of an intermediate mercurinium ions, *e.g.*, **45** or its equivalent,[33] by the hemiacetal hydroxyl group to afford **2a** can ultimately dominate. This proposed mechanism follows from earlier reports by Brown and coworkers that in THF and other aprotic solvents adduct formation between an olefin and mercuric trifluoroacetate is both rapid and reversible.[13,34] The strongest evidence in favor of the proposed mechanism is the observed rapid disappearance of hemiacetal **5** when mercuric trifluoroacetate is added, and the corresponding slow build-up of the cyclic adduct **2a**. Consistent also with this mechanism is the observed cis stereochemistry of the cyclic chloromercuri adduct **32**.

Of particular mechanistic interest is the unprecedented kinetic preference for formation of the seven-membered ring 1,3-dioxepane adducts **27** and **28** when hemiacetals **22** and **24** are treated with mercuric trifluoroacetate in THF. Presumably these adducts do not result from external capture by the hemiacetal hydroxyl group of intermediate **46**,[33] since it is well established that kinetic formation of



six-membered rings is faster than that of seven-membered rings by several orders of magnitude.[35] Although the inductive effect of the hemiacetal group should, to some extent, favor nucleophilic addition at C-4,[30] it seems unlikely that this effect would be large enough to reverse the usual large kinetic preference for six-membered ring formation. One explanation for this unusual observation is that the hemiacetal hydroxyl group is not an external nucleophile, but rather is coordinated to mercury. Collapse of such an internally solvated intermediate, *e.g.*, mercurinium ion **47**, would not have the kinetic bias for six-membered ring formation expected of an external nucleophile and could result in formation of significant amounts of the seven-membered ring adduct **48**. The internal addition of anions in the coordination sphere of a solvated mercurinium ion intermediate has recently been suggested by Bach[19d] to account for the large amount of cis addition observed when bicyclo[2.2.2]octene is oxymercurated in nonpolar solvents. Studies aimed at clarifying this proposed mechanism for the case of the presumably analogous but simplier 5-alken-1-ols are in progress.

Experimental Section[36]

The solvents used were analytical reagent grade. No increase in yield resulted if THF was freshly distilled from $LiAlH_4$. Mercuric trifluoroacetate was prepared by Brown's procedure.[6a] 2-Cyclohexen-1-ol, (*E*)-2-hexen-1-ol, (*E*)-3-hexen-1-ol, (*Z*)-3-hexen-1-ol, (*E*)-3-hepten-1-ol, 2,4-hexadien-1-ol, and cinnamyl alcohol were purchased from Aldrich Chemical Co. or Chemical Samples Corp. *cis*- and *trans*-4-*tert*-butyl-*cis*-1,2-cyclohexanediol (**1b** and **1c**)[37] and 1-hydroxymethylcyclohexan-1-ol[1b] were prepared by literature procedures. 1,2α,4aβ,5,6,7,8,8aα-Octahydro-2-naphthol (**10**) was prepared from the isomeric axial alcohol[38] by oxidation[39] followed by reduction with $LiAlH_4$ at −78°. Authentic samples of aliphatic diols were prepared as follows: 1,3-hexanediol by $LiAlH_4$ reduction of ethyl 3-hydroxyhexanoate;[40] 1,4-hexanediol by hydroboration[41] of 1-hexen-4-ol; 1,3-heptanediol by hydroboration[41] of 1-hepten-3-ol; 1,4-heptanediol by hydroboration[41] of 1-hepten-4-ol. *cis*-1,2-Diols were prepared from the corresponding alkenes by the procedure of Woodward and Brutcher.[42] The diols were converted to the diacetates by treatment with acetic anhydride in pyridine and the diacetates were purified by preparative gc on a 5 ft × 0.25 in. column of 5% QF-1 on 60/80 Chromosorb B. For the determination of gc yields, internal standards (naphalene, *p*-dichlorobenzene, or diethyl adipate) were added to the crude reaction mixture before the isolation[36a] procedure.

Mercuration–Demercuration of Chloral Hemiacetal Derivatives of Cyclic Alcohols. *cis*-4-*tert*-Butyl-*cis*-1,2-(2-trichloromethylethylenedioxy)cyclohexane (3b). A mixture of **1b** (0.979 g, 6.36 mmol), chloral (1.3 ml, 13 mmol), and THF (20 ml) was

treated with mercuric trifluoroacetate (2.72 g, 6.36 mmol) and the resulting solution was stirred under nitrogen at room temperature for 48 hr. The solution was then cooled to 0° and reduced by adding 20 ml of 2.0 *M* NaOH, followed by 20 ml of 0.5 *M* sodium borohydride in 2.0 *M* NaOH. After stirring for 2 hr at 25°, the water layer was saturated with K_2CO_3 and the product was isolated[36a] with ether to afford 1.88 g of a white solid. Sublimation at 50° (0.1 Torr) yielded 1.20 g (74%) of **3b**, mp 84–88°, 99% pure by gc. Two singlets in the nmr spectrum at τ 4.77 and 4.87 in a 95:5 ratio indicated that this sample was a mixture of epimers at the CCl_3-bearing carbon.

The analytical sample was prepared by recrystallization from ethanol–water to afford white needles: mp 91.5–92.5°; ν_{max} (Nujol) 1133 (CO) and 803 cm^{-1} (CCl); nmr τ 4.77 (s, 1 H, $CHCCl_3$), 5.32–5.85 (m, 2 H, CHOR), 9.12 [s, 9 H, $C(CH_3)_3$].

Anal. Calcd for $C_{12}H_{19}O_2Cl_3$: C, 47.78; H, 6.35. Found: C, 47.84; H, 6.48.

***cis*-1,2-(2-Trichloromethylethylenedioxy)cyclohexane (3a).** In a similar manner a mixture of **1a** and chloral was treated for 60 hr with 1.0 equiv of mercuric trifluoroacetate to afford after distillation in 62% yield **3a**: bp 70–73° (0.1 Torr); ν_{max} (film) 1138 (CO) and 809 cm^{-1} (CCl); nmr ($CDCl_3$) τ 4.59 and 4.76 (singlets in 92:8 ratio, 1 H, $CHCCl_3$ epimers), 5.28–5.83 (m, 2 H, CHOR).

Crystallization from hexane at −78° afforded a pure sample of the major epimer, mp 32.0–34.5° (lit.[9] mp 34.5–35°).

Anal. Calcd for $C_8H_{11}Cl_3O_2$: C, 39.13; H, 4.52; Cl, 43.32. Found: C, 38.91; H, 4.31; Cl, 43.28.

Addition of ytterbium tris(2,2,6,6-tetramethylheptanedionate) [Yb(dpm)$_3$] to the epimer mixture resulted in shifts for the $CHCCl_3$ hydrogens shown in Figure 2.

1-Hydroxymethylcyclohexan-1-ol Trichloroacetaldehyde Acetal (8). In a similar manner a mixture of **7** and chloral was treated for 28 hr with 1.0 equiv of mercuric trifluoroacetate to afford after distillation in 71% yield **8**, bp 96–97° (0.5 Torr).

The analytical sample was prepared by preparative gc (5% SE-30): ν_{max} (film) 1342 (CO) and 812 cm^{-1} (CCl); nmr τ 4.80 (s, 1 H, $CHCCl_3$) and 6.20 (s, 2 H, CH_2OR).

Anal. Calcd for $C_9H_{13}O_2Cl_3$: C, 41.65; H, 5.05. Found: C, 41.55; H, 5.12.

Reductive cleavage of **8** with sodium in ether afforded in 96% yield diol **9** which was identical (ir, melting point, mixture melting point) with the diol obtained by conventional[8b] mercuration–demercuration of alcohol **7**.

1,2α,3α,4,4aβ,5,6,7,8,8aα-Decahydro-2,3-(2-trichloromethylethylenedioxy)naphthalene (11). In a similar manner a mixture of **10** (containing 80% of the equatorial hydroxyl isomer) and chloral was treated for 66 hr with 1.05 equiv of mercuric trifluoroacetate to afford after sublimation (70°, 0.1 Torr) in 67% yield (based on the equatorial isomer) **11**, mp 101–106°, 85% pure by gc.

The analytical sample was prepared by preparative gc (5% SE-30) and was recrystallized from hexane at −78°: mp 109.5–112°; ν_{max} (Nujol) 1338 (CO) and 808 cm^{-1} (CCl), 4.77 and 4.92 (singlets, 1 H total, $CHCCl_3$ epimers), and 5.13–5.80 (m, 2 H, CHOR).

Anal. Calcd for $C_{12}H_{17}Cl_3O_2$: C, 48.10; H, 5.72; Cl, 35.50. Found: C, 47.81; H, 5.51; Cl, 35.72.

Reduction of **11** with sodium in ether afforded in 85% yield diol **12**, which was identical (ir, melting point, mixture melting point) with an authentic sample[43] prepared[42] from *trans*-2-octalin.

Reductive Cleavage of Chloral Acetals. A. Cleavage of Acetal 3b with Sodium in Ether. Sodium dispersion (300 mg, 5.2 mmol, Alfa, 40% in mineral oil) was washed three times with hexane and added to a solution of **3b** (255 mg, 0.843 mmol) in anhydrous ether (15 ml). After stirring for 12 hr at 25°, the excess sodium was destroyed by carefully adding wet ether. Brine solution (20 ml) was added and the product was isolated[36a] with ether and crystallized (hexane–ether) to afford 137 mg (94%) of **4b**, mp 105–111°, 95% pure by nmr.

The analytical sample was prepared by two recrystallizations from CCl_4: mp 115–116.5°;[44] ν_{max} (KBr) 3400 cm^{-1} (OH); nmr ($CDCl_3$) τ 6.13 (m, 1 H, $W_{1/2}$ = 7.5 Hz, equatorial CHOH), 6.47 (m, 1 H, $W_{1/2}$ = 18 Hz, axial CHOH), 6.94 (broad s, 1 H, OH), 9.14 [s, 9 H, $C(CH_3)_3$].

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.90; H, 11.96.

B. Cleavage of Acetal 3a with Zinc and Acetic Acid. A mixture of **3a** (3.60 g, 14.6 mmol) and zinc dust (5.0 g, 76 mmol) in acetic acid (30 ml) was refluxed with stirring for 12 hr. The acetic acid was removed *in vacuo* and the product was isolated[36a] with ether to afford after distillation 2.18 g (75%) of *cis*-1,2-diacetoxycyclohexane, bp 72–73° (0.05 Torr), 95% pure by gc. Removal of the acetyl groups with NaOMe in methanol afforded after sublimation *cis*-1,2-cyclohexanediol (**4a**) in 85% yield, mp 96.5–98.5°, mmp 96–98° (lit.[48] 96–98°).

Mercuration–Demercuration of Hemiacetal Derivatives of Acyclic Alcohols. Cyclization of Hemiacetal 15. A mixture of (*E*)-2-hexen-1-ol (1.00 g, 10 mmol), chloral (2 ml, 20 mmol), and THF (10 ml) was treated at 25° with mercuric trifluoroacetate (4.28 g, 10 mmol). After 23 hr this solution was reductively worked up as described for **3b** to afford 2.4 g of a yellow oil. Bulb-to-bulb distillation afforded 1.93 g (79%) of a mixture of 4-*n*-propyl-2-trichloromethyl-1,3-dioxane (**18**) and 4-*n*-butyl-2-trichloromethyl-1,3-dioxolane (**21**), bp 70–76° (0.1 Torr). The nmr spectrum showed three $CCl_3CH<$ methine hydrogen singlets at τ 5.29, 4.79, and 4.72 in a 47:11:42 ratio. The peak at τ 5.29 is assigned to **18** by comparison with the nmr spectrum of the acetal mixture formed from **22**. An identical isomer ratio was observed at 6 hr.

Anal. Calcd for $C_8H_{13}Cl_3O_2$: C, 38.82; H, 5.29; Cl, 42.96. Found: C, 39.01; H, 5.43; Cl, 42.71.

The diacetate mixture obtained by reductive cleavage (Na) of this acetal mixture followed by acetylation is described in Table II.

Cyclization of Hemiacetal 22. In a similar manner a mixture of (*E*)-3-hexen-1-ol and chloral was treated with 1.0 equiv of mercuric trifluoroacetate. The build-up of the cyclic trichloroacetal was followed by gc and reached a maximum (44%) at 60 hr and began to slowly decline thereafter. Reductive work-up at 60 hr afforded in 32% yield a mixture of 4-*n*-propyl-2-trichloromethyl-1,3-dioxane (**18**) and 4-ethyl-2-trichloromethyl-1,3-dioxepane (**27**), bp 78–79° (0.2 Torr). The nmr spectrum showed two large CCl_3CH methine hydrogen singlets at τ 5.29 and 5.11 in a 53:47 ratio. At shorter reaction times (1–24 hr) four isomers were apparent: singlets at τ 5.29, 5.11, 5.18, and 5.07 in a 39:51:3:7 ratio. The major peaks at τ 5.29 and 5.11 are assigned to **18** and **27**, respectively.

Anal. Calcd for $C_8H_{13}Cl_3O_2$: C, 38.82; H, 5.29. Found: C, 39.15; H, 5.50.

The mixture of diacetates obtained by reductive cleavage (Na) of the kinetic acetal mixture (9 hr) followed by acetylation is described in Table II. The gc assignment was confirmed by isolation of the 1,3- and 1,4-diacetoxyhexanes by preparative gc (10% QF-1) and comparison (ir and nmr) with authentic samples.

Cyclization of Hemiacetal 23. In a similar manner (*Z*)-3-hexen-1-ol and chloral were treated for 48 hr with 1.0 equiv of mercuric trifluoroacetate to afford after distillation a mixture of **18** and **27** in 72% yield, bp 76–78° (0.1 Torr). The nmr spectrum showed singlets at τ 5.29 and 5.11 in a ratio of 65:35 for **18** and **27**, respectively. The isomer ratio was identical at 22 hr.

The mixture of diacetates obtained by reductive cleavage of this acetal mixture followed by acetylation is described in Table II.

Cyclization of Hemiacetal 24. In a similar manner (*E*)-3-hepten-1-ol and chloral were treated for 48 hr with 1.05 equiv of mercuric trifluoroacetate to afford, after distillation, in 45% yield a mixture of 4-*n*-butyl-2-trichloromethyl-1,3-dioxane (**26**) and 4-*n*-propyl-2-trichloromethyl-1,3-dioxepane (**28**). The nmr spectrum showed two trichloromethyl methine hydrogen singlets at τ 5.30 and 5.12 in a 60:40 ratio. Since at 6 hr the ratio of these peaks is 40:60 (50:50 at 24 hr), the τ 5.30 peak is assigned to **26** and the τ 5.12 peak to **28**.

The mixture of diacetates obtained by reductive cleavage (Na) of this acetal mixture followed by acetylation is described in Table II.

Cyclization of Hemiacetal 17. In a similar manner 2,4-hexadien-1-ol (a mixture of isomers) was treated with 1.0 equiv of mercuric trifluoroacetate for 48 hr to afford after distillation 4-propenyl-2-trichloromethyl-1,3-dioxane (**20**) in 37% yield, bp 70–74° (0.1 Torr). The nmr spectrum showed one major absorption for the $>CHCCl_3$ methine hydrogen at τ 5.20.

Hydrogenation (Pd/C) followed by reductive cleavage (Na) and acetylation afforded the mixture of diacetates described in Table II.

Cyclization of Hemiacetal 40. A solution of (*E*)-2-hexen-1-ol (1.06 g, 10.6 mmol), benzaldehyde (25 ml, 245 mmol), mercuric trifluoroacetate (4.53 g, 10.6 mmol), and THF (10 ml) was stirred under nitrogen for 6 days at 25°. Demercuration as described for **3b** and isolation[36a] with ether afforded the crude acetal, which was dissolved in dry THF and reduced with $LiAlH_4$ (to convert any benzaldehyde to benzyl alcohol). Distillation afforded 2-phenyl-4-*n*-propyl-1,3-dioxane (**42**), bp 73° (0.01 Torr).

The analytical sample was prepared by preparative tlc on silica

gel using hexane–ethyl acetate (9:1) as eluent: ν_{max} (film) 1105 (CO), 749, and 696 cm^{-1}; nmr τ 2.4–2.9 (m, 5 H, C_6H_5), 4.68 (s, 1 H, >CHPh), and 5.4–6.5 (m, 3 H, CHOR).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 76.06; H, 8.35. Found: C, 76.00; H, 8.54.

Hydrolysis with 1 *M* HCl in refluxing THF–H_2O followed by acetylation afforded 1,3-diacetoxyhexane (94%) contaminated with 6% or 1,2-diacetoxyhexane.

Cyclization of Hemiacetal 39. A solution of trifluoroacetaldehyde[49] (20 ml, 0.9 *M*) in ether at −78° was treated with (*E*)-2-hexen-1-ol (0.929 g, 9.3 mmol). Upon warming to room temperature excess fluoral was lost by degassing and the nmr spectrum showed a complex multiplet centered at τ 5.2 for the >$CHCF_3$ methine hydrogen of **39**. Mercuric trifluoroacetate (4.28 g, 9.3 mmol) was added and the solution was maintained at 25° for 90 hr and demercurated as described for **3b**. Isolation[36a] with ether afforded 1.207 g (52%, 80% pure by gc) of crude 4-*n*-propyl-2-trifluoromethyl-1,3-dioxane (**41**). The nmr spectrum indicated the predominant formation of a single cyclic acetal isomer, as only one quartet centered at τ 5.25 [$J(^{19}F\text{-}H)$ = 3.5 Hz] was observed for the >$CHCF_3$ methine hydrogen. At shorter reaction times (24–36 hr) two isomers were apparent—quartets centered at τ 5.25 and 4.87 in a ratio of 85:15. Preparative gc (5% QF-1) afforded **41** (96% pure by gc): ν_{max} (film) 1299 and 1183 cm^{-1} (CF); nmr τ 5.25 (q, 1 H, $CHCF_3$, J = 3.5 Hz) and 3.9 (m, 3 H, CHOR).[53]

Reductive cleavage of **41** with sodium in ether followed by acetylation afforded 1,3-diacetoxyhexane (96%) contaminated with 4% of 1,2-diacetoxyhexane.

***cis*-3-Chloromercuri-*cis*-1,2-(2-trichloromethylethylenedioxy)cyclohexane (32).** A solution of **1a** (1.96 g, 20 mmol), chloral (4.0 ml, 40 mmol), and mercuric trifluoroacetate (9.32 g, 22 mmol) in THF (20 ml) was stirred for 48 hr at 25°. The addition of 10% sodium chloride solution (40 ml) produced an oily precipitate, which was isolated[36a] with $CHCl_3$ to afford 6.4 g of a white semisolid (70% **32** by nmr). Crystallization from ethanol–H_2O and recrystallization from 1:1 ethanol–hexane afforded 1.56 g (16%) of **32**, mp 142.5–143.5°.

The analytical sample was prepared by two recrystallizations from benzene to afford fine white needles: mp 142.5–144°; ν_{max} (Nujol) 1131 (CO) and 830 cm^{-1} (CCl); nmr ($CDCl_3$) τ 4.53 (s, 1 H, $CHCCl_3$), 5.05–5.60 (m, 2 H, CHOR), 7.23 (m, 1 H, $W_{1/2}$ = 19 Hz, axial CH-HgCl).

Anal. Calcd for $C_8H_{10}O_2Cl_4Hg$: C, 19.99; H, 2.10. Found: C, 20.17; H, 1.89.

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Registry No.—**1a**, 822-67-3; **1b**, 26819-49-8; **3a** α epimer, 51014-77-8; **3a** β epimer, 51014-78-9; **3b** α epimer, 51014-79-0; **3b** β epimer, 51014-80-3; **4a**, 1792-81-0; **4b**, 19793-86-3; **7**, 4845-04-9; **8**, 39257-35-7; **10**, 18314-48-2; **11** α epimer, 51014-81-4; **11** β epimer, 51096-40-3; **15**, 51014-82-5; **17**, 51015-02-2; **18**, 51015-03-3; **20**, 51015-04-4; **21**, 51015-05-5; **22**, 51014-83-6; **23**, 51014-84-7; **24**, 51014-85-8; **26**, 51022-61-8; **27**, 51022-62-9; **28**, 51015-06-6; **32**, 51015-07-7; **39**, 51014-86-9; **40**, 51014-87-0; *cis*-**41**, 51014-88-1; *trans*-**41**, 51014-89-2; **42**, 51015-08-8; chloral, 75-87-6; mercuric trifluoroacetate, 1600-27-7; *cis*-1,2-diacetoxycyclohexane, 2396-76-1; (*E*)-2-hexen-1-ol, 928-95-0; (*E*)-3-hexen-1-ol, 928-97-2; (*Z*)-3-hexen-1-ol, 928-96-1; (*E*)-3-hepten-1-ol, 2108-05-6; 2,4-hexadien-1-ol, 111-28-4; benzaldehyde, 100-52-7; trifluoroacetaldehyde, 75-90-1.

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(5) In CCl_4 this hydrogen appears as a singlet for all the secondary alcohols we have studied and indicates that the equilibrium of eq 1 is faster than the nmr time scale, since two diastereoisomers are possible. In basic solvents such as THF this hydrogen appears as an unresolved multiplet which we take to indicate that not only is the equilibrium of, *e.g.*, eq 1 slower in such a hydrogen-bonding solvent but also that coupling of the methine hydrogen to the hydroxyl group is observed. As expected this multiplet collapses to a singlet upon the addition of trifluoroacetic acid.

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(47) Samples for comparison were kindly provided by Professor Rickborn.
(48) "Dictionary of Organic Compounds," Vol. 2, 4th ed, 1965, p 783.
(49) Fluoral was prepared from fluoral hydrate by a modification of the procedure described by Pautrant.[50] In this modification the apparatus of Pautrant was evacuated to 100 Torr and the crude hydrate (Columbia Chemicals Co., contaminated with the ethyl hemiacetal of fluoral) was then added portionwise to the polyphosphoric acid solution. Redistillation of the condensate afforded fluoral in approximately 50% yield: ν_{max} (gas) 2857, 1786, 1370, 1299, and 1190 cm^{-1}.[51] Liquid fluoral or solutions in ether could be stored at −78° for several weeks with no noticeable polymerization. An alternate procedure for preparing solutions of fluoral in benzene–chloroform proved unsuccessful.[52]
(50) R. Pautrat, J. Marteau, and R. Cheritat, *Bull. Soc. Chim. Fr.*, 1182 (1968).
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Pyrolysis of Amino Acids. Mechanistic Considerations

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Pyrolysis (*ca.* 500°) of a number of structurally different amino acids has been studied to determine the effects on mechanisms and product distribution exerted by geometrical isomerism. Aliphatic protein amino acids decompose predominantly by decarboxylation and condensation reactions as primary steps. β-Amino acids lose ammonia to give unsaturated acids. α-Amino acids containing α-alkyl substituents undergo a novel S_Ni reaction losing ammonia and forming an intermediate α-lactone that subsequently yields a ketone upon decarbonylation. γ- and δ-amino acids give 2-pyrrolidinone and 2-piperidone, respectively, as major pyrolysis products. The ε-amino acid, while producing some lactam, yields several chain-shortened amines and nitriles with no single predominant product.

The use of pyrolysis for the analysis of complex molecules and polymers has grown steadily in recent years. Modern techniques utilize pyrolysis methods in conjunction with gas chromatography (gc) and mass spectrometry (ms) or, in many instances, both for the analysis of complex systems.

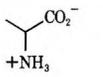
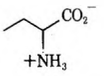
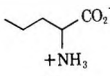
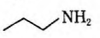
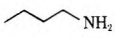
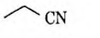
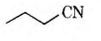
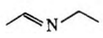
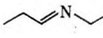
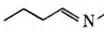
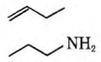
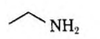
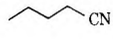
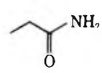
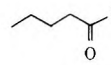
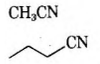
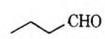
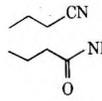
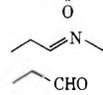
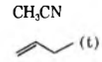
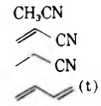
Applications are increasingly growing in the fields of synthetic polymers[2] and biological research.[3] Pyrolysis has been used to study nucleotides,[4,5] mycolic acid,[6] steroids,[7] and acetycholine,[8] and for amino acid[9] and peptide identification.[10]

Recently, the field has grown to include attempts to characterize strains or species of microorganisms by pyrolysis coupled with gc, ms, and gc–ms.[11,12] While the use of this technique for analytical purposes is possible without a detailed understanding of the mechanisms involved, the full potential for pyrolysis can only be realized when the fragmentation products can be related to starting materials *via* logical mechanisms.

One important class of compounds is the amino acids. In addition to their obvious biological significance, a suite of amino acids has been found in the Murchison[13,14] and Orgueil[15] meteorites that are considered to be of extraterrestrial origin. Since NASA plans to include a pyrolysis gc–ms experiment aboard a Viking spacecraft (scheduled to land on Mars in mid-1976), a knowledge of thermally induced fragmentation processes of this apparently important class of compounds would assist the interpretation of any results forthcoming from that experiment.

We have previously reported on the thermal fragmentation of a selected group of protein amino acids.[16] Our studies have been expanded to include additional homologs to that series and labeled substrates which provide evidence for the mechanisms proposed. In addition, a variety of positional isomeric monoamino monocarboxylic acids have been investigated. From these data, a more consistent scheme can be developed to describe the pathways by which amino acids thermally decompose.

Table I
Products Obtained from the Pyrolysis of α-Amino Acids

Yield[a]	Alanine	α-Amino-n-butyric acid	Norvaline
			
		1	2
A	CO_2	CO_2	CO_2
	H_2O	H_2O	H_2O
			
B	CH_3CN		
			
	DKP	DKP	DKP
	NH_3	NH_3	NH_3
C	C_2H_4	C_2H_4	
	C_2H_6	C_2H_6	
			
			
		CH_3CN	
	CH_3CHO		
			
			
D	CO	CH_4	CO
	CH_4	CO	CH_4
	 (t)[b]	CH_3CN	C_2H_4
	CH_3NH_2 (t)	 (t)	C_2H_6
			CH_3CN
			

[a] Yield ranges (per cent of total pyrolysate): A, 20% or more; B, 5–20%; C, 0.5–5%; D, 0.05–0.5%. [b] Trace amounts (t), <0.05%.

Experimental Section

Methods. A detailed description of the pyrolysis gc–ms apparatus used in these experiments has previously been reported.[17] In brief, approximately 0.5–1 mg of each crystalline amino acid was carefully weighed into a 2.5-cm (0.158-cm i.d.) stainless steel tube attached directly to the front of the chromatographic column. A small furnace that fits snugly around the pyrolysis tube was used to raise the temperature of the sample to 500° in approximately 10 sec. Chromatographic columns, 2.4 m long with a 0.158-cm o.d. and a 0.127-cm i.d., were packed with either Chromosorb 103 (Johns-Manville) or Tenax-GC (Applied Science Laboratories).

The majority of experiments, however, were conducted using the Tenax column, which proved to be particularly useful in resolving the wide range of products found in the pyrolysates. Typically, columns were temperature programmed from 25 to 285° at 7.5°/min. Mass spectra were obtained directly from the effluent of the gc column, after enrichment through a single-stage jet separator, on an EAI Quadrupole 300 mass spectrometer (Palo Alto, Calif.).

Where possible, individual thermal fragments were identified by comparing their mass spectra with published spectra.[18] Where spectra were unavailable, tentative identification was confirmed by synthesis and comparison of the mass spectra fragmentation pattern of the synthesized compound with that of the pyrolysis product.

Relative yields of products were determined by calibrating the ion current with standard mixtures. The compounds listed as products from the pyrolysis of the substrates studied are those we observed or inferred from our results. The possibility remains that some compounds might have been formed which were either too large or too polar to permit chromatographic analysis under our experimental conditions. These, of course, would not have been detected. Since the nature of a pyrolysis gc–ms experiment makes mass balance extremely difficult, we cannot be sure what per cent of our starting material is represented by the products. While we are confident that we have accounted for the majority of the products, and certainly the major ones, the possibility remains that the techniques employed have resulted in the loss of minor constituents.

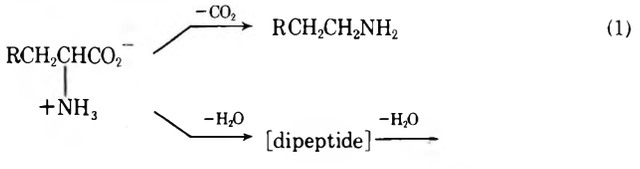
Reagents. Neutral amino acids were obtained from a number of commercial sources. 2-Methylalanine, isovaline and β-aminoisobutyric acid were purchased from K and K Laboratories. β-Amino-n-butyric acid was supplied by Aldrich Chemical Co. and α-amino-n-butyric acid by Nutritional Biochemicals Corp. The alanine polymers and norvaline were obtained from CalBiochem Corp. All amino acids were DL and of the highest purity available. Alanine-^{15}N was obtained from Prochem with 95% enrichment.

Results and Discussion

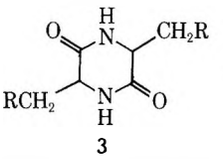
α-Amino Acids. Both α-amino-n-butyric acid (1) and norvaline (2) represent homologs of the group of protein amino acids studied previously[16] and should therefore yield products predictable from earlier results. Table I lists the thermal fragments formed from these two compounds; previous results for alanine are included for comparison. The data are listed in terms of yield ranges to facilitate discussion. For purposes of this study, it is more critical to establish major and minor products and approximate yields than to determine whether a substance represents 1 or 5% of the total pyrolysate. Discussion of the general pathways leading to the observed products would not be altered by a more precise determination of product yields. Where discussion warrants, relative yields within groups will be presented. When absolute yields are presented, they indicate per cent yield based on total product.

Throughout this paper, reactions are depicted as arising *via* the zwitterion form of the amino acids. While the equilibrium constant favors the zwitterion by 10^5 at room temperature, the free acid–base form is favored at pyrolysis temperatures (*ca.* 500°).[19] Since no data are available on the rates for either the equilibration process or the decomposition reactions, speculation regarding the nature of the species decomposing is difficult. Only when one of the structures is suggested by the mechanistic arguments being presented is the nature of the substrate important.

As expected from our previous study, the α-amino acids 1 and 2 (Table I) undergo a decarboxylation reaction to produce n-propyl- and n-butylamine, respectively, as the major organic products.



(1)

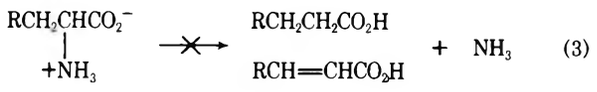


(2)

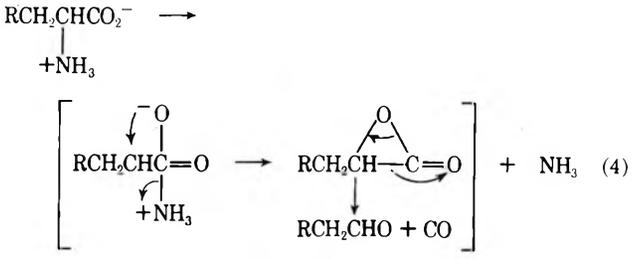
3

A second process (eq 2), also considered to be a primary decomposition mode, involves a double dehydration reaction yielding first a dipeptide and subsequently a diketopiperazine 3 (DKP). The presence of the dipeptide is only inferred, since its analysis under our experimental conditions is precluded. The presence of water and the diketopiperazine, however, provide strong evidence for its involvement.

In our previous report,[16] deamination was suggested to be a primary, although minor, pathway. The absence of the corresponding carboxylic acids (eq 3), however, always

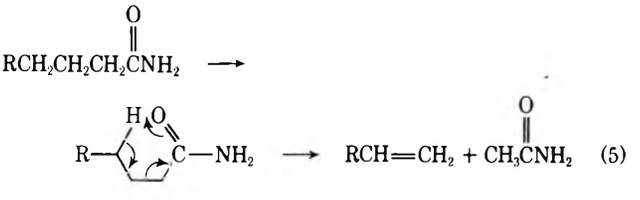


presented interpretative problems, and more recent work (*vide infra*) indicates that ammonia is formed predominantly as a product from secondary reactions. The possibility of a minor pathway in which ammonia may be formed as a primary product, however, cannot be eliminated. Aldehydes containing one carbon less than the parent amino acid are present in the pyrolysate of all members of this class. Although these compounds represent minor products here (0.1–0.5%), their presence is significant. We originally proposed[16] an intramolecular reaction involving an intermediate α-lactone followed by decarbonylation (eq 4) to account for the observed aldehydes, and,



in light of our studies on α-amino acids containing α-alkyl substituents (*vide infra*), this process appears more firmly established. Therefore, while representing only a minor pathway for this class of compounds, aldehyde formation *via* eq 4 seems to represent a primary decomposition step.

A fourth mode of decomposition, possibly representing primary fragmentation, involves chain homolysis and leads to a series of both saturated and unsaturated hydrocarbons. Homolysis, however, even for the longer chain homologs, represents at most a minor part of the reaction, since total hydrocarbon yields never exceed 3%. In addition, olefins might arise from secondary decompositions of several products, particularly those susceptible to the formation of six-membered transition states such as amides[20] (eq 5). The presence of amines and *N*-alkylaldimines of chain length shorter than that expected from the parent amino acid also indicate the presence of some chain homolysis, particularly methyl group cleavage, but these processes remain minor.

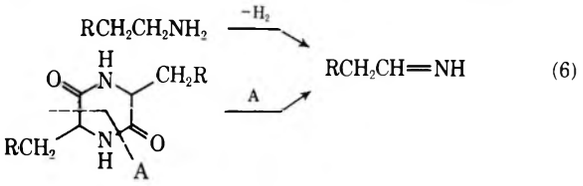


Following these primary processes, a significant number of products arise from secondary decompositions. Major among these secondary products are *N*-alkylaldimines and nitriles containing one carbon less than the parent amino acid. The imines are always a significant product and normally represent 8–12% of the total product yield, although on some occasions even greater amounts were produced. The nitrile yields are generally less than those of the imines, varying between 5 and 10%, and are comparable to the yields of diketopiperazines.

Both the nitriles and *N*-alkylaldimines represent secondary products that may arise from simple aldimines. The aldimines, in turn, may result from the decomposition of either amines[9,21] or diketopiperazines.

Methylamine, for example, undergoes pyrolysis at 500° to yield HCN and hydrogen as major products.[22] The HCN was proposed to result from the decomposition of methyleneimine, formed in a radical chain process.

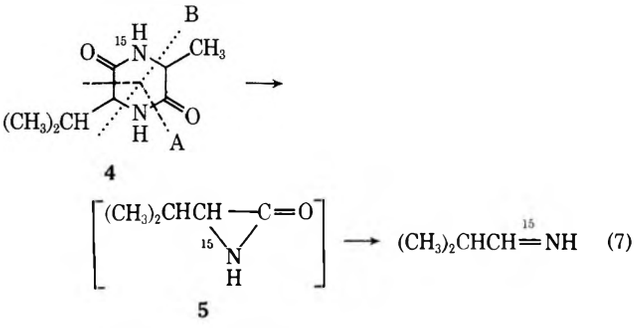
Diketopiperazines of valine, alanine, and glycine were prepared and pyrolyzed under our conditions. For valine and alanine DKP, nitriles corresponding to cleavage through A (eq 6) followed by dehydrogenation were major



products. For glycine DKP, HCN was a major product, again conforming to the proposed pathway.

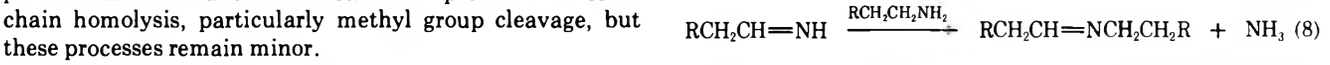
An additional process may also be involved, giving rise to nitriles *via* aldimines. When valine and alanine-^{15}N (1:1) were pyrolyzed together, isobutyronitrile containing ^{15}N (15–30%) was found. This, of course, necessitates a bimolecular process between valine and alanine which also allows for carbon-chain reduction. A diketopiperazine again offers a reasonable possibility.

The diketopiperazine 4 can cleave either through A (eq 7) or B. Cleavage through A will produce the necessary



imine intermediate but with no label. If cleavage through B, however, is accompanied by a concomitant ring closure to the α-lactam 5, decarbonylation, similar to that for aldehyde formation (*vide supra*) would produce the labeled imine directly. The nitrile product, therefore, would be expected to contain labeled nitrogen. At present, it is not possible to estimate accurately the relative extent to which each pathway occurs; however, the low yields of CO indicate that pathways leading to nitriles involving the diketopiperazine are of minor importance.

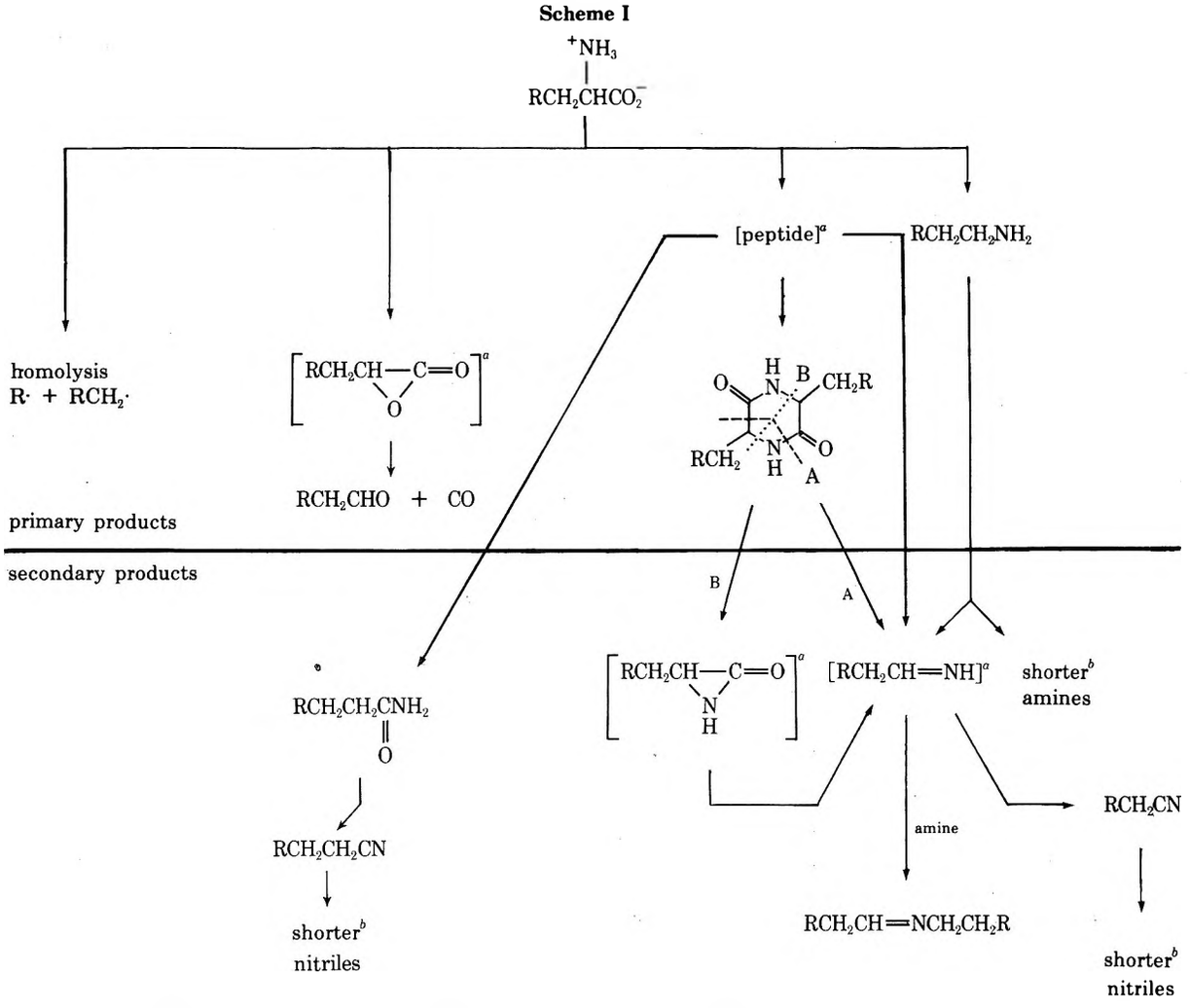
In the present system, a large quantity of amine is present following decarboxylation and a transalkylidenation reaction (eq 8) represents a pathway that provides for the formation of both ammonia and the *N*-alkylaldimines.



Further, preliminary studies suggest that the yields of *N*-alkylaldimine and ammonia are directly correlated when conditions to reduce or increase their yields relative to the nitrile are introduced.

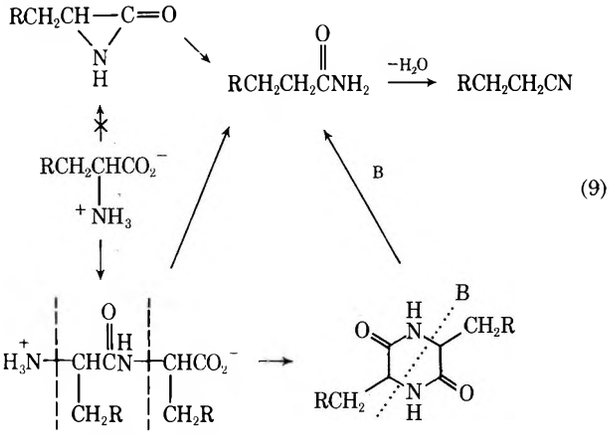
A second nitrile always present in these reactions contains the same carbon number as the parent amino acid. Their presence can best be explained by the dehydration of an amide (eq 9). Amides containing the same carbon number as the parent amino acid are present in all reactions, varying in yield from 0.5 to 2%. Since carboxylic acids are absent, the amides cannot be accounted for from a bimolecular reaction between acid and ammonia. Originally,[16] we proposed three other sources for the formation of amides and the corresponding nitriles (eq 9). The α-lactam, while offering conceptual simplicity, can now be eliminated, since pyrolysis of a mixture of valine and alanine-^{15}N resulted in the formation of 3-methylbutyramide containing the ^{15}N label, thus necessitating a bimolecular

Scheme I



[a] Compounds in brackets were not found, but inferred from other information. [b] These may result from chain homolysis, particularly for the longer chain precursors.

process. While reductive fragmentation of diketopiperazines was expected to yield amides, the pyrolysis of both alanine and valine DKP failed to produce any detectable amide products. Peptides, on the other hand, produce large yields of amides when pyrolyzed under conditions similar to those for the free amino acids. Cleavage through the bonds indicated in eq 9 for the dipeptide accounts not

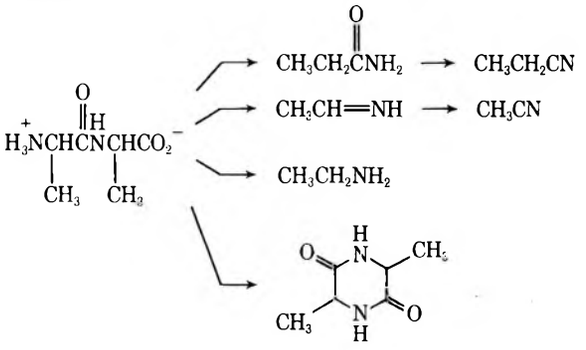


(9)

only for the formation of amides, but also for the observed label incorporation.

The peptide may also be an additional source for aldimines and, consequently, the chain-shortened nitriles previously discussed. Alanylalanine, for example, gives significant yields of acetonitrile in addition to the amide and nitrile homologs mentioned above.

The major products resulting from the pyrolysis of alanylalanine are shown in eq 10. Of some interest is the fact



(10)

that pyrolysis of a series of alanine polymers with two to five residues and polyalanine gave nearly identical product yields with a few exceptions.

Scheme I summarizes the reactions we feel are largely responsible for the products observed from the pyrolysis of this class of amino acids. Simple decarboxylation is certainly the major process that occurs. The importance of the peptide formation and the extent to which it or the diketopiperazine give rise to secondary products is largely speculative, although the use of labels and mixed reactants suggests that each is involved to some extent.

The complexity of the secondary processes makes an understanding of the extent to which each reaction is involved very difficult to obtain.

Amino Group Isomerism. To provide a contrast to the α-amino acids and to study the effects exerted by positional isomerism of the two functional groups, a series of amino acids with the amino group in the β, γ, δ, and ε positions was studied.

Table II lists the results for a group of β-amino acids. Results for β-alanine (8) were reported previously,[16] but additional information has been obtained pertinent to this study. The pyrolytic decomposition of the new members of the group, β-amino-*n*-butyric acid (6) and β-aminoisobutyric acid (7), is similar to that of β-alanine. The most striking difference between the thermal decomposition of the α- and β-amino acids is the almost total distinction between their primary modes of decomposition. Whereas the α-amino acids undergo decarboxylation with at most very minor deamination, the β-amino acids produce unsaturated acids and ammonia as major products. In addition, where more than one olefinic acid can form, all are observed. β-Amino-*n*-butyric acid, for example, produces both *cis*- and *trans*-crotonic acid as well as 3-butenoic acid. While the α,β-unsaturated acids are the more abundant products, the ratio of these to the β,γ-unsaturated acid is not necessarily indicative of their relative rates of formation.

$$RCH_2\underset{\displaystyle {}^{+}NH_3}{\underset{|}{C}}HCH_2CO_2^- \longrightarrow RCH_2CH{=}CHCO_2H + NH_3 \quad (11)$$

Propene, also a significant pyrolysis product, is probably the result of decarboxylation of the 3-butenoic acid.

$$CH_2{=}CHCH_2CO_2H \longrightarrow \left[\begin{array}{c} H \\ O \\ \| \\ C{=}O \end{array}\right] \longrightarrow CH_2{=}CHCH_3 + CO_2 \quad (12)$$

The formation of β,γ unsaturation appears to be required for facile decarboxylation of an unsaturated carboxylic acid. Acrylic acid, for example, decomposes only slightly at 500°,[23] and β,β-dimethylacrylic acid resists decarboxylation at least to 300°.[24] Here, apparently no mechanism for isomerization was available.

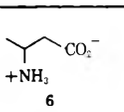
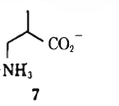
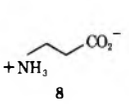
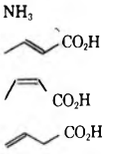
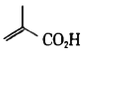
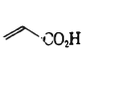
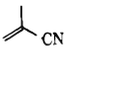
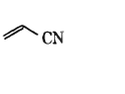
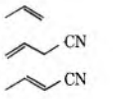
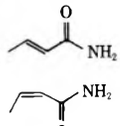
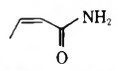
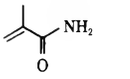
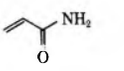
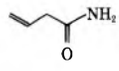
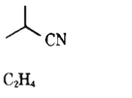
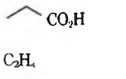
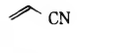
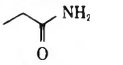
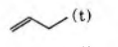
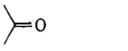
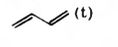
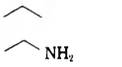
These data further reinforce our suggestion that direct deamination to form acids does not occur in the α-amino acids. Were this process involved, acrylic acid should have been produced from alanine pyrolysis and valine should have yielded β,β-dimethylacrylic acid.

Among secondary products resulting from the β-amino acids, nitriles of the same carbon number as the parent amino acid predominate. This contrasts again with the α-amino acids, where, of the nitriles present, those reduced by one carbon were the major product. Only in the case of **6** were nitriles of reduced carbon number observed and even here the yields were very low (<0.5%). The nitriles are most reasonably accounted for through dehydration of an amide, similar to the α-amino acids.

Once again, providing an unequivocal pathway for amide formation is difficult. The major products from β-alanine pyrolysis are shown in eq 13. Taking the amide and nitrile yields to represent original amide production, we find amide formation approximately 75% of the acid produced, which is significantly larger than that observed in the α-amino acids and certainly represents a major process. In all the β-amino acids studied, the combined yield of nitrile and amide was 60–80% of the observed acid yield.

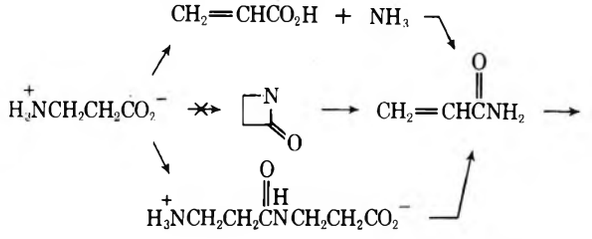
$$H_3\overset{+}{N}CH_2CH_2CO_2^- \longrightarrow \begin{array}{ll} CH_2{=}CHCO_2H & (20\%) \\ CH_2{=}CHCONH_2 & (3\%) \\ CH_2{=}CHCN & (12\%) \end{array} \quad (13)$$

Table II
Products Obtained from the Pyrolysis of β-Amino Acids

Yield[a]	β-Amino-*n*-butyric acid	β-Aminoisobutyric acid	β-Alanine
			
	6	**7**	**8**
A	NH_3	NH_3	H_2O
		H_2O	NH_3
			
B	CO_2		
	H_2O		
			
C		CO_2	CO_2
			
			
D	C_2H_4	C_2H_4	C_2H_4
		C_2H_6	C_2H_6
	CH_3CO_2H		
			
			
	C_2H_6 (t)		
			CH_3CN

[a] Yield ranges are the same as those in Table I.

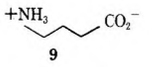
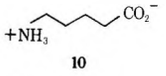
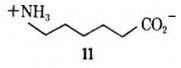
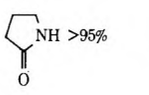
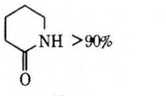
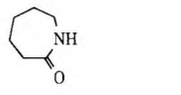
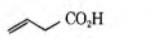
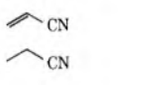
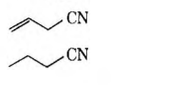
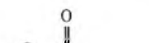
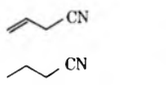
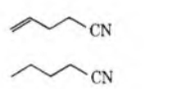
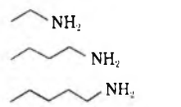
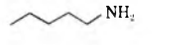
Three possible sources for amide production are shown in eq 14. The β-lactam intermediate was ruled out by labeling studies involving alanine-^{15}N. When a 5:1 mixture of alanine-^{15}N and β-alanine was pyrolyzed, both the acrylamide and acrylonitrile contained the ^{15}N label.



$$CH_2{=}CHCN \quad (14)$$

Of the remaining pathways, the bimolecular reaction between acrylic acid and ammonia is more acceptable. The presence of large yields of both acid and ammonia in the initial products indicates that the substrates necessary for bimolecular amide production are readily available. This is in contrast to the α-amino acids, where no acid was detected in the product mixture. Secondly, if the peptide were responsible for the amide formation, the significantly increased yields of amide and nitrile, by comparison with the α-amino acids, would indicate that peptide formation is greatly enhanced in the β-alanine system. That the yields of amide and nitrile were not sub-

Table III
Products Obtained from the Pyrolysis of ω-Amino-n-alkanoic Acids

Yield[a]	4-Amino-*n*-butyric acid	5-Amino-*n*-valeric acid	6-Amino-*n*-hexanoic acid[b]
			
	9	10	11
A			
		12	
	H_2O	H_2O	CO
			CO_2
			NH_3
			C_2H_4
			C_2H_6
			
B			
			
			
			
C			CH_3CN
			
			
	CO		
	CO_2		
	NH_3	CO	
		CO_2	
		NH_3	

[a] Yield ranges are the same as those in Table I. [b] No single product was predominant from **11**. Yields of all products are of the same order of magnitude.

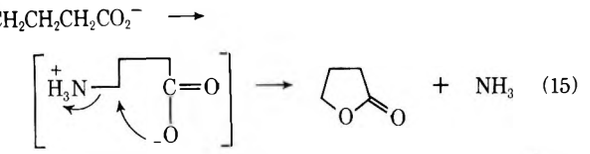
stantially diminished when alanine and β-alanine (1:1) were run together makes peptide formation even less likely as a significant pathway to amide formation.

These results indicate, therefore, that with minor exceptions β-amino acids decompose almost exclusively by deamination with the remaining products arising *via* secondary processes.

The formation of saturated products, chiefly propionic acid and propionamide, suggests that some hydrogen is available for reduction, although the predominance of unsaturation would indicate that it is minor.

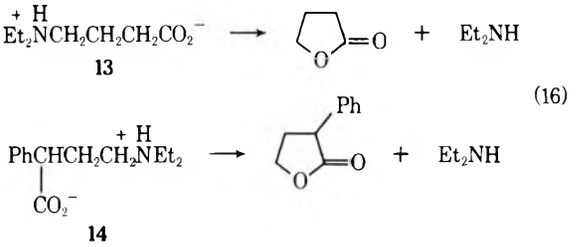
The results for the remaining members of the series, the γ-, δ-, and ε-amino acids, are listed in Table III. Both the 4-amino-*n*-butyric (**9**) and the 5-amino-*n*-valeric acid (**10**) yielded five- and six-membered cyclic lactams, respectively. For 6-amino-*n*-hexanoic acid (**11**), the corresponding seven-membered lactam was formed, although not as a major product.

The minor and secondary products for each compound differed and produced an interesting trend. The γ-amino acid **9** produced two products similar to those from β-alanine. Both 3-butenoic acid and the corresponding amide were formed, presumably *via* processes similar to those occurring for β-alanine. In addition, small yields (*ca.* 1%) of γ-butyrolactone were formed and most likely resulted from an intramolecular nucleophilic attack by oxygen. Clark[25] found a similar process occurring for a series of



(15)

γ-amino acids. When pyrolyzed at only 225°, for example, **13** produced diethylamine and γ-butyrolactone while **14** gave a 73% yield of the corresponding phenyl-substituted lactone.

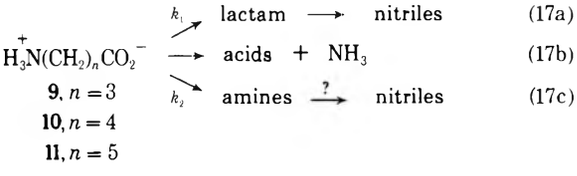


(16)

In contrast, the minor products from 5-amino-*n*-valeric acid (**10**) were one chain shortened carboxylic acid and a series of both saturated and unsaturated nitriles of varying chain length. Pyrolysis of 2-piperidone (**12**) under similar conditions produced small amounts of the corresponding nitrile series and, consequently, may be their source in a secondary process.

The ε-amino acid **11** (as mentioned previously) produced only small quantities of the seven-membered lactam, but a large series of nitriles, amines, and hydrocarbons, all of similar yield. Chain fragmentation seems to be more significant here than in the shorter chain homologs.

The origins of the products are not well understood for this series (**9**–**11**), but may be discussed in terms of eq 17.



(17a)
(17b)
(17c)

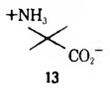
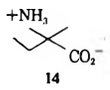
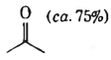
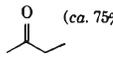
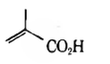
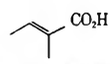
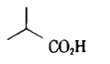
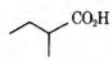
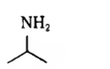
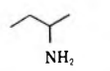
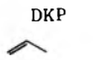
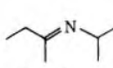
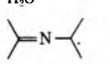
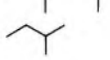
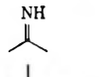
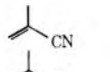
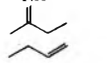
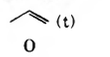
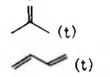
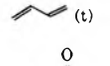
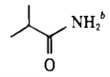
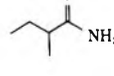
The absence of acids in **11** and the minor occurrence of a single carboxylic acid in **10** indicate that the deamination pathway so prominent for β-alanine becomes less important as the amino group is moved farther from the acid group.

It is interesting that no unsaturated amines were found in **11**, while the nitrile series was formed with both saturated and unsaturated members of each carbon number. Further, the unsaturated nitriles from both **10** and **11** were exclusively unsaturated at the terminal end. In addition, compound **10** gave no detectable amines, suggesting therefore that the amines and nitriles found in **11** arise from different sources.

If, as in eq 17c, nitriles are considered to result from amine decomposition, three difficulties arise. First, the presence of nitriles in **10** yet the absence of amines must be explained. Second, in the dehydrogenation of an amine to a nitrile an intermediate aldimine results (eq 6). These aldimines would be expected to react with the free amines available (similar to the α-amino acids) to give *N*-alkylaldimines. None were observed. Third, in **11** the nitriles all contain unsaturated members, while the amines were fully saturated.

These data suggest, therefore, that the nitriles may arise by secondary decomposition of the lactam (eq 17a), this process occurring to a greater extent for **11** than for **10**.

Table IV
Products Obtained from the Pyrolysis of α-Amino Acids Containing α-Methyl Substituents

Yield[a]	2-Methylalanine	Isovaline
	 13	 14
A	 (*ca.* 75%)	 (*ca.* 75%)
	CO	CO
	NH_3	NH_3
B		
		
		
	DKP	
C		
	CO_2	
	H_2O	
		
	DKM	CO_2
	NH	H_2O
		DKP
		DKM
		NH
		
		 (t)
		 (t)
		 (t)
D		

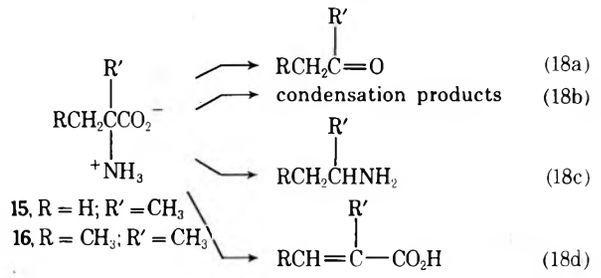
[a] Yield ranges are the same as those in Table I. [b] Compounds not positively identified.

The formation of amines in **11** probably results from a direct decomposition of the parent compound.

With the increased chain length in **11**, the relative rates k_1 and k_2 (eq 17) are more nearly equal; consequently products from both processes occur. In **10**, however, the facile formation of the six-membered lactam makes $k_1 > k_2$ to an extent that products from eq 17c are not observed.

α-Methyl-α-amino Acids. To determine what effects might be exerted by alkyl substitution at the α-carbon position, two amino acids containing α-methyl groups were pyrolyzed. The results for the thermolysis of α-methylalanine (**15**) and isovaline (**16**) are listed in Table IV.

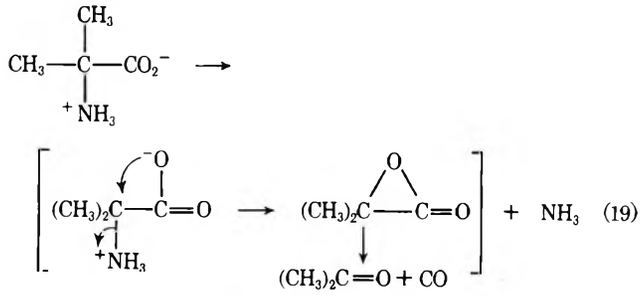
The additional methyl substitution at the C-2 position substantially alters the primary decomposition of α-amino acids. The major organic product (*ca.* 75%) is a ketone of



one carbon less than the parent amino acid. Other primary but minor pathways include decarboxylation, deamination, and condensation reactions.

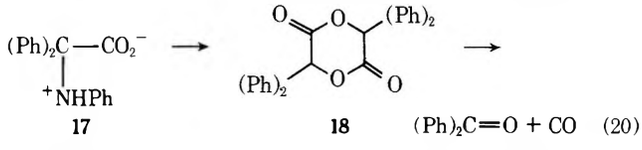
The formation of acetone from **15** and 2-butanone from **16**, while surprising from the standpoint of yield, can be viewed as analogous to the aldehyde formation from simple α-amino acids (see eq 4).

The formation of these ketones is best described by an intramolecular reaction involving an intermediate α-lactone (eq 19). Other routes, while conceptually reasonable,

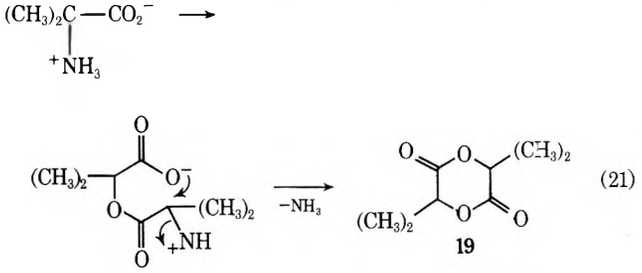


are less appealing. Ritchie[26] observed ketones and CO during the pyrolysis of both acrylic and crotonic acids. During the pyrolysis of the β-amino acids, where acids of the type Ritchie, *et al.*, studied were major products, we found ketones in only trace quantities. This rules out acids as a significant source for ketone formation.

From the thermal decomposition (in solution at 250°) of the diphenyl amino acid **17**, McGee and Ritchie[27] found benzophenone to be a major product and suggested lactide **18** as an intermediate (eq 20). Subsequently, Golomb and

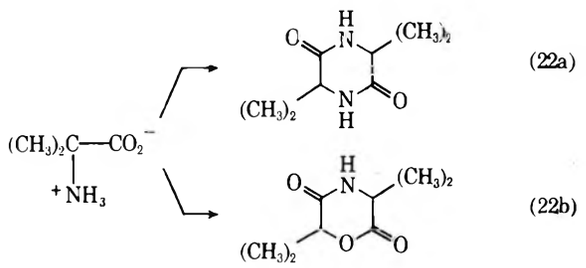


Ritchie[28] prepared lactide **19** from the corresponding α-hydroxy acid and pyrolyzed it. While acetone and CO were the major products, only 69% decomposition occurred. Lactide **19** is a possible intermediate from the pyrolysis of α-methylalanine, arising by the following sequence (eq 21). The high yields of ketone in our system,



however, suggest that the lactide is not a major contributor, since Golomb and Ritchie[28] found decomposition to be incomplete, and we observed no trace of the lactide. While some lactide formation remains a possibility, the intramolecular process (eq 19) appears more reasonable to account for the majority of the ketone. Confirmation of this point, however, could be obtained only through the use of a doubly labeled substrate.

Two bimolecular condensation products are formed from each amino acid. These represent additional primary processes, although the total yields of both remain low (*ca.* 5%). In addition to the formation of diketopiperazines (eq 22a), diketomorpholines (DKM) are formed (eq 22b). Both could arise *via* a common intermediate dipeptide; however, the amino acid might also first undergo a bimolecular displacement reaction to yield an ester followed



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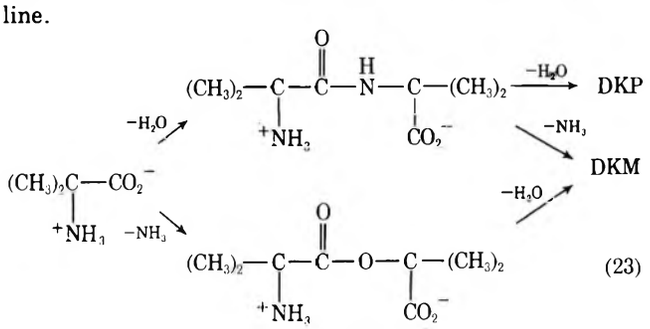
by a subsequent dehydration to yield the diketomorpholine.



From 2-methylalanine the DKP to DKM ratio was approximately 4, whereas from isovaline the yields of the corresponding products were nearly equal.

The formation of diketomorpholines from amino acids is not a new observation, as McGee and Ritchie[27] found them in the low-temperature pyrolysate of a number of amino acids containing α-alkyl substituents.

The formation of both ketones and diketomorpholines suggests that a quasi-heterolytic process is occurring. This concept has been growing for many years and has been reviewed by Maccoll and Thomas.[29] For example, in the gas-phase pyrolysis of a series of alkyl chlorides,[30] the trend in reactivity follows that of the same compounds undergoing solvolysis in polar solvents. Ingold,[31] in fact, has formulated a mechanism for these reactions involving halogen heterolysis with no hydrogen loosening as the rate-controlling step. Consequently, the formation of aldehydes from the protein amino acids[16] and their homologs (Table I) indicates the occurrence of a pathway that becomes prominent through alkyl substitution at the reaction center.

The formation of ketones can therefore be described by a transition state where partial heterolytic bond cleavage of the ammonia–α-carbon bond has occurred, thereby placing a partial positive charge on the α-carbon atom. This charge and, consequently, the transition state are stabilized by the inductive effect of the alkyl substituent and the concomitant formation of the carbon–oxygen bond. When this bond is intramolecular, the initial stage of reaction is formally analogous to an S_Ni process occurring in solution and ketones result from subsequent decomposition of the α-lactone. When the bond is intermolecular, the diketomorpholines result. The preponderance of the ketone is not unreasonable, since, even though the formation of an α-lactone is energetically less favorable than the formation of the morpholine derivative, entropy considerations for the two processes greatly favor the intramolecular formation of a three-membered ring.

A decomposition pathway similar to that for the simple α-amino acids is seen in the formation of amines from both 2-methylalanine and isovaline. In addition, *N*-alkylaldimines are present in both systems and represent products whose formation have been discussed in detail previously.

Two pathways, however, are probably responsible for the presence of *N*-alkylaldimines from these compounds. Amines can undergo condensation reactions with either the ketones or the simple ketimines. The large yields of ketones make condensation reactions with amines quite likely. The low yields of aldehydes and CO in the pyrolysates of the simple α-amino acids compelled us to suggest the involvement of aldimines in the formation of the *N*-alkylaldimines from those systems. In the present system, however, ketones are abundant. In addition, acetone ketimine and butanone ketimine were found in small yields from the pyrolysis of 2-methylalanine and isovaline, respectively. The formation of these compounds lends further support to the suggestion that aldimines are the important intermediates in the α-amino acid pyrolysis.

In the present system, however, no further dehydrogenation can occur as in the formation of nitriles from aldimines. Consequently, any ketimine not undergoing a transalkylidination reaction remains as a reaction product.

The fourth primary mode of decomposition seems to reflect that of β-alanine. Carboxylic acids resulting from deamination are formed in yields equivalent to those of the aliphatic amines (*ca.* 2–5%). The simple α-amino acids, it will be recalled, do not undergo deamination reactions to produce acids. The addition of the α-methyl group apparently provides enough stability at the α carbon to allow deamination to be competitive.

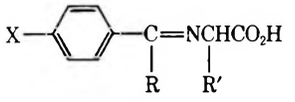
Although amides were not positively identified, nitriles of chain length equivalent to the parent amino acid were present, and amide involvement is assumed. Diketopiperazines, however, also remain a possible source for the nitriles. In addition, acids and nitriles were formed as both saturated and unsaturated isomers. In all cases, however, the unsaturated isomer exceeded the saturated counterpart by a factor of approximately 2.

A summary of the important reactions occurring during the pyrolysis of the α-alkyl-substituted α-amino acids is provided in Scheme II.

Comparison of Results

The most obvious dichotomy resulting from this study involves the differences in the major primary decomposition steps of the α-amino acids (*i.e.*, alanine) and the β-amino acids (*i.e.*, β-alanine). For the former, decarboxylation is the predominant process, while, for the latter, deamination appears to be the predominant reaction.

Brown[32] has reviewed data which show that, in general, decarboxylation of heterocyclic systems containing nitrogen is increased when the zwitterion is present. Furthermore, Baddar and Sherif[33] found that, for decarboxylation of amino acids in the presence of substituted aryl ketones, electron-withdrawing substituents in the aromatic ring increased the rate of decarboxylation which was suggested to occur from the intermediate imino acid **21**. Here, however, resonance interaction of the developing negative charge is possible with the aromatic ring. For simple α-amino acids, no resonance interaction between the nitrogen and the developing charge is possible; however, the ammonium group is at the α carbon and can aid decarboxylation by inductive charge neutralization. Inductive σ values for the $-NR_3^+$ species have been calculated to be approximately +0.9.[34] Experimentally, a value of +0.60 was found for σ_I of $-NH_3^+$.[35] In light of this relatively large inductive σ value, it is not unreasonable for decarboxylation to occur readily for the simple aliphatic amino acids.



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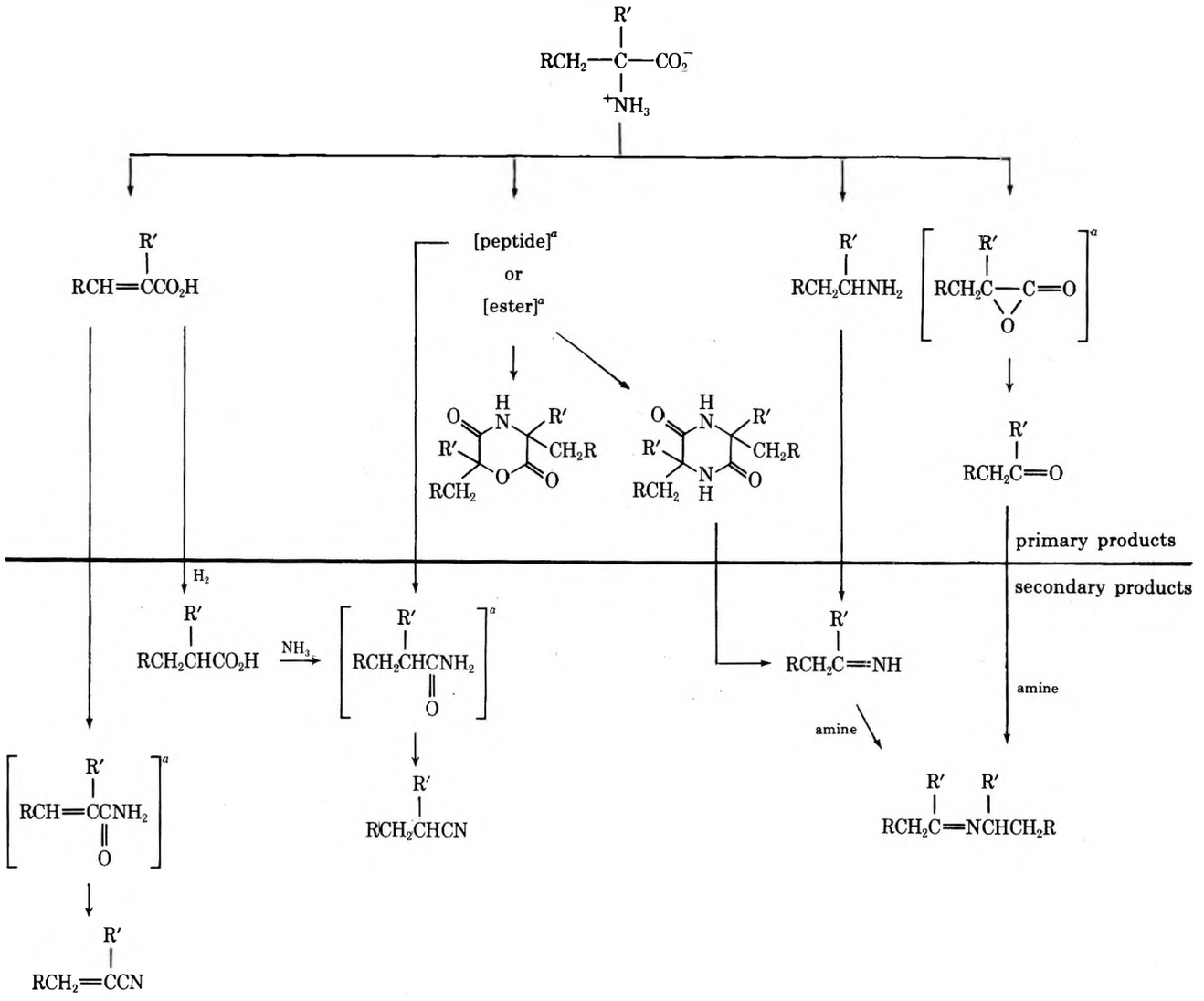
Scheme II

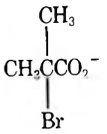


a Compounds in brackets were not found, but inferred from other information.

The β-amino acids, on the other hand, contain an additional methylene bridge between the reactive centers, thereby greatly reducing the rate enhancement provided the α-amino acids. The β-amino acids therefore do not decarboxylate. Deamination becomes dominant, perhaps partly owing to the product stability provided by the formation of the α,β-unsaturated acid. Furthermore, deamination most likely proceeds by an E1-like mechanism from the zwitterion. If ammonia were lost from the free acid–base molecule through a four-centered reaction, no charge would develop in the transition state and some deamination would be expected from the α-amino acid. The fact that significant deamination occurs for β- and not α-amino acids further strengthens the concept that the zwitterion is important.

The effect of the α-methyl group in 2-methylalanine is consistent with the foregoing discussion. In this case, both deamination and decarboxylation occur. The deamination must be aided by the inductive effect of the additional methyl group ($\sigma_I \sim 0.0$ to -0.3),[35] which would provide additional stabilization to the developing positive charge.

The major reaction, however, involves ketone formation by a similar process, albeit one where the carboxyl group is involved in an SNi-like reaction. The intermediate α-lactone then loses CO to form the ketone. There are analogous data in the solvolysis literature. The relative rate for the solvolysis of **22** and **23** (k_{22}/k_{23}) was found to be



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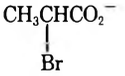

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$\sim$250.[36] For both cases carboxyl assistance was said to be operative. While both alanine and α-methylalanine apparently undergo this type of decomposition, other pathways compete.

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Registry No.—**1**, 2835-81-6; **2**, 760-78-1; **6**, 2835-82-7; **7**, 144-90-1; **8**, 107-95-9; **9**, 56-12-2; **10**, 660-88-8; **11**, 60-32-2; **13**, 62-57-7; **14**, 595-39-1; DL-alanine, 302-72-7.

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Cyclic Phenylboronates as Hydroxyl Protecting Groups in the Synthesis of Monoesters of Macrolide Aglycones

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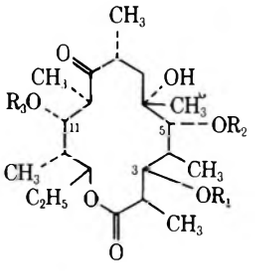
Benzeneboronic acid reacts readily with the cis-related 1,3-diols present in 14-membered macrolide aglycones. These cyclic phenylboronates were found to be useful protecting groups of the C-3 and C-5 hydroxyls of erythronolides, allowing the esterification of the C-11 hydroxyl. Removal of the phenylboronate from the erythronolide 11-esters was not possible under the usual hydrolytic conditions, so the protecting group was removed by treatment with dilute peroxide and hydrolysis of the presumed borate ester intermediate. Attempts to prepare 11-acetylerythromycin by microbial conversion of 11-acetylerythronolide B or its 6-deoxy analog were unsuccessful. The major product in both cases was 3-*O*-(α-L-mycarosyl)-11-acetylerythronolide B.

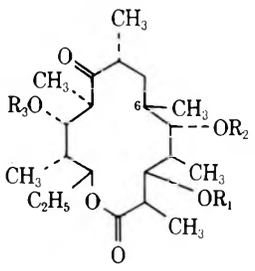
In our studies of the chemistry and conformation of erythromycin aglycones[1] we had need for monoacetyl derivatives of the three secondary hydroxyls in the erythronolide and 6-deoxyerythronolide molecules (**1** and **6**). Such compounds might also serve as potential substrates for microbial transformation in the study of blocked mutants of *S. erythreus*.[2] We were successful in obtaining monoacetylation of the hydroxyls at C-3 and C-5 as well as diacetylation at these positions using reaction conditions less strenuous than that necessary for triacetylation.[1a] Mixtures of these compounds could be separated conveniently by chromatography on Sephadex LH-20. The relative reactivity of the C-11 hydroxyl prevented selective acetylation at this position, however; so a cyclic phenylboronate ester was selected as a possible means of protecting the C-3 and C-5 hydroxyls during acetylation.

Cyclic phenylboronates have been used for protecting glycoside hydroxyls during acetylation[3] because of their facile formation from 1,2- and 1,3-diols[4] and their easy removal with water or polyalcohols.[3,4] Cyclic phenylboronate esters have also proven to be useful derivatives in the macrolide aglycone series[1c,2b] because of their selective and nearly quantitative reaction with the cis-related or 1,3-syn-periplanar diols present in these compounds. The preparation of erythronolide B 3,5-phenylboronate (**11**) occurred readily by refluxing an equimolar mixture of the macrolide and benzeneboronic acid in acetone for a short time. Other macrolide aglycones were similarly reactive. The aglycone of lankamycin,[5] 11-acetyllankolide, reacted with benzeneboronic acid to give the 3,5-phenylboronate **16** in good yield. This compound was prepared to study the conformational similarity among macrolide aglycones. The nmr analysis of phenylboronates has been discussed in detail in a separate communication.[6]

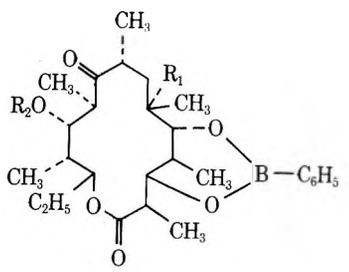
The formation of the 11-acetyl-3,5-phenylboronates of erythronolide B (**12**) and 6-deoxyerythronolide B (**15**) with acetic anhydride in pyridine proceeded smoothly using the fairly lengthy times necessary for acetylating the unreactive C-11 hydroxyl. Acetylation of this hydroxyl could also be accomplished with other acid anhydrides or acid chlorides. For instance, 11-benzoylerythronolide B 3,5-phenylboronate (**13**) could also be prepared in good yield. When attempts were made to hydrolyze the phenylboronate ester of these derivatives, however, using hydrolytic conditions normally successful for removing this group,[3,4] no reaction occurred. The presence of an ester function at C-11 apparently was responsible for preventing hydrolysis, since a 3,5-phenylboronate group on erythronolide B was easily removed under these conditions. It thus became necessary to find another mild method for removing phenylboronate protecting groups without destroying the macrolide ring.



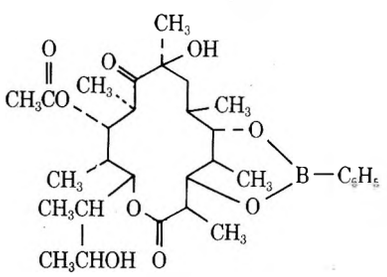
	R_1	R_2	R_3
1	H	H	H
2	CH_3CO	H	H
3	H	CH_3CO	H
4	H	H	CH_3CO
5	CH_3CO	CH_3CO	H



	R_1	R_2	R_3
6	H	H	H
7	CH_3CO	H	H
8	H	CH_3CO	H
9	H	H	CH_3CO
10	CH_3CO	CH_3CO	H



	R_1	R_2
11	OH	H
12	OH	CH_3CO
13	OH	C_6H_5CO
14	H	H
15	H	CH_3CO



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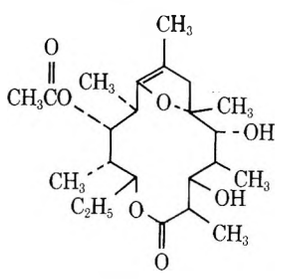

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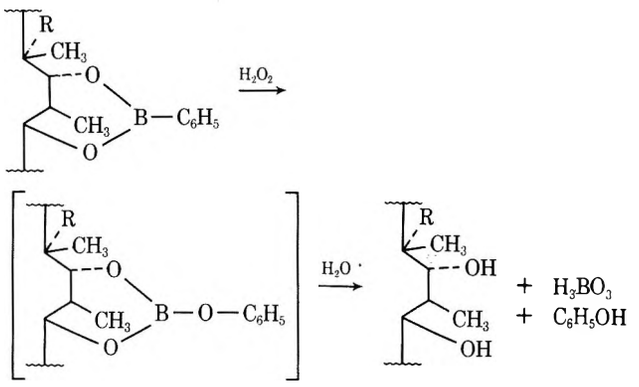
Earlier studies of the chemistry of benzeneboronic acid had shown that this compound reacts quite readily with dilute hydrogen peroxide, the products being boric acid and phenol resulting from insertion of an oxygen between boron and the aromatic carbon followed by hydrolysis.[7] It seemed reasonable to expect that phenylboronate esters would react in the same manner with peroxide. If this occurred with the erythronolide phenylboronates, the resulting borate esters might be more readily hydrolyzed than their precursors (Scheme I).

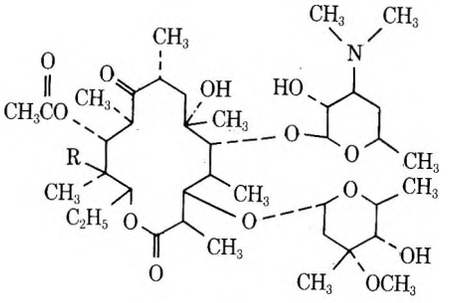
Treatment of 11-acetylerythronolide B 3,5-phenylboronate with hydrogen peroxide in aqueous ethanol did indeed produce detectable amounts of phenol. The product obtained from the reaction, however, was not the desired 11-acetylerythronolide B (4) but its 6,9-enol ether derivative 17. The formation of the enol ether apparently resulted from the presence of the boric acid formed in the reaction, since acidic conditions are known to catalyze the formation of enol ethers in the erythronolide and erythromycin series.[1a,8] To overcome this problem the reaction was conducted with suspended $NaHCO_3$ as a buffering agent. In this manner 11-acetylerythronolide B (4) was obtained. The presence of phenol sometimes prevented crystallization of the product; so the most convenient method for obtaining the 11-acetyl derivative was by chromatographic purification. A similar procedure was used to prepare 11-acetyl-6-deoxyerythronolide B (9).

Scheme I

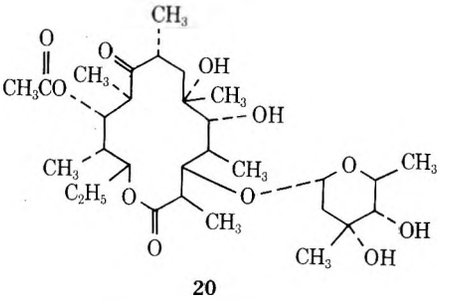


The nmr chemical shifts for the acetate esters of erythronolide B and 6-deoxyerythronolide B are shown in Table I. These compounds proved to be valuable for the conformational analysis of the erythronolide ring. Detailed examination of the nmr spectra and circular dichroism spectra of these compounds has been discussed by Egan in a separate communication.[6]

The 11-acetylerythronolides 4 and 9 were used as potential substrates for microbiological conversion to 11-acetylerythromycins A or B (18 and 19) by addition of these



	R
18	OH
19	H



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compounds to fermentations of early blocked mutants of *S. erythreus* capable of converting known erythromycin progenitors to the complete antibiotic. While there was evidence for conversion of each of these substrates to a mixture of basic antibiotics, the major product in both cases was the neutral glycoside 3-*O*-(α-L-mycarosyl)-11-

Table I
Chemical Shifts of Acetyl Esters of Erythronolide B and 6-Deoxyerythronolide B

Compd	Compd no.	δ (CDCl₃, ambient) CH₃CO	H-3	H-5	H-11
3-Acetylerythronolide B	**2**	2.09	5.07	3.54	3.84
5-Acetylerythronolide B	**3**	2.10	3.79	4.52	3.79
11-Acetylerythronolide B	**4**	2.02	3.96	4.05	4.89
3,5-Diacetylerythronolide B	**5**	2.02, 2.08	5.23	4.60	3.83
3,5,11-Triacetylerythronolide B[a]		2.02, 2.05, 2.07	5.40	4.70	5.13
3-Acetyl-6-deoxyerythronolide B	**7**	2.08	5.19	3.49	3.67
5-Acetyl-6-deoxyerythronolide B	**8**	2.08	3.73	4.68	3.37
11-Acetyl-6-deoxyerythronolide B	**9**	2.00	3.92	4.07	4.91
3,5-Diacetyl-6-deoxyerythronolide B	**10**	2.00, 2.10	5.19	4.71	3.58
3,5,11-Triacetyl-6-deoxyerythronolide B[b]		2.02, 2.03, 2.07	5.20	4.79	4.89
6-Deoxyerythronolide B	**6**		3.90	3.98	3.69

[a] Reference 1a. [b] Reference 2b.

acetylerythronolide B (**20**). The elemental analysis of this compound indicated an empirical formula of $C_{30}H_{52}O_{11}$, and the high-resolution mass spectrum contained peaks at *m/e* 570, corresponding to the loss of water from the parent, and at *m/e* 443 and 427 due to cleavage of mycarose (with and without the glycosidic oxygen)[9] from the parent molecule. The appearance of a fragment ion due to loss of H_2O at the highest mass is a common occurrence in the mass spectrum of neutral macrolides.[10] The uv spectrum of this compound contained a normal peak at 285 nm due to the carbonyl at C-9, and the nmr spectrum showed a close correspondence with those of other mycarosylerythronolides.[2a,c] Particularly important was the resonance at 5.05 ppm ($CDCl_3$) due to the anomeric proton of mycarose, and the coupling constants of this proton ($J_{1,2}$ = <1, 3.0) provided evidence for the α configuration.[2a,2c]

The inability to produce major amounts of 11-acetylerythromycins by a combination chemical–microbiological synthesis was a disappointment. Subsequently, a chemical route was found to produce these compounds in good yield.[11]

Experimental Section

Melting points were determined with a microscope hot stage. Ir spectra were obtained as $CHCl_3$ solutions by Mr. W. H. Washburn and associates on a Perkin-Elmer Model 521 instrument. Uv spectra were recorded for 95% EtOH solutions with a Cary Model II spectrophotometer. Nmr spectra were determined in $CDCl_3$ on a Varian HA-100 instrument. High-resolution mass spectra were obtained by Mrs. S. Mueller with an AEI MS-9 instrument. CD data (EtOH) were provided by Dr. L. A. Mitscher, The Ohio State University.

Acetylation of Erythronolide B (1). Erythronolide B (2.0 g) was dissolved in 30 ml of pyridine and 3.0 ml of acetic anhydride was added. The reaction mixture was allowed to stand at room temperature for 6.5 hr, then poured into ice–water and extracted with ethyl acetate. The extracts were washed with water, dried ($MgSO_4$), and evaporated. Residual pyridine was removed by azeotroping with benzene, giving 2.25 g of oil. Tlc examination of the oil showed starting material and three faster moving components. The oil was chromatographed on a column (2.5 × 35 cm) of silica gel prepared in $CHCl_3$. Elution with increasing concentrations of CH_3OH in $CHCl_3$ gave fractions examined by tlc. Those fractions containing a single component were pooled and evaporated to dryness. The first component eluted (233 mg) was **3,5-diacetylerythronolide B (5).** Crystallization from ethyl acetate–hexane gave colorless needles: mp 204–205°; $[\theta]_{292}$ −11,103; $[\theta]_{216}$ +3170.

Anal. Calcd for $C_{25}H_{42}O_9$: C, 61.71; H, 8.70. Found: C, 61.44; H, 8.71.

The second component eluted (546 mg) was **5-acetylerythronolide B (3).** The compound was obtained as a glass which resisted crystallization, $[\theta]_{288}$ −10,750, $[\theta]_{216}$ −1234.

Anal. Calcd for $C_{23}H_{40}O_8$: C, 62.13; H, 9.07. Found: C, 61.95; H, 9.34.

The third component eluted (479 mg) was **3-acetylerythronolide B (2).** Crystallization from ethyl acetate–hexane gave needles, mp 187–189°, $[\theta]_{290}$ −11,626.

Anal. Calcd for $C_{23}H_{40}O_8$: C, 62.13; H, 9.07. Found: C, 61.98; H, 9.13.

Acetylation of 6-Deoxyerythronolide B (6). 6-Deoxyerythronolide B (1.0 g) was acetylated in 15 ml of pyridine with 3.0 ml of acetic anhydride for 6 hr at ice-bath temperature. Work-up as above gave 977 mg of oily residue. Tlc examination showed the presence of starting material and three faster moving components. The mixture of three products was separated from starting material by chromatography on silica gel prepared in $CHCl_3$. Elution with 0.3% CH_3OH in $CHCl_3$ gave 469 mg of glassy residue. The glassy residue was fractionated by passage through a column (2.0 × 90 cm) of Sephadex LH-20 prepared in $CHCl_3$. Elution with $CHCl_3$ first gave fractions containing **3,5-diacetyl-6-deoxyerythronolide B (10).** Crystallization from ethyl acetate–hexane gave 172 mg: mp 130–131°; $[\theta]_{291}$ −16,260; $[\theta]_{230}$ −1305.

Anal. Calcd for $C_{25}H_{42}O_8$: C, 63.81; H, 9.00. Found: C, 64.08; H, 9.23.

The second component eluted was **5-acetyl-6-deoxyerythronolide B (8).** Crystallization as above gave 124 mg: mp 142–143°; $[\theta]_{289}$ −16,371; $[\theta]_{212}$ −5300.

Anal. Calcd for $C_{23}H_{40}O_7$: C, 64.46; H, 9.41. Found: C, 64.22; H, 9.34.

The third component eluted was **3-acetyl-6-deoxyerythronolide B (7).** Crystallization gave 102 mg: mp 160–162°; $[\theta]_{289}$ −17,128; $[\theta]_{220}$ −2320.

Anal. Calcd for $C_{23}H_{40}O_7$: C, 64.46; H, 9.41. Found: C, 64.51; H, 9.19.

Erythronolide B 3,5-Phenylboronate (11). A solution of 10.0 g (25 mmol) of erythronolide B (1) and 3.0 g (25 mmol) of benzeneboronic acid in 500 ml of anhydrous acetone was refluxed for 3–5 hr. The solution was then concentrated to a volume of about 75 ml and cooled to room temperature, yielding 8.4 g of crystalline product, mp 160–165°. Further concentration gave an additional 3.2 g. The total yield was 86% as the acetone solvate. The acetone could be removed by drying under vacuum at 140°. The ir spectrum contained a band at 1310 cm^{-1} characteristic for phenylboronates;[3a] $[\theta]_{292}$ −15,690.

Anal. Calcd for $C_{27}H_{41}O_7B$: C, 66.39; H, 8.46; O, 22.93; B, 2.22. Found: C, 66.50; H, 8.49; O, 23.14; B, 2.03.

The phenylboronate group of 11 could be removed easily by refluxing in a 1:1 acetone–water solution containing mannitol and sodium bicarbonate.[4a]

11-Acetylerythronolide B 3,5-Phenylboronate (12). A solution of 3.0 g of 11 (as the solvate) and 3.0 ml of acetic anhydride in 30 ml of anhydrous pyridine was allowed to stand at room temperature under a drying tube for 2 days. The solution was then poured into ice water and the precipitate was collected, washed with water, and dried, giving 2.3 g, mp 142–147°. A recrystallization from ethanol–water gave 1.9 g (65%): mp 150–153°; ir 1315 cm^{-1} (B–O); nmr δ 2.03 (CH_3CO); $[\theta]_{292}$ −33,290.

Anal. Calcd for $C_{29}H_{43}O_8B$: C, 65.66; H, 8.17; B, 2.04. Found: C, 65.48; H, 8.38; B, 1.78.

11-Acetyl-6-deoxyerythronolide B 3,5-Phenylboronate (15). The procedure above was used to prepare **15** from 5.0 g of 6-deoxyerythronolide B 3,5-phenylboronate[2b] (**14**), giving 4.0 g (74%) of crystalline product: mp 133–134°; ir 1315 cm^{-1} (B–O); nmr δ 2.00 (CH_3CO); $[\theta]_{294}$ −24,060.

Anal. Calcd for $C_{29}H_{43}O_7B$: C, 67.71; H, 8.42; B, 2.10. Found: C, 67.78; H, 8.49; B, 2.30.

11-Benzoylerythronolide B 3,5-Phenylboronate (13). A solution of 2.0 g (4 mmol) of **11** in 20 ml of anhydrous pyridine was cooled in ice while 1.15 ml (10 mmol) of benzoyl chloride was added. The solution was kept at 0° for 1 hr, then at room temperature for 24 hr, after which it was poured into ice water. The gummy solid obtained was allowed to stand in the aqueous solution overnight until it became crystalline. The solid was filtered, washed with water, and suspended in 5% $NaHCO_3$ solution for a few hours, then filtered, washed with water, and dried, giving 2.5 g of product. A recrystallization from 95% ethanol gave 1.6 g (74%), mp 191–193, ir 1315 cm^{-1} (B–O).

Anal. Calcd for $C_{34}H_{45}O_8B$: C, 68.92; H, 7.65; B, 1.83. Found: C, 68.81; H, 7.71; B, 2.08.

11-Acetyllankolide 3,5-Phenylboronate (16). A solution of 50 mg of 11-acetyllankolide[5a] and 12 mg of benzeneboronic acid in benzene was refluxed for 2 hr. The benzene was removed by distillation and the oil obtained was crystallized from $CHCl_3$–hexane, giving 27 mg, mp 150–155°.

Anal. Calcd for $C_{31}H_{47}O_9B$: C, 64.81; H, 8.25. Found: C, 64.61; H, 8.30.

11-Acetylerythronolide B (4). A solution of **12** (6.7 g) in 200 ml of 95% ethanol was stirred with suspended $NaHCO_3$ while 4.5 ml of 30% H_2O_2 was added. Stirring was continued for 23 hr and then a small amount of platinum oxide was added and the suspension was stirred for 7 hr more. The solid was filtered and 100 ml of water was added to the filtrate. The clear solution was reduced in volume *in vacuo* until a solid began to precipitate. The product which crystallized from the solution was filtered, giving 4.4 g: mp 163–165° (79%); uv λ_{max} 285 nm (ϵ 46); $[\theta]_{292}$ −17,875; $[\theta]_{218}$ −3200.

Anal. Calcd for $C_{23}H_{40}O_8$: C, 62.13; H, 9.07; O, 28.80. Found: C, 62.29; H, 8.95; O, 28.84.

The presence of phenol in the reaction solution sometimes prevented crystallization of the product. In this case the aqueous solution was extracted with ether and the oil obtained from the evaporated extract was chromatographed on Sephadex LH-20 prepared in CH_3OH. The product was crystallized from EtOH–H_2O.

When the reaction was conducted under the same conditions but without adding bicarbonate to control the pH, the product obtained was **8,9-anhydro-11-acetylerythronolide B 6,9-hemiacetal (17)**: mp 215–218°; nmr δ 2.06 (CH_3CO), 1.56 ($CH_3C{=}C$); uv no λ_{max} at 260–350 nm.

Anal. Calcd for $C_{23}H_{38}O_7$: C, 64.76; H, 8.98; O, 26.26. Found: C, 64.89; H, 8.96; O, 26.08.

11-Acetyl-6-deoxyerythronolide B (9). The procedure used to prepare **4** was followed. From 5.2 g of **15** was obtained 3.3 g of **9**: mp 155–157° (76%); $[\theta]_{290}$ −17,400; $[\theta]_{222}$ −3815.

Anal. Calcd for $C_{23}H_{40}O_7$: C, 64.46; H, 9.41; O, 26.13. Found: C, 64.71; H, 9.71; O, 26.14.

Fermentation of 11-Acetyl-6-deoxyerythronolide B (9) by a Blocked Mutant of *Streptomyces erythreus* (Abbott 2NU153). *Streptomyces erythreus* (Abbott 2NU153) was grown in complex fermentation medium as previously described.[2] Finely divided **9** (900 mg) was evenly distributed among 36 500-ml Erlenmeyer flasks each containing 50 ml of a 24-hr fermentation culture. Incubation was continued for 144 hr, then the flask contents were pooled and clarified as described previously. The clarified fermentation broth at pH 7.2 was extracted with one-half volume of ethyl acetate. The ethyl acetate extract was partitioned two times with one-half volumes of 0.1 *M* phosphate buffer at pH 4.5, washed with water, and dried (Na_2SO_4). Removal of the ethyl acetate *in vacuo* left 1.23 g of yellow oil. The oil was chromatographed on a column of silica gel (3.0 × 35 cm) prepared in chloroform. Elution with increasing concentrations of methanol in chloroform gave fractions containing only a material with R_f 0.35–0.39. These fractions were combined and the solvent was removed, leaving 598 mg of light yellow oil. The oil was dissolved in methanol and treated with Darco G60. Crystallization from ethyl acetate–hexane gave 310 mg of 3-*O*-(α-L-mycarosyl)-11-acetylerythronolide B (**20**) as colorless needles. An analytical sample had mp 212–214°; ir 3605, 3500, 1733, 1705 cm^{-1}; uv λ_{max} 285 nm (ϵ 41.5); $[\theta]_{290}$ −12,950; $[\theta]_{218}$ −2340.

Anal. Calcd for $C_{30}H_{52}O_{11}$: C, 61.20; H, 8.90. Found: C, 61.06; H, 8.98.

Fermentation of 11-Acetylerythronolide B (4) by a Blocked Mutant of *Streptomyces erythreus* (Abbott 2NU153). 11-Acetylerythronolide B (1.2 g) was incubated with *S. erythreus* (Abbott 2NU153) as described above. Ethyl acetate extraction of the clarified broth gave 1.52 g of yellow oil. Chromatography of the neutral fraction gave 862 mg of light yellow oil which was treated with Darco G60 in methanol. Crystallization from ethyl acetate–hexane gave 521 mg of 3-*O*-(α-L-mycarosyl)-11-acetylerythronolide B (**20**), mp 208–210°. The identity of this compound with that from the previous fermentation was confirmed by all physical and spectroscopic data.

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Registry No.—**1**, 3225-82-9; **2**, 50740-66-4; **3**, 50740-74-4; **4**, 32908-56-8; **5**, 50740-67-5; **6**, 15797-36-1; **7**, 50740-68-6; **8**, 50740-69-7; **9**, 50740-70-0; **10**, 50740-71-1; **11**, 50740-72-2; **12**, 50897-98-8; **13**, 51021-69-3; **14**, 50740-73-3; **15**, 50740-75-5; **16**, 51021-70-6; **17**, 51021-71-7; **20**, 51021-72-8; 11-acetyllankolide, 51021-73-9.

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N-Cyano-N,N,N-trialkylammonium Salts. Synthesis and Reactions

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Stable N-cyano-N,N,N-trialkylammonium fluoroborates have been prepared and their reactivity examined. With nucleophiles there are at least two types of reactions—the alkylation reaction observed by von Braun and the cyanation reaction observed for the first time on stable N-cyanoammonium salts. The alkylation reaction proceeds with arylamines such as N-methylaniline and some other weak nucleophiles such as DMF. With strong nucleophiles such as isobutylamine, benzenethiol, and triphenylphosphine the reaction proceeds by cyanation, giving a variety of NuCN derivatives which react further in different ways.

N-Cyanoammonium bromides have been postulated as reactive intermediates in the von Braun reaction of tertiary amines and cyanogen bromide.[2] The reaction, discovered by von Braun[2] and independently by Scholl and Noerr,[3] has been extensively studied as a method of degrading tertiary amines to secondary cyanamides.[4,5] In his pioneering work on the cyanogen bromide reaction, von Braun[2] proposed that the nitrogen atom of a tertiary amine attacks cyanogen bromide to form bromide ion and N-cyano-N,N,N-trialkylammonium ion. The cation of the intermediate is subsequently attacked by bromide ion to form a dialkylcyanamide and an alkyl bromide.

$$R_3N + CNBr \longrightarrow \left[R_3\overset{+}{N}-CN\ Br^-\right] \longrightarrow R_2N-CN + RBr$$

Concurrent with our report of the preparation of N-cyano-N,N,N-trialkylammonium fluoroborates,[6] Fodor and Abidi reported the characterization of the 1:1 adducts of cyanogen bromide and tertiary amines stabilized as tosylates.[7] It was also reported that the N-cyano-N,N,N-trialkylammonium hexachloroantimonates were prepared using antimony pentachloride–cyanogen chloride complex as shown below.

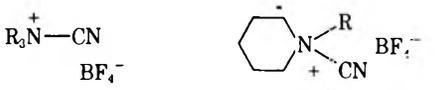
$$R_3N: + CNCl-SbCl_5 \longrightarrow R_3\overset{+}{N}-C\equiv N\ SbCl_6^-$$

Fodor and Abidi subsequently reported an nmr spectroscopic kinetic study of the reaction of excess cyanogen bromide and N-methyldecahydroquinoline.[7] The kinetic data were explained by the fast formation of the intermediate N-cyanoammonium ion followed by its rate-determining decomposition to the cyanamide and methyl bromide.

The data available led us to believe that the primary reason for the instability of this class of compounds is the nucleophilic attack by the anion to regenerate the original reactants or to cleave an alkyl group. To stabilize the unstable cations, halide ion was replaced by other, less nucleophilic, anions such as fluoroborate anion.[8] To provide a source of fluoroborate under anhydrous conditions, a forcing anion exchange reaction was devised whereby the undesired anions were removed by alkylation with triethyloxonium fluoroborate.[9] Using an equivalent amount of triethyloxonium fluoroborate, the fluoroborate salts were obtained in pure forms, and were further purifiable by recrystallization. Some of the compounds prepared by this

$$R_3N: + CNBr \xrightarrow[-78^\circ]{} R_3\overset{+}{N}-CN\ Br^- \xrightarrow[-(CH_3CH_2)_2O]{(CH_3CH_2)_3O^+BF_4^-,\ -CH_3CH_2Br} R_3\overset{+}{N}-CN\ BF_4^-$$

method have been previously reported in preliminary form.[6] In all cases the compounds had structures 1 or 2,



1 R = Et, Bu, Hex

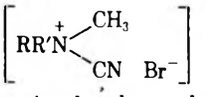
2 R = Me, Et, Pr, Bu

showed sharp melting points, and were readily soluble in polar organic solvents. The compounds showed weak absorptions at 2260–2270 cm^{-1} which were different from those of cyanogen bromide[10] and, based on the increased frequency and decreased intensity, were consistent with the presence of a N-cyanoammonium fluoroborate.[11-15] The nmr spectra differed from those of the corresponding tertiary or quaternary ammonium fluoroborates. The combined physical and spectral data suggested that the compounds were N-cyanoammonium fluoroborates.

The use of triethyloxonium fluoroborate was not universally applicable and met with failures when too reactive or too unreactive tertiary amines were used. Trimethylamine and N,N-dimethylcyclohexylamine reacted very rapidly to give only tetraalkylammonium salts as the sole solid prod-

$$RR'N-CH_3 + CNBr \longrightarrow$$

$$RR'N-CN + CH_3Br \xrightarrow{RR'N-CH_3} RR'\overset{+}{N}(CH_3)_2\ Br^-$$



ucts. This type of reaction has been observed with tertiary amines having N-methyl groups in the von Braun cyanogen bromide reaction.[16] Although the quaternization reaction has been assumed to occur by the alkylation of the formed methyl bromide, it may also proceed by the alkylation of the intermediate N-cyanoammonium bromide. In the other extreme, when the tertiary amine was not reactive enough at low temperature, neither an increase of the reaction temperature nor the addition of triethyloxonium fluoroborate to the partially formed adducts gave any desired products. This type of failure was observed with hindered tertiary amines such as diisopropylethylamine or dicyclohexylethylamine or with aromatic amines such as N,N-dimethylaniline. N-Benzylpiperidine and pyridine failed to give the expected products.

It is theoretically possible that a nucleophile can attack either on the alkyl groups (path a) or on the cyano group (path b). Since path a is similar to the originally suggest-

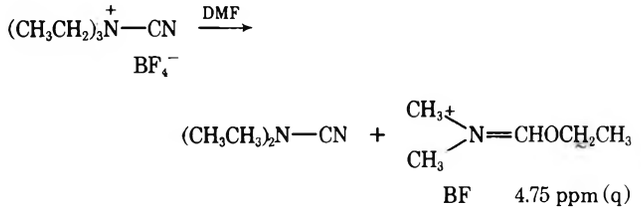
$$R_2N-CN + R-Nu: + HF/BF_3$$

$$R_3\overset{+}{N}-CN + HNu: \xrightarrow[\text{path b}]{\text{path a}}$$

$$R_3\overset{+}{N}H\ BF_4^- + :Nu-CN$$

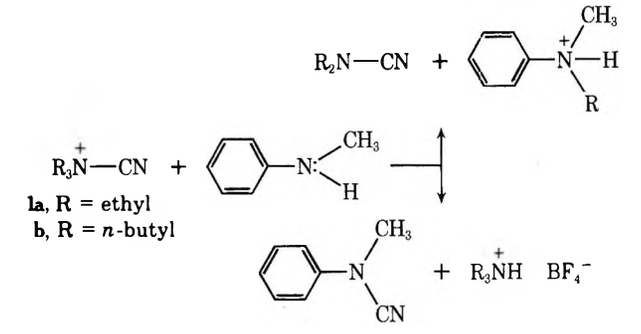
ed mechanism of the von Braun cyanogen bromide reaction, the *N*-cyanoammonium salts were expected to be good alkylating reagents. Path b might also be quite possible considering that the cyano group is bonded to a highly electron-withdrawing tertiary ammonium group.

To test the reactivity of *N*-cyanoammonium fluoroborates a small amount of a nucleophilic reagent, dimethylformamide or some other reagent, was added to an nmr sample tube containing a solvent and the *N*-cyanoammonium fluoroborate; this was placed in a spectrometer; spectral changes were observed during the first 1 or 2 hr. For dimethylformamide a quartet was observed at about δ 4.02 ppm which disappeared as the time proceeded, and a new quartet gradually appeared at about δ 4.75 ppm. The reaction was explained as being due to the attack of the nucleophile on the ethyl group of the *N*-cyanoammonium fluoroborate as shown below. The half-lives of some *N*-



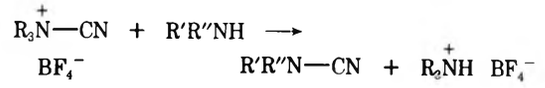
cyanoammonium fluoroborates obtained by this method were as follows: *N*-cyano-*N*,*N*,*N*-triethylammonium fluoroborate, 35 min with 8 equiv of D_2O in CH_3CN, 11 min with about 4 equiv of DMF in CH_3CN; *N*-cyano-*N*,*N*,*N*-tri-*n*-butylammonium fluoroborate, 12 min with about 4 equiv of DMF in CH_3CN, about 10 min in dimethyl sulfoxide-d_6.

The nmr spectra of the ether-soluble products of reaction of *N*-cyanoammonium salts with *N*-methylaniline showed principally the presence of dialkylcyanamides derived from the *N*-cyanoammonium fluoroborates. A very small peak at δ 3.24 ppm, assigned to the *N*-methyl group of *N*-methylcyananilide, was detected and calculated to be less than 5%. The reaction thus occurred by nucleophilic attack on the alkyl groups of the *N*-cyanoammonium fluoroborates, which is in agreement with the pattern observed in the von Braun cyanogen bromide reaction. Di-



ethylcyanamide (R = ethyl) and di-*n*-butylcyanamide (R = *n*-butyl) were obtained by distillation in 82 and 89% yield, respectively. The minor product, *N*-methylcyananilide, was obtained in low yields and identified by comparison with an authentic sample. The dialkylanilines were obtained in comparable yields to further substantiate the alkylation reaction.

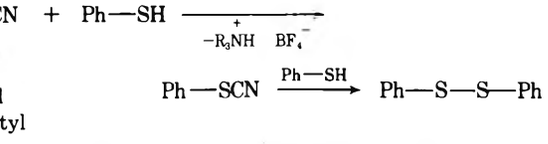
The exothermic reaction of the *N*-cyanoammonium fluoroborates with primary and secondary aliphatic amines proceeded to give exclusive cyano group cleavage. Thus the reaction of *N*-methylcyclohexylamine and isobutylamine gave in high yield with *N*-cyanoammonium salts the expected cyanamides, *N*-methylcyclohexylcyanamide and isobutylcyanamide, and the tertiary amine salts. It



1a, R = ethyl
b, R = *n*-butyl
2c, R_3N = *N*-*n*-propylpiperidine

has been reported that cyanogen bromide, the only readily available cyanating reagent, could not be efficiently used for the cyanation of secondary and primary amines because of the formation of the amine hydrobromide salts, which often react with the cyanamides formed to yield guanidines.[17] The use of *N*-cyanoammonium fluoroborates as cyanating reagents for amines seems highly promising.

When a 1:1 molar ratio of *N*-cyano-*N*,*N*,*N*-triethylammonium fluoroborate and thiophenol were allowed to react, a small amount of phenyl disulfide and 67% of phenyl thiocyanate were obtained. When the *N*-cyano-



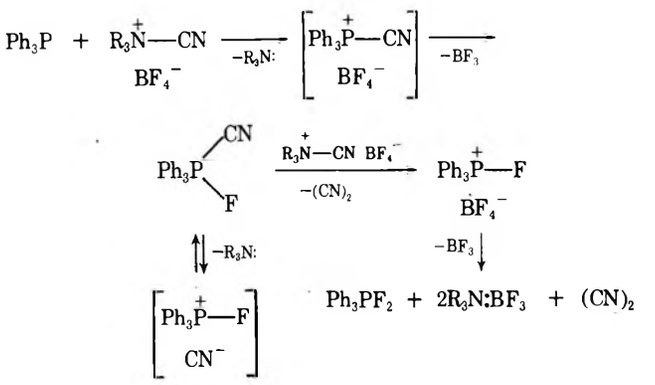
N,*N*,*N*-tri-*n*-butylammonium fluoroborate and thiophenol were allowed to react in 1:2 molar ratio the yield of phenyl disulfide was 83% and the rest (11%) was phenyl thiocyanate. The reaction of *N*-cyanoammonium fluoroborates with thiophenol can be explained by the nucleophilic attack of thiol group on the cyano group only. The formation of phenyl disulfide can be ascribed to further reaction of the thiocyanate with unreacted thiol. The formation of disulfide by this scheme has been proposed as a very favorable path,[18] and recently alkyl disulfides were reported to be prepared by the reaction of thiols and cyanogen bromide directly.[19] Among other known methods alkyl thiocyanates have been prepared by the use of cyanogen bromide on lead or alkali metal mercaptides,[20] on thiols with an equivalent of tertiary amines,[21] or on dialkyl sulfides.[22,23]

Sodium thiophenolate reacted with *N*-cyano-*N*,*N*,*N*-tri-*n*-butylammonium fluoroborate in 2:1 molar ratio to give 94% of relatively pure phenyl disulfide.

The reaction of *N*-cyanoammonium fluoroborate with triphenylphosphine in 1:1 molar ratio gave difluorotriphenylphosphorane in 51% yield. The yield was increased to about 93% when the *N*-cyanoammonium salt was used in 2:1 molar ratio. The reaction was exothermic at room temperature, and, since the product was not soluble in the reaction medium, it was obtained in good crystalline forms when the reaction mixture was allowed to cool to room temperature. The ^{19}F nmr spectrum of difluorotriphenylphosphorane agreed with that reported:[24] ^{19}F nmr (acetone, internal $CFCl_3$) δ 38.72 ppm (doublet), J_{P-F} = 665.2 Hz [^{19}F nmr ($CHCl_3$, internal $CFCl_3$) δ 40.4 ppm, J_{P-F} = 660 Hz]. The mass spectral fragmentation pattern could also be explained by the assigned structure.

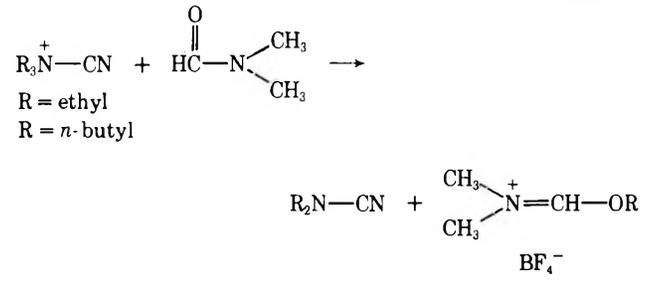
The reaction mechanism for the formation of difluorotriphenylphosphorane was not studied but a plausable pathway through the intermediacy of cyanotriphenylphosphonium fluoroborate,[25] fluorocyanotriphenylphosphorane, and fluorotriphenylphosphorium[26] cyanide can be devised. This pathway, as shown below, requires that dicyanogen and amine–BF_3 complex be major products in the reaction. We did not attempt to isolate dicyanogen but we did identify an amine–BF_3 complex as expected.

Difluorotriphenylphosphorane has been prepared in low yields (40–50%) by using sulfur tetrafluoride on triphenylphosphine or triphenylphosphine oxide in a pressurized



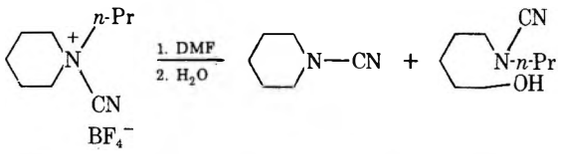
bottle at elevated temperature,[27a] or by fluorination of triphenylphosphine with tetrafluorohydrazine.[27b]

The reaction of *N*-cyanoammonium fluoroborates with dimethylformamide yielded only the alkyl group cleaved products. The dialkylcyanamides (R = ethyl and R = *n*-butyl) and dimethylammoniun fluoroborate obtained by



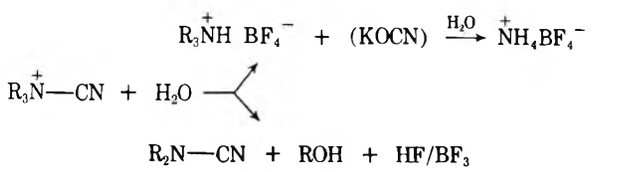
hydrolyses were isolated in about 80% yield. No cyanation products of DMF were detected.

When *N*-cyano-*N*-*n*-propylpiperidinium fluoroborate was used in the reaction the alkyl group cleavage occurred in two ways as shown below. About 30% of piperidine cy-



anamide and 52% of 5-hydroxypentyl-*n*-propylcyanamide were obtained. This ratio corresponds to about 37% of the former and 63% of the latter, assuming that the alkyl group cleavage products were isolated in 100% yield. In the von Braun cyanogen bromide reaction of *N*-*n*-propylpiperidine the ratio of the propyl group cleavage product to the ring-cleavage product was 40:60.[28]

With water the cyano group cleavage product is cyanic acid. The detection of the formed cyanic acid was not attempted, but its hydrolysis product was obtained in about 15 and 14% yields, respectively, with the *N*-cyanoammonium salts (R = Et, R = Bu). The tertiary amine salts (R = ethyl and R = *n*-butyl) were obtained in 84% yields, indicating that the cyano group cleavage occurred at least to the extent of 84%. The dialkylcyanamides (R = ethyl and R = *n*-butyl) were obtained in 12 and 9% yields, respectively, from the alkyl group cleavage of the *N*-cyanoammonium salts. Ethanol was tentatively identified (nmr evidence) in the distillate of the reaction solvent of *N*-cyano-*N,N,N*-triethylammonium fluoroborate.



In summary, the cyanation reaction (path B) was observed with most strong nucleophiles such as aliphatic amines, thiophenol, sodium thiophenolate, triphenylphosphine, and water. The potential use of *N*-cyanoammonium salts as cyanating reagents in the reaction with carboxylic acids has been reported.[29] Alkyl-group cleavage (path A) was observed with dimethylformamide and *N*-methylaniline. The reasons for the highly selective reactions, either path A or path B, are not at all clear and require further study. It seems that *N*-cyanoammonium fluoroborates might not be useful as alkylating agents, contrary to original expectations, but may serve as versatile cyanating agents in a variety of reactions.

Experimental Section[30]

Preparation of *N*-Cyano-*N,N,N*-triethylammonium Fluoroborate. To a solution of 15 g (0.014 mol) of cyanogen bromide in 50 ml of ether cooled at −78° were added in small portions 10.1 g (0.10 mol) of triethylamine in 50 ml of ether cooled at −78°. Colorless crystals began to form immediately. The solution was stirred for 2 hr at −78° and 18.9 g (0.01 mol) of triethyloxonium fluoroborate in 50 ml of dry methylene chloride cooled to −78° was added at once. After stirred for several minutes the reaction mixture was allowed to warm up until room temperature was reached. The supernatant solvent was decanted from the colorless crystals under a dry nitrogen atmosphere and washed with 2:1 ether–methylene chloride mixed solvent three times. Drying *in vacuo* gave 20–21 g (93–98%) of *N*-cyano-*N,N,N*-triethylammonium fluoroborate. The product was recrystallized from acetonitrile by adding ethyl acetate: mp 63–64°; ir (Nujol mull) 2270 (weak, CN) and 1050–1100 cm^{-1}; nmr (acetone-d_6) δ 1.67 (t, CH_3, 9 H) and 4.30 (q, CH_2N^+, 6 H).

Anal. Calcd for $C_7H_{15}N_2BF_4$ (214.02): C, 39.28; H, 7.06; N, 13.09. Found: C, 39.12; H, 7.01; N, 13.27.

***N*-Cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate** was prepared by the same procedure as that of *N*-cyano-*N,N,N*-triethylammonium fluoroborate with the extension of the time for the adduct formation to about 5 hr (97% yield) and was recrystallized from ethyl acetate by adding petroleum ether: mp 79–80°; ir (Nujol mull) 2265 (weak, CN) and 1050–1100 cm^{-1}; nmr (acetone-d_6) δ 1.01 (t, CH_3, 9 H), 1.27–1.77 (m, CH_2, 6 H), 1.83–2.40 (m, CH_2, 6 H), and 4.15–4.27 (m, CH_2N^+, 6 H); uv tail (acetonitrile) 240 nm (E 40).

Anal. Calcd for $C_{13}H_{27}N_2BF_4$ (298.19): C, 52.36; H, 9.13; N, 9.40. Found: C, 52.50; H, 9.17; N, 9.30.

***N*-Cyano-*N*-methylpiperidinium fluoroborate** was prepared by the same procedure as that of *N*-cyano-*N,N,N*-tri-*n*-butylammonium floroborate (86% yield): mp 83–85°; ir (Nujol mull) 2260 (weak, CN) and 1000–1100 cm^{-1}; nmr (acetonitrile) δ 3.81 (s, CH_3N^+, 3 H), and 3.70–4.76 (m, CH_2N^+, 4 H).

Anal. Calcd for $C_7H_{13}N_2BF_4$ (212.01); C, 39.65; H, 6.18; N, 13.22. Found: C, 39.80; H, 5.91; N, 13.50.

***N*-Cyano-*N*-ethylpiperidinium fluoroborate** was prepared by the same procedure as that of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate (91% yield): mp 108–110°; ir (Nujol mull) 2263 (weak, CN) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.63 (t, CH_2, 3 H), 1.33–2.60 (br, CH_2, 6 H), and 3.74–4.73 (br, CH_2N^+, 6 H).

Anal. Calcd for $C_8H_{15}N_2BF_4$ (226.02): C, 42.51; H, 6.69; N, 11.65. Found: C, 42.45; H, 6.76; N, 12.10.

***N*-Cyano-*N*-*n*-propylpiperidinium fluoroborate** was prepared by the same procedure as that of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate (86% yield): mp 83–85°; ir (Nujol mull) 2260 (weak, CN) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.11 (5, CH_3, 3 H), 1.40–2.50 (br, CH_2, 8 H), and 3.74–4.4 (m, CH_2N^+, 6 H).

Anal. Calcd for $C_9H_{17}N_2BF_4$ (240.05): C, 45.03; H, 7.14; N, 11.76. Found: C, 44.85; H, 7.40; N, 11.45.

***N*-Cyano-*N*-*n*-butylpiperidinium fluoroborate** was prepared by the same procedure as that of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate (85% yield): mp 68–69°; ir (Nujol mull) 2270 (weak, CN) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.00 (t, CH_3, 3 H), 1.10–2.50 (m, CH_2, 10 H), and 3.74–4.73 (br, CH_2N^+, 6 H).

Anal. Calcd for $C_{10}H_{19}N_2BF_4$ (253.29): C, 47.27; H, 7.54; N, 11.03. Found: C, 47.20; H, 7.40; N, 11.10.

Reaction of *N*-Methylaniline with *N*-Cyanoammonium Fluoroborates. 1. *N*-Cyano-*N,N,N*-triethylammonium Fluoroborate. To a solution of 2.14 g (0.01 mol) of *N*-cyano-*N,N,N*-triethylammonium fluoroborate in 10 ml of acetonitrile was added 1.07 g (0.01 mol) of *N*-methylaniline. The solution was allowed to

stand for 1 day. It was refluxed for 5 min, the solvent was removed by azeotropic distillation with isopropyl ether (bp 63.5–68°), and the residue was extracted with ether (4.50 ml) to separate the ammonium salt. The ether layer was washed with water (15 ml), dried (Na_2SO_4), and evaporated on a rotary evaporator at room temperature to give a pale yellow oil. The oil was dissolved in 200 ml of ether and washed with 30 ml of 1 *N* HCl solution to remove unreacted *N*-methylaniline. The ether layer was washed with a small amount of water, dried (Na_2SO_4), and distilled to give 0.89 g (88%) of diethylcyanamide. The distillation residue contained *N*-methylcyananilide as the major component which was further purified by column chromatography on deactivated silica gel using 10:1 cyclohexane–ethyl acetate as solvent. *N*-Methylcyananilide was identified by comparison of nmr spectra with those of an authentic sample prepared by the reaction of cyanogen bromide with *N,N*-dimethylaniline.[1] The nmr signal of an impurity appeared at δ 0.8–1.9 ppm in CCl_4. The ether-insoluble products were dissolved in 30 ml of water and treated with 1.50 g of sodium hydroxide under 200 ml of ether. The ether-extracted portion was distilled to give 1.10 g (82%) of *N*-methyl-*N*-ethylaniline. Diethylcyanamide was analyzed as follows: ir (thin film) 2213 cm^{-1} (strong, CN); nmr (CCl_3) δ 1.25 (t, CH_3, 6 H) and 3.20 (q, CH_2, 4 H); mass spectrum *m/e* (rel abundance) 98 (M^+, 34), 87 (6), 85 (42), 84 (6), 83 (6), 70 (11), 69 (12), 58 (25), 56 (6), 55 (100), 53 (6), 49 (9), 48 (10), 47 (22), 44 (9), 43 (98), 42 (20), 41 (6).

Anal. Calcd for $C_5H_{10}N_2$ (98.15): C, 61.18; H, 10.27; N, 28.55. Found: C, 61.30; H, 10.42; N, 28.02.

2. *N*-Cyano-*N,N,N*-tri-*n*-butylammonium Fluoroborate. Three grams (0.01 mol) of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate and 1.07 g (0.01 mol) of *N*-methylaniline were allowed to react in 10 ml of acetonitrile as in 1 to give 1.50 g of ether-soluble product mixture which was shown to contain di-*n*-butylcyanamide as the major component and a minor component which had a singlet at δ 3.24 ppm in CCl_4. The crude product was purified by column chromatography on silica gel using 10:1 cyclohexane–ethyl acetate as solvent to give 0.87 g (56.5%) of di-*n*-butylcyamide as the second fractions. The first fractions contained most of the *N*-methylcyananilide and weighed about 0.05 g. The ether-insoluble portion gave, after base treatment, 1.40 g (83%) of *N*-methyl-*N*-*n*-butylaniline, which was purified by column chromatography on silica gel using 10:1 cyclohexane–ethyl acetate as solvent. The nmr spectrum (CCl_4) had signals at δ 0.91 (t, CH_3, 3 H), 1.07–1.80 (br, CH_2, 4 H), 2.85 (s, CH_3, 3 H), 3.17 (t, CH_2, 2 H), 6.43–6.63 (m, phenyl ring, 3 H), 6.91–7.23 (m, phenyl ring, 2 H). Di-*n*-butylcyanamide was characterized as follows: bp 70–71° (0.5 mm); ir (thin film) 2205 cm^{-1} (strong, CN); nmr (CCl_4) δ 0.97 (t, CH_3, 6 H), 1.20–1.90 (m, CH_2, 8 H), 2.97 (t, CH_2, 4 H); mass spectrum *m/e* (rel abundance) 154 (M^+, 23), 139 (7), 125 (9), 112 (10), 111 (44), 98 (9), 97 (7), 86 (8), 83 (7), 70 (11), 69 (100), 57 (44), 55 (19), 43 (13), 42 (10), 41 (41), 39 (8).

Reaction of *N*-Methylcyclohexylamine with *N*-Cyanoammonium Fluoroborates. 1. *N*-Cyano-*N,N,N*-triethylammonium Fluoroborate. To a solution of 2.14 g (0.01 mol) of *N*-cyano-*N,N,N*-triethylammonium fluoroborate in 10 ml of acetonitrile was added 1.13 g (0.01 mol) of *N*-methylcyclohexylamine. The reaction mixture was allowed to stand at room temperature for several hours. The solvent was removed on a rotary evaporator at room temperature, and the residue was extracted with ether (3 × 100 ml), which was washed with 15 ml of water, dried (Na_2SO_4), and evaporated at room temperature to give 1.13 g (85%) of crude *N*-methylcyclohexylcyanamide. The nmr spectrum of this product in CCl_4 showed small peaks at around δ 3 ppm, but the impurity was not characterized. Distillation, bp 72° (0.32 mm), of this product gave an analytically pure sample which was characterized as follows: ir (thin film) 2200 cm^{-1} (strong, CN); nmr (CCl_4) δ 1.75 (br, CH_2, 10 H), 2.83 (br, CH, 1 H), 2.85 (s, CH_3, 3 H); mass spectrum *m/e* (rel abundance) 138 (M^+, 55), 137 (11), 123 (8), 121 (5), 111 (5), 110 (11), 109 (15), 105 (8), 98 (8), 97 (8), 96 (17), 95 (88), 84 (11), 83 (93), 82 (26), 81 (15), 77 (6), 71 (6), 70 (15), 69 (26), 68 (13), 76 (38), 58 (6), 57 (98), 56 (15), 55 (100), 54 (22), 53 (18), 44 (11), 43 (68), 41 (87), 40 (6), 39 (32).

Anal. Calcd for $C_8H_{14}N_2$ (138.21): C, 69.52; H, 10.21; N, 20.27. Found: C, 69.54; H, 10.00; N, 20.10.

2. *N*-Cyano-*N,N,N*-tri-*n*-butylammonium Fluoroborate. Three grams (0.01 mol) of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate and 1.13 g (0.01 mol) of *N*-methylcyclohexylamine were allowed to react as in 1 in 10 ml of acetonitrile to give 1.40 g (99%) of crude *N*-methylcyclohexylcyanamide, which was distilled in a Hickman still (80°) to give an analytically pure sample of *N*-methylcyclohexylcyanamide.

3. *N*-Cyano-*N*-*n*-propylpiperidinium Fluoroborate. Three grams (0.0125 mol) of *N*-cyano-*N*-propylpiperidinium fluoroborate and 1.50 g (0.13 mol) of *N*-methylcyclohexylamine were allowed to react as in 1 in 10 ml of acetonitrile to give 1.67 g (97%) of crude *N*-methylcyclohexylcyanamide, which gave, after distillation in a Hickman still (80°), a clear oil whose ir and nmr spectra were identical with those obtained previously.

Reaction of Isobutylamine with *N*-Cyanoammonium Fluoroborates. 1. *N*-Cyano-*N,N,N*-triethylammonium Fluoroborate. To a solution of 2.14 g (0.01 mol) of *N*-cyano-*N,N,N*-triethylammonium fluoroborate in 10 ml of acetonitrile was added 0.75 (0.01 mol) of isobutylamine. The solution was allowed to stand at room temperature for several hours, and the solvent was removed on a rotary evaporator at room temperature. The residue was extracted with ether (3 × 100 ml) and the ether layer was washed with 15 ml of water, dried (Na_2SO_4), and distilled to give 0.8 g (81.5%) of crude isobutylcyanamide as a residue whose nmr spectrum in CCl_4 did not show any peaks at around δ 3 ppm. Distillation at 73° (0.35 mm) gave a clear oil of isobutylcyanamide which was characterized as follows: ir (thin film) 3166 (strong, NH) and 2218 cm^{-1} (strong, CN); nmr ($CDCl_3$) δ 0.92 (d, CH_3, 6 H), 1.83 (m, CH, 1 H), 2.83 (d, CH_2, 2 H), and 4.68 (br, NH, 1 H). This cyanamide was trimerized on standing to a solid, which was characterized as follows: mp 86–90°; ir (thin film) 3346 (strong, NH), 1613, and 1492 cm^{-1}; mass spectrum *m/e* (rel abundance) 294 (M^+, 3), 279 (7), 237 (6), 223 (6), 182 (12), 181 (9), 167 (12), 140 (22), 127 (20), 126 (20), 99 (5), 98 (40), 97 (6), 84 (7), 83 (53), 70 (14), 69 (16), 58 (6), 57 (15), 56 (13), 55 (100), 53 (5), 44 (4), 43 (14), 42 (14), 41 (12).

Anal. Calcd for $C_{15}H_{30}N_6$ (294.45): C, 61.18; H, 10.27; N, 28.54. Found: C, 61.30; H, 10.10; N, 28.60.

2. *N*-Cyano-*N,N,N*-tri-*n*-butylammonium Fluoroborate. To a solution of 1.50 g (0.005 mol) of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate in 10 ml of acetonitrile, 0.38 (0.005 mol) of isobutylamine was added. The solution was allowed to react and worked up as in 1 to give 0.47 g (99%) of isobutylcyanamide, which was short-path distilled [82° (0.45 mm)] to give a clear oil whole ir and nmr spectra were identical with those obtained in 1.

Reaction of Thiophenol with *N*-Cyanoammonium Fluoroborates. 1. *N*-Cyano-*N,N,N*-triethylammonium Fluoroborate. To a solution of 0.88 g (0.041 mol) of *N*-cyano-*N,N,N*-triethylammonium fluoroborate in 10 ml of acetonitrile was added 0.49 g (0.0045 mol) of thiophenol. The mixture was allowed to stand at room temperature for several hours and refluxed briefly, followed by removal of the solvent by azeotropic distillation with isopropyl ether (bp 63.5–68°). The residue was extracted with ether (3 × 100 ml), and the ether portion was evaporated on a rotary evaporator without heating to give a pale yellow oil whose nmr spectrum showed only phenyl groups. The oil was dissolved in 300 ml of ether, and the ether solution was washed with 10 ml of 2 *N* NaOH solution and 15 ml of water, dried (Na_2SO_4), and distilled in a short-path distillation column to give 0.45 g (67%) of phenyl thiocyanate. The residue was a small amount of phenyl disulfide, which was identified by comparison with an authentic sample by ir and nmr spectroscopy. Phenyl thiocyanate was characterized as follows: ir (thin film) 2156 cm^{-1} (strong, SCN); nmr ($CDCl_3$) δ 7.37 (m, phenyl ring); mass spectrum showed molecular ion at *m/e* 135.

Anal. Calcd for C_7H_5NS (135.18): C, 62.19; H, 3.73; N, 10.36. Found: C, 62.15; H, 3.82; N, 10.48.

2. *N*-Cyano-*N,N,N*-tri-*n*-butylammonium Fluoroborate. A solution of 3.00 g (0.01 mol) of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate in 20 ml of acetonitrile and 2.30 (0.021 mol) of thiophenol were allowed to react and worked up as in 1 to give 2.0 g of ether-soluble product mixture. Distillation [130° (0.20 mm)] in a short-path distillation column gave 0.15 g (11%) of crude phenyl thiocyanate and 1.80 g (82.5%) of phenyl disulfide as residue. Phenyl disulfide was recrystalized from ethanol and characterized as follows: mp 59–59.5° (lit.[31] mp 61–62°); ir (Nujol mull) 1517, 1432, 1375, 1069, 1022, 896, 834, 737, and 685 cm^{-1}; nmr ($CDCl_3$) δ 7.25 (m, phenyl ring); mass spectrum showed molecular ion at *m/e* 218.

Anal. Calcd for $C_{12}H_{10}S_2$ (218.33): C, 66.01; H, 4.62. Found: C, 65.75; H, 4.77.

3. *N*-Cyano-*N*-*n*-propylpiperidinium Fluoroborate. A solution of 3.00 g (0.0125 mol) of *N*-cyano-*N*-*n*-propylpiperidinium fluoroborate in 20 ml of acetonitrile and 1.65 g (0.015 mol) of thiophenol were allowed to react and worked up as in 1 to give 1.25 g of crude phenyl thiocyanate, bp 116° (0.15 mm), and 0.61 g of phenyl disulfide. (The minimum yield of the formed thiocyanate was calculated to be 92%.)

Reaction of Sodium Thiophenolate with *N*-Cyanoammonium Fluoroborates. 1. *N*-Cyano-*N,N,N*-triethylammonium Fluoroborate. A solution of 1.58 g (0.0074 mol) of *N*-cyano-*N,N,N*-triethylammonium fluoroborate in 20 ml of acetonitrile was added to 1.78 g (0.0135 mol) of sodium thiophenolate (prepared from sodium and thiophenol in ethanol). The reaction mixture was allowed to stand at room temperature for several hours. The solvent was removed on a rotary evaporator and the residue was extracted with ether (3 × 100 ml). Distillation gave 1.32 g (89.5%) of phenyl disulfide as residue.

2. *N*-Cyano-*N,N,N*-tri-*n*-butylammonium Fluoroborate. A solution of 3.00 g (0.01 mol) in 10 ml of acetonitrile was added to 2.80 g (0.021 mol) of sodium thiophenolate. The solution was allowed to react and worked up as in 1 to give 2.09 g (95%) of phenyl disulfide, which gave, after recrystalization from ethanol, identical ir and nmr spectra with those obtained in the previous experiment.

Reaction of Triphenylphosphine with *N*-Cyanoammonium Fluoroborates. 1. *N*-Cyano-*N,N,N*-triethylammonium Fluoroborate. To a solution of 2.14 g (0.01 mol) of *N*-cyano-*N,N,N*-triethylammonium fluoroborate in 20 ml of acetonitrile, 1.31 g (0.005 mol) of triphenylphosphine was added. The reaction mixture was allowed to stand at room temperature for several hours. The precipitated colorless crystals were collected, washed with ether, and dried under vacuum to give 0.76 g (51%) of a compound eventually identified as difluorotriphenylphosphorane. The mother liquor was evaporated on a rotary evaporator at room temperature, and the residue was extracted with petroleum ether (2 × 100 ml) to give, by distillation of the solvent, 0.07 g of diethylcyanamide. The unextracted material could not be purified by continuous extraction with ether. It was treated with decolorizing carbon in 100 ml of ethyl acetate and the addition of ether precipitated 1.40 g of very unstable, colorless crystals which were dried under vacuum for several days. The crystals gave very similar ir and nmr spectra to those of the adduct of triethylamine and boron trifluoride formed in ether, but satisfactory elemental analysis could not be obtained owing to the instability. Difluorotriphenylphosphorane was characterized as follows: mp 147–149° (lit.[28] mp 158–162°); nmr (acetone-d_6) δ 7.50, 7.90, and 8.10 (m's in 2:1:1 ratio); ^{19}F nmr (acetone, internal $CFCl_3$) ϕ 38.72 (doublet, J_{P-F} = 665.2 Hz (lit.[24] ϕ 40.4, J_{P-F} = 660 Hz in $CHCl_3$); mass spectrum *m/e* (rel abundance) 300 (M^+, 0.4), 281 (3), 279 (3), 223 (21), 205 (11), 204 (100), 203 (22), 202 (4), 183 (5), 154 (17), 152 (5), 127 (23), 77 (24), 51 (12).

Anal. Calcd for $C_{18}H_{15}PF_2$ (300.275): C, 71.99; H, 5.04. Found: C, 72.10; H, 5.06.

2. *N*-Cyano-*N,N,N*-tri-*n*-butylammonium Fluoroborate. To a solution of 3.00 g (0.01 mol) of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate in 20 ml of acetonitrile was added 1.31 g (0.005 mol) of triphenylphosphine. The solution was allowed to react and worked up as in 1 to give 1.46 g (93%) of difluorotriphenylphosphorane.

Reaction of Water with *N*-Cyanoammonium Fluoroborates. 1. *N*-Cyano-*N,N,N*-triethylammonium Fluoroborate. To a solution of 2.14 g (0.01 mol) of *N*-cyano-*N,N,N*-triethylammonium fluoroborate in 20 ml of acetonitrile was added 0.20 ml of water. The reaction mixture was allowed to stand at room temperature for 3 days. It was refluxed briefly and the solvent was removed by distillation. The distillate showed a quartet at δ 3.47 ppm (in acetonitrile). The distillation residue was extracted with ether (3 × 100 ml) and the ether layer was evaporated on a rotary evaporator at room temperature to give 0.12 g (11%) of crude diethylcyanamide, which was distilled in a Hickman still as a clear oil whose nmr and ir spectra were identical with those obtained earlier. The ether-insoluble product mixture was dissolved in 100 ml of acetonitrile and filtered to give the undissolved colorless crystals of ammonium fluoroborate weighing 0.19 g (15%). The acetonitrile solution was evaporated to give crude triethylammonium fluoroborate weighing 1.50 g (84%), whose ir and nmr spectra were identical with those of an authentic sample. Elemental analysis of ammonium fluoroborate was as follows.

Anal. Calcd for NH_4BF_4 (129.07): H, 3.85; N, 13.40. Found: H, 4.04; N, 13.15.

2. *N*-Cyano-*N,N,N*-tri-*n*-butylammonium Fluoroborate. To a solution of 1.50 g (0.005 mol) of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate in 20 ml of acetonitrile, 0.20 ml of water was added and the solution was allowed to react and worked up in 1; 0.14 g (9.1%) of di-*n*-butylcyanamide, 0.09 g (14%) of ammonium fluoroborate, and 1.14 g (83.5%) of tri-*n*-butylammonium fluoroborate were obtained. Di-*n*-butylcyanamide was purified by column chromatography on silica gel using 1:1 hexane–ethyl acetate as solvent. The three products gave ir and nmr spectra identical with those of authentic samples obtained earlier.

Reaction of Dimethylformamide with *N*-Cyanoammonium Fluoroborates. 1. *N*-Cyano-*N,N,N*-triethylammonium Fluoroborate. To a solution of 2.14 g (0.01 mol) of *N*-cyano-*N,N,N*-triethylammonium fluoroborate in 20 ml of acetonitrile was added 0.75 g (0.01 mol) of dimethylformamide. The solution was allowed to stand for 2 days at room temperature and refluxed for 2 hr, followed by the addition of 0.20 ml (0.011 mol) of water. The solution was refluxed for an additional 2 hr and the solvent was removed by azeotropic distillation with isopropyl ether (bp 63.5–68°). The distillation residue was extracted with ether (3 × 100 ml), and the ether portion was washed with 15 ml of water, dried (Na_2SO_4), and evaporated on a rotary evaporator at room temperature to give 0.79 g (80.6%) of diethylcyanamide, which was short-path distilled to give a clear oil whose ir and nmr spectra were identical with those obtained earlier. The ether-insoluble product was 1.10 g (82.5%) of crude dimethylammonium fluoroborate as determined by nmr spectroscopy.

2. *N*-Cyano-*N,N,N*-tri-*n*-butylammonium Fluoroborate. To a solution of 1.50 g (0.005 mol) of *N*-cyano-*N,N,N*-tri-*n*-butylammonium fluoroborate in 20 ml of acetonitrile was added 0.37 g (0.005 mol) of dimethylformamide. The solution was allowed to react and worked up as in 1 to give 0.62 g (82%) of di-*n*-butylcyanamide, which was distilled in a Hickman still to give a clear oil whose ir and nmr spectra were identical with those obtained earlier.

3. *N*-Cyano-*N*-*n*-propylpiperidinium Fluoroborate. To a solution of 3.0 g (0.0125 mol) of *N*-cyano-*N*-*n*-propylpiperidinium fluoroborate in 20 ml of acetonitrile, 0.95 g (0.013 mol) of dimethylformamide was added. The solution was allowed to react as in 1. The reaction mixture was distilled, and the distillate was examined by nmr spectroscopy to show two different triplets at about δ 4.08 and 3.40 ppm in acetonitrile. (The former triplet was assigned to the methylene protons of the expected *n*-propyl formate.) The distillation residue was extracted with methylene chloride (3 × 100 ml) and distilled to give 0.41 g (30%) of piperidine cyanamide and 1.10 g (52%) of 5-hydroxypentyl-*n*-propylcyanamide. Piperidine cyanamide contained a small amount of dimethylformamide, which was removed by washing with water. The methylene chloride insoluble portion was crystalized and washed with ether in a continuous-extraction column to give 1.61 g (97%) of dimethylammonium fluoroborate. Piperidine cyanamide was characterized as follows: bp 41° (0.65 mm); ir (thin film) 2203 cm^{-1} (strong, CN); nmr ($CDCl_3$) δ 1.60 (br, CH_2, 6 H) and 3.17 (br, CH_2N, 4 H); mass spectrum *m/e* (rel abundance) 110 (M^+, 100), 111 (8), 109 (78), 95 (6), 83 (5), 82 (10), 81 (5), 69 (64), 67 (10), 58 (12), 57 (28), 56 (13), 55 (44), 54 (13), 53 (10), 44 (22), 43 (40), 42 (99), 41 (39), 40 (5), 39 (15).

Anal. Calcd for $C_6H_{10}N_2$ (110.16): C, 65.41; H, 9.15; N, 25.44. Found: C, 65.45; H, 9.25; N, 25.00.

5-Hydroxypentyl-*n*-propylcyanamide was characterized as follows: bp 140° (0.65 mm); ir (thin film) 2203 cm^{-1} (strong, CN); nmr ($CDCl_3$) δ 0.97 (t, CH_3, 3 H), 1.40–1.90 (m, CH_2, 8 H) 2.90–3.40 (m, CH_4, 4 H), and 3.60 (t, CH_2, 2 H); mass spectrum *m/e* (rel abundance) 170 (M^+, 4), 155 (15), 142 (4), 141 (10), 128 (19), 127 (8), 126 (5), 125 (10), 123 (6), 114 (16), 113 (6), 112 (7), 111 (10), 110 (4), 105 (8), 100 (11), 99 (9), 98 (22), 97 (35), 88 (6), 96 (8), 88 (5), 86 (6). 85 (51), 84 (7), 83 (13), 82 (7), 81 (43), 80 (15), 79 (8), 77 (17), 75 (39), 72 (22), 71 (5), 70 (25), 69 (48), 58 (8), 57 (21), 56 (14), 55 (100), 54 (16), 53 (11), 51 (7), 45 (6), 44 (18), 43 (68), 42 (22), 41 (85), 39 (28).

Anal. Calcd for $C_9H_{18}N_2O$ (170.25): C, 63.49; H, 10.65; N, 16.46. Found: C, 63.60; H, 10.40; N, 16.25.

Registry No.—1 (R = Et), 30684-36-7; 1 (R = Bu), 30684-37-8; 2 (R = Me), 30759-79-6; 2 (R = Et), 51108-21-5; 2 (R = Pr), 51108-23-7; 2 (R = Bu), 30759-80-9; cyanogen bromide, 506-68-3; triethylamine, 121-44-8; triethyloxomium fluoroborate, 368-39-8; tri-*n*-butylamine, 102-82-9; *N*-methylpiperidine, 626-67-5; *N*-ethylpiperidine, 766-09-6; *N*-propylpiperidine, 5470-02-0; *N*-*n*-butylpiperidine, 4945-48-6; *N*-methylaniline, 100-61-8; diethylcyanamide, 617-83-4; *N*-methyl-*N*-*n*-butylaniline, 3416-49-7; *N*-methylcyclohexylamine, 100-60-7; *N*-methylcyclohexylcyanamide, 49677-01-2; isobutylamine, 78-81-9; isobutylcyanamide, 13519-17-0; isobutylcyanamide trimer, 51056-91-8; thiophenol, 108-98-5; phenyl thiocyanate, 5285-87-0; phenyl disulfide, 882-33-7; sodium thiophenolate, 930-69-8; triphenylphosphine, 603-35-0; difluorotriphenylphosphorane, 845-64-7; water, 7732-18-5; ammonium fluoroborate, 13826-83-0; dimethylformamide, 68-12-2; piperidine cyanamide, 1530-87-6; 5-hydroxypentyl-*n*-propylcyanamide, 51056-92-9.

References and Notes

(1) Taken in part from the Ph.D. Thesis of M. Kim, Kansas State University, 1973. Financial support from the National Science Foundation Grant No. GP 15334 and a grant to the Department of Chemistry for the purchase of XL-100-15 and T-60 nmr spectrometers is gratefully acknowledged.
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N-Alkoxycarbonyl-*N,N,N*-trialkylammonium Fluoroborates. Formation of Carbonic Anhydrides in Peptide Synthesis

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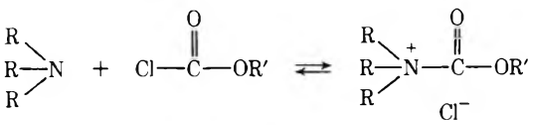
A variety of *N*-alkoxycarbonyl-*N,N,N*-trialkylammonium fluoroborates have been synthesized from tertiary amines and alkyl chloroformates. The salts are stable and can be used in the mixed anhydride method of peptide synthesis. The yields of peptides are similar to those observed previously but the amount of racemization is apparently reduced as determined by the Anderson test. The salts also react readily with primary and secondary amines to give urethanes.

The occurrence of simple *N*-alkoxycarbonyl-*N,N,N*-trialkylammonium salts has been postulated many times[3-8] but stable salts have been isolated only rarely.[9-11] The highly stabilized derivatives of 4-(*N,N*-dimethylamino)pyridine[10] and *N*-methylimidazole[11] may not even be in a strict sense *N*-alkoxycarbonylammonium salts. Thus there remains only the report of simple *N*-alkoxycarbonylammonium salt preparation by reaction of urethanes with methyl fluorosulfonate[9] followed by rearrangement.

Our interest in preparing the *N*-alkoxycarbonylammonium salts required preparation of wide variety of structures and high yields for use in the mixed anhydride method of peptide synthesis. We felt that if such salts can be made and used then the mixed anhydride method would be completely free of excess bases (in the formation of the mixed anhydride) that might lead to racemization.[12] Currently the *N*-alkoxycarbonylammonium salts are prepared by mixing tertiary amino and alkyl chloroformates.[12-16] Chloride ion is a fairly good nucleophile;

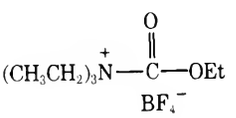


thus the reaction can never be completely free of base because the reaction is always somewhat reversible. If the reagents can be readily formed then it also may be useful in the formation of N, O, and S protecting groups.

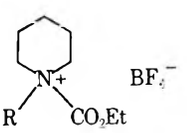
To eliminate the problem of reversibility we chose to exchange the chloride for fluoroborate. The fluoroborate ion is less nucleophilic[17] and in our experience yields stable, nonhydroscopic salts.[18,19]

The adducts of tertiary amines and alkyl chloroformates were obtained by mixing the two reactants in ether at −78°. The addition compounds were generally observed as colorless crystals and appeared stable at room temperature under ether. Detailed examination by nmr spectroscopy and elemental analysis indicated that the substances were usually a mixture.

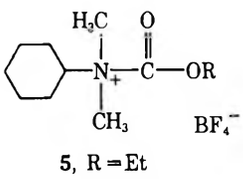
The anion exchange reaction was facile when the HF/BF_3 mixture was added to the adducts of tertiary amines and alkyl chloroformates at −78°. Stirring until room temperature was reached gave colorless crystals of *N*-alkyloxycarbonylammonium fluoroborates (**1**–**12**) in 89–99% yield. Most salts showed sharp melting points and varied in their stability. The pyridine derivatives were very unstable, and among those derived from aliphatic amines the stability increased as the alkyl groups became bulkier. The derivatives of *N,N*-dimethylcyclohexylamine and isopropyl, *sec*-butyl, or isobutyl chloroformate were the most stable *N*-alkyloxycarbonylammonium salts, allowing easy



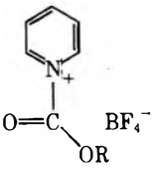
1



2, R = Et
3, R = *n*-Pr
4, R = *n*-Bu



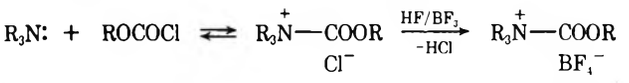
5, R = Et
8, R = CH_2Ph
9, R = *i*-Bu
11, R = *s*-Bu
12, R = *i*-Pr



6, R = Et
7, R = CH_2Ph
10, R = *i*-Bu

handling under ordinary available anhydrous experimental conditions.

The reaction scheme of the anion exchange reaction is formulated as shown below. The adduct of a tertiary



amine and an alkyl chloroformate is assumed to be the ionic intermediate from which the *N*-alkyloxycarbonylammonium fluoroborate is formed upon the addition of HF/BF_3 mixture by losing one HCl molecule.

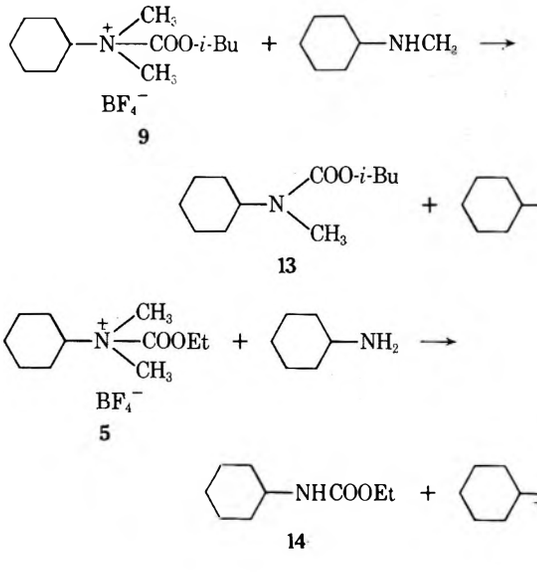
The main feature of the infrared spectra of *N*-alkyloxycarbonylammonium fluoroborates (1–12) is that each has a strong carbonyl bond absorption at around 1812–1822 cm^{-1} (except the salt 8). Since alkyl chloroformates usually absorb strongly at around 1760–1880 cm^{-1} owing to the carbonyl bonds,[20] the carbonyl absorptions of *N*-alkyloxycarbonylammonium fluoroborates are higher by about 10–20 cm^{-1}. This is a trend similar to that observed in the infrared spectra of *N*-cyanoammonium fluoroborates.[18]

Nuclear magnetic resonance spectra of *N*-alkyloxycarbonylammonium fluoroborates were consistent with the proposed structures. The alkyl groups derived from alkyl chloroformates appeared in a chemical shift region similar to those of alkyl chloroformates. The protons adjacent to the nitrogen atom showed a drastic change in chemical shifts when comparing the *N*-alkyloxcarbonylammonium salts with ordinary tertiary ammonium salts. The chemical shifts (δ) were about 3.8 ppm for methylene protons, 3.2–3.45 ppm for methyl protons, and 4.0–4.3 ppm for methine protons in acetone-d_6. For tertiary ammonium salts the values are about 3.0, 2.95, and 3.1 ppm, respectively.

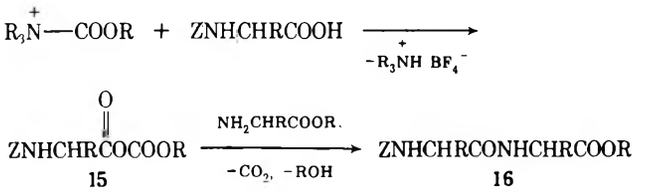
The present method of preparation of *N*-alkyloxycarbonylammonium fluoroborates using HF/BF_3 mixture resulted in several failures. The products obtained from *N*-methylpiperidine, trimethylamine and quinuclidine, and isobutyl chloroformate were crystalline substances, but too unstable to be characterized. In the other extreme, the reactions of most hindered tertiary amines and alkyl chloroformates were too slow at the low temperatures employed to give crystalline products. Thus, the reaction of *N,N*-dimethyl-*tert*-butylamine, tri-*n*-butylamine, and *N,N*-diethylcyclohexylamine with ethyl or isobutyl chloroformate did not give the desired products.

It was apparent that the alkyl groups of the alkyloxycarbonylammonium fluoroborates could be cleaved by the attack of a nucleophile as observed in several intermediates[3-9,12-16] but the cleavage of the alkyloxycarbonyl groups was also expected as in the reaction of *N*-cyanoammonium fluoroborates.[18,19] The present study dealt only with the acyl group cleavages, especially the suitability of these ammonium salts as mixed anhydride and urethane forming reagents.

The reaction of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate (9) with *N*-methylcyclohexylamine gave a 93% yield of the carbamate 13. *N*-Ethyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate (5) reacted with cyclohexylamine to give a 99% yield of the carbamate 14. From the two examples it is clear that urethanes can be formed in high yield using reagents. The use as selective urethane-forming reagents is being explored.



The attempted peptide synthesis using *N*-alkyloxycarbonylammonium fluoroborates proceeded to give moderate yields of oligopeptides. The carboxyl group of the N-protected amino acid attacks on the alkyloxycarbonyl group of the ammonium salt to form the mixed anhydride 15, which is attacked by the added N-terminal amino acid to form the dipeptide derivative[16] accompanied by the liberation of carbon dioxide and an alcohol. The procedure



of this peptide synthesis was that of the generally known "mixed anhydride method" using directly tertiary amines and alkyl chloroformates. Thus, the reaction was done at about −10°, and the solution was kept overnight after the addition of the N-terminal amino acids. In most cases crystallizable products were obtained, and the best yields were observed with the isobutyl (9), isopropyl (12), and *sec*-butyl (11) derivatives of *N,N*-dimethylcyclohexylamine. The results are recorded in Tables I and II.

Table I lists the coupling reagents, solvents, and yield of the indicated products. The first four entries constitute a limited test of various coupling reagents keeping the same solvent. Entries 7 and 8 constitute the Anderson test using two coupling reagents. In general there does not seem to be any advantage to use of IBAF or IPAF, the two most promising reagents, as they give similar yields in all cases. Table II is a test for coupling of Z-Gly-OH and H-Gly-OEt under identical conditions in a variety of solvents. Since the yields are 71–90% and no effort has been made to optimize the yield, there does not seem to be any significant advantage in any solvent. The yields are generally comparable with those of original mixed anhydride method where the alkyl chloroformates are used directly.[14] The similar yields can probably be explained as being due to similar or essentially the same reaction mechanism.

Table I

	C-Terminal Amino Acid	N-Terminal Amino Acid	Coupling reagent	Solvent	Peptide product	Yield, %
1	Z-Gly-OH	Gly-OEt	IBAF (**9**)	DMF	Z-Gly-Gly-OEt	90
2	Z-Gly-OH	Gly-OEt	SBAF (**11**)	DMF	Z-Gly-Gly-OEt	83
3	Z-Gly-OH	Gly-OEt	EAF (**5**)	DMF	Z-Gly-Gly-OEt	60
4	Z-Gly-OH	Gly-OEt	IBPF (**10**)	DMF	Z-Gly-Gly-OEt	34
5	Z-DL-Val-OH	Gly-OEt	IBAF (**9**)	DMF	Z-DL-Val-Gly-OEt	80
6	Z-DL-Val-OH	Gly-Gly-OEt·HOAc/TEA[a]	IBAF (**9**)	DMF	Z-DL-Val-Gly-Gly-OEt	76
7	Z-Gly-L-Phe-OH	Gly-OEt	IBAF (**9**)	THF	Z-Gly-L-Phe-Gly-OEt (all L)	89
8	Z-Gly-L-Phe-OH	Gly-OEt	IPAF (**12**)	THF	1-Gly-Phe-Gly-OEt (3% DL, the rest L)	97
9	Z-Gly-OH	L-Phe-OEt·HCl/TEA[a]	IBAF (**9**)	CH_3CO_2Et	Z-Gly-L-Phe-OEt	74
10	Z-Gly-OH	Gly-OEt·HCl/TEA[a]	IPAF (**12**)	CH_3CO_2Et	Z-Gly-Gly-OEt	69
11	Z-Gly-OH	Gly-OEt·HCl/TEA[a]	IPAF (**12**)	CH_3CN	Z-Gly-Gly-OEt	73

[a] TEA: triethylamine.

Table II

$$\text{Z-Gly-OH} + \text{HGly-OEt} \xrightarrow{\text{IBAF}} \text{Z-Gly-Gly-OEt}$$

Solvent	Yield, %
DMF	90
$CHCl_3$	81
THF	83
$CHCl_2$	78
CH_3CN	71
CH_3CO_2Et	77

The use of *N*-alkyloxycarbonylammonium fluoroborates in peptide synthesis was expected to give low racemization owing to the presence of reduced amounts of excess base. Excess base may arise from several sources if chloride is the anion: (1) inexact stoichiometry in weighing of the components; (2) reaction of *N*-alkyloxycarbonylammonium chlorides to give free base and chloroformate, *i.e.*, the reverse of the formation reaction; (3) ionization of the tertiary ammonium salt formed during the formation of the mixed anhydride. In all three cases the use of stable *N*-alkyloxycarbonylammonium fluoroborates will reduce the amount of free base that is present. Under ideal conditions as described by Kemp, Bernstein, and Rebek, the mixed anhydride method may show as little as 0.01% racemization.[12b] Departure from exact stoichiometry results in a greater than tenfold increase in racemization.[12b] To test the degree of racemization of this method, Anderson's method[21] was chosen among other methods.[22-24] This method has been known to be able to detect at least about 2% of racemization.[24,25] According to the procedure,[21] carbobenzoxyglycyl-L-phenylalanine was coupled with glycine ethyl ester using *N*-isobutyloxycarbonyl-*N*,*N*-dimethylcyclohexylammonium fluoroborate (**9**) and yielding 89% of the tripeptide; racemized product could be obtained from this tripeptide by fractional crystallization. However, when isopropyloxycarbonyl-*N*,*N*-dimethylcyclohexylammonium fluoroborate (**12**) was used the yield of crude product was 97%, from which about 3% of the racemized product crystallized out. The differences observed for the two reagents are barely significant considering the sensitivity of the test. However, it is highly significant that the overall amount of racemization was very low.[25]

$$\text{Z—Gly—L—Phe—OH} + \text{NH}_2\text{CH}_2\text{COOEt} \begin{cases} \rightarrow \text{Z—Gly—L—Phe—Gly—OEt} \\ \rightarrow \text{Z—Gly—D—Phe—Gly—OEt} \end{cases}$$

More sensitive tests for racemization will be needed to determine if in fact *N*-alkoxycarbonyl-*N*,*N*,*N*-trialkylammonium fluoroborates have any advantages in decreasing racemization. The first results reported here look very promising. Because the reagents are readily prepared in high yield and can be stored for months at room temperature with a little care to keep them dry, the mixed anhydride reactions will be much easier to run on a routine basis. Finally, the possibility of introducing benzyloxycarbonyl and *tert*-butyloxycarbonyl protecting groups with the same reagents adds considerably to the utility of the reagents. All aspects of the chemistry of *N*-alkoxycarbonyl-*N*,*N*,*N*-trialkyammonium fluoroborate are still under study.

Experimental Section[26]

General Procedure for the Preparation of *N*-Alkoxycarbonyl-*N*,*N*,*N*-trialkylammonium Fluoroborates. To a solution of chloroformate (0.02 mol) in 50 ml of ether cooled to −78° was added in drops a solution of tertiary amine (0.01 mol) in 50 ml of ether while stirring. It was allowed to stand for 5 hr at −78° and for 2 hr at −10 to 20°. The adduct was cooled to −78°, and a 1:1 mixture of condensed hydrogen fluoride which had been added to boron trifluoride etherate (0.015 mol) was added at once. (A stock solution of HF/BF_3 in ether could be prepared and kept in a polyethylene bottle.) After the cooling bath was removed the solution was stirred until room temperature was reached. Precipitated colorless crystals were collected, washed with ether three times, and dried under vacuum.

***N*-Ethyloxycarbonyl-*N*,*N*,*N*-triethylammonium Fluoroborate (Yield 92%).** The crystals were very unstable, and their ir and nmr spectra showed some decomposition: ir (Nujol mull) 1822 (strong, C=O) and 1000–1100 cm^{-1}; nmr (acetonitrile) δ 1.35 (t, CH_3, 9 H), 3.70 (q, CH_2N^+, 6 H), and 4.65 (q, CH_2O, 2 H).

***N*-Ethyloxycarbonyl-*N*-ethylpiperidinium fluoroborate** (yield 86%) had mp 34–35°; ir (Nujol mull) 1817 (strong, C=O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.54 (t, CH_3, 3 H), 1.50–2.20 (br, CH_2, 6 H), 3.84 (q, CH_2N^+, 2 H), 3.22–4.37 (br, CH_2N^+, 4 H), and 4.75 (q, CH_2O, 2 H).

Anal. Calcd for $C_{10}H_{20}NO_2BF_4$ (273.09): C, 43.89; H, 4.39; N, 5.13. Found: C, 43.70; H, 7.40; N, 5.40.

***N*-Ethyloxycarbonyl-*N*,*n*-propylpiperidinium fluoroborate** (yield 91%) had mp 32–33°; ir (Nujol mull) 1812 (strong, C=O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 0.98 (t, CH_3, 3 H), 1.48 (t, CH_3, 3 H), 1.70–2.24 (br, CH_2, 6 H), 3.40–4.40 (br, CH_2N^+, 6 H), and 4.75 (q, CH_2O, 2 H).

Anal. Calcd for $C_{11}H_{22}NO_2BF_4$ (287.04): C, 46.03; H, 7.70; N, 4.88. Found: C, 46.30; H, 7.90; N, 4.97.

***N*-Ethyloxycarbonyl-*N*-*n*-butylpiperidinium fluoroborate** (yield 96%) had mp 65–66°; ir (Nujol mull) 1812 (strong C=O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 0.95 (t, CH_3, 3 H), 1.48 (t, CH_3, 3 H), 1.60–2.24 (br, CH_2, 6 H), 3.40–4.40 (br, CH_2N^+, 6 H), and 4.75 (q, CH_2O, 2 H).

Anal Calcd for $C_{12}H_{24}NO_2BF_4$ (301.14): C, 47.86; H, 8.03; N, 4.65. Found: C, 48.10; H, 8.00; N, 4.53.

***N*-Ethyloxycarbonyl-*N*,*N*-dimethylcyclohexylammonium fluoroborate** (yield 99%) had mp 108°; ir (Nujol mull) 1812 (strong, C=O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.47 (t, CH_3, 3 H), 1.60–2.40 (br, CH_2, 10 H), 3.42 (s, CH_3N^+, 6 H), 3.80–4.15 (br, CHN^+, 1 H), and 4.67 (q, CH_2O, 2 H).

Anal. Calcd for $C_{11}H_{22}NO_2BF_4$ (287.10): C, 46.02; H, 7.73; N, 4.88. Found: C, 46.00; H, 7.60; N, 4.80.

***N*-Benzyloxycarbonylpyridinium fluoroborate** (yield 98%) had mp 100–100.5°; ir (Nujol mull) 1822 (strong, C=O) and 1000–1120 cm^{-1}; the compound decomposed when dissolved in most usually available organic solvents and on storing.

***N*-Ethyloxycarbonylpyridinium fluoroborate** (yield 95%) had mp 62–63°; ir (Nujol mull) 1822 (strong, C=O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.50 (t, CH_3, 3 H), 4.80 (q, CH_2O, 2 H), 8.38 (t, 3-H, 2 H), 9.07 (t, 4-H, 1 H), and 9.67 (d, 2-H, 2 H).

Anal. Calcd for $C_8H_{10}NO_2BF_4$ (238.99): C, 40.20; H, 4.22; N, 5.86. Found: C, 40.40; H, 4.43; N, 5.76.

***N*-Benzyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 98%) had mp 90–91°; ir (Nujol mull) 1796 (strong, C=O) and 1030–1100 cm^{-1}; nmr ($CDCl_3$) δ 0.92–2.10 (br, CH_2, 1 OH), 3.44 (s, CH_3N^+, 6 H), 3.44–3.96 (br, CHN^+, 1 H), 5.55 (s, CH_2O, 2 H), and 7.43 (m, phenyl ring, 5 H).

Anal. Calcd for $C_{16}H_{24}NO_2BF_4$ (349.18): C, 55.03; H, 6.93; N, 4.01. Found: C, 55.30; H, 7.27; N, 3.96.

***N*-Isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 96%) had mp 50–50.5°; ir (Nujol mull) 1812 (strong, C=O) and 1000–1100 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (d, CH_3, 6 H), 1.20–2.35 (br, CH_2 and CH, 11 H), 3.33 (s, CH_3N^+, 6 H), 3.45–4.0 (br, CHN^+, 1 H), and 4.33 (d, CH_2O, 2 H).

Anal. Calcd for $C_{13}H_{26}NO_2BF_4$ (315.17): C, 49.54; H, 8.32; N, 4.45. Found: C, 49.80; H, 8.50; N, 4.49.

***N*-Isobutyloxycarbonylpyridinium fluoroborate** (yield 98%) had mp 69.5–70°; ir (Nujol mull) 1822 (strong, C=O) and 1020–1130 cm^{-1}; nmr (acetone-d_6) δ 1.08 (d, CH_3, 6 H), 2.30 (m, CH, 1 H), 4.57 (d, CH_2O, 2 H), 8.37 (t, 3-H, 2 H), 9.02 (t, 4-H, 1 H), and 9.61 (d, 2-H, 2 H). The nmr spectrum showed some decomposition.

Anal. Calcd for $C_{10}H_{14}NO_2BF_4$ (267.02): C, 44.95; H, 5.28; N, 5.25. Found: C, 44.60; H, 5.39; N, 5.45.

***N*-*sec*-Butyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 98%) had mp 81.5–82°; ir (Nujol mull) 1822 (strong, C=O) and 1000–1130 cm^{-1}; nmr ($CDCl_3$) δ 0.97 (t, CH_3, 3 H), 1.46 (d, CH_3, 3 H), 1.77 (q, CH_2, 2 H), 1.20–2.30 (br, CH_2, 10 H), 3.28 (s, CH_3N^+, 6 H), 3.50–4.0 (br, CHN^+, 1 H), and 5.16 (m, CHO, 1 H).

Anal. Calcd for $C_{13}H_{26}NO_2BF_4$ (315.17): C, 47.86; H, 8.02; N, 4.65. Found: C, 47.80; H, 7.90; N, 4.76.

***N*-Isopropyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 99%) had mp 91–92.5°; ir (Nujol mull) 1812 (strong, C=O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.50 (d, CH_3, 6 H), 1.40–2.18 (br, CH_2, 10 H), 3.40 (s, CH_3N^+, 6 H), 3.70–4.20 (br, CHN^+, 1 H), and 5.33 (m, CHO, 1 H); uv (acetonitrile), no absorptions between 240 and 400 nm.

Anal. Calcd for $C_{12}H_{24}NO_2BF_4$ (301.14): C, 47.86; H, 8.02; N, 4.65. Found: C, 47.80; H, 7.90; N, 4.76.

Reaction of *N*-Ethyloxycarbonyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Cyclohexylamine. To a solution of 0.55 g (0.0019 mol) of *N*-ethyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 10 ml of methylene chloride was added 0.17 g (0.0017 mol) of cyclohexylamine. The solution was allowed to stand for 1 hr at room temperature, and the solvent was removed on a rotary evaporator. The residue was extracted with ether (3 × 20 ml) and the ether portion was washed with a small amount of water. Evaporation of the solvent gave 0.29 g (99%) of crude *N*-cyclohexylcarbamic acid ethyl ester, mp 54–56.5° (lit.[27] mp 57°); ir and nmr spectra were in agreement with the structure.

Anal. Calcd for $C_9H_{17}NO_2$ (171.24): C, 63.12; H, 10.00; N, 8.18. Found: C, 62.85; H, 9.90; N, 8.27.

Reaction of *N*-Isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *N*-Methylcyclohexylamine. To a solution of 1.65 g (0.0053 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 10 ml of acetonitrile was added 0.57 g (0.005 mol) of *N*-methylcyclohexylamine at −10°. The solution was allowed to stand for several hours at room temperature, and the solvent was removed on a rotary evaporator without heating. The residue was extracted with ether (3 × 100 ml), and the ether portion was washed with a small amount of water, dried (Na_2SO_4), and distilled to give 1.01 g (93%) of oil as residue. Hickman still distillation [87° (0.35 mm)] gave 0.88 g of a clear oil of *N*-methylcyclohexylcarbamic acid isobutyl ester: ir (thin film) 1665 cm^{-1} (strong, C=O); nmr (CCl_4) δ 0.91 (d, CH_3, 6 H), 1.17–2.03 (br, CH_2, 10 H), 2.70 (s, CH_3, 3 H), 3.75 (d, CH_2, 2 H), and 3.80 (br, CH, 1 H).

Anal. Calcd for $C_{12}H_{23}NO_2$ (213.31): C, 67.56; H, 10.87; N, 6.57. Found: C, 67.78; H, 10.60; N, 6.45.

Reaction of *N*-Alkyloxycarbonylammonium Fluoroborates with *N*-Benzyloxycarbonyl Amino Acids. Synthesis of *N*-Benzyloxycarbonylglycylglycine Ethyl Ester. To a cooled (−10°), stirred solution of 2 09 g (0.01 mol) of *N*-benzyloxycarbonylglycine in 20 ml of dimethylformamide was added in small portions 4.20 g of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate. The mixture was stirred for 15 min at −10° and for 15 min at room temperature, and cooled to −10°. To this 1.31 g (0.013 mol) of ethyl glycinate was added in small portions while stirring. The solution was allowed to stand for 1 day at ordinary temperature followed by the removal of the solvent on a rotary evaporator. The residue was dissolved in 75 ml of ethyl acetate and washed with 25 ml of water, 25 ml of 5% $NaHCO_3$ solution, 25 ml of 1 *N* HCl solution, and 25 ml of water. It was dried (Na_2SO_4) and evaporated to give a syrupy residue which was crystallized when triturated with petroleum ether. The yield was 2.64 g (90%) of *N*-benzyloxycarbonylglycylglycine ethyl ester whose ir and nmr spectra were in agreement with those reported, mp 78–90° (lit.[28] mp 77–85°).

Anal. Calcd for $C_{14}H_{18}N_2O_5$ (294.30): C, 57.13; H, 6.16; N, 9.52. Found: C, 57.30; H, 6.31; N, 9.45.

The same procedure was followed using different solvents to give the yields indicated in Table I.

Synthesis of *N*-Benzyloxycarbonyl-DL-valylglycine Ethyl Ester. The same procedure was followed with 1.25 g (0.005 mol) of *N*-benzyloxycarbonyl-DL-valine, 2.10 g (0.0066 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 0.77 g (0.006 mol) of ethyl glycinate in 20 ml of dimethylformamide to give 1.40 g (80%) of *N*-benzyloxycarbonyl-DL-valylglycine ethyl ester: mp 147–150°; ir (Nujol mull) 1742 (strong, CO), 1690 (strong, C=O), and 3240 cm^{-1} (strong, NH); nmr ($CDCl_3$) δ 0.93 (br, CH_3, 6 H), 1.23 (t, CH_3, 3 H), 2.03 (m, CH, 1 H), 3.59 (d, CH_2, 2 H), 3.59 (br, CH, 1 H), 4.17 (q, CH_2, 2 H), 5.09 (s, CH_2, 2 H), 5.83 (d, NH, 1 H), 7.10 (br, NH, 1 H), and 7.30 (m, phenyl ring, 5 H).

Anal. Calcd for $C_{17}H_{24}N_2O_5$ (336.38): C, 60.70; H, 6.98; N, 8.17. Found: C, 60.70; H, 6.90; N, 8.20.

Synthesis of *N*-Benzyloxycarbonyl-DL-valylglycylglycine Ethyl Ester. The same procedure was followed with 1.25 g (0.005 mol) of *N*-benzyloxycarbonyl-DL-valine, 1.80 g (0.0057 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 1.20 g (0.0055 mol) of ethyl glycylglycinate [prepared by hydrogenolysis of *N*-benzyloxycarbonylglycylglycine ethyl ester using Pd/C (10%) as catalyst[29]] with 0.55 g (0.0055 mol) of triethylamine in 20 ml of dimethylformamide to give 1.50 g (76.2%) of *N*-benzyloxycarbonyl-DL-valylglycylglycine ethyl ester, recrystallized from ethanol: mp 119–120°; ir (Nujol mull) 3321, 3000, 1753, 1737, 1692, 1667, 1646 cm^{-1} (all sharp); nmr ($CDCl_3$) δ 0.97 (two d, CH_3, 6 H), 1.23 (t, CH_3, 3 H), 3.93 (t, CH_2, 4 H), 4.13 (q, CH_2, 2 H), 3.93–4.13 (br, NH, 1 H), 5.83 (s, CH_2, 2 H), 6.03 (d, NH, 1 H), and 7.30 (m, phenyl ring, 5 H).

Anal. Calcd for $C_{19}H_{27}N_3O_6$ (393.43): C, 58.00; H, 6.92; N, 10.68. Found: C, 58.33; H, 6.80; N, 10.48.

Synthesis of *N*-Benzyloxycarbonylglycyl-L-phenylalanine. The same procedure was followed with 4.10 g (0.0196 mol) of *N*-benzyloxycarbonylglycine, 6.52 g (0.021 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 4.0 g (0.02 mol) of ethyl L-phenylalaninate hydrochloride with 2.02 g of triethylamine in 100 ml of ethyl acetate to give 5.50 g (74%) of an amorphous product. It was dissolved in 50 ml of 1 *N* NaOH solution containing 10 ml of methanol, and stirred for 2 hr to hydrolyze. The solution was acidified with 1 *N* HCl solution (Congo Red), and the solvent was removed to give an amorphous residue which was crystallized from 1:5 acetone–water mixture. The yield was 4.50 g (90%) of *N*-benzyloxycarbonylglycyl-L-phenylalanine: mp 126–127° (lit.[21] mp 127.5°); ir (Nujol mull) 3326, 1735, 1690, 1650 cm^{-1} (all sharp); nmr (acetone-d_6) δ 3.03–3.25 (m, CH_2, 2 H), 3.83 (d, CH_2. 2 H), 4.78 (m, CH, 1 H), 5.10 (s, CH_2, 2 H), 6.40–6.80 (br, NH, 1 H), 7.23 (m, phenyl ring, 5 H), 7.33 (m, phenyl ring, 5 H), 7.33 (br, NH, 1 H), 916–9.66 (br, COOH, 1 H),

Anal. Calcd for $C_{19}H_{20}N_2O_5$ (356.37): C, 64.03; H, 5.66; N, 7.86. Found: C, 63.83; H, 5.66; N, 7.73.

Synthesis of *N*-Benzyloxycarbonylglycyl-L-phenylalanylglycine Ethyl Ester. The same procedure was followed with 3.60 g (0.0101 mol) of *N*-benzyloxycarbonylglycyl-L-phenylalanine, 3.45 g (0.011 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 1.15 g (0.011 mol) of ethyl glycinate in 30 ml of tetrahydrofuran (dried over lithium aluminum hydride) to give 3.93 g (89.2%) of an amorphous product. It was dissolved in 192 ml of absolute ethanol (2% solution) and kept in a refrigerator at about −5°.[21] After about 2 weeks the crystalliza-

tion of the L tripeptide began: the small fraction was collected, which melted at 119.2–119.7° (lit.[21] mp 116.5–119.5°). Continuous refrigeration gave more crystals of the same material. The residual peptide was obtained by reducing the volume of the solution amounting to 3.50 g, and about 0.26 g of oil was left uncrystallized: ir (Nujol mull) 3225, 1750, 1715, 1688, 1665, 1650 cm^{-1} (all sharp); nmr ($CDCl_3$) δ 1.20 (t, CH_3, 3 H), 3.05 (d, CH_2, 2 H), 3.70–3.93 (two d, CH_2, 4 H), 4.10 (q, CH_2, 2 H), 4.83 (d, CH, 1 H), 5.05 (s, CH_2, 2 H), 5.85 (br, NH, 1 H), 7.15 (br, NH, 1 H), 7.15 (s, phenyl ring, 5 H), and 7.30 (s, phenyl ring, 5 H).

Anal. Calcd for $C_{23}H_{27}N_3O_5$ (441.47): C, 62.57; H, 6.17; N, 9.52. Found: C, 62.80; H, 6.04; N, 9.40.

The above procedure was followed with 3.56 g (0.01 mol) of *N*-benzyloxycarbonylglycyl-L-phenylalanine, 3.30 g (0.011 mol) of *N*-isopropyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 1.15 g (0.011 mol) of ethyl glycinate in 30 ml of tetrahydrofuran. The yield of the amorphous tripeptide derivative was 4.30 g (97%). A 2% solution of the peptide in absolute ethanol gave, after about 3 weeks of refrigeration, the first fraction of crystals amounting to 0.13 g (3%) of DL tripeptide melting at 129–130° (lit.[21] mp 132–133°). After 2 days 0.07 g of crystals was obtained melting at 120–121°, and soon the L tripeptide began to appear amounting to 3.12 g, melting at 119–120.5°. The residue was obtained in crude crystals. The elemental analysis of this product was identical with that of the product in the first part of this synthesis.

Registry No.—**1,** 51157-30-3; **2,** 51056-73-6; **3,** 51108-18-0; **4,** 51056-75-8; **5,** 51056-77-0; **6,** 51056-79-2; **7,** 51056-81-6; **8,** 51056-83-8; **9,** 51056-85-0; **10,** 51056-87-2; **11,** 51108-20-4; **12,** 51056-89-4; triethylamine, 121-44-8; *N*-ethylpiperidine, 766-09-6; *N,N*-dimethylcyclohexylamine, 98-94-2; pyridine, 110-86-1; *N*-*n*-propylpiperidine, 5470-02-0; *N*-*n*-butylpiperidine, 4945-48-6; ethyl chloroformate, 541-41-3; benzyl chloroformate, 501-53-1; isobutyl chloroformate, 543-27-1; *sec*-butyl chloroformate, 17462-58-7; isopropyl chloroformate, 108-23-6; cyclohexylamine, 108-91-8; *N*-methylcyclohexylamine, 100-60-7; *N*-benzyloxycarbonylglycine, 1138-80-3; *N*-benzyloxycarbonyl-DL-valylglycine ethyl ester, 7801-65-2; *N*-benzyloxycarbonyl-DL-valine, 3588-63-4; *N*-benzyloxycarbonyl-DL-valylglycylglycine ethyl ester, 51056-90-7; *N*-benzyloxycarbonylglycyl-L-phenylalanine, 1170-76-9; *N*-benzyloxycarbonylglycyl-L-phenylalanylglycine ethyl ester, 2073-59-8.

References and Notes

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N-Acyl-*N,N,N*-Trialkylammonium Fluoroborates. Synthesis and Reactions

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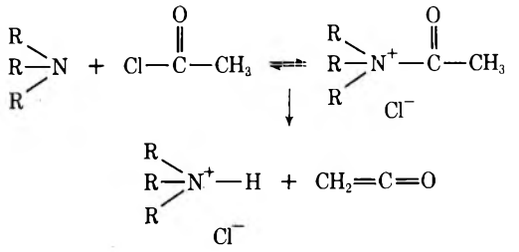
Stable *N*-acyl-*N,N,N*-trialkylammonium fluoroborates have been prepared from tertiary amines and acyl halides followed by exchange of anion to fluoroborate with HF/BF_3. The stable salts react with various nucleophiles such as amines, acids, alcohols, and thiols to form the acylated derivatives. The primary alcohols react rapidly, the secondary alcohols only partially, and tertiary alcohols do not react at all.

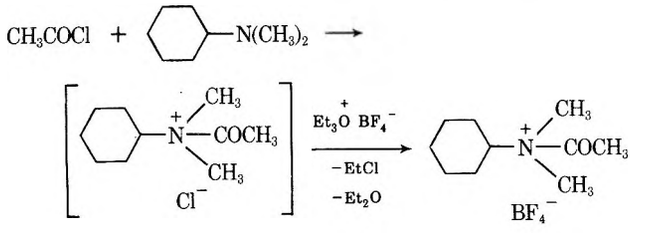
N-Acyl-*N,N,N*-trialkylammonium salts have been examined extensively for a variety of purposes.[3-6] The salts that have been examined have been highly reactive and quite frequently impure, precluding detailed examination of their structure and properties.[7-13] The best evidence was obtained by ir from adducts prepared at liquid nitrogen temperatures.[14] However, even these showed adsorptions at around 2300–2700 cm^{-1}, indicating that the hydrohalides were present.[15] Preparation by alkylation of amides was only partially successful.[16] Thus while the compounds have been prepared in impure form many times and have been assumed as intermediates in many other reactions,[17-20] very little can be accepted without some reservations.

Our interest in *N*-cyano- and *N*-alkyloxycarbonyl *N,N,N*-trialkylammonium salts[2] as reagents in peptide synthesis led us to consider *N*-acylammonium salts as possible reagents for preparation of protecting groups. In *N*-acylammonium salts the size of the tertiary amine can be readily varied, thus allowing the possibility of stereoselective acylating reagents. We assumed from our previous experience[2] that the major cause of instability was the nucleophilic nature of the anion, which could regenerate the tertiary amine, thus allowing dehydrohalogenation

reactions.[4] We chose to convert the unstable salts to the considerably more stable fluoroborates.

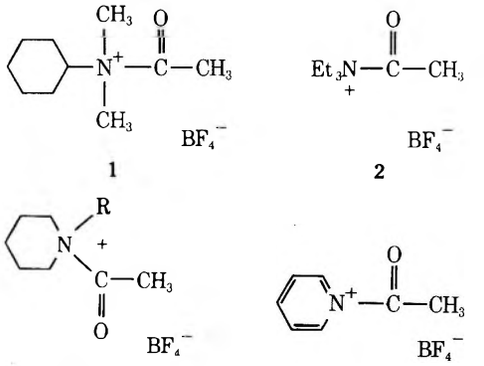


The use of triethyloxonium fluoroborate as the exchange reagent[1] was satisfactory when the tertiary amine was *N,N*-dimethylcyclohexylamine, giving 87% of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate. How-



1

ever, the treatment of the adducts of other tertiary amines, such as triethylamine, *N*-ethylpiperidine, and pyridine, gave mixtures containing the hydrohalide salts. When a mixture of HF/BF_3 was used as the anion exchange reagent,[2] colorless crystals of *N*-acetylammonium fluoroborates were obtained. They were stable under ether or as solids in a dry atmosphere at room temperature. The compounds **1–6** were recrystallizable from anhydrous organic solvents and were obtained in 85–98% yield except acetylpyridinium fluoroborate (**6**), where a large amount of pyridinium hydrofluoroborate was removed by washing with dry acetone, giving only 19% yield.



1 **2**

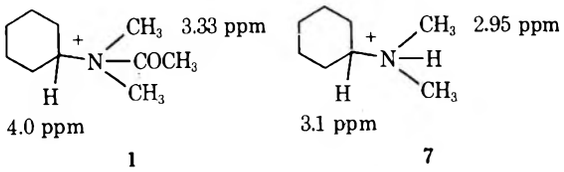
3, R = Et
4, R = *n*-Pr
5, R = *n*-Bu

6

The *N*-acetylammonium fluoroborates decomposed rather rapidly in open air. The apparently most stable salt was *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate (**1**), and the pyridinium salt **6** was the least stable. All of the salts were soluble in acetonitrile and all except the salts **2** and **6** were soluble in acetone. The salt **6** was soluble in trifluoroacetic acid, but reacted slowly to form unidentified products as observed by nmr spectroscopy.

The infrared spectra of the *N*-acetylammonium fluoroborates showed a strong carbonyl bond absorption at around 1806–1826 cm^{-1}, somewhat higher than that of acetyl chloride, which occurs at 1807 cm^{-1}.[21] This is in agreement with the observation made by Cook,[14] and explainable as being due to the presence of the positive charge on the nitrogen atom in the obtained compounds.

Nuclear magnetic resonance spectra of *N*-acetylammonium fluoroborates **1–6** exhibited signals for the acetyl groups appear at about δ 2.85–2.90 ppm in acetone-d_6 and at around δ 2.70–2.80 ppm in acetonitrile. These chemical shifts are generally lower by about 0.1 ppm than that of acetyl chloride in similar solvents. The acetyl group of *N*-acetylpyridinium fluoroborate (**6**) appeared at δ 3.13 ppm in trifluoroacetic acid and at δ 3.01 ppm in acetonitrile. The presence of the acetyl group in *N*-acetylammonium fluoroborates also produced a considerable downfield shift of methine, methylene, and methyl protons adjacent to the nitrogen atom. The chemical shifts of the methine and methyl protons of compounds **1** and **7** are indicative,

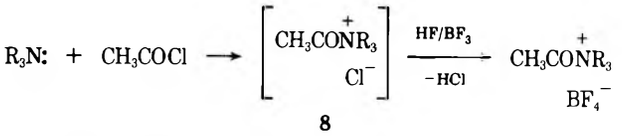


1 **7**

where the presence of the acetyl group on the nitrogen atom is apparent. The methylene protons of *N*-acetylammonium fluoroborates appeared at around δ 3.4–4.4 ppm in acetone-d_6, and these values are about 0.5–0.6 ppm lower than that of methylene protons of the corresponding ammonium salts. The ring protons of *N*-acetylpyridinium fluoroborate (**6**) appeared in three groups, and the C_2 protons are assigned to the doublet at δ 9.47 ppm in trifluoroacetic acid. The similar protons of pyridinium hydrofluoroborate salt appeared at about 0.6 ppm higher, indicating that the acetyl group on the nitrogen atom shifted the adjacent hydrogens. (The C_2 protons of *N*-acetylpyridinium hexafluoroantimonate appeared at δ 8.17 ppm in liquid sulfur dioxide at −60°.[22])

Although the ionic nature of the *N*-acetylammonium fluoroborates was not tested by a more direct method, the infrared and nmr spectroscopic results and physical properties such as solubility are those of ionic compounds. Thus it seems certain that the structural assignment of the *N*-acetylammonium fluoroborates is correct.

It is noteworthy that the addition of HF/BF_3 mixture to the adducts of acetyl chloride and tertiary amines did not bring about the formation of the tertiary amine hydrofluoroborates. This indicates that the adduct-forming equilibrium is complete to the side of the *N*-acetylammonium chlorides. The general similarity of some pertinent absorptions in the infrared spectra of the *N*-acetylammonium fluoroborates and the adducts of acetyl halides and tertiary amines observed by Cook[14] indicates that the adducts **8** are ionic. The general course of reaction can be represented as shown below.



8

Tri-*n*-butylamine, *N,N*-dimethyl-*tert*-butylamine, other hindered amines, and *N,N*-dimethylaniline appeared to react with acetyl chloride but on addition of HF/BF_3 gave only the ammonium salts. The same result was observed with triethylamine and benzoyl chloride, pivaloyl chloride, or *n*-butyryl chloride. With trimethylamine and *N*-methylpiperidine the adduct formation of the amines and acetyl chloride appeared to be complete but the *N*-acetylammonium fluoroborates never formed or if formed were too reactive for isolation.

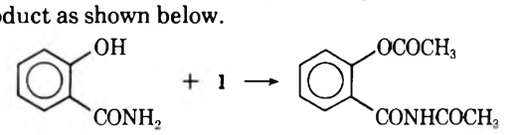
Reactions to test the acylating ability of the *N*-acetylammonium fluoroborates were tried to determine if the pure products differed in any form from the addition compounds of tertiary amines and acyl chloride. The reaction of water with the adduct of pyridine and acetyl chloride has been known to give acetic acid and acetic anhydride.[7] The same adduct was found to be a good acetylating agent for alcohols and phenols,[23] and suggested to be an analytical reagent for the determination of active hydroxyl groups.[24] The same adduct also has been known to acetylate hydrogen sulfide[25] and primary amides.[26]

To test the reactivity of *N*-acetylammonium fluoroborates the nmr spectral changes were followed after adding a small amount of deuterium oxide. In all cases spectral changes could be observed instantly in *N*-acetyl-*N*-*n*-propylpiperidinium fluoroborate (4). The singlet of the acetyl group at δ 2.85 ppm disappeared, and a new peak appeared at about δ 2.3 ppm which is very similar to that of acetic anhydride. Also the multiplet at about δ 3.8 ppm moved to about δ 3.3 ppm, which corresponds to the change of the methylene protons adjacent to the nitrogen atom of the compound 4 to those of the tertiary amine hydrogen ion salt. The observed changes can be explained as being due to rapid hydrolysis of the *N*-acetylammonium salt 4 by deuterium oxide to give acetic acid, which reacted further to give acetic anhydride.

The most stable *N*-acetylammonium fluoroborate (1) was chosen as the model compound for a large-scale product study. The nucleophiles examined were amines, thiophenol, amides, and acids.

The reaction of 25% excess of the model compound with *dl*-α-phenethylamine gave a nearly quantitative yield of crude *dl*-α-phenethylacetamide. *N*-Methylcyclohexylamine was acetylated similarly to give the acetamide in 91% yield. With *N*-methylaniline the yield of the amide was only 51%, apparently owing to some side reactions as was indicated by the appearance of a blue color in the reaction medium. Thiophenol was acetylated to give 88% of thiophenyl acetate. *N*-Benzyloxycarbonylglycine was allowed to react with the model compound, and the expected acid anhydride reacted with ethyl glycinate to give a 65% yield of the dipeptide.

The reaction of the model compound with alcohols proceeded to some extent, the degree of which depended upon the nature of the hydroxyl groups. Thus benzyl alcohol reacted to give 97% of benzyl acetate under strenuous conditions, but cyclohexanol gave only a mixture of the acetylated product and the unreacted alcohol in 68:32 ratio (by glpc) under similar reaction conditions. *tert*-Butyl alcohol could be recovered unreacted from a similar reaction. The reaction of salicylamide gave the diacetylated product as shown below.



Methylglycinate hydrochloride did not react with the model compound 1 in acetonitrile in the presence of 1 equiv of triethylamine or pyridine. Methyl benzyl ketone did not react with the model compound 1 in acetonitrile.

There might be several advantages or disadvantages in using this type of *N*-acetylammonium salts as acylation reagents. Possible disadvantages will be the low solubility in less polar organic solvents and their general instability. Although they seemed to be good acetylation reagents for strong nucleophiles, the instability did not permit the use of more strenuous reaction conditions such as high temperature for weak nucleophiles. The decreased reactivity of some *N*-acetylammonium fluoroborates toward hindered alcohols may be attributed to the bulky ammonium groups. This fact might be usefully employed for selective acetylation of less hindered hydroxyl groups.

Experimental Section[27]

Preparation of *N*-Acetyl-*N*,*N*-dimethylcyclohexylammonium Fluoroborate Using Triethyloxonium Fluoroborate. To a solution of 1.50 g (0.02 mol) of acetyl chloride in 50 ml of ether cooled to −78° was added in drops 1.27 g (0.01 mol) of *N*,*N*-dimethylcyclohexylamine in 50 ml of ether while stirring vigorously. After the completion of the addition the mixture was allowed to stand at −76° for 5 hr and at −10 to −20° for 2 hr. It was cooled again to −78°, and 1.89 g (0.01 mol) of triethyloxonium fluoroborate in 50 ml of methylene chloride cooled to −78° were added at once. After the cooling bath was removed, the solution was stirred until room temperature was reached. Precipiated colorless crystals were collected and washed with 2:1 ether–methylene chloride mixed solvent several times under a dry nitrogen atmosphere, and dried under vacuum. The yield was 2.24 g (84%); mp 64.5–66°; ir (Nujol mull) 1829 (strong, C=O and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.20–2.35 (br, CH_2, 10 H), 2.90 (s, CH_3CO, 3 H), 3.33 (s, CH_3N^+, 6 H), and 3.85–4.35 (br, CHN^+, 1 H).

Anal. Calcd for $C_{10}H_{20}NOBF_4$ (257.09): C, 46.72; H, 7.84; N, 5.45. Found: C, 46.70; H, 8.10; N, 5.60.

General Procedure for the Preparation of *N*-Acetyl-*N*,*N*,*N*-trialkylammonium Fluoroborates. To a solution of acetyl chloride (0.02 mol) in 50 ml of anhydrous ether cooled to −78° was added in drops a solution of tertiary amine (0.01 mol) in 50 ml of anhydrous ether while stirring. It was allowed to stand for 5 hr at −78° and for 2 hr at −10 to 20°. The adduct was cooled to −78°, and a 1:1 mixture of hydrogen fluoride and boron trifluoride (0.015 mol) was added at once. After the cooling bath was removed, the solution was stirred until room temperature was reached. Precipitated colorless crystals were collected, washed with anhydrous ether three times, and dried under vacuum. (Moisture was kept low by using a reaction system closed by calcium chloride–sodium hydroxide drying tubes where the reagents and solvents were transported by pressurized dry nitrogen. Analytical samples were prepared in a drybox.)

***N*-Acetyl-*N*,*N*,*N*-triethylammonium fluoroborate** (yield 98%) was recrystallized from 1:10 acetonitrile–ethyl acetate mixed solvent by adding anhydrous ether: mp 60–61°; ir (Nujol mull) 1814 (strong, C=O) and 1000–1120 cm^{-1}; nmr (acetonitrile) δ 1.21 (t, CH_3, 9 H), 2.72 (s, CH_3CO, 3 H), and 3.57 (q, CH_2N^+, 6 H); uv tail (acetonitrile) 240 nm (ϵ 70).

Anal. Calcd for $C_8H_{18}ONBF_4$ (231.05): C, 41.58; H, 7.85; N, 6.06. Found: C, 41.10; H, 8.14; N, 6.08.

***N*-Acetyl-*N*-ethylpiperidinium fluoroborate** (yield 90%) was recrystallized from 1:10 acetonitrile–ethyl acetate by adding anhydrous ether: mp 92–93°; ir (Nujol mull) 1817 (strong, C=O) and 980–1120 cm^{-1}; nmr (acetone-d_6) δ 1.28 (t, CH_3, 3 H), 1.50–2.20 (br, CH_2, 6 H), 2.86 (s, CH_3CO, 3 H), 3.85 (q, CH_2N^+, 2 H), and 3.40–4.15 (br, CH_2N^+, 4 H).

Anal. Calcd for $C_9H_{18}ONBF_4$ (243.06): C, 44.47; H, 7.46; N, 5.76. Found: C, 44.50; H, 7.35; N, 5.76.

***N*-Acetyl-*N*-*n*-propylpiperidinium fluoroborate** (yield 87%) was recrystallized from 1:10 acetonitrile–ethyl acetate mixed solvent by adding anhydrous ether: mp 68–69.5°; ir (Nujol mull) 1818 (strong, C=O and 990–1120 cm^{-1}; nmr (acetone-d_6) δ 0.98 (t, CH_3, 3 H), 150–2.25 (br, CH_2, 8 H), 2.85 (s, CH_3CO, 3 H), and 3.40–4.35 (br, CH_2N^+, 6 H).

Anal. Calcd for $C_{10}H_{20}ONBF_4$ (257.09): C, 46.72; H, 7.84; N, 5.45. Found: C, 46.95; H, 7.95; N, 5.58.

***N*-Acetyl-*N*-*n*-butylpiperidinium fluoroborate** (yield 99%) was recrystallized from 1:10 acetonitrile–ethyl acetate mixed solvent by adding anhydrous ether: mp 76–77°; ir (Nujol mull) 1808 (strong, C=O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 0.95 (t, CH_3, 3 H), 1.22–2.25 (br, CH_2, 10 H), 2.86 (s, CH_3CO, 3 H), and 3.35–4.35 (br, CH_2N^+, 6 H).

Anal. Calcd for $C_{11}H_{22}ONBF_4$ (271.12): C, 48.73; H, 8.18; N, 5.17. Found: C, 48.50; H, 8.05; N, 4.93.

***N*-Acetyl-*N*,*N*-dimethylcyclohexylammonium fluoroborate** (yield 97%) had ir and nmr spectra identical with those obtained earlier using triethyloxonium fluoroborate as the anion exchange reagent.

***N*-Acetylpyridinium Fluoroborate.** The reaction product was shown to contain about 40% of pyridinium fluoroborate salt as examined by nmr spectroscopy. The impurity was removed by washing with dry acetone (5 × 10 ml for 0.01 mol of product mix-

ture): mp 105–106° dec; ir (Nujol mull) 1806 (strong, C=O) and 1000–1100 cm^{-1}; nmr (CF_3COOH) δ 3.13 (s, CH_3CO, 3 H), 8.30 (t, 3-H, 2 H), 8.91 (t, 4-H, 1 H), and 9.46 (d, 2-H, 2 H).

Anal. Calcd for $C_7H_8ONBF_4$ (208.96): C, 40.23; H, 3.86; N, 6.70. Found: C, 39.90; H, 3.83; N, 7.04.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *N*-Methylcyclohexylamine. To a solution of 1.15 g (0.0045 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 0.60 g (0.005 mol) of *N*-methylcyclohexylamine. (Heat evolution!) The solution was allowed to stand for several hours at room temperature, and the solvent was removed on a rotary evaporator at room temperature. The residue was extracted with ether (3 × 100 ml), and the ether layer was washed with 10 ml of 1 *N* HCl solution and 10 ml of water, dried (Na_2SO_4), and evaporated on a rotary evaporator without heating to give 0.71 g (91%) of crude *N*-methylcyclohexylacetamide as residue. Short-path distillation [88° (0.9 mm)] gave 0.51 g of clear oil whose ir and nmr spectra were identical with those of *N*-methylcyclohexylacetamide.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *N*-Methylaniline. To a solution of 2.30 g (0.009 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 0.90 g (0.0084 mol) of *N*-methylaniline. The solution was allowed to stand overnight at room temperature. (Deep blue color appeared.) The solvent was removed on a rotary evaporator, and the residue was extracted with ether (3 × 100 ml). The ether layer was washed with 10 ml of 1 *N* HCl and 10 ml of water, dried (Na_2SO_4), and evaporated to give 0.64 g (51%) of *N*-methylacetanilide, recrystallized from ethanol: mp 99.5°; ir (Nujol mull) 1658 cm^{-1} (strong, C=O); nmr (CCl_4) δ 1.78 (s, CH_3, 3 H), 3.20 (s, CH_3, 3 H), and 7.00–7.37 (m, phenyl ring, 5 H).

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *dl*-α-Phenethylamine. To a solution of 3.20 g (0.0125 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 1.20 g (0.01 mol) of *dl*-α-phenethylamine. The solution was allowed to stand for 1 hr, and the solvent was removed on a rotary evaporator without heating. The residue was extracted with ether (3 × 100 ml), and the ether layer was washed with 20 ml of 1 *N* HCl solution and 20 ml of water and dried (Na_2SO_4). Evaporation of the solvent gave 1.63 g (99%) of crude *dl*-α-phenethylacetamide, which was distilled [125° (0.5 mm)] to give a clear oil which crystallized later: mp 73–75°; ir (thin film) 3220 (strong, NH) and 1680 cm^{-1} (strong, C=O); nmr (CCl_4) δ 1.35 (d, CH_3, 3 H), 1.77 (s, CH_3, 3 H), 4.93 (m, CH, 1 H), 7.15 (m, phenyl ring, 5 H), and 8.33 (d, NH, 1 H).

Anal. Calcd for $C_{10}H_{13}NO$ (163.21): C, 73.59; H, 8.03; N, 8.58. Found: C, 73.31; H, 8.14; N, 8.39.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Thiophenol. To a solution of 1.15 g (0.0045 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 0.60 g (0.0054 mol) of thiophenol. The solution was allowed to stand for 1 day at room temperature. After refluxing for a few minutes the solvent was removed by azeotropic distillation with isopropyl ether (bp 63.5–68°), and the residue was extracted with ether (3 × 100 ml). The ether layer was washed with 20 ml of 2 N NaOH solution and 20 ml of water and dried (Na_2SO_4). Evaporation on a rotary evaporator at room temperature gave 0.60 g (88%) of crude thiophenyl acetate, which was distilled [70° (0.9 mm)] in a Hickman still to give a clear oil: ir (thin film) 1706 cm^{-1} (strong, C=O); nmr (CCl_4) δ 2.28 (s, CH_3, 3 H) and 7.30 (m, phenyl ring, 5 H); mass spectrum showed molecular ion at *m/e* 152.

Anal. Calcd for C_8H_8SO (152.21): C, 63.12; H, 5.30. Found: C, 63.35; H, 5.24.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Benzyl Alcohol. To a solution of 3.45 g (0.0133 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 1.26 g (0.01 mol) of benzyl alcohol. The solution was allowed to stand for 1 day at room temperature and refluxed for 30 min followed by removal of the solvent by distillation. The residue was extracted with ether (3 × 100 ml), and the ether portion was washed with water (4 × 10 ml), dried (Na_2SO_4), and evaporated on a rotary evaporator without heating to give 1.38 g (92%) of crude benzyl acetate, which was distilled in a short-path distillation column [90° (1.20 mm)] to give a clear oil: ir (thin film) 1839 (strong, C=O) and 1250 cm^{-1} (strong, CO); nmr (CCl_4) δ 1.97 (s, CH_3, 3 H), 4.97 (s, CH_2, 2 H), and 7.23 (m, phenyl ring, 5 H); mass spectrum showed molecular ion at *m/e* 150.

Anal. Calcd for $C_9H_{10}O_2$ (150.17): C, 71.98; H, 6.71. Found: C, 72.20; H, 6.62.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Cyclohexanol. To a solution of 3.20 g (0.0125 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 1.0 g (0.01 mol) of cyclohexanol. The solution was allowed to stand for 1 day at room temperature and for 5 hr at about 60–70°. The solvent was removed on a rotary evaporator without heating, and the residue was extracted with ether (3 × 100 ml). The ether layer was washed with a small amount of water, dried (Na_2SO_4), and evaporated to give 1.10 g of oil. Glpc analysis indicated 68% of cyclohexyl acetate and 32% of unreacted cyclohexanol (6 ft × 0.25 in., 15% Carbowax 20M on Chromosorb P, 125°, 180 ml/min). The acetate was collected and identified by ir and nmr spectra, which were in agreement with those of authentic material.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Salicylic Amide. To a solution of 7.71 g (0.03 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 50 ml of acetonitrile was added 1.30 g (0.0095 mol) of salicylic amide. The solution was allowed to stand at room temperature for 1 day followed by refluxing for about 30 min. The solvent was removed by distillation, and the residue was extracted with ether (2 × 100 ml). The ether portion was washed with a small amount of water, dried (Na_2SO_4), and distilled in a Hickman still [150° (1.4 mm)] to give 1.54 g (72.6%) of *N*-acetylsalicylic amide acetate as a clear oil which later crystallized as a low-melting solid: ir (thin film) 1779 (strong, C=O), 1718 (strong, C=O), and 1701 cm^{-1} (strong, C=O); nmr (CCl_4) δ 2.23 (s, CH_3, 3 H), 2.43 (s, CH_3, 3 H), and 6.97–7.43 (m, phenyl ring, 4 H); mass spectrum showed molecular ion at *m/e* 221.

Anal. Calcd for $C_{11}H_{11}NO_4$ (221.21): C, 59.72; H, 5.01; N, 6.35. Found: C, 60.05; H, 5.05; N, 6.56.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *N*-Benzyloxycarbonylglycine. To a solution of 2.30 g (0.09 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 2.09 g (0.01 mol) of *N*-benzyloxycarbonylglycine in small portions while stirring at about −10°. The solution was swirled for 15 min at −10° and for 15 min at room temperature, and cooled again to −10°. To this a solution of 1.40 g (0.01 mol) of ethyl glycinate hydrochloride and 1.01 g (0.01 mol) of triethylamine was added in drops while stirring. The reaction mixture was allowed to react and worked up as usual (as in the mixed anhydride method of peptide synthesis) to give 1.70 g (65%) of crude *N*-benzyloxycarbonylglycylglycine ethyl ester, which was recrystallized from ethanol. The final product gave identical ir and nmr spectra with those of authentic material.[1]

Registry No.—**1**, 51051-39-9; **2**, 51051-41-3; **3**, 51051-43-5; **4**, 51051-45-7; **5**, 51051-47-9; **6**, 51051-48-0; triethyloxonium fluoroborate, 368-39-8; acetyl chloride, 75-36-5; *N,N*-dimethylcyclohexylamine, 98-94-2; triethylamine, 121-44-8; *N*-ethylpiperidine, 766-09-6; *N*-*n*-propylpiperidine, 5470-02-0; *N*-*n*-butylpiperidine, 4945-48-6; pyridine, 110-86-1; *N*-methylcyclohexylamine, 100-60-7; *N*-methylaniline, 100-61-8; *N*-methylacetanilide, 579-10-2; *dl*-α-phenethylamine, 300-62-9; *dl*-α-phenethylacetamide, 36065-27-7; thiophenol, 108-98-5; thiophenyl acetate, 934-87-2; benzyl alcohol, 100-51-6; benzyl acetate, 140-11-4; cyclohexanol, 108-93-0; salicylic amide, 65-45-2; *N*-acetylsalicylic amide acetate, 51051-49-1; *N*-benzyloxycarbonylglycine, 1138-80-3.

References and Notes

(1) Financial support from the National Science Foundation to the Department of Chemistry for purchase of XL-100-15 and T-60 nmr spectrometers is gratefully acknowledged.
(2) Taken in part from the Ph.D. Thesis of M. G. Kim, Kansas State University, 1973.
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(27) All melting points were taken on a Nalge microscopic hot stage and are uncorrected except those used for comparison. Infrared spectra were obtained on a Perkin-Elmer 137 double beam recording spectrometer. Nmr spectra were determined on Varian T-60, A-60, or XL-100 recording spectrometers. Mass spectra were obtained using an AEI MS-9 recording spectrometer. Microanalysis were performed by the Chemistry Department, Kansas State University, Manhattan, Kan. Temperatures for short-path distillations were pot temperatures.

N-Cyanoammonium Salts as Intermediates in the von Braun Cyanogen Bromide Reaction

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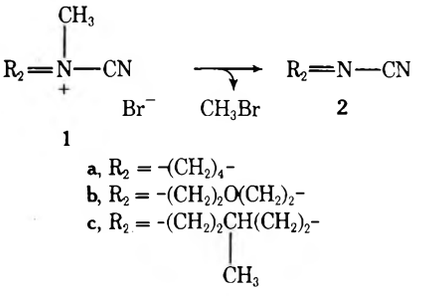
Cyanogen bromide was treated in a 1:1 ratio with a variety of tertiary amines (*e.g.*, *N*-methylpiperidine, *N*-methyl-*trans*-decahydroquinoline) to give *N*-cyanoammonium bromides (**1**), which have been trapped at temperatures of −50 to −10° for the first time, in crystalline form, and analyzed. Spontaneous decomposition of the bromides (**1**) led to methyl bromide and a secondary cyanamide (**2**). A low-temperature nmr kinetic study of step **1** → **2** in a variety of solvents yielded first-order rate constants. This two-step, low-temperature technique gave *sec*-cyanamides and, in turn, amines in yields superior to previous ones. In addition, no protection of hydroxyl groups is needed. Replacement of bromide by nonnucleophilic anions gave a number of stable cyanoammonium salts. N diastereoisomers (92:8) of *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium fluoroborate (**3b** and **4b**) have been separated and their configurations determined by combined pmr, ^{13}C nmr, and X-ray crystallographic studies, whereby equatorial preference of N-cyanation was established. These stable cyanoammonium salts were then reconverted into the epimeric bromides (**3a** and **4a**), and relative reaction rates of axial cyano *vs.* equatorial cyano epimers in the step **1** → **2** were determined. Furthermore, the decomposition of the chiral intermediate, (*S*)-(+)-*N*-cyano-*N*-*sec*-butyl-4-methylpiperidinium bromide (**15a**), gave (*R*)-(−)-*sec*-butyl bromide (**16**) with inversion. Some synthetic aspects of the cyanoammonium salt intermediates are outlined.

The von Braun cyanogen bromide reaction[1] (illustrated in Scheme I) has been extensively applied[2] over the past 70 years, but no mechanistic study has been undertaken, except some early unsuccessful approaches based on analogies with triphenylphosphine–cyanogen bromide[3] or with arsines.[4] The first circumstantial evidence for the mechanism was presented by Harper, *et al.*,[5] and Casy, *et al.*,[6] respectively. Methadone, a tertiary amine containing a carbonyl group, gave with cyanogen bromide no incorporation of bromide ion, but an unexpected cyclic, nitrogen-free compound: a tetrahydrofuran derivative. Therefore, an *N*-cyanoammonium salt structure was suggested for the first time as a possible intermediate, which underwent cleavage by carbonyl oxygen as an internal nucleophile. Along similar lines Albright and Goldman[7] recently succeeded in converting different alkaloids into cyclic ethoxy cyanamides with cyanogen bromide, using ethanol as a protic solvent. The incorporation of ethoxide instead of bromide occurred, and the overall steric course was one of inversion. This is further circumstantial evidence for the same type of intermediate, with no carbon–bromide bond; displacement by alkoxide ion should have otherwise resulted in a double inversion, equaling overall retention.

Preparation of *N*-Cyanoammonium Salts. We have undertaken a different study[8a,b] with the aim of finding direct evidence by trapping the postulated cyanoammonium salts for the first time. The present paper gives a full account of the experiments we have done in this field during the last 3 years. As a preliminary approach a stable cyanoammonium salt was sought, because any nucleophilic ion would very easily result in the breaking of the rather weakened *N*-methyl or other *N*-alkyl carbon bond.

Scheme I



There was no reagent known that would contain a cyanium cation compensated by any of the known nonnucleophilic anions, such as fluoroborate. However, a complex salt of cyanogen chloride and antimony pentachloride, described by Woolf[9] in the 1950's, gave cyanogen at the cathode upon electrolysis. It thus seemed an appropriate cyanium cation donor. In the meantime ^{13}C nmr studies were undertaken[10] on this complex salt, which showed that it is certainly not a cyanium hexachloroantimonate, but has the antimony coordinated with the nitrogen, not the chlorine, of cyanogen chloride. Nonetheless, the crystalline complex salt still held the promise of being a potential CN cation donor.

Therefore, we treated $CNCl \cdot SbCl_5$ with triethylamine in nitromethane; the ir spectrum of the product showed a strong C≡N stretch around 2200 cm^{-1}. The nmr spectrum indicated a strong downfield shift (by 0.8 ppm) of the methylene protons adjacent to nitrogen, indicative of the conversion of the amine nitrogen into a quaternary

Table I
Cyanoammonium Salts and Related Compounds

Registry no.	*N*-Cyanoammonium ion	Anion	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % X	Found, % C	Found, % H	Found, % N	Found, % X
51075-32-2	*N*-Methylpiperidinium	Chloroantimonate	78–80	$C_7H_{13}Cl_6N_2Sb$	18.2	2.9	5.4	46.5[b]	18.07	3.31	5.19	44.86[b]
51075-33-3	*N*-Methylpiperidinium	Bromide	0 dec	$C_7H_{13}BrN_2$	40.97	6.34	13.65	39.04[a]	41.10	6.32	13.81	
51075-34-4	*N*-Methylpiperidinium	Methanesulfonate	78–80	$C_8H_{16}N_2O_3S$	43.63	7.30	12.72	14.54[c]	44.24	7.43	12.50	15.07[c]
51075-36-6	*N*-Ethylpiperidinium	Methanesulfonate	74–75	$C_9H_{18}N_2O_3S$	46.05	7.69	11.96	13.67[c]	44.86	8.28	11.50	13.17[c]
51157-32-5	*N*-Methylmorpholinium	Methanesulfonate	92.5	$C_7H_{14}N_2O_4S$				14.50[c]				15.54[c]
51075-37-7	4-Hydroxypiperidine		Liquid	$C_5H_{10}N_2O$	57.14	7.93	22.22		56.91	8.06	22.26	
51075-39-9	3-β-Hydroxytropanium	Fluoroborate	142	$C_9H_{15}BF_4N_2O$	42.55	5.91	11.02		42.22	6.00	10.80	
51075-41-3	3-Oxotropanium	Fluoroborate	158–159	$C_9H_{13}BF_4N_2O$	42.86	5.16	11.11		43.09	5.12	11.04	
51075-42-4	3-Oxotropanium	Bromide	5 dec	$C_9H_{10}BrN_2O$	44.08	5.31	11.42		44.42	5.37	11.69	
51075-44-6	1-Hydroxymethylquinolizidinium	Fluoroborate	162–163	$C_{11}N_{19}BF_4N_2O$	46.81	6.74	9.98		46.91	6.65	10.11	
51153-93-6	*N*-Methyl-*trans*-decahydroquinolinium	Bromide	20 dec	$C_{11}N_{19}BrN_2$	50.96	7.34	10.81	30.89[a]	51.25	7.26	11.08	
51153-95-8	*N*-Methyl-*trans*-decahydroquinolinium	Chloroantimonate	175–180	$C_{11}N_{19}Cl_6N_2Sb$			5.45				5.45	
	N-Methyl-*trans*-decahydroquinolinium	Fluoroborate epimers		$C_{11}N_{19}BF_4N_2$	49.66	7.14	10.54	28.59[d]	49.53	7.05	10.76	28.42[d]
51075-45-7	*N*-Methyl-*trans*-decahydroquinolinium	Fluoroborate CN equatorial	135–136	$C_{11}H_{19}BF_4N_2$	49.66	7.14	10.54	28.59[d]	49.75	7.15	10.52	28.53[d]
51075-46-8	*N*-Methyl-*trans*-decahydroquinolinium	Fluoroborate CN axial	148–152	$C_{11}H_{19}BF_4N_2$	49.66	7.14	10.54	28.59[d]	49.95	7.40	10.47	
51075-47-9	*N*-Cyano-*trans*-decahydroquinoline			$C_{10}H_{16}N_2$	73.17	9.75			73.30	9.59		
51075-48-0	*N*-*sec*-Butyl-4-methylpiperidine		Bp 82 (22 mm)	$C_{10}H_{21}N$	77.42	13.54			77.24	13.53		

[a] Bromine. [b] Chlorine. [c] Sulfur. [d] Fluorine.

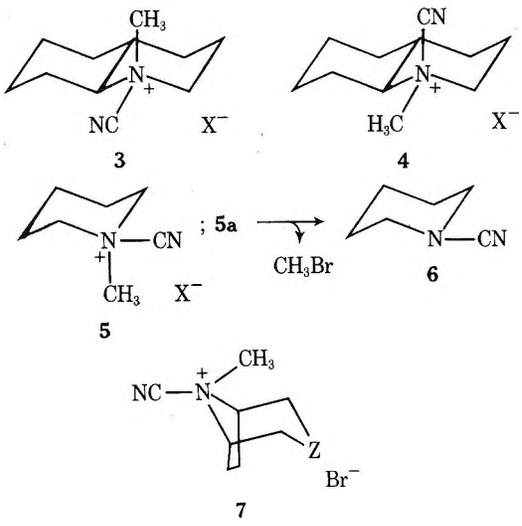
Table II
Significant Spectral Data of Cyanoammonium Salts, Cyanamides, and Some Related Compounds

Registry no.	*N*-Cyanoammonium ion	Anion	Ir, cm^{-1} (C≡N)	$^+NCH_3$ or $^+N(CN)CH_3$	$^+NCH_2$ or ^+NCH	Remote CH_2 and CH	Other protons
51075-49-1	Triethylammonium	Hexachloroantimonate	2200[a]	3.35 (t)	1.42 (q)		
51075-50-4	Triethylammonium	Bromide		2.86[e]	3.35[e] (q)	2.00[e]	
				3.08[b]	3.22[b] (q)	2.10[b]	
	N-Methylpiperidinium	Hexachloroantimonate	2200[j,k]	3.05 (s)	3.81,[c] 3.68	2.15[c]	
				3.22[b] (s)	3.95, 3.76 (m)	1.93[b]	
				3.15[b] (s)			
51075-51-5	*N*-Methylpiperidinium	Hexafluoroantimonate	2200[m]	3.14 (broad, s)	3.65 (m)	2.00	
	N-Methylpiperidinium	Methanesulfonate	2278[i]	2.88[b]	3.68	3.10 (CH_3SO_3)	
				2.90[c]	3.55[c]	3.18[c]	
				2.85[d]	3.55[d]	3.10[d]	

1530-87-6	Piperidine[h]		2205[f]		3.18[c,e]	1.62[c,e]	
	N-Ethylpiperidinium	Methanesulfonate	2200[i]	2.72[d]	3.7–3.4 3.10	1.42 (CH_2CH_3)	3.10 (CH_3SO_3)
51075-53-7	*N*-2,6-Trimethylpiperidinium	Methanesulfonate	2200[i]	3.02[c] (eq) 2.86[c] (ax)	3.2[c] (broad)	1.70[c]	3.30[c] (CH_3SO_3) 1.55 (d, J = 7 Hz, CCH_3)
51075-54-8	*N*-2,6-Trimethylpiperidinium[f]	*p*-Toluenesulfonate	2275[i]	2.93[c] (major) 2.60 (minor)	3.55[c] (broad)	1.82[c]	2.50[c] Ar–CH_3 major 1.47 (d, J = 6 Hz, CCH_3) 1.35 (d, J = 6 Hz, CCH_3)
	N-Methylmorpholinium	Methanesulfonate	2200[i]	2.78[d]	3.45[d]	4.15[d] (OCH_2)	
51157-34-7	*N*-Methyl-4-hydroxypiperidinium	Methanesulfonate	2220[i]	2.67[c]	3.48[c]	2.2	2.97 (CH_3SO_3)
51157-35-8	*N*-Methyl-4-hydroxypiperidinium	*p*-Toluenesulfonate	2215[i]	2.90[d]	3.42[d]	4.15 (CHOH)	2.52[d] ($ArCH_3$)
1530-89-8	Morpholine[h]		2215[f]		3.26[d] (NCH_2)	3.75[d] (OCH_2)	
	3β-Hydroxytropanium	Fluoroborate	2280[i]	3.68[d] (s)	4.82[d] (H-1,5)	1.95[d] (H-2,3,6,7)	4.0 (CHOH) 2.70 (OH)
	3-Oxotropanium	Fluoroborate	2280[i]	4.01[d]	5.1[d] (H-1,5)	2.0[d]	2.8 (CH_2CO)
	N-Methyl-*trans*-decahydroquinolinium	Hexachloroantimonate	2220[i]	3.10[b,f] (eq, major) 3.02 (ax, minor)	3.85[b,f] (H-2 eq) 3.68 (H-2 ax) 2.9 (H-9)	1.9[b,f]	
51153-96-9	*N*-Methyl-*trans*-decahydroquinolinium	Methanesulfonate	2280[i]	2.56[b,f]	3.55[b,f] (H-2,9) (broad)	1.72	3.20 3.10 (CH_3SO_3)
	N-Methyl-*trans*-decahydroquinolinium	Fluoroborate (CN eq)	2280[i]	3.63[d] 4.00[e]	4.34[d] (H-2 eq) 4.25 (H-2 ax) 4.13 (H-9)	1.70[d]	
	N-Methyl-*trans*-decahydroquinolinium	Fluoroborate (CN axial)	2280[i]	3.74[d]	4.36 (H-2 eq) 3.96 (H-2 ax) 3.87 (H-9)	1.70[d]	
51157-36-9	*N*-*sec*-Butyl-2-(3-bromopropyl)-cyclohexylamine[h]		2200[i]		3.48 (q, J = 7.1 Hz, CH_3CH)	1.65	1.21 (J = 7.1 Hz, CH_3CH) 0.95 (J = 6 Hz, CH_3CH_2)
51075-56-0	*N*-*sec*-Butyl-4-methylpiperidinium	Fluoroborate	2220[i]		3.50[e] (CH_2) 4.80[e] (CH)	1.72[e]	1.05 (CH_2CH_3) ($CHCH_3$) 1.35 (4-CH_3)
20696-86-0	4-Methylpiperidine[h]		2200[f]		2.8[g]	1.1[h]	0.68 (d, CCH_3)
51075-57-1	*N*-*sec*-Butyl-4-methylpiperidine[g]	Fluoroborate			3.2[e] 2.8	1.75[e]	0.95 (CH_2CH_3, $CHCH_3$) 1.35 (4-CH_3) 4.2 (NH)
51075-58-2	*N*-*sec*-Butyl-4-methylpiperidine[g]	Hydrobromide			3.3[e] 2.75	2.00[e]	1.08 (2 d, s, CH_2CH_3, $CHCH_3$) 1.45 (4-CH_3)
	1-Hydroxymethylquinolizidinium	Fluoroborate	2275[m]		4.7–4.0[d] (m, s, H-4,5,10)	2.00 (m, 12 H) 2.58 (H-1)	3.45 (CH_2O) 2.75 (OH)
10159-79-2	1-Hydroxymethylquinolizidine[g]				2.80[d] (H-4,5 eq)	2.0[d] 1.6	3.57 (CH_2O) 4.0 (OH)
51075-60-6	Methylpyrrolidinium	Fluoroborate	2200[i]	3.80[d]	4.40[d]	2.00[d]	
51075-61-7	*N*-Methyl-4-bromobutanamine[h]			2.82			
51075-62-8	*N*-4-(*N'*-methyl)piperidinium *N*-methylbutanamine bromide[h]			3.40[e] 2.80 $CH_3N(CN)$	3.70[e] (6 H)	1.80	

[a] Nitromethane. [b] DMSO-d_6. [c] Acetone-d_6. [d] Acetonitrile-d_3. [e] Chloroform-d. [f] Mixture of chloroform-d and acetonitrile-d_3. [g] Not a cyano compound. [h] Cyanamide. [i] Film. [j] Nitromethane. [k] Nujol. [l] Dimethylformamide. [m] Dinethyl sulfoxide.

Scheme II



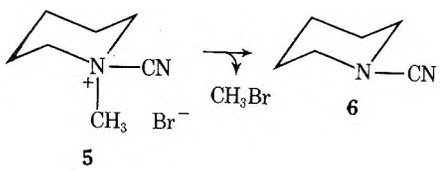
3 4 5 6 7

a, X = Br^-
b, X = BF_4^-
c, X = $O_3SCH_3^-$
d, X = $O_3S\text{-}C_6H_4CH_3\text{-}p^-$
e, X = $SbCl_6^-$

a, Z = CO
b, Z = CH(OH) ax
c, Z = CH(OH)eq

ammonium ion. Similarly, the chemical shift of the *N*-methyl signal of *N*-methylpiperidine, in its addition compound with the $CNCl\cdot SbCl_5$ complex, moved downfield by 0.82 ppm. Those shifts were of the same order of magnitude as those in the general quaternization of tertiary nitrogen into an ammonium ion center.[12c] Thus, we have indeed isolated *N*-cyanoammonium salts, *e.g.*, **5e** (Scheme II).

Although a variety of cyanoammonium hexachloroantimonates have now been prepared and analyzed (Tables I and II), these stabilized salts were not suitable for further study on any nucleophilic displacements of cyanoammonium salts because of solubility reasons. Therefore, as the next step, we intended to isolate the actual intermediates of the cyanogen bromide reaction. In ethereal solution at temperatures ranging from −10 to −50° we succeeded in isolating a white precipitate[8a,b] which could be filtered and dried. These cyanoammonium bromides were white, crystalline solids that have been kept for several days under vacuum at −16°. However, depending on their alkyl group, they decomposed between −10 and 10° and gave the cyanamides in very high yields. Thus, they proved to be the real intermediates in the von Braun reaction. They were immediately analyzed. Elemental analyses gave carbon, hydrogen, and nitrogen values close to the calculated ones for these unstable cyanoammonium bromides (Table I). On the other hand, *N*-cyano-*N*-methylpiperidinium bromide (**5a**) gave only the final displacement products, *N*-cyanopiperidine (**6**) and methyl bromide, the latter of which was trapped and quantitatively analyzed as *N*-ethylpiperidine methobromide. The cyanoammonium bromides, although sensitive, could be converted at −20° into "stabilized" salts, by ion exchange with silver methanesulfonate, *p*-toluenesulfonate, hexafluoroantimonate, or fluoroborate. Shortly after these experiments[8a] a different and independent approach was published in a communication by Paukstelis and Kim,[11] who converted the reaction mixtures of a few tertiary amines with cyanogen bromide into *N*-cyanoammonium fluoroborates with triethyloxonium fluoroborate, *i.e.*, the Meerwein salt.



5 6

The cyanoammonium bromides, *e.g.*, **1a-c, 3a, 4a, 5a, 7a-c,** etc., we have prepared were derived from *N*-methyl- and *N*-ethylpiperidine, 4-hydroxy-*N*-methylpiperidine, *N*-methylmorpholine, tropine, pseudotropine, tropinone, lupinine, *N*-methyl-*trans*-decahydroquinoline, 1,4-diazabicyclo[2.2.2]octane, and quinine. Most of these bromides were converted into the stable salts *via* ion exchange.

Table I indicates most physical and analytical properties of a number of both unstable and stabilized cyanoammonium salts. Table II contains the spectral data. Infrared spectra are consistent with their structure, the C≡N bond appearing as a sharp, medium-intensity band between 2200 and 2280 cm^{-1}.

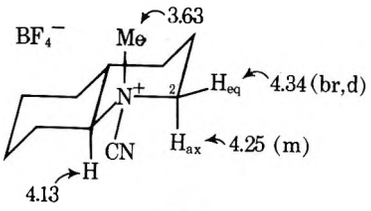
Structure and Stereochemistry. Our technique of low-temperature precipitation of the cyanoammonium bromide with subsequent conversion into the *stabilized* cyanoammonium salt gave near-quantitative yields of the latter. With these stable salts we were in the position to determine the preferred steric course of cyanation. The model we have used was (±)-*N*-methyl-*trans*-decahydroquinoline because of its configurational and conformational rigidity. Cyanation thereof by cyanogen bromide (addition of cyanide ion is now known as cyanylation[13]) was immeasurably fast and nearly quantitative. No traces of the tertiary amine could be detected by spectral methods, at as low as −65°, in a variety of solvents (after adding 1 mol of cyanogen bromide per mole of the tertiary amine). Cyanation may be regarded as a special case of quaternizations of nitrogen. *N*-Methyl-*trans*-decahydroquinoline in ethereal solution gave a very high yield of a crystalline product, which, based upon integration of the two pmr methyl signals (at δ 3.63 and 3.74 ppm; see Table II and Scheme III), consisted of the two N-epimeric bromides **3a** and **4a** in a ratio of 92:8. Those were separated by fractional crystallization after conversion into the fluoroborates **3b** and **4b** (Scheme III).

The crude product melted at 127–130° after recrystallization. The purified major product had mp 156°. The *cT* diagram of mixtures of the pure isomers showed a eutectic point at 100° and 50% composition; thus they gave a *definite* mixture melting point depression.

These cyanoammonium fluoroborates could also be prepared *in situ* if the reactions were done in acetonitrile with subsequent addition of silver fluoroborate; removal of silver bromide and freeze drying (or vacuum evaporation at low temperature) afforded the mixture of the stereoisomeric fluoroborates **3b** and **4b.** The Meerwein salt technique did not allow isolation of the minor isomer. The individual isomers, as well as their mixture, gave correct elemental analysis data (Table I). Both have been subjected to detailed spectroscopic study. Moreover, the major stereoisomer was analyzed by X-ray crystallography.[12b]

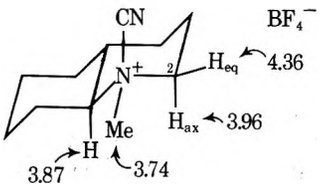
Nuclear Magnetic Resonance Studies. Extensive pmr measurements at 250 and 100 MHz enabled unequivocal determination of relative configurations about the chiral nitrogen atom. Only the most important and pertinent data are given in Table II and Scheme III. The major stereoisomer (**3b**) showed three deshielded protons at δ 4.13, 4.25, and 4.34 ppm. The minor isomer (**4b**) contained the equivalent protons at δ 3.87, 3.96, and 4.36 ppm, respectively. The difference is striking regarding the first two chemical shifts. Therefore, the δ 4.13 and 4.25 ppm signals were assigned to H-9 and to H-2 axial, these protons being deshielded by an adjacent electronegative (*i.e.*, CN) group

Scheme III

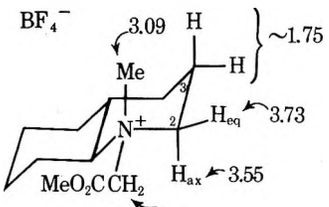


$J_{Me,2\text{-}Hax} = 0.4$ Hz

3b

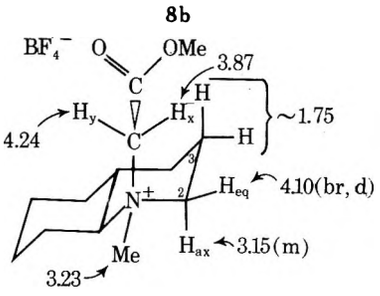


4b



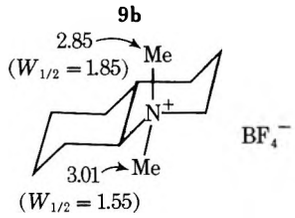
$J_{Hx,Hy} = 16.5$ Hz

8b



$J_{Hy,2\text{-}Hax} = 1.6$ Hz
$J_{Hx,Me} = 0.85$ Hz
$J_{Hx,Hy} = 16.5$ Hz

9b



10b

in the major product. The signals at δ 3.87 and 3.96 ppm were assigned to H-9 and H-2 axial in the minor stereoisomer, these being shielded by the adjacent equatorial *N*-methyl group. The two low-field signals at δ 4.34 and 4.36 ppm, in practically the same position in the two epimers, were attributed to the less affected equatorial protons at C-2. This by itself is evidence that the cyano group is equatorial in the major product, hence it must be axial in the minor product. In addition a long-range *W* coupling (J = 0.4 Hz) between *N*-methyl and H-2 axial of the major isomer could be decoupled by double irradiation of either signal at δ 3.63 or 4.25 ppm. There was no appreciable coupling between NCH_3 and H-9 protons.

In addition, methoxycarbonylmethylation of the same amine resulted in a 4:1 ratio of two N stereoisomers (**8a** and **9a**). The fluoroborate of the major and the minor products, **8b** and **9b**, respectively, indicated two diastereotopic methylene signals of the methoxycarbonylmethyl group at δ 4.29 and 4.09 ppm (J = 16.5 Hz) and at δ 4.24 and 3.87 ppm (J = 16.5 Hz), respectively. Also in the minor product the protons at C-3 have been located at approximately δ 1.75 ppm, by decoupling of the H-2 signals at δ 4.10 and 3.15 ppm. Furthermore, ^{14}N decoupling resulted in significant change in signal shape about δ 1.75 ppm, in agreement with results that β protons are more strongly coupled[14] to ^{14}N than are other protons. Irradiation at δ 1.75 ppm resulted in a 10% nuclear Overhauser effect (NOE) in the δ 3.87 ppm signal, which we assigned as H_x. Therefore, the methoxycarbonylmethyl group is axial in the minor product. The two C-2 proton assignments were made on the basis of their splitting patterns. It should be noted that, in accordance with the configuration derived from the NOE, *W*-type couplings were observed on the one hand between H_y and H-2 axial, and on the other between H_x and *N*-methyl. The two couplings show that rotation of the axial methoxycarbonylmethyl group is restricted in **9**.

A further reference compound, *N,N*-dimethyl-*trans*-decahydroquinolinium fluoroborate (**10b**), showed a difference in chemical shift between the two methyl signals of δ 2.85 and 3.01 ppm, respectively, and there was a considerable difference in half-height peak width (1.85 and 1.55 Hz). The greater half-height width is due to the *W* coupling of the higher field protons with H-2 axial and H-9 axial, which can only be the case if that methyl group was itself axial. The chemical shifts of the axial methyl group and methylene protons appeared at higher field than those of their equatorial counterparts in a number of other *trans*-decahydroquinoline derivatives.[12b]

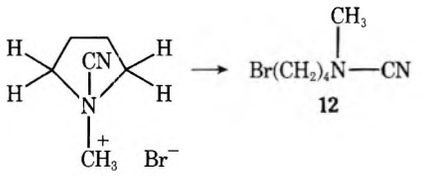
In conclusion, evidence based on pmr spectra point to the fact that cyanation of *N*-methyl-*trans*-decahydroquinoline took place preferentially in the equatorial position. In addition an extensive ^{13}C nmr spectroscopic study of compounds **3b**, **4b**, **8b**, **9b**, and **10b** was also undertaken. Details of that work will be published.[15] Wenkert, *et al.*[15] have shown that the *N*-methyl carbon atom of the major product of cyanation of the same base resonated at 8.7 ppm higher field than the one in the minor product. Furthermore, the C-3 and C-10 signals appeared at 3.4 and 4.1 ppm higher field than in the minor product, respectively. The conformational effect, in particular the 1,3-diaxial interaction of the two protons at C-10 and C-3 with axial *N*-methyl, would result in considerable shielding of carbons 10 and 3, while the axial cyano group in the major epimer does not as greatly affect those ^{13}C nmr shifts (similar to related cyclohexane derivatives[16]).

X-Ray Crystallography. X-Ray measurements were made at room temperature using a Picker four-circle diffractometer with Cu Kα radiation, proving structure **3b** for the major product of cyanation. Details of that X-ray crystallographic study will be published elsewhere.[17]

Thus, the combined pmr, ^{13}C nmr, and X-ray crystallographic studies[12b] have confirmed the complete geometry of the N-epimeric *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium fluoroborates, and are in complete agreement with other quaternization studies carried out with the same type of compound.

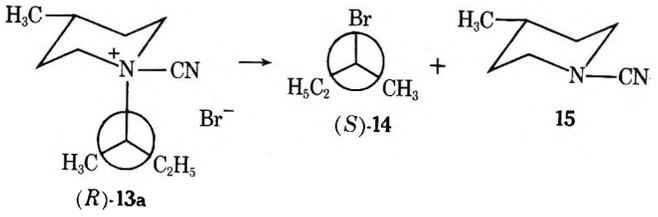
Reactions of *N*-Cyanoammonium Salts. Interionic Reaction. The reaction we studied most extensively is nucleophilic displacement of one of the alkyl groups from the chiral (or pseudo-chiral) nitrogen of the *N*-cyanoammonium salts. Two models in particular have been studied: *N*-methyl-*N*-cyanopiperidinium bromide (**5a**) and *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium bromide (**3a** and **4a**). In addition, preliminary studies have been undertaken with *N*-cyano-*N*-methylpyrrolidinium bromide

Scheme IV



11a

Scheme V



(R)-13a

(11a). For solubility reasons most of our kinetic studies were carried out with 3a and 4a. All *N*-cyanoammonium bromides we have isolated or prepared *in situ* are spontaneously decomposed at temperatures ≥0°. None were stable above 25° (see Kinetic Studies).

The bromides were attacked by other nucleophiles as well, such as alcohols or pyridine. The stable cyanoammonium methanesulfonates, *p*-toluenesulfonates, fluoroborates, or hexafluoroantimonates were decomposed in solution upon the addition of lithium bromide, whereby the bromide ion displaced the *N*-methyl group in most cases. With *N*-ethyl-*N*-cyanopiperidinium salts, however, ring cleavage occurred to a considerable extent concomitantly with ethylation. Similarly, *N*-methyl-*N*-cyanomorpholinium bromide (1b) also underwent ring cleavage. In the case of *N*-cyano-*N*-methylpyrrolidinium bromide (11a), the fluoroborate 11b could be isolated. However, the major pathway was that of ring cleavage of the bromide 11a (Scheme IV) into 4-(*N*-cyano-*N*-methylbutyl) bromide (12).[18] Most likely, in the cyanoammonium ion that forms in the course of the reaction, the strongly eclipsed C-2 and C-5 hydrogens interfered with the cis-positioned cyano or methyl groups attached to the ring nitrogen. Therefore, these additional nonbonded interactions may considerably weaken a ring C–N bond, ultimately resulting in ring cleavage. In addition, steric factors in the transition state may have a definite effect on the course of this reaction, but at present we are unable to assess their relative importance. *N*-Cyano-*N*-*sec*-butyl-4-methylpiperidinium bromide (13a) (Scheme V) prepared *in situ* was decomposed by mild heating into the expected cyanamide (6) and *sec*-butyl bromide (14). A mixture of 1- and 2-butenes and some *N*-sec-butyl-4-methylpiperidinium bromide were also isolated, as identified by their nmr spectra. The possible mechanism for olefin and amine salt formation could involve removal of a proton from the *sec*-butyl group of the cyanoammonium ion by the unchanged tertiary amine, *i.e.*, a Hofmann-type elimination instead of a nucleophilic attack of bromide upon the secondary butyl carbon atom.

Reactions with Other Nucleophiles. When the cyanoammonium bromide from either *N*-methylpiperidine or *N*-methyl-*trans*-decahydroquinoline was dissolved in acetone and sodium iodide was added, an instant coloration appeared, which upon titration showed that about 30% iodine had formed, by oxidation. Since the cyanoammonium cation cannot be an oxidizing agent, while cyanogen bromide is known to be, one reason[19] for this reaction was the dissociation of the cyanoammonium bromide into the tertiary amine and cyanogen bromide. The latter would then oxidize the iodide. One may object that there is no spectral evidence for any free base in the presence of cyanogen bromide. However, even if present in infinitesimally small amounts, rapid oxidation of iodide by cyanogen bromide could result in a shift of the equilibrium, in addition to the "normal" interionic reaction leading to the cyanamide and methyl bromide.

Reduction of the cyanoammonium salt 3b with sodium borohydride (in methanol) at 0° leads to an 80% yield of *N*-methyl-*trans*-decahydroquinoline. No other product could be isolated. Solvolysis of a 92:8 mixture of 3b and 4b with methanol-d_4 at 26.5 and 28.5°, respectively, resulted in the formation of *N*-methyl-*trans*-decahydroquinoline, characterized by its nmr spectrum. It showed no infrared stretch in the 2200-cm^{-1} region. That reaction was also monitored by pmr kinetics.

Action of sodium methoxide [$\delta(CH_3)$ 3.2 ppm] upon the salt 3b gave a product with a *N*-methyl signal at rather high field (δ 2.15, s) which can be assigned to *N*-methyl-*trans*-decahydroquinoline. However, no signal indicating the presence of dimethyl ether was detected. It is apparent that reduction of the cyanoammonium salt competed with alkylation. In spite of this, *N*-cyanotrialkylammonium salts can be used in synthesis as potential alkyl cation donors.

Reactions with Electrophiles. *N*-Cyano-*N*-methylpiperidinium fluoroborate reacts with trifluoroacetic acid. As shown by its pmr spectrum the N^+-methyl signal at δ 3.3 ppm slowly disappeared, giving rise to a new doublet of increasing intensity at δ 2.95 ppm. This product was identified as the trifluoroacetate of *N*-methylpiperidine. The fate of the CN group remains unclear. However, in the light of recently published experiments,[20] trifluoroacetic acid may react with the cyanoammonium salts to form $CF_3COOC{\equiv}N$ and/or $(CF_3CO)_2O$. The cyano group is thus removed, and the resulting tertiary base can subsequently form the salt with additional trifluoroacetic acid. A similar experiment with trifluoroacetic acid was carried out in acetonitrile-d_3. The major methyl signal appeared at δ 3.8 ppm. Upon addition of a drop of D_2O a doublet appeared in the δ 2.72 ppm region. The intensity of that signal increased while the one of the N^+-methyl signal decreased. At the end of addition of D_2O that signal became predominant. The doublet was again typical of the trifluoroacetate of the tertiary base. It is not easy to interpret that reaction; however, the product indicates an acidolytic or hydrolytic removal of the cyano group. Such a reaction would not be unexpected in the case of a cyanoammonium bromide, because dissociation thereof should lead to cyanogen bromide and the tertiary amine, the latter being protonated; hence the equilibrium slowly shifted. However, an analogous reaction with the fluoroborate leading to cyanium tetrafluoroborate was unlikely. The latter was not accessible from cyanogen bromide and silver fluoroborate.

Kinetic Studies. Kinetic data were obtained by measuring the decrease in intensity of the *N*-methyl signal in the pmr spectrum of the various cyanoammonium compounds under the appropriate reaction conditions. *N*-Cyano-*N*-methyl-*trans*-decahydroquinolinium bromide (3a + 4a) was found to be reasonably soluble in chloroform-*d*, acetonitrile-d_3, and nitromethane-d_3, and, in addition, the *trans*-decahydroquinoline skeleton is conformationally more rigid than that of piperidine. Thus, the greater part of the kinetic measurements were carried out in the *trans*-decahydroquinoline series.[12a,b]

The kinetic studies were essentially in three parts: (A) on mixed axial and equatorial N stereoisomers (3a + 4a) in the above three solvents (Figures 1 and 2); (B) on the separated N stereoisomers (3b or 4b) in the same three sol-

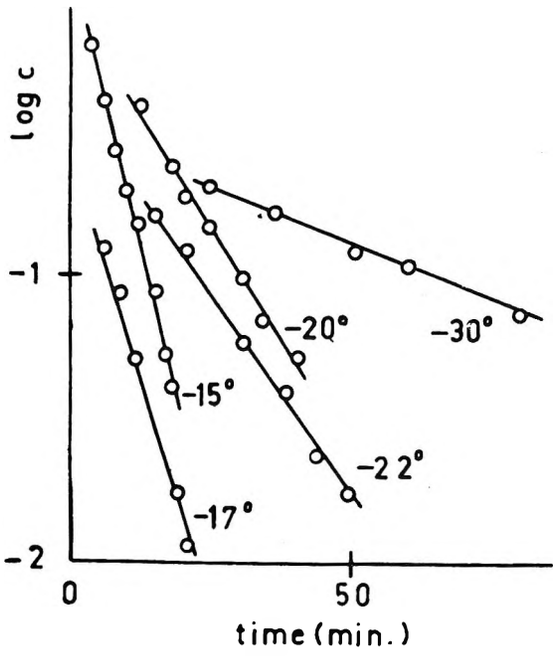


Figure 1. First-order plots for the decomposition of 3a + 4a in $CDCl_3$ at various temperatures.

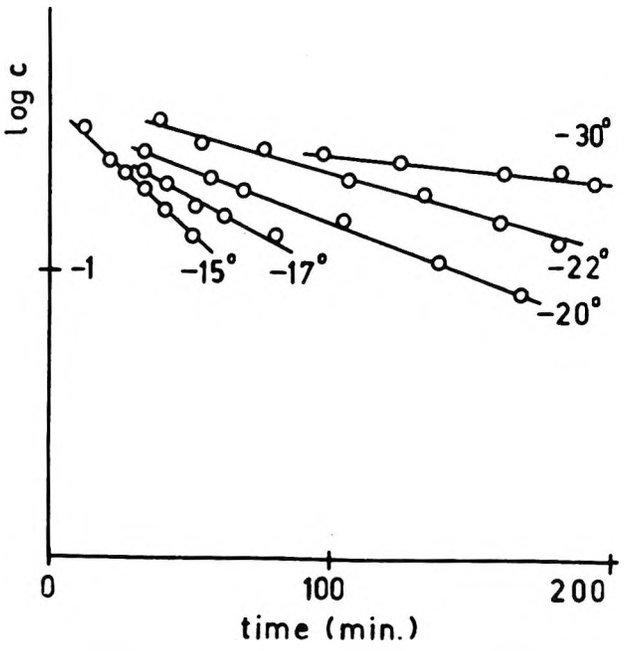


Figure 2. First-order plots for the decomposition of 3a + 4a in CD_3CN at various temperatures.

vents; and (C) on the separated N stereoisomers (3b or 4b) in CH_3OD. No difference was observed in the kinetic behavior whether the cyanation was carried out in one of these solvents or whether the cyanoammonium bromide (3a + 4a) was precipitated at −40 to −50° from ethereal solution and subsequently dissolved in the precooled reaction solvent. In addition to the molecularity of the reaction, these kinetic studies have allowed supporting conclusions to be drawn regarding the preferred steric course of the first step of cyanation, and of the configurational effect of substituents about the quaternary nitrogen upon the rate of decomposition of the cyanoammonium intermediate.

The decomposition rate of *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium bromide (3a + 4a) is ten times greater in chloroform-*d* than in acetonitrile-d_3 but only 2.5 times greater than in nitromethane-d_3. The decrease in rate tends to follow the order of increasing basicity and increasing *Z* value[21] (chloroform < nitromethane < acetonitrile) rather than an increase in the dipole moment (chloroform < acetonitrile < nitromethane).[22] The energies of activation are calculated to be 19 kcal mol^{-1} in chloroform and 22 kcal mol^{-1} in acetonitrile. Increase in the overall concentration of the salt or of the original cyanogen bromide did not affect the reaction rates. Added common ion (*e.g.*, from lithium bromide) to the acetonitrile solution only resulted in "salting out" the crystalline cyanoammonium bromide. However, the addition of 0.3 mol of lithium perchlorate per mole of cyanoammonium salt produced a considerable (*ca.* fivefold) rate attenuation, indicating a negative kinetic salt effect. These results can be explained by assuming a less polar transition state in the step 1 → 2, and that the reactant ions are solvated to a greater degree in acetonitrile.

The entropy of activation in chloroform-*d* was calculated to be +1.5 ± 3.0 eu, and in acetonitrile-d_3 it was +9.5 ± 3.0 eu (see Table III, Figures 1 and 2). The positive value in both of the above-mentioned cases is consistent with the above assumption of a transition state which is less polar (less strongly solvated) than the reactant ions in the step 1 → 2. In addition, the small positive ΔS^* in chloroform and the relatively larger value in acetonitrile suggests an intimate ion pair for the cyanoammonium bromide in chloroform, while in acetonitrile the more strongly solvated individual ions may give it a more "normal" salt structure. This conclusion is reached on the basis that an ion pair requires less reorganization of the solvent shell and loss of fewer solvent molecules in going from reactant to transition state than does a salt which is solvated as free, individual ions.

Conductance measurements taken at room temperature and at −42° in these solvents clearly show that there are a greater number of conducting species in the acetonitrile solution, there being a 1000-fold difference in conductivity between the two solvents; the conductivity is almost negligible in chloroform (Table IV).

We have followed Ross's analysis[23] in fitting the raw kinetic data to various rate laws. This analysis shows that, if the reacting salt is present in solution as all ion pairs, first-order kinetics will be observed; if free ions are present, second-order kinetics will be expected; if triple ions are present two-thirds-order kinetics will follow; and if quadruples are the predominant aggregates, one-half-order kinetics will be obtained. Intermediate reaction orders may indicate mixtures of species.

Our preliminary kinetic studies indicate that, in chloroform and in nitromethane at all temperatures investigated, first-order kinetics were followed. In acetonitrile at the relatively higher temperatures first-order kinetics were also observed, but both first-order and second-order plots became nonlinear below −20°. Taken together all of these physical data indicate that there is extensive ion pairing under the experimental conditions which we have used. However, the deviation from linearity below −20° in acetonitrile indicates that neither first- nor second-order kinetics are valid. Therefore, we interpret this as indicating in acetonitrile at these lower temperatures that the reacting species are most probably higher aggregates, *i.e.*, triple ions. We would suggest that the ion pair in chloroform is a tight ion pair and that in nitromethane and in acetonitrile it could be considered a solvent-separated ion pair.[24] The exact nature of the solvent cage about the ion aggregates is expected to be different in nitromethane and acetonitrile.

The influence of configuration about the ammonium nitrogen atom on reaction rates can be seen in the following data. The rate constant for the axial methyl derivative of *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium fluorobo-

Table III
First-Order Rate Constants[a] of the Decomposition of 3b and 4b into *N*-Cyano-*trans*-decahydroquinoline and Methyl Bromide at Different Temperatures

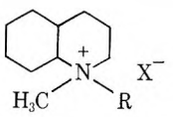
Solvent	−30°	−22°	−20°	−17°	−15°
Chloroform-*d*	3.0×10^{-4}	1.1×10^{-3}	1.2×10^{-3}	2.0×10^{-3}	3.0×10^{-3}
Acetonitrile-d_3	3.0×10^{-5}	1.0×10^{-4}	1.4×10^{-4}	2.0×10^{-4}	3.3×10^{-4}
Nitromethane-d_3			6.5×10^{-4}		1.2×10^{-3}

Calculated Activation Parameters

Solvent	E_a, kcal mol^{-1}	ΔG^* kcal mol^{-1}	ΔH^{*b} kcal mol^{-1}	ΔS^*, ev
Chloroform-*d*	19	18.1	18.5	+1.5
Acetonitrile-d_3	22	19.2	21.5	+9.5

[a] In reciprocal seconds. [b] ΔH^* calculated at −30 and −15°. For $CDCl_3$: 18.52 kcal mol^{-1} at −30°, 18.49 kcal mol^{-1} at −15°. For CD_3CN: 21.52 kcal mol^{-1} at −30°, 21.49 kcal mol^{-1} at −15°.

Table IV
Equivalent Conductance of Various *N*-Cyano-*trans*-decahydroquinoline Salts in Three Solvents



R	X	Solvent	Temp, °C	Δ, Mho/cm
CN	BF_4	CH_3CN	22.8	131.1
CN	BF_4	CH_3CN	−41.9	61.32
CN	Br	CH_3CN	−42.0	23.80
CN	BF_4	CH_3NO_2	22.7	78.17
CN	BF_4	$CHCl_3$	22.7	2.712×10^{-2}
CN	Br	$CHCl_3$	−42.0	"0"
C_2H_5[a]	Br	$CHCl_3$	22.7	14.07×10^{-2}
$(n\text{-Pr})_4{}^+NBr^-$[b]		$CHCl_3$	22.6	28.42×10^{-2}

[a] Registry no., 51075-63-9. [b] Registry no., 1941-30-6.

rate (reacts as the bromide) is 2.1×10^{-4} sec^{-1}, while that of the minor product, the equatorial *N*-methyl isomer, is 2.9×10^{-4} sec^{-1}; thus $k_{eq}/k_{ax} = 1.38$. This may be interpreted by assuming that the axial methyl group is somewhat hindered, or at least the equatorial methyl group is more easily attacked by the bromide ion.

Steric Course of the Decomposition of a Chiral Cyanoammonium Salt. Further insight into the mechanism of the interionic reaction was gained from the synthesis and decomposition of a cyanoammonium salt with a chiral *N*-alkyl group. 4-Methylpiperidine was butylated with (*S*)-(+)-2-butyl *p*-toluenesulfonate[25] of 59% optical purity to form (*R*)-(−)-*N*-*sec*-butyl-4-methylpiperidine, $[\alpha]^{20}_{4359}$ −26.97° (neat). This is similar to the preparation of (*R*)-(+)-*N*-*sec*-butylpiperidine.[25] The optical purity of this product could only be estimated at 27% [comparison with optically pure (*R*)-(+)-*N*-*sec*-butylpiperidine, $[\alpha]^{25}_{4359}$ +99° (neat)], since we have not yet completely resolved 4-methyl-*N*-*sec*-butylpiperidine. Reaction of the latter with cyanogen bromide led to isolation of the cyanoammonium bromide **13a**, which was characterized as the fluoroborate **13b**. Upon decomposition the chiral bromide **13a** gave rise to (*S*)-(+)-*sec*-butyl bromide (**14**), $[\alpha]^{20}_{4359}$ +7.3° (ether); optically pure (*S*)-(+)-butyl bromide[26,27] shows $[\alpha]^{20}_{4360}$ +70.5° (neat). On the other hand (*S*)-(+)-*sec*-butyl tosylate of 80% optical purity gave (*R*)-(−)-*sec*-butyl bromide, $[\alpha]^{20}_{4359}$ −58.2° (ether). That value was corrected to an optically pure bromide, $[\alpha]^{20}_{4359}$ −72.7°. Therefore, the optical purity of the bromide from **13a** was only 10%. The steric course of the N-debutylation, however, corresponds to 36% inversion, if the low optical purity of our *N*-*sec*-butyl-4-methylpiperidine is taken into account. This warrants the statement that the interionic dealkylation step leading to *sec*-butyl bromide occurred with inversion, which thus implies an SN2-type displacement of the nitrogen from the *sec*-butyl carbon 2.

The product of this reaction was the expected *N*-cyano-4-methylpiperidine (**15**) in high yield. In addition a mixture of 1- and 2-butenes, probably formed by the action of unchanged *N*-butylpiperidine upon the cyanoammonium bromide, *i.e.*, by Hofmann elimination, was detected. Furthermore, a 10% yield of *N*-*sec*-butyl-4-methylpiperidine hydrobromide (**16**) was isolated, in agreement with the elimination mechanism. Compound **16**, or rather its bromide ion, was responsible for considerable racemization of the (*S*)-(+)-*sec*-butyl bromide formed in the reaction **13a** → **14** + **15**. This was proven by distilling added optically pure *sec*-butyl bromide from the same salt in a control experiment, which resulted in complete racemization thereof. That undesirable process was somewhat minimized by precipitating the hydrobromide with ether immediately following the von Braun reaction of **13a** carried out at 10°, and subsequently distilling the (*S*)-(+)-*sec*-butyl bromide, now practically free of bromide ions.

Experimental Section

General. Nmr spectra were recorded on a Varian HA-60, HA-100, or T-60 spectrometer unless otherwise specified; chemical shifts are given in parts per million (δ) downfield from TMS as internal reference. Ir spectra were recorded on a Beckman IR-8 spectrophotometer. Melting points were taken on an Electrothermal Model 1A 6304 apparatus. Optical rotations were measured at 25° with a Perkin-Elmer Model 141 M electric polarimeter. Elemental analyses were partly carried out on F & M Model 185 C, H, N Analyser by Mr. R. Dulude, and partly by Galbraith Laboratories, Knoxville, Tenn.

All solvents employed in the preparation of *N*-cyanoammonium salts were carefully purified before use. Acetonitrile was dried over phosphorus pentoxide overnight and then distilled. Commercial anhydrous ether was refluxed with lithium aluminum hydride for 2 hr and then distilled directly into the reaction flask. Cyanogen bromide was distilled from calcium carbonate–magnesium oxide (1:1). Other liquid reagents were distilled and solid reagents were recrystallized to ensure purity.

General Procedure for the Preparation of Quaternary *N*-Cyanoammonium Bromides (for Details See Tables I and II). A solution of 1.9 g (0.018 mol) of cyanogen bromide in 15 ml of anhydrous ether was cooled to −50°, and 0.016 mol of the tertiary amine in 20 ml of anhydrous ether was added dropwise over a period of 30 min with efficient stirring. The reaction mixture was stirred for an additional 3 min, and the temperature was maintained between −50 and −60°. At the end of this period the voluminous precipitate was transferred as rapidly as possible to a sintered glass funnel equipped with an evacuated cooling jacket and suction filtered, first at the water aspirator and then with an oil pump. The yield of the dry solid was in the range of 95–98%. Attempts to dissolve either *N*-cyano-*N*-methylpiperidinium bromide (**5a**) or *N*-cyanotropinonium bromide (**7a**) in available nmr solvents at temperatures below −40° were unsuccessful. *N*-Cyano-

N-methyl-*trans*-decahydroquinolinium bromide (**3a + 4a**), on the other hand, dissolved readily in chloroform-*d*, acetonitrile-d_3, or nitromethane-d_3. For physical and spectral data see Tables I and II.

General Procedure for the Thermal Decomposition of *N*-Cyanoammonium Bromides. All experiments were carried out under strictly anhydrous conditions. For example, 6.15 g (0.03 mol) of *N*-cyano-*N*-methylpiperidinium bromide, which had been kept at −80°, was placed in a 100-ml round-bottom flask being immersed in a Dry Ice–acetone bath. The flask was connected to a short-path distillation unit equipped with a cold finger condenser; the receiver was cooled in a Dry Ice–acetone bath. Upon warming gradually to room temperature, the solid mass began to appear deliquescent on the surface. When gentle heating was applied with a hot air gun, the solid disintegrated completely, yielding a gas, which was condensed into the cold receiver, and a liquid. The gas was identified as methyl bromide (2.47 g, 88%), a sample of which had superimposable nmr and ir spectra and identical chemical properties with authentic material. The liquid was distilled, yielding 3 g (92%) of *N*-cyanopiperidine: bp 104° (10 mm) [lit.[28] bp 102–104° (10 mm)]; ir 2200 cm^{-1} (s, C≡N); nmr spectrum was identical with that of an authentic sample. Thermal decomposition of *N*-cyanotropinonium bromide (**7a**) by the same method gave 85 and 86% yield of methyl bromide and *N*-cyanotropinone, respectively. Similarly *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium bromide (**3a + 4a**) was thermally decomposed to give methyl bromide (91%) and *N*-cyano-*trans*-decahydroquinoline (98%). The latter cyanamide boiled at 102–103° (0.09 mm) and showed no difference from the compound obtained by direct N-cyanation of *trans*-decahydroquinoline with cyanogen bromide.

General Procedure for the Preparation of Stabilized *N*-Cyanoammonium Salts. The *N*-cyanoammonium bromide was prepared by the method described above. To a very well stirred suspension of that salt in ether at −50° a solution of an equivalent amount of silver tetrafluoroborate (or silver *p*-toluenesulfonate) was slowly added in acetonitrile. The mixture was stirred at −50° for another 1 hr and then allowed to warm to room temperature. The solvents were evaporated at reduced pressure and room temperature; the remaining solid was then thoroughly triturated with acetonitrile. The silver bromide was removed by filtration, leaving behind a clear solution of the stable *N*-cyanoammonium salt. Reduced-pressure evaporation of the solvent at 10–20° afforded the crude product, which was analyzed by nmr. Recrystallization, usually from acetonitrile–ether, gave the pure *N*-cyanoammonium tetrafluoroborate (or *p*-toluenesulfonate). The yields and melting points of some products were as follows: *N*-cyano-*N*-methylpiperidinium methanesulfonate, 75%, mp 78–80°; *N*-cyano-*N*-ethylpiperidinium methanesulfonate, 64%, mp 75–75°; *N*-cyanopseudotropinium tetrafluoroborate, 95%, mp 142°; *N*-cyanotropinonium tetrafluoroborate, 90%, mp 158–159°; *N*-cyanolupininium tetrafluoroborate, 88%, mp 162–163°.

***N*-Cyano-*N*-methylpiperidinium Hexachloroantimonate (5e).** The cyanogen chloride–antimony pentachloride complex salt was prepared according to the method of Woolf.[9] The pure crystalline material was obtained as colorless prisms by sublimation (10^{-3} mm) at room temperature: mp 124–125° dec; ir 2220 cm^{-1} (C≡N); λ_{max} (CH_3CN) 268 mμ. A solution of *N*-methylpiperidine (0.74 g, 7.5 mmol) in 5 ml of dry nitromethane was added dropwise to a cold, stirred solution (−10°) of the fresh sublimed complex salt (2.7 g, 7.5 mmol) in 10 ml of dry nitromethane. Freeze-drying of the reaction mixture left a solid product (3 g, 94%), mp 79–80°.

***N*-Methyl-*trans*-decahydroquinoline.** The Eschweiler procedure was used as modified by Clarke, Gillespie, and Weisshaus.[29] *trans*-Decahydroquinoline (25 g, 0.18 mol) was heated[30a] to 95–100° with 45 ml of 91% formic acid and 45 ml of 37% aqueous formaldehyde for 10 hr. The cooled reaction solution was evaporated to dryness after addition of 100 ml of 4 *N* hydrochloric acid, and the tertiary amine was liberated by subsequent addition of a 20% potassium hydroxide solution. The crude product was purified by vacuum distillation. The yield of *N*-methyl-*trans*-decahydroquinoline was 21.4 g (78%); bp 73° (3 mm) [lit.[30b] bp 204° (721 mm)]; ir 2750 cm^{-1}; nmr ($CDCl_3$) δ 2.01 (NCH_3, 3 H, s).

Preparation and Separation of N Stereoisomers 3b and 4b, *N*-Cyano-*N*-methyl-*trans*-decahydroquinolinium Tetrafluoroborate. The crude cyanoammonium salt was obtained in 95% yield from the reaction of *N*-methyl-*trans*-decahydroquinoline with cyanogen bromide at −30° in ether or acetonitrile (see general procedure). Subsequent treatment of the resulting intermediates with silver tetrafluoroborate and integration of the $^+NCH_3$ nmr signals of the stabilized salt indicated a mixture consisting of 95% major product (**3b**) and 5% minor product (**4b**). The epimers were separated by fractional crystallization. Anhydrous ether was added gradually to a solution of 11 g of the crude product (**3b** and **4b**) in 150 ml of acetonitrile until the solution became faintly turbid and kept at 0–5° for a few hours. The CN-equatorial epimer (**3b**) had crystallized out as colorless needles (2.3 g, 21%), mp 135°.

Repeated recrystallization by the same procedure afforded two more crops of pure major compound **3b** from the mother liquor, yielding a total of 3.9 g (35.4%) of monoclinic crystals. The intermediate fractions contained mixtures (50:50 mixture, mp 100°) while the final two fractions contained a total of 0.2 g (1.8%) of the pure CN-axial epimer (**4b**). The latter melted at 156°.

Reaction of an *N*-Cyanoammonium Tetrafluoroborate with Lithium Bromide. Anhydrous lithium bromide (1.15 g, 0.013 mol) was dissolved in 25 ml of acetonitrile, and a solution of 2.44 g (0.0091 mol) of *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium tetrafluoroborate (**3b**) in 10 ml of acetonitrile was added. A white precipitate formed immediately, the mixture was diluted with ether, and the precipitate was filtered and washed with ether. The filtrate and the ethereal solution were combined. Removal of the solvents followed by vacuum distillation yielded 1.33 g (89%) of *N*-cyano-*trans*-decahydroquinoline which was spectrally identical with an authentic specimen.

Optically Active 2-Butyl *p*-Toluenesulfonate. (*S*)-(+)-2-Butanol), $[\alpha]^{25}_{4359}$ +16.15°, was supplied by Professor J. L. Wolfhagen of the University of Maine. However, later a product of higher optical purity, $[\alpha]^{25}_{4359}$ +22.08°, was obtained from Norse Laboratories and used for most of our experiments. By a method reported elsewhere[25] the latter alcohol (15.33 g, 0.27 mol) was treated with *p*-toluenesulfonyl chloride (89.5 g, 0.4 mol) in 300 ml of pyridine at 0° to give 27.3 g (73%) of *sec*-butyl *p*-toluenesulfonate, $[\alpha]^{25}_{4359}$ +10.35° (neat). The (*S*)-(+)-2-butanol of lower rotation gave a tosyl ester: $[\alpha]^{25}_{4359}$ +7.76° (neat); bp 80° (0.01 mm) [lit.[25] bp 95° (0.1 mm)]; ir 668, 820, 910, 1190, 1360, 1605, 3000, 3050 cm^{-1}, Kenyon, Phillips, and Pittman[25] reported $[\alpha]^{20}_{4359}$ +12.98° (neat).

Optically Active *N*-*sec*-Butyl-4-methylpiperidine. A mixture of 33.66 g (0.34 mol) of freshly distilled 4-methylpiperidine and of (*S*)-(+)-*sec*-butyl *p*-toluenesulfonate, $[\alpha]^{25}_{4359}$ +7.76°, was stirred at 85° overnight. As the reaction proceeded, the clear solution separated gradually into two layers. At the end of the reaction, the bottom layer solidified upon cooling. The solid, 4-methylpiperidine hydrobromide, was separated by filtration, washed thoroughly with several portions of ether, dissolved in water, and finally treated with 20% aqueous KOH solution, and dried (K_2CO_3). The ether was evaporated on a rotary evaporator, and the residual oil was fractionally distilled to yield 20.2 g (77%) of (*R*)-(−)-*N*-*sec*-butyl-4-methylpiperidine, bp 82° (22 mm), $[\alpha]^{25}_{4359}$ −26.96° (neat). This was approximately 27% optically pure; ir and nmr spectra of this material matched perfectly those of the corresponding optically inactive compound which had been previously prepared. For analytical data see Table I.

Cyanogen Bromide Reaction of Optically Active *N*-*sec*-Butyl-4-methylpiperidine. A solution of 7.75 g (0.05 mol) of (*S*)-(+)-*N*-*sec*-butyl-4-methylpiperidine in 10 ml of anhydrous ether was added with constant stirring to a precooled solution (−60°) of 6.36 g (0.06 mol) of cyanogen bromide in 10 ml of anhydrous ether, similar to the general preparation of quaternary *N*-cyanoammonium bromides. After the NCH_3 signal in the pmr spectrum of the free tertiary amine had completely disappeared the reaction mixture was kept at −60° for 2 hr. The solution of **13a** was then allowed to warm to room temperature. After 30 min, 20 ml of dry ether was added to precipitate *N*-sec-butyl-4-methylpiperidine hydrobromide, mp 211° (4.7 g, 50.6%). Also isolated was 0.85 g (14.55%) of (*S*)-(+)-*sec*-butyl bromide (**16**), bp 90–92°, $[\alpha]^{25}_{4359}$ +7.3° (ether, c 0.85). The optical purity of the latter compound was 10% relative to the optically pure (*S*)-(+)-*sec*-butyl bromide, $[\alpha]^{25}_{4359}$ +7.05° (neat[27]), +72.9° (ether). A part of the butyl residue was detected by pmr as a mixture of 1- and 2-butene. The residue afforded 2.9 g (48%) of *N*-cyano-4-methylpiperidine (**15**), bp 75–76° (0.5 mm) [lit.[31] bp 78° (1 mm)]. The above experiment, when repeated with 15.5 g (0.1 mol) of (*R*)-(−)-*N*-*sec*-butyl-4-methylpiperidine and 10.6 g (0.1 mol) of cyanogen bromide in bromobenzene, gave 1.1 g (8%) of *sec*-butyl bromide, $[\alpha]^{27}_{4359}$ +1.22° (neat), corresponding to 1.74% optical purity, and about 6.4% inversion. The considerable loss of optical purity is due to secondary racemization by bromide ion as shown by the following control experiment.

Racemization of (*R*)-(−)-*sec*-Butyl Bromide by Bromide

Ion. Optically active (*R*)-(−)-*sec*-butyl bromide (1.37 g, 0.01 mol), $[\alpha]^{25}_{4359}$ −56° (neat), prepared[25] from (*S*)-(+)-*sec*-butyl tosylate, and 2.35 (0.01 mol) of racemic *N*-*sec*-butyl-4-methylpiperidine were dissolved in 30 ml of bromobenzene and then distilled to give 1 g (73%) of *sec*-butyl bromide, bp 90–91°, $[\alpha]^{25}_{4359}$ 0°, completely racemized.

Kinetic Measurements. Decomposition of *N*-Cyano-*N*-methyl-*trans*-decahydroquinolinium Bromide. All of the solutions for low-temperature nmr studies were 2 *M* concentration of the sample in chloroform-*d*, acetonitrile-d_3, or nitromethane-d_3. Sample temperatures were maintained by a Varian V-4340 low-temperature probe and were calibrated by recording the temperature as a function of the difference in chemical shifts of the hydroxyl proton and methyl protons of methanol. The rates of decomposition of the *N*-cyanoammonium bromide were measured at −30, −22, −20, −17, and −15 ± 0.05° by following changes in intensity of the $^+NCH_3$ signal at δ 4.0 ppm in chloroform-*d* (δ 3.67 ppm in acetonitrile-d_3, δ 3.86 ppm in nitromethane-d_3). In a typical run, solutions of *N*-methyl-*trans*-decahydroquinoline (0.122 g, 0.8 mmol) in 0.4 ml of the deuterated solvent and cyanogen bromide (0.085 g, 0.8 mmol) in 0.4 ml of the same solvent, in separate vials, were thermally equilibrated and then mixed in a thermally equilibrated nmr tube. The tube was then sealed with a torch. The mixture was analyzed by integration (mean of three runs) of the nmr signals in the $^+NCH_3$ region of the spectrum. The extent of reaction was normally followed to 90% completion.

Rate constants were obtained by standard procedures from the slopes of logarithmic plots. Activation parameters were also determined. All analyses were performed in duplicate and the data were reproducible within the limit of experimental error.

N Stereoisomers (3b and 4b) of *N*-Cyano-*N*-methyl-*trans*-decahydroquinolinium Tetrafluoroborate. The pure N stereoisomer (either the major or the minor product) of *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium tetrafluoroborate (0.093 g, 0.35 mmol) in 0.5 ml of CD_3CN at −9° was converted *in situ* into *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium bromide (**3a** or **4a**) upon mixing, in a thermally equilibrated nmr tube, with an equivalent quantity of *N,N*-dimethyl-*trans*-decahydroquinolinium bromide in 0.5 ml of chloroform-*d* at −9°. The rate of decomposition of the isomeric *N*-cyanoammonium bromide at that temperature (−9°) was followed spectroscopically by nmr and the rate constant was computed as before. In cases of both the major and the minor isomer there was observed a good linear relationship between the logarithms of concentrations of the *N*-cyanoammonium bromide and the reaction times.

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Registry No.—*N*-Methylpiperidine, 626-67-5; *N*-ethylpiperidine, 766-09-6; *N*-methylmorpholine, 109-02-4; 4-hydroxypiperidine, 5382-16-1; 3-β-hydroxytropane, 135-97-7; 3-oxotropane, 5632-84-8; *N*-methyl-*trans*-decahydroquinoline, 875-63-8; triethylamine, 121-44-8; *N*,2,6-trimethylpiperidine, 669-81-8; *N*-methyl-4-hydroxypiperidine, 106-52-5; *N*-*sec*-butyl-4-methylpiperidine, 51075-48-0; methylpyrrolidine, 120-94-5; cyanogen bromide, 506-68-3; cyanogen chloride–antimony pentachloride complex, 24273-94-7; *trans*-decahydroquinoline, 767-92-0; lithium bromide, 7550-35-8; (*S*)-(+)-2-butanol, 4221-99-2; (*S*)-*sec*-butyl *p*-toluenesulfonate, 50896-54-3; (*R*)-(−)-*N*-*sec*-butyl-4-methylpiperidine, 51075-64-0; (*S*)-(+)-*N*-*sec*-butyl-4-methylpiperidine, 51075-65-1; (*S*)-(+)-*sec*-butyl bromide, 5787-32-6; (*R*)-(−)-*sec*-butyl bromide, 5787-33-7; racemic *N*-*sec*-butyl-4-methylpiperidine, 51153-97-0.

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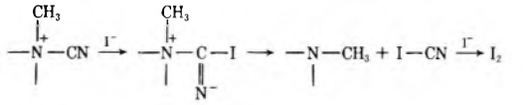
(19) Another might be expressed in the following mechanism, based on recent work,[20] as kindly suggested to us by referee II.



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Kinetics of Decomposition of Certain Benzhydryl Nitrosobenzamides. Evidence for a Rearrangement Step

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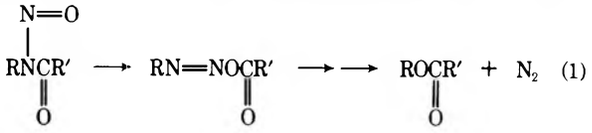
N-Benzhydryl-*N*-nitrosobenzamide and the 4-chloro- and 4-methoxybenzhydryl analogs were prepared and decomposed in benzene, acetonitrile, and acetic acid solvents. The rates of decomposition were all fairly similar, suggesting that a direct ionization to give benzhydryl carbonium ions is not occurring. Instead, these nitrosoamides appear to react by the normal pathway involving a rearrangement to the corresponding diazo ester in the first step.

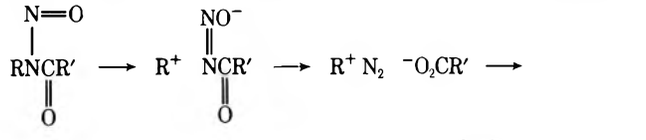
N-Nitrosoamides of primary amines (**1**) decompose in both polar and nonpolar solvents to yield the corresponding esters (eq 1).[1,2] Various studies have shown that, for



1 **2** (1)

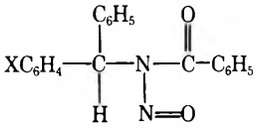
nitrosoamides of simple alkylamines (**1**, R = alkyl, benzyl, etc.), the first step in the reaction is a rearrangement of **1** into an isomer, the diazo ester **2**; subsequent reactions lead to the corresponding ester (eq 1).[1,2] The rate-determining step, the rearrangement,[2] has a relatively nonpolar transition state as shown by the following observations: (1) the nitrosoamide reaction of simple alkylamines proceeds readily in nonpolar solvents such as hexane,[1,2] (2) only a small solvent effect has been noted,[3] and (3) only a small electronic effect of substituents on the rates of decomposition has been observed.[4]

The purpose of the present work was to investigate the possibility that a direct ionization mode of decomposition (eq 2) might be competitive under certain circumstances.



(2)

Alkyl groups, R, that form stable carbonium ions could conceivably change the course of the decomposition to favor an S$_N$1 mode of reaction (eq 2). The benzhydryl system was chosen for the present study in this context because it has been used in studies relating the deamination reaction to solvolysis,[5] and because the benzhydryl carbonium ion is the most stable of the carbonium ions studied in an alkyl nitrosoamide decomposition to date[2] (the triphenylmethyl system has not yet been examined). This paper covers the preparation of the nitrosobenzamides of benzhydrylamine (**3a**) and the 4-chloro (**3b**) and 4-methoxy (**3c**) derivatives, and the measurement of their rates



3a, X = H
b, X = 4-Cl
c, X = 4-CH_3O

of decomposition. The reactions were followed in benzene, acetonitrile, and acetic acid, and the results show that these nitrosoamides also follow the pathway outlined in eq 1.

Results

N-Benzhydryl-, *N*-(4-chlorobenzhydryl)-, and *N*-(4-methoxybenzhydryl)benzamides were nitrosated with dinitrogen tetroxide[6] to yield compounds **3a-c**. These nitrosoamides were not subjected to purification procedures because of their instability. The changes in the infrared spectra on nitrosation are large,[6,7] however, and the most reasonable impurities can be readily detected. The nitrosoamides used in the rate studies were pure as shown by their infrared spectra; these showed no detectable amounts of the starting amides or the product esters. The rates of decomposition were followed by the decrease in intensity of the visible absorption band of the nitroso group at ~425 nm.[7,8] A concentration of 10^{-2} *M* was chosen to give a convenient optical density for a cell of 1-cm path length. A commercial Haake circulator and temperature controller was used as a constant-temperature bath. With this apparatus it was possible to maintain a given temperature in the bath to within 0.01°; the thermometer could be read to 0.1° and estimated to within 0.01°. All runs were conducted at 25 ± 0.01°. For each run, the cell and the solvent were equilibrated at 25° in the constant-temperature bath, the nitrosoamide was quickly dissolved in the solvent of choice, and the spectra were taken on a Cary spectrometer Model 14, the cell chamber of which was connected to the Haake circulator. The initial optical density A_0 was obtained by extrapolation of the optical densities to time zero.

Runs varied from 2 to 3 half-lives and 7–14 points were used to establish the linearity of the first-order plots. The rate constants were determined from these by graphical methods.[9] The nitrosoamides proved not to be very soluble in acetic acid. In the acetic acid runs, they were first dissolved in a small amount of methylene chloride and then the acetic acid was added; the final concentration of methylene chloride in the acetic acid was 2–7%.

The data for a typical run are given in Table I. In all of the cases, linear plots of log A_0/A *vs* time were obtained and from these, the first-order rate constants were calculated; the data are given in Table II.

Discussion

In all of the solvents used, the 4-methoxybenzhydryl compound (**3c**) decomposed faster than the 4-chlorobenzhydryl analog (**3b**). The rate enhancement factor was 1.5 in benzene, 1.7 in acetonitrile, and 1.4 in acetic acid. This effect of the methoxy group is small relative to that to be expected if the reaction were to proceed *via* eq 2, however. For example, the rates of methanolysis of benzhydryl chlorides with the same suite of substituents increase in the order 4-Cl (0.47), 4-H (1.0), 4-CH_3O (~5000).[10] Further, the rate constants for the solvolysis of the corresponding benzhydryl 4-nitrobenzoates in 90% aqueous acetone fall in the order 0.5, 1.0, and >1300.[11]

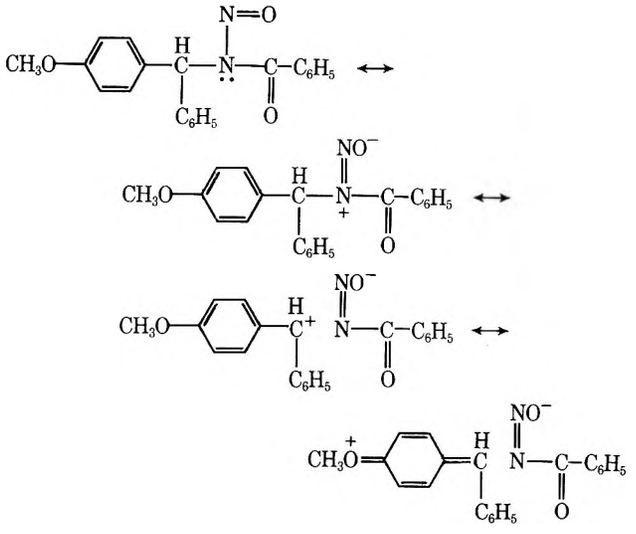
Table I
Decomposition of *N*-Nitroso-*N*-benzhydrylbenzamide (3a) in Benzene

Time, sec	A^a	Log A_0/A	k_1,[b] min^{-1}
0	0.720[c]	0.000	
235	0.620	0.065	3.8×10^{-2}
480	0.535	0.129	3.6×10^{-2}
710	0.470	0.185	3.4×10^{-2}
930	0.410	0.245	3.7×10^{-2}
1140	0.367	0.293	3.2×10^{-2}
1385	0.320	0.352	3.4×10^{-2}
1610	0.280	0.410	3.6×10^{-2}
1825	0.250	0.459	3.2×10^{-2}
2445	0.175	0.614	3.4×10^{-2}
3030	0.130	0.743	3.0×10^{-2}
			Av $3.4^4 \times 10^{-2}$

[a] A = optical density. [b] First-order rate constant calculated for each point. [c] Obtained by extrapolating the experimental points to time zero.

The small rate increase noted upon substitution of a methoxy group into a benzhydrylnitrosoamide shows that, even for benzhydryl groups, the nitrosoamide reaction is not diverted from the normal path outlined in eq 1 to the ionization mode outlined in eq 2. Of course, nitrosoamides bearing groups that would yield more stable carbonium ions (*e.g.*, **1**, R = triphenylmethyl) might follow eq 2. It appears, however, that all the nitrosoamides prepared to date decompose *via* the pathway outlined in eq 1.[12]

The small rate enhancement that was observed for series **3a–c** (Table II) is probably a result of inductive and resonance interactions (4) influencing the nucleophilicity of the oxygen atom in the nitroso group.



4

Experimental Section

Instrumentation. Infrared spectra were obtained on a Perkin-Elmer Model 337 grating spectrophotometer. A Cary 14 recording spectrophotometer was used to obtain uv spectra. Proton magnetic resonance spectra were obtained with a Varian Model A-60. Chemical shifts are reported in δ units using tetramethylsilane as internal reference. Melting points, obtained on a Thomas-Hoover apparatus, were uncorrected.

4-Methoxybenzophenone Oxime. 4-Methoxybenzophenone oxime was prepared on 70% yield from 4-methoxybenzophenone and hydroxylamine hydrochloride.[13] A mixture of syn and anti oximes was obtained: mp 115–139° (lit.[13a] mp 115–116° for anti and 137–138° for syn isomer); ir ($CDCl_3$) 3590, 3300 (broad), 2910, 1615, and 990 cm^{-1}; nmr (acetone-*d*) δ 3.32 and 3.37 (3 H, s, OCH_3), ~6.70 (9.1 H, m, C_6H_5 and C_6H_4), impurities at 1.6 (m), and 2.6 (s).

4-Methoxybenzhydrylamine Hydrochloride. Reduction of 6.0 g (26.4 mmol) of 4-methoxybenzophenone oxime with sodium in ethanol and formation of the hydrochloride yielded the salt:[14] 5.30 g (21.3 mmol, 82%); mp 218–220° (lit.[14a] mp 190°, lit.[15] mp 229°); ir (KBr) 2900 (broad), 1600, 1500, and 1030 cm^{-1}; nmr (DMSO-d_6) δ 3.35 (2.5 H, s, NH_3^+), 3.75 (3 H, s, OCH_3), 6.90 and 7.50 (10 H, m, C_6H_5, C_6H_4, CH).

Table II
First-Order Rate Constants for the Decomposition of the *N*-Nitrosobenzamides of Three Benzhydrylamines [3, $RN(NO)COC_6H_5$] at 25°

Solvent	R	Registry no.	k, min^{-1}	Half-life, min
Benzene	4-Chlorobenzhydryl	16469-42-4	2.7×10^{-2}	26
	Benzhydryl	16469-41-3	3.5×10^{-2}	20
	4-Methoxybenzhydryl	51271-73-9	3.9×10^{-2}	18
Acetonitrile	4-Chlorobenzhydryl		3.0×10^{-2}	23
	4-Methoxybenzhydryl		5.2×10^{-2}	13
Acetic Acid	4-Chlorobenzhydryl		3.8×10^{-2}	18
	4-Methoxybenzhydryl		5.4×10^{-2}	13

***N*-Benzhydrylbenzamides.** *N*-Benzhydrylbenzamide, *N*-4-chlorobenzhydrylbenzamide, and *N*-4-methoxybenzhydrylbenzamide were prepared from the corresponding amines and benzoyl chloride using pyridine as a solvent. The corresponding melting points follow: *N*-benzhydrylbenzamide, 174–175° (lit.[16] 172°); *N*-4-chlorobenzhydrylbenzamide, 178–180° (lit.[17] 180–181°); and *N*-4-methoxybenzhydrylbenzamide, 180–181° (lit.[18] 174°).

***N*-Nitroso-*N*-benzhydrylbenzamides.** *N*-Nitroso-*N*-benzhydrylbenzamide, *N*-nitroso-*N*-4-chlorobenzhydrylbenzamide, and *N*-nitroso-*N*-4-methoxybenzhydrylbenzamide were prepared by nitrosating the corresponding amides. A procedure slightly modified from that reported in the literature[6,17] was used. The amides were dissolved in methylene chloride, sodium acetate (~35-fold molar excess) was added and the mixture was cooled to −70°. Dinitrogen tetroxide (~20-fold molar excess with respect to the amide) was added and the temperature was raised to about −15 to −5°. The reaction mixture was stirred for about 2.5 hr and then worked up in a cold room. The final solution of the nitrosoamide in methylene chloride was washed with ice-cold 5% sodium carbonate solution and with saturated sodium chloride. The solution was dried over anhydrous sodium sulfate and the solvent was removed at −10° (*ca.* 0.05 Torr). Because of their instability, the nitrosoamides were not purified. The course of the nitrosation could be readily followed in the ir by the loss of the amide carbonyl band at 1675 cm^{-1} and the growth of the nitrosoamide carbonyl band at 1710 cm^{-1} as well as the double-bond stretch of the nitroso group at 1510 cm^{-1}. The samples used for the kinetic studies were free of amide and the corresponding ester (formed on decomposition). Two absorptions in the uv are associated with the *N*-nitroso group: 405–409 (ϵ 70–73) and 423–426 nm (ϵ 71–75).[7,8]

Acknowledgment. We thank the National Science Foundation (GP-8993) and the Johns Hopkins University for financial support.

Registry No.—*syn*-4-Methoxybenzophenone oxime, 10147-61-2; *anti*-4-methoxybenzophenone oxime, 10147-60-1; 4-methoxybenzhydrylamine hydrochloride, 5427-61-2.

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Syntheses of Some 1,2,3,4-Tetrahydropyrazino[1,2-*a*]benzimidazoles

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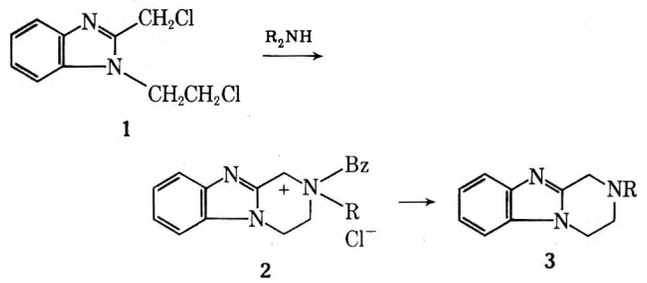
A general and convenient method for the synthesis of 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazoles has been developed. Evidence is presented for the existence of the 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]benzimidazole system.

It was the purpose of this work to develop a general and convenient synthetic route to 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole and its derivatives. Saunders[1] prepared *N*-carbethoxy-1,2,3,4-tetrahydropyrazino-[1,2-*a*]benzimidazole in low yield by pyrolyzing 2-(4′-carbethoxypiperazine)phenyl azide. This method has been improved and extended by Garner, Garner, and Suschitzky.[2] Schmutz and Kunzle[3] prepared the ring system by treating 1-(β-chloroethyl)-2-chloromethylbenzimidazole with secondary amines. When one of the alkyl groups was



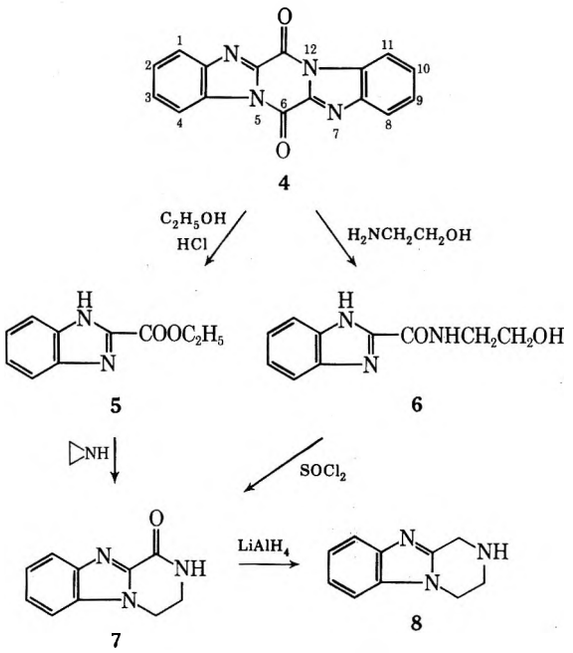
1 2 3

benzyl, hydrogenolysis gave the corresponding 2-alkyl derivative. A similar but more direct synthesis involved treating 1-(β-chloroethyl)-2-chloromethylbenzimidazole with primary amines. This leads directly to the 2-alkyl derivative.[4]

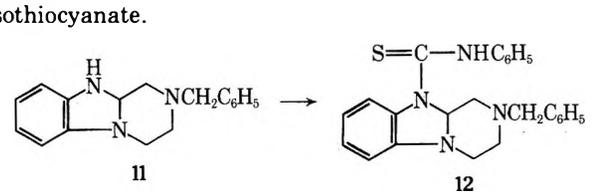
Freedman[5] explored a new synthetic pathway to this ring system which is shown in Scheme I. In this work,[5] difficulties were encountered in the conversion of **7** into **8**. This scheme, at this stage, was not very efficient. It appeared, however, to have one advantage, namely ease of procurement of starting materials. It was decided therefore to restudy the procedure, with special emphasis on the conversion of **7** into **8**. This has now been completed and we now have a convenient general method for the preparation of 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazoles in good yields.

The starting compound, dibenzimidazo[1,2-*a*,1′,2′-*a*]tetrahydropyrazine-6,13-dione (**4**), was prepared by a known method.[6] We found that the conversion of **6** into **7** proceeded in higher yield than the conversion of **5** into **7**. Initially the reduction of **7** with lithium aluminum hydride gave air-sensitive products from which only small amounts of 8 could be isolated. Suspecting the overreduc-

Scheme I



tion of **7**, we investigated the $LiAlH_4$ reduction of the more easily reducible 2-benzyl-1,2,3,4-tetrahydropyrazino-[1,2-*a*]benzimidazol-1-one (**10**). Compound **10** was prepared by the synthesis outlined in Scheme I, using 2-benzylaminoethanol in place of 2-aminoethanol. An analytical sample of the reduction product could not be obtained because of its instability. The product was shown to be 2-benzyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]benzimidazole (**11**). The nmr and ir assignments agreed with this structure, and the product formed a stable thiourea derivative (**12**) in high yield when **10** was treated with phenyl isothiocyanate.



11 12

Dehydrogenation of **11** at room temperature over Pd on carbon gave 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole (**13**) which was converted into **8** by debenzylation. Reexamination of the lithium aluminum hydride reduction of **7** showed that good yields of **8** were obtained when the crude reduction product was treated immediately with palladium on carbon. It would appear, from these observations, that the benzimidazole nucleus is reduced by lithium aluminum hydride to a benzimidazoline that is difficult to isolate in analytically pure form and that reverts to a benzimidazole in the presence of air (low conversion) or in the presence of palladium (high conversion).[7]

The following 2-substituted derivatives of **8** were prepared for biological testing purposes: 2-ethyl (**14**), 2-propyl (**15**), 2-cyanomethyl (**16**), 2-aminoethyl (**17**), and 2-(*p*-methoxybenzyl (**18**).

Experimental Section

All melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. The nuclear magnetic resonance spectra were determined with either a Varian Model HA-60EL or Model A-60A spectrometer. Infrared spectra were measured on a Perkin-Elmer Model 521 spectrophotometer. Ultraviolet spectra were obtained with a Cary Model 14 spectrophotometer.

***N*-(2-Hydroxyethyl)-2-benzimidazolecarboxamide (6).** To a cooled solution of 147.5 g (0.246 mol) of 2-aminoethanol in chloroform was added, with stirring, 50 g (0.1732 mol) of dibenzimidazo[1,2-*a*,1′,2′-*a*]tetrahydropyrazine-6,13-dione (**4**). The mixture was refluxed for 2 hr. The chloroform was removed *in vacuo* and the residual oil was poured into 400 ml of water. After cooling overnight, the solid was removed and recrystallized from ethanol, yield 80%, mp 219–220°.

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.49. Found: C, 58.55; H, 5.35; N, 20.53.

1,2,3,4-Tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (7). A solution of 19.1 g (0.1 mol) of *N*-(2-hydroxyethyl)-2-benzimidazolecarhoxamide (**6**), in 180 ml of dry dimethylformamide, was cooled to 0–5°. Thionyl chloride (12.6 g, 0.105 mol), in 80 ml of dry DMF, was added dropwise with stirring. A solid separated. The mixture was heated under reflux for 2 hr. The resulting solution was treated with decolorizing carbon and filtered hot. The DMF was removed *in vacuo* and the residual gummy solid was washed with 10% sodium hydroxide solution and then with cold water. The product was recrystallized from water: yield 65%; mp 292–294°; ir (KBr) 1680 cm^{-1}.

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.15; H, 4.86; N, 22.44. Found: C, 64.24; H, 4.82; N, 22.35.

This compound (**7**) was obtained in lower yield by treating ethyl 2-benzimidazolecarboxylate (**5**) with ethylenimine. A solution of 4.4 g (0.023 mol) of (**5**), 1.3 ml (0.023 mol) of ethylenimine and 1 drop of ethanolic hydrogen chloride in 50 ml of ethanol was placed in a pressure flask and heated on a steam bath for 8 hr. After cooling, the solid was removed and recrystallized from water, yield 28%, mp 292–294°.

***N*-Benzyl-*N*-(2-hydroxyethyl)-2-benzimidazolecarboxamide (9).** Dibenzimidazo[1,2-*a*,1′,2′-*a*]tetrahydrapyrazine-6,13-dione (50 g) was added with stirring to a solution of 165 g (1.17 mol) of 2-benzylaminoethanol in 400 ml of benzene. A clear solution was obtained in about 1 hr. The benzene was removed *in vacuo* and the residual oil was solidified by washing with water. The solid was recrystallized from benzene: yield 55%; mp 143.5–145°; ir (KBr) 1620 cm^{-1}; nmr (DMSO) complex multiplet at δ 7.28–7.69 (9 H, aromatic protons), singlet at 5.70 (1 H, amino), singlet at 4.88 (2 H, benzylmethylene), multiplet at 3.97 (4 H, ethane protons), multiplet at 3.61 (1 H, hydroxyl proton). The absorptions at 5.70 and 3.61 disappeared on deuteration.

Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.28; H, 5.97; N, 14.34.

2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (10). Compound **10** was prepared by the method used for making compound **7**, using *N*-benzyl-*N*-(2-hydroxyethyl)-2-benzimidazolecarboxamide as the starting material. The product was recrystallized from ethanol: yield 79%; mp 200–201°; ir (KBr) 1660 cm^{-1}; nmr (DMSO) multiplet at δ 7.30–7.79 (9 H, aromatic protons), singlet at 4.76 (2 H, benzyl methylene), multiplet at 3.96 (4 H, ethane protons).

Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.66; H, 5.30; N, 15.32.

1,2,3,4-Tetrahydropyrazino[1,2-*a*]benzimidazole (8). Method A. Reduction of 1,2,3,4-Tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (7). To a cooled mixture of 2.42 g (0.08 mol) of lithium aluminum hydride in 100 ml of dry tetrahydrofuran was added, portionwise with stirring, 3.74 g (0.02 mol) of 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (**7**). The solution was heated under reflux for 68 hr and cooled to −78°. Water was added with stirring until all of the excess lithium aluminum hydride and its salts were destroyed. The solution was filtered directly into a mixture of 0.37 g of 10% palladium on carbon in 25 ml of ethanol, placed under nitrogen atmosphere, and stirred overnight. The solution was filtered free of catalyst, and excess dry hydrogen chloride gas was added. The resulting insoluble salt was collected by filtration, dissolved in water, and made basic (pH 9) with sodium bicarbonate. The water solution was continuously extracted with chloroform for 24 hr. The chloroform was dried ($MgSO_4$) and removed under reduced pressure to give 2.50 g (72.5%) of **8**, mp 129–130°. Recrystallization from benzene afforded an analytical sample: mp 130–131.5°; yield 60%; ir showed no carbonyl absorption; nmr ($CHCl_3$) multiplet at δ 7.63 (1 H, for the 9 proton), multiplet at 7.20 (3 H, for the 6, 7, and 8 protons), singlet at 4.00 (2 H, methylene protons), triplet at 3.04 (2 H, J = 5.7 Hz, ethane protons), triplet at 3.64 (2 H, ethane protons), and a singlet at 2.32 (1 H, NH proton, disappeared on deuteration).

Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.34; H, 6.41; N, 24.25. Found: C, 69.26; H, 6.23; N, 24.11.

Method B. Two-Step Reduction of 2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (10). Preparation of 2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole (13). To a mixture of 1.14 g (0.03 mol) of lithium aluminum hydride in 150 ml of dry ether was added 4.11 g (0.015 mol) of 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (**10**). The mixture was refluxed for 70 hr and cooled at 0°, and 5 ml of water was added dropwise, with stirring. The solid was removed and washed with cold ether. The filtrate, plus washings, was dried ($MgSO_4$). The ether was removed *in vacuo*. Ethanol (50 ml) and 0.4 g of 10% Pd on carbon was added to the residue. The mixture was stirred for 24 hr in a nitrogen atmosphere. The mixture was filtered and the filtrate was saturated with hydrogen chloride. The solution was concentrated to 20 ml, cooled, and filtered. The hydrochloride (mp 290–294°) was dissolved in water, and the solution was neutralized with sodium bicarbonate to yield the free base. The free base was recrystallized from cyclohexane: yield 76%; mp 124–124.75°; ir showed no carbonyl absorption; nmr ($CDCl_3$) multiplet at δ 7.70 (1 H, the 9 proton), complex multiplet at 7.28 (8 H, benzyl aromatic protons and 6, 7, and 8 protons), two triplets at 2.86 and 3.92 (2 H, represent the 3 and 4 methylene protons), singlet at 3.66 (2 H, benzyl methylene protons), singlet at 3.87 (2 H, one methylene protons).

Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.53; H, 6.51; N, 15.96. Found: C, 77.45; H, 6.49; N, 16.10.

Debenzylation of 2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole (13) to 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole (8). Dry hydrogen chloride was passed into a solution of 1.38 g (0.005 mol) of 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole in 30 ml of ethanol to form the hydrochloride. Palladium (10%) on carbon (0.07 g) was added and the solution was hydrogenated for 7 hr at 50° and 50 psi. The product precipitated from the solution. It was removed and dissolved in water, and the solution was neutralized with sodium bicarbonate. The solution was continuously extracted with chloroform for 10 hr. The extract was dried ($MgSO_4$) and the chloroform removed *in vacuo*. The residue was recrystallized from benzene, yield 97%, mp 130–131.5°. The ir and nmr spectra were identical with the spectra of an authentic sample.

A better overall yield of 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole was obtained by method B when it was made a one-step method. An example of this method follows. A mixture of 4.56 g (0.12 mol) of lithium aluminum hydride and 16.58 g (0.06 mol) of 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole in 400 ml of dry tetrahydrofuran was refluxed for 60 hr. The mixture was cooled to 0° and 15 ml of water was added dropwise with stirring. The insoluble solutions were removed and washed with cold ether. The ether solutions were dried ($MgSO_4$) at −15° and the ether then removed under reduced pressure. To the resulting oil was added 1.66 g of 10% Pd on carbon and 175 ml of ethanol, and the mixture was stirred for 12 hr in a nitrogen atmosphere. The catalyst was removed and hydrogen chloride was passed into the filtrate to form the hydrochloride. Palladium (1.66 g of 10%

Pd/C) was added and the mixture was hydrogenated at 55° and 58 psi for 7 hr. The product and catalyst were removed by filtration and the product was removed from the precipitate by extraction with water. The aqueous extract was neutralized with sodium bicarbonate and the solution was then continuously extracted with chloroform for 24 hr. The chloroform solution was dried ($MgSO_4$) and the chloroform was then removed *in vacuo*. The solid, so obtained, was recrystallized from benzene, yield 88%, mp 130.5–131.5°. It was identical in all respects with the previous samples.

Evidence for the Formation of 2-Benzyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole (11). 2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazol-1-one (**10**) (4.11 g, 0.015 mole) was added to a stirred mixture of 1.14 g (0.03 mole) of lithium aluminum hydride in 150 ml of dry ether. The mixture was refluxed for 60 hr. After cooling to 0°, 5 ml of water was added dropwise with stirring. The insoluble salts were removed and the filtrate was dried ($MgSO_4$) at −15°. The ether was removed *in vacuo*. Scratching the walls of the flask caused the oil to crystallize. Because of its sensitivity to air, the product was collected under nitrogen. It was washed with a small amount of cold ether and sucked dry in a nitrogen atmosphere. It was sealed in a vial, under nitrogen, and stored at −15°, yield 62%, mp 82–88°. Because of its instability a good analytical sample could not be obtained. The ir spectrum (CCl_4) showed a band at 3390 cm^{-1} (N–H) and bands at 1600 and 1485 for aromatic C=C skeletal in-plane vibrations but no band was observed for a C=N group. The nmr ($CDCl_3$) showed a singlet at δ 7.29 (5 H, C_6H_5), multiplet at 6.54 (4 H, C_6H_4), quartet at 4.79 (1 H, 10a, X part of ABX with $J_{ax} + J_{bx} = 6$ Hz), multiplet at 3.50 (3 H, NH and 1 CH_2), singlet at 3.49 (2 H, $CH_2C_6H_5$), multiplet at 2.73 (2 H, 4 CH_2) and a multiplet at 2.18 (2 H, 3 CH_2).[8]

Phenylthiourea Derivative of 2-Benzyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole (12). To a solution of 0.14 g (0.001 mol) of phenyl isothiocyanate in dry toluene (under nitrogen) was added 0.27 g (0.001 mol) of crude 2-benzyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole (**11**) and the solution allowed to stand overnight. The solid, which separated, was recyrstallized from petroleum ether, yield 79%, mp 137° dec.

Anal. Calcd for $C_{24}H_{24}N_4S$: C, 71.97; H, 6.04; N, 13.99; S, 8.00. Found: C, 71.84; H, 6.04; N, 13.86; S, 8.14.

Alkylation Products of 1,2,3,4-Tetrahydropyrazino[1,2-a]-benzimidazole, 2-Ethyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (14). A solution of 0.43 g (0.0025 mol) of 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (**8**), 0.27 g (0.0025 mol) of ethyl bromide, and 0.25 g (0.0025 mol) of triethylamine in 25 ml of acetone was refluxed for 138 hr. The volatile materials were removed *in vacuo*. The triethylamine hydrobromide was removed from the residue by extraction with water and the remaining solid was recrystallized from cyclohexane, yield 36%, mp 107–108°.

Anal. Calcd for $C_{12}H_{15}N_3$: C, 71.61: H, 7.51; N, 20.88. Found: C, 71.77; H, 7.42; N, 21.02.

2-Propyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (15). This compound was prepared similarly to **14** using *n*-propyl bromide. It was recrystallized from hexane, yield, 26%, mp 75.5–77°.

Anal. Calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.67; H, 7.83; N, 19.66.

2-Cyanomethyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (16). The alkylating agent was chloroacetonitrile in this case and the solution was refluxed for 48 hr. The product was recrystallized from acetone, yield 70%, mp 176–176.5°.

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.06; H, 5.77; N, 26.58.

2-(2-Aminoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole Trihydrochloride (17). 2-Cyanomethyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (0.53 g, 0.0025 mol) in 10 ml of dry tetrahydrofuran was added slowly to a stirred suspension of 0.284 g (0.0075 mol) of lithium aluminum hydride in 40 ml of THF. The mixture was refluxed for 72 hr. The mixture was cooled to −78° and 2 ml of water in 20 ml of THF was added dropwise with stirring. The cold mixture was then filtered into a mixture of 0.1 g of 10% Pd/C in 25 ml of ethanol. After stirring for 20 min, the catalyst was removed by filtration and the solvent was removed *in vacuo*. Ten milliliters of 20% ethanolic hydrogen chloride was added to the residual oil to convert it into the trihydrochloride. The salt was recrystallized from ethanol–concentrated hydrochloric acid, yield 40%, mp 256° dec.

Anal. Calcd for $C_{12}H_{19}Cl_3N_4$: C, 44.16; H, 5.88; Cl, 32.66; N, 17.20. Found: C, 43.91; H, 6.08; Cl, 32.44; N, 16.99.

2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (13). Benzyl chloride was the alkylating agent and the solution was refluxed for 31 hr. The product was recrystallized from cyclohexane, yield 66%, mp 124–124.75°. The product was identical in all respects with the one previously prepared from 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazol-1-one.

2-(p-Methoxybenzyl)-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (18). *p*-Methoxybenzyl chloride was the alkylating agent and the solution was refluxed for 18 hr. The compound was recrystallized from cyclohexane, yield 57%, mp 150–150.25°.

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53; N, 14.32. Found: C, 73.96; H, 6.46; N, 14.16.

Registry No.—**4**, 14483-72-8; **5**, 1865-09-4; **6**, 14484-06-1; **7**, 51052-05-2; **8**, 4744-53-0; **9**, 51052-06-3; **10**, 51052-07-4; **11**, 51052-08-5; **12**, 51052-09-6; **13**, 51052-10-9; **13** HCl, 51052-11-0, **14**, 51052-12-1; **15**, 15052-13-2; **16**, 51052-14-3; **17**, 51052-15-4; **18**, 51108-09-9; 2-aminoethanol, 141-43-5; ethylenimine, 151-56-4; 2-benzylaminoethanol, 104-63-2.

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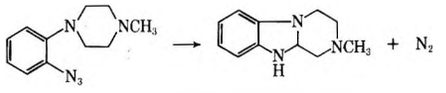
(7) Just as the present work was completed, R. Garner, G. V. Garner, and H. Suschitzky (ref 2) reported the preparation of hexahydropyrazino[1,2-a]benzimidazoles by the decomposition of azides as shown by the following example.



They also prepared hexahydropyrido[1,2-a]benzimidazole by the $LiAlH_4$ reduction of the corresponding benzimidazole.
(8) A four-line pattern centered at δ 3.23 was observed which may be the A part of the ABX pattern of the 1 CH_2 and 10a H; if so, J_{AB} = 11 Hz.

Syntheses of C-Amino- and C-Azido-1,2,4-triazoles

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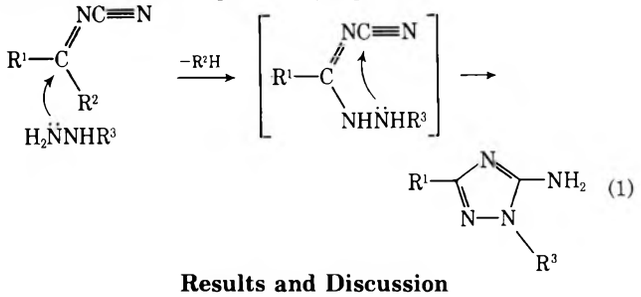
A series of C-amino-1,2,4-triazoles, substituted with methyl, dimethylamino, methoxy, and methylthio groups, was prepared from the appropriate N-cyanoazomethines and either hydrazine or methylhydrazine (eq 1). C-Azido-1,2,4-triazoles were prepared from the corresponding amines by diazotization followed by reaction with azide ion. When these diazotization reactions were carried out, the C-amino-1,2,4-triazoles derived from methylhydrazine, unlike those derived from hydrazine, yielded varying quantities of products depending on the acidity of the reaction media. Ir and proton nmr spectra of the C-azido-1,2,4-triazoles in various solvents indicated that none of them participates in imidoyl azide–tetrazole tautomerism, even at −82°.

C-Amino- and C-azido-1,2,4-triazoles were synthesized as part of an investigation of the possible imidoyl azide–tetrazole tautomerism of the azides. The C-amino-1,2,4-triazoles were prepared by the reaction of hydrazines with N-cyanoazomethines containing at least one good leaving group bonded to the azomethine carbon, an old but little-used method.[2-6] This reaction has been visualized as taking place by attack of the hydrazine, first on the azomethine carbon, and then on the carbon of the cyano group (eq 1).[2] We have used this method to obtain a series of C-amino-1,2,4-triazoles because it facilitates the preparation of 1,2,4-triazoles substituted with various groups, most of which have not been previously reported.



(1)

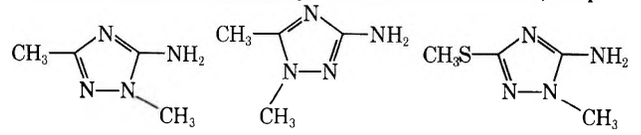
Results and Discussion

C-Amino-1,2,4-triazoles. The reactants used and products formed when the method described above was implemented are listed in Table I.

Either the primary or secondary amino nitrogen atom of methylhydrazine can attack the azomethine carbon, giving rise to isomeric C-amino-1,2,4-triazoles. As indicated in Table I, both isomers (**6** and **7**) were isolated from the reaction of methylhydrazine with **1**. Only **11** was isolated from the reaction of methylhydrazine with **4**, although nmr spectra indicated the presence of two isomeric products.

Structures were assigned to isomers **6** and **7** on the basis of a previous preparation of **6**[14] and the assignments were confirmed when the nmr spectrum of **17** (prepared from **6**) proved to be identical with that of 1,3-dimethyl-1,2,4-triazole.[15]

Assignments of **6** and **11** to the major products formed in the reactions of methylhydrazine with **1** and **4**, respec-



6 **7** **11**

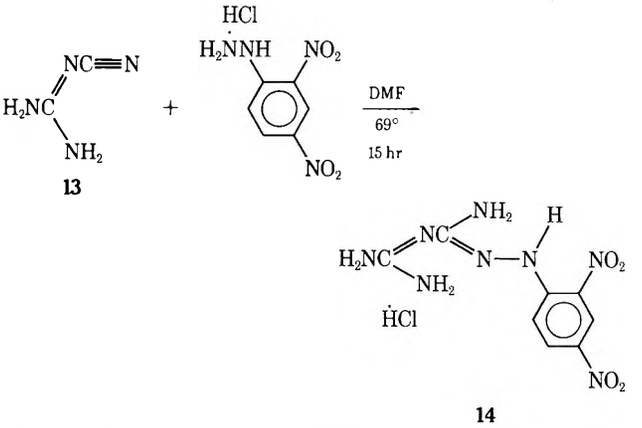
tively, mean that the less hindered primary amino nitrogen preferentially attacks the azomethine carbon (eq 1), consistent with the reactions of methylhydrazine with simpler acylating agents.[16-18]

A change from polar to nonpolar solvents decreased the reaction rates of methylhydrazine with both **1** and **4**. Reactions of **4** in various solvents (acetonitrile, 95% ethanol, benzene) resulted in percentages of isomers which changed little (94–100% **11**); however, in reactions of **1** the per cent of **6** increased from 65 to 91% when the solvent was changed from 95% ethanol to benzene. We suggest that this increase in per cent of **6** may be due to a more selective attack by the least sterically hindered nitrogen atom of methylhydrazine with the decreased reaction rate.

Although the reactions of N-cyanoazomethines and hydrazines, indicated in Table I, proceeded readily, it is not a completely general method for preparing C-amino-1,2,4-triazoles. No reaction occurred when a solution of N-cyano-S-methylisothiourea (**12**), p-bromophenylhydrazine, and dimethylformamide (DMF) was refluxed for 12 hr.

When **12** and 2,4-dinitrophenylhydrazine were refluxed in DMF for 48 hr in an attempt to prepare 3,5-diamino-1-(2,4-dinitrophenyl)-1,2,4-triazole, the only compound that could be isolated from the reaction mixture was m-dinitrobenzene. It is probable that this transformation occurred by the action of atmospheric oxygen under the severe reaction conditions, since m-dinitrobenzene has been formed by the oxidation of 2,4-dinitrophenylhydrazine with manganese dioxide[19] and by the oxidation of 2,4-dinitrophenylhydrazones with ozone.[20]

Another method[21,22] was used in a second attempt to prepare 3,5-diamino-1-(2,4-dinitrophenyl)-1,2,4-triazole. When a suspension of cyanoguanidine (**13**), 2,4-dinitrophenylhydrazine hydrochloride, and DMF was heated, a solid precipitated which was formulated as **14** on the basis

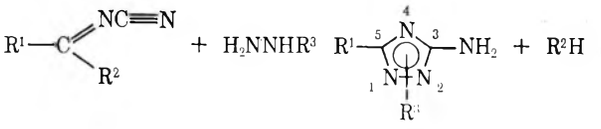


13 **14**

of its elemental analysis and nmr spectrum. The attack of amine salts on the cyano carbon of cyanoguanidine has been observed previously.[23,24]

Unlike certain methylthio groups bonded to the 1,2,4-triazine nucleus,[25-27] the methylthio group of **10** could not be displaced by hydrazine. Hydrazine and **10** were refluxed in both 95% ethanol and acetonitrile for 22 hr without any reaction whatever.

Table I
C-Amino-1,2,4-triazoles Prepared from N-Cyanoazomethines



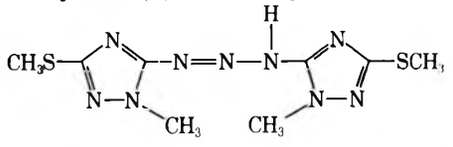
N-Cyanoazomethine	R^1	R^2	R^3 (position on ring)	Triazole	Yield, %
1	CH_3	OC_2H_5	H[a]	5	59
1	CH_3	OC_2H_5	CH_3 (2)	6	83
1	CH_3	OC_2H_5	CH_3 (1)	7	
2	$(CH_3)_2N$	SCH_3	H[a]	8	95
3	CH_3O	OCH_3	H[a]	9	79
4	CH_3S	SCH_3	H[a]	10	92
4	CH_3S	SCH_3	CH_3 (2)	11	81

[a] 1,2,4-Triazoles of this type exist as tautomeric mixtures in which the hydrogen atom is bonded, primarily, to N-1 or N-2.[7-13]

C-Azido-1,2,4-triazoles. 5-Chloro-3-methylthio-1,2,4-triazole (**20**) was prepared by a method[28] in which the diazonium chloride formed from **10** was decomposed; however, the chloro group of **20**, like the methylthio group of **10**, proved to be unreactive toward nucleophilic substitution.[29] Compound **20** was refluxed together with equimolar quantities of sodium azide and ammonium chloride in DMF for 24 hr[30] and with equimolar quantities of hydrazine and triethylamine under the same conditions, but no reaction occurred in either case.

Reports of the preparation of five-membered heteroaromatic (pyrazole[31] and 1,3-thiazole[32]) azides by treating the diazonium salts with azide ion suggested that C-azido-1,2,4-triazoles could be obtained in the same way. Table II shows compounds, including the azides, that were prepared from C-amino-1,2,4-triazoles *via* the unisolated diazonium salts.

The diazotization reactions leading to **15** and **18–21** were relatively insensitive to the acidity of the media. In contrast, Table III illustrates how the percentages of products varied with the acidity of the aqueous solution when **11** was treated consecutively with nitrous acid and azide ion. In each reaction, in order to standardize conditions, the temperature was maintained below 1° while first a solution of sodium nitrite and then a solution of sodium azide was added; also, the second solution was added immediately following the first. The immediate addition of sodium azide solution was necessary since 1,3-bis(1-methyl-3-methylthio-1,2,4-triazol-5-yl)triazene (**23**) began



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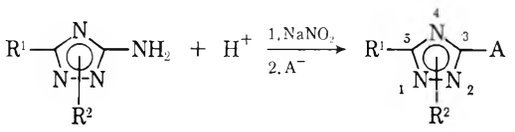
precipitating during the addition of sodium nitrite solution in the reaction carried out at lowest acidity.

When the acidity of the reaction medium was greatest, the percentage of recovered amine starting material was greatest. Since the free base and not its conjugate acid is the species that is diazotized, at high concentrations of acid less amine is diazotized and, upon neutralization of the reaction mixture, most of it can be recovered.[33] On the other hand, when the acidity of the aqueous solution was lowest, the percentage of triazene formed was greatest. This is explained by the fact that the lower the hydrogen ion concentration, the greater the concentration of free base and the more likely it is to react with diazonium ion to form the triazene.

Table II
Compounds Prepared from the Diazonium Salts of C-Amino-1,2,4-triazoles



Product	R^1	R^2 (position on ring)	A	Normality[a]	Yield, %
15	CH_3	H[b]	N_3	2.0	76
16	CH_3	CH_3 (2)	N_3	0.72	10
17	CH_3	CH_3 (2)	H	0.41	36
18	$(CH_3)_2N$	H[b]	N_3	0.28	72
19	CH_3O	H[b]	N_3	0.54	80
20	CH_3S	H[b]	Cl	12	73
21	CH_3S	H[b]	N_3	0.81	70
22	CH_3S	CH_3 (2)	N_3	0.71	28

[a] Normality of the acidic solution before the addition of $NaNO_2$. [b] See footnote *a*, Table I.

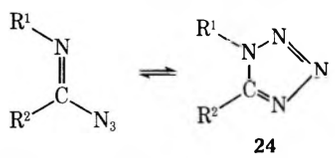
Table III
Variation of Product Percentages with Acidity of the Media in the Diazotization of 5-Amino-1-methyl-3-methylthio-1,2,4-triazole (11)

	Mol % of material recovered[a]		
Normality[b]	Amine **11**[c]	Azide **22**[c]	Triazene **23**[d]
10	70	30	
2.1	57	30	13
0.71		69	31

[a] At least 80% of the weight of **11** was accounted for. [b] Normality of the acidic solution before the addition of $NaNO_2$. [c] Percentages were determined by nmr spectroscopy. [d] Percentages were determined by weighing the isolated product.

Problems similar to those illustrated by Table III also arose when the preparations of **16**, **17**, and the isomer of **16**, 3-azido-1,5-dimethyl-1,2,4-triazole, were attempted. It should be noted that in all of these cases a methyl group, instead of hydrogen, is bonded to one of the ring nitrogen atoms. When 3-amino-5-alkyl-4-aryl-1,2,4-triazoles were diazotized, various products were formed depending on the acidity of the reaction medium;[34] however, other workers did not report differences in the diazotization reactions of N-substituted and unsubstituted C-amino-1,2,4-triazoles.[35]

The Absence of Imidoyl Azide–Tetrazole Tautomerism in C-Azido-1,2,4-triazoles. It has been found that the tetrazole tautomer (**24**) is favored when (1) R^1 and R^2



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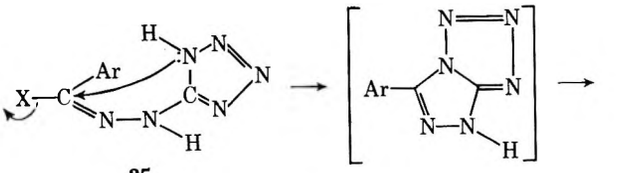
are electron donating; (2) the solvent is polar; and (3) the temperature is low.[36-39] It was reported that, when tetrazolyl hydrazine halides (**25**) were dissolved in 95% ethanol, an intramolecular displacement occurred which did not produce the expected triazolotetrazoles (**26**), but their valence tautomers, 3-aryl-5-azido-1,2,4-triazoles (**27**).[40] We have studied C-azido-1,2,4-triazoles with more varied substituents in various solvents and at low temperature.

In addition to the sampling methods used to obtain the ir spectra reported in the Experimental Section, solutions of the C-azido-1,2,4-triazoles in $CHCl_3$ and DMSO-d_6 were examined by ir spectroscopy. Nmr spectra were obtained of solutions of C-azido-1,2,4-triazoles in $CDCl_3$ at 35°, acetone-d_6 at 25 and −82°,[41] and DMSO-d_6 at 35, 76,

125, and 175°. Since all the nmr spectra (except those of the samples in DMSO-d_6 at 175°) displayed the number of methyl group resonances (chemical shifts were constant for a given solvent regardless of temperature) expected for one of the tautomers, and all the ir spectra showed an azide band between 2120 and 2140 cm^{-1}, compounds **15, 16, 18, 19, 21,** and **22** all exist only as the azide tautomer.



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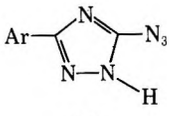

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While the nmr samples were being heated to 175°, the Teflon caps were blown off the tubes, with the loss of sample, and the solutions became darker in color. The spectra taken after temperature equilibration showed peaks at the original chemical shifts along with a number of others of varying intensities. That these observations and spectra indicated decomposition of the azides, rather than a reversible change in the tautomerism, was proved since the spectra of the recooled samples were not identical with those taken before the sample had been heated.

The nonexistence of tetrazole tautomer in the case of *C*-azido-1,2,4-triazoles, regardless of the substituents, is probably due to the electron-withdrawing effect of the triazole ring itself. There are several instances in which the absence of tetrazole tautomer is attributed to the electron-withdrawing effect of a heteroaromatic ring fused to the ring bearing the azido group.[42-44]

Experimental Section

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Boiling points are also uncorrected. Uv spectra were recorded on a Bausch and Lomb Spectronic 505 spectrophotometer. Ir spectra were determined using Beckman IR-8 and Perkin-Elmer Model 137-B spectrophotometers.[45] Nmr spectra were obtained using Varian T-60 and HA-60-EL instruments employing tetramethylsilane as an internal standard. The mass spectra were determined with a Nuclide 12-90-G single-focusing instrument operating at 70 eV.[46] Both the solids and liquids were introduced *via* the direct inlet at the lowest temperature at which a spectrum could be obtained. The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Ethyl *N*-Cyanoacetimidate (1). A modification of the method reported by Huffman and Schaefer[5] was used to prepare this compound in 66% yield: bp 33° (0.1 Torr) [lit.[5] bp 95–96° (15 Torr)]; n_D 1.4512; uv max (95% EtOH) 232 nm (ϵ 1500); ir (capillary film) 3000 (m), 2205 (s), 1610 (s), 1410 (s), 1380 (s), 1320 (s), 1155 (m), 1040 (s), and 885 cm^{-1} (m); nmr ($CDCl_3$) δ 1.34 (t, 3, J = 7 Hz, CH_2CH_3), 2.40 (s, 3, CH_3), 4.30 (q, 2, J = 7 Hz, CH_2CH_3); mass spectrum (70 eV) m/e (rel intensity) 112 (13), 85 (15), 84 (12), 70 (18), 69 (15), 67 (17), 43 (100), 29 (18).

Dimethyl Cyanodithioimidocarbonate (4). A modification of the procedure by Hantzsch and Wolvekamp[47] was used to prepare this compound in 72% yield: mp 52.5–53.5° (lit.[47] mp 57°); ir (KBr) 2190 (s), 1470 (vs), 1310 (m), 1035 (s), and 945 cm^{-1} (s); nmr ($CDCl_3$) δ 2.66 (s, CH_3); mass spectrum (70 eV) m/e (rel intensity) 146 (91), 99 (100), 74 (73), 47 (48), 45 (64).

***N,N*-Dimethyl-*N'*-cyano-*S*-methylisothiourea (2).** This compound was prepared from 4 by the method of Wieland[48] in 100% yield, nmr ($CDCl_3$) δ 2.77 (s, 3, SCH_3), 3.27 [s, 6, $N(CH_3)_2$].

Dimethyl *N*-Cyanoimidocarbonate (3). A modification of the procedure of Wieland[48] was used to prepare this compound from 4 in 53% yield: mp 52–56° (lit.[48] mp 58–59°); ir ($CHCl_3$) 2220 (m), 1620 (s), 1485 (m), 1345 (s), 1035 (w), and 1000 cm^{-1} (w); nmr ($CDCl_3$) δ 4.00 (s, CH_3).

***N*-Cyano-*S*-methylisothiourea (12).** A procedure modeled after that of Davidson[49] was used to prepare this compound from 4 in 88% yield: mp 171–174° (lit.[50] mp 175°); uv max (H_2O) 244 nm (ϵ 9020); ir (fluorolube and Nujol mulls) 3310 (s), 3110 (s), 2200 (s), 2170 (s), 1660 (s), 1530 (s), 1480 (s), 1200 (s), and 985 cm^{-1} (s); nmr (DMSO-d_6) δ 2.46 (s, 3, CH_3), 8.50 (s, 2, NH_2); mass spectrum (70 eV) m/e (rel intensity) 115 (37), 68 (100), 60 (13), 48 (37), 47 (19), 45 (22), 43 (19).

Cyanoguanidine (13). A method similar to that described by Haag[51] was employed to prepare this compound in 88% yield: mp 209–211° (lit.[51] mp 205°); uv max (H_2O) 230 nm (ϵ 905); ir (fluorolube and Nujol mulls) 3440 (s), 3400 (s), 3340 (s), 3160 (s), 2210 (s), 2160 (s), 1640 (s), 1565 (s), 1500 (s), 1255 (s), 930 (m), 720 (m), and 665 cm^{-1} (m); nmr (DMSO-d_6) δ 6.60 (s, NH_2); mass spectrum (70 eV) m/e (rel intensity) 84 (100), 68 (50), 44 (13), 43 (54), 42 (25), 41 (12).

***C*-Amino-1,2,4-triazoles (Table I). General Procedure.** To a magnetically stirred solution of the *N*-cyanoazomethine (100 mmol) and acetonitrile (20 ml), surrounded by a cold water bath, was added the appropriate hydrazine (100 mmol). After the initial exothermic reaction, a precipitate formed, the water bath was removed, and the reaction mixture was stirred overnight. The precipitate was collected by suction filtration and washed with cold acetonitrile (10 ml) to give the following five compounds.

A. 3-Amino-5-methyl-1,2,4-triazole (5)[5] as white crystals: yield 59%; mp 149–150° (lit.[52] mp 148°); uv max (H_2O) 222 nm (ϵ 850); ir (fluorolube and Nujol mulls) 3420 (s), 3330 (s), 3220 (s), 3050 (s), 2700 (s, br), 1625 (s), 1595 (s), 1540 (s), 1475 (s), 1415 (s), and 1065 cm^{-1} (s); nmr (DMSO-d_6) δ 2.10 (s, 3, CH_3), 5.65 (s, 2, NH_2), 11.9 (s, 1, NH).

B. 3-Amino-5-dimethylamino-1,2,4-triazole (8) as white crystals in a yield of 95%, mp 187–189°. Sublimation (125°, 0.1 Torr) of this hygroscopic material gave an analytical sample: mp 189–191°; ir (fluorolube and Nujol mulls) 3200 (s, br), 1630 (s), 1555 (s), 1460 (s), 1405 (s), 1080 (m), 1050 (m), 930 (s), and 740 cm^{-1} (m); nmr (DMSO-d_6) δ 2.78 (s, 6, CH_3), 5.43 (s, 2, NH_2).

Anal. Calcd for $C_4H_9N_5$: C, 37.78; H, 7.13; N, 55.08. Found: C, 37.65; H, 7.07; N, 55.30.

C. 3-Amino-5-methoxy-1,2,4-triazole (9) as white crystals in a yield of 79%, mp 172–174°. Sublimation (110°, 0.1 Torr) of this hygroscopic material gave an analytical sample: mp 168–170°; ir (fluorolube and Nujol mulls) 3530 (m), 3350 (s), 3180 (s), 1660 (s), 1570 (s), 1490 (s), 1400 (s), 1345 (s), 1100 (m), 1040 (m), 1025 (m), and 980 cm^{-1} (m); nmr (DMSO-d_6) δ 3.75 (s, 3, CH_3), 5.90 (s, 2, NH_2), 11.15 (s, 1, NH).

Anal. Calcd for $C_3H_6N_4O$: C, 31.58; H, 5.30; N, 49.10. Found: C, 31.48; H, 5.29; N, 49.27.

D. 3-Amino-5-methylthio-1,2,4-triazole (10)[3] as white crystals in a yield of 92%, mp 138–139°. Recrystallization from acetonitrile gave an analytical sample: mp 139–140° (lit.[3] mp 135°); uv max (H_2O) 234 nm (ϵ 1740); ir (fluorolube and Nujol mulls) 3450 (s), 3320 (m), 3150 (s), 1645 (s), 1590 (s), 1500 (s), 1480 (m), 1465 (m), and 1280 cm^{-1} (s); nmr (DMSO-d_6) 2.43 (s, 3, CH_3) 5.98 (s, 2, NH_2), 11.94 (s, 1, NH).

Anal. Calcd for $C_3H_6N_4S$: C, 27.68; H, 4.65; S, 24.63. Found: C, 27.75; H, 4.76; S, 24.56.

E. 5-Amino-1-methyl-3-methylthio-1,2,4-triazole (11) as light yellow crystals in a yield of 81%, mp 103–106°. Recrystallization from acetonitrile gave an analytical sample: mp 105–106°; uv max (H_2O) 246 nm (ϵ 3200); ir (fluorolube and Nujol mulls) 3420 (s), 3340 (s), 3230 (s), 1620 (s), 1545 (s), 1475 (s), 1350 (s), 1310 (m), 1140 (m), and 745 cm^{-1} (m); nmr ($CDCl_3$) δ 2.60 (s, 3, SCH_3), 3.60 (s, 3, NCH_3), 4.48 (s, 2, NH_2).

Anal. Calcd for $C_4H_8N_4S$: C, 33.32; H, 5.59; N, 38.86. Found: C, 33.48; H, 5.74; N, 38.80.

The acetonitrile was evaporated from the original filtrate at reduced pressure to give 2.7 g of solid, the nmr ($CDCl_3$) spectrum of which showed the peaks due to **11**, listed above, as well as the following: δ 2.50 (s, 3), 3.57 (s, 3), 4.42 (s, 2). Assuming that the isomeric 3-amino-1-methyl-5-methylthio-1,2,4-triazole was responsible for these peaks, it comprised 30% of the solid or 6% of the total triazole produced in this reaction.

5-Amino-1,3-dimethyl-1,2,4-triazole (6). To a magnetically stirred solution of 1 (16.0 g, 143 mmol) and benzene (700 ml), surrounded by a cold water bath, was added methylhydrazine (8.0 ml, 153 mmol). The cooling bath was not replenished, and during continued stirring the solution became increasingly yellow and crystals precipitated. After 6 days, the reaction mixture was heated to boiling, the solution was decanted, and, upon recrystal-

lization, the yellow crystals (8.4 g) were collected by suction filtration. Concentration of the filtrate produced a second crop (5.0 g) for a total yield of 83% triazole.

The first crop consisted of **6** which was recrystallized from benzene to give an analytical sample of white leaflets: mp 155–156° (lit.[14] mp 156°); uv max (H_2O) 222 nm (ϵ 1070); ir (fluorolube and Nujol mulls) 3320 (s), 3130 (s), 1650 (s), 1580 (s), 1535 (s), 1395 (s), 1350 (s), and 1115 cm^{-1} (m); nmr ($CDCl_3$) δ 2.20 (s, 3, CCH_3), 3.55 (s, 3, NCH_3), 5.23 (s, 2, NH_2).

Anal. Calcd for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.97. Found: C, 42.82; H, 7.20; N, 50.01.

An nmr ($CDCl_3$) spectrum of the second crop showed that it consisted of 75% **6** and 25% **7**. Therefore, the minor component, **7**, comprised 9% of the total triazole obtained in this reaction.

Isolation of 3-Amino-1,5-dimethyl-1,2,4-triazole (7). A 2:1 mixture (9 g) of **6** and **7** was placed on a column of silica gel (300 g). The mixture was eluted with 40% acetone–60% trichloromethane. Fractions containing the first 1.5 g of triazole were combined and recrystallized from trichloromethane to give **7** (1.0 g). Recrystallization from benzene afforded an analytical sample of white crystals: mp 216–217° in a sealed tube; uv max (H_2O) 227 nm (ϵ 1350); ir (fluorolube and Nujol mulls) 3340 (s), 3190 (s), 1650 (s), 1560 (s), 1525 (s), 1425 (s), 1390 (s), and 655 cm^{-1} (s); nmr ($CDCl_3$) δ 2.32 (s, 3, CCH_3), 3.62 (s, 3, NCH_3), 4.10 (s, 2, NH_2).

Anal. Calcd for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.97. Found: C, 43.08; H, 7.18; N, 50.07.

5-Methylamino-1,3-dimethyl-1,2,4-triazole Hydriodide (28). A magnetically stirred solution of **6** (100 mg, 0.834 mmol), iodomethane (1.0 ml, 16 mmol), and acetonitrile (5 ml) was heated at 87° for 22 hr. After the solution was allowed to cool, the crystallized white crystals were collected by suction filtration to yield **28** (45 mg, 21%): mp 229–230° dec; ir (KBr) 3260 (m), 3080 (m), 1670 (vs), 1600 (m), 1440 (m), 1165 (m), and 760 cm^{-1} (s); nmr (D_2O) δ 2.40 (s, 3, CCH_3), 3.54 (s, 3, NCH_3), 3.70 (s, 3, $^+NCH_3$), 4.64 (s, 2, $^+NH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 128 (71), 127 (33), 126 (100), 125 (32), 69 (29), 57 (84), 42 (33).

Anal. Calcd for $C_5H_{11}IN_4$: C, 23.63; H, 4.36; N, 22.05. Found: C, 23.80; H, 4.30; N, 22.13.

Reaction of *N*-Cyano-*S*-methylisothiourea (12) with 2,4-Dinitrophenylhydrazine. A magnetically stirred solution of **12** (1.00 g, 8.70 mmol), 2,4-dinitrophenylhydrazine (1.72 g, 8.69 mmol), and DMF (10 ml) was refluxed for 48 hr. The reaction mixture was diluted with water (70 ml) and the dark precipitate (1 g) was collected by filtration. This material was boiled with acetonitrile and the insoluble portion (0.2 g) was removed by filtration. After the acetonitrile had been evaporated at reduced pressure, the residue was recrystallized from acetone–cyclohexane to yield *m*-dinitrobenzene (0.48 g, 33%). Recrystallization from ethanol–water gave a sample which melted at 87–88° (lit.[53] mp 89.5°). The ir and nmr spectra were identical with the published spectra[54] of *m*-dinitrobenzene.

Reaction of Cyanoguanidine (13) with 2,4-Dinitrophenylhydrazine Hydrochloride. A magnetically stirred mixture of **13** (1.00 g, 11.9 mmol), 50% aqueous 2,4-dinitrophenylhydrazine hydrochloride (5.58 g, 11.9 mmol), and DMF (10 ml) was heated at 69°. As the temperature increased, the reaction mixture became homogeneous, but within 1 hr a precipitate formed. After 17 hr, the precipitate was collected by suction filtration and washed thoroughly with acetone to give 1-(2,4-dinitroanilino)biguanide hydrochloride (**14**) as orange crystals (2.2 g, 58%), mp 246–247° dec. Recrystallization with DMF–95% EtOH afforded an analytical sample of fine orange needles, mp 250–251° dec. Silver chloride was precipitated when aqueous solutions of **14** and silver nitrate were combined. Compound **14** has the following spectral properties: ir (fluorolube and Nujol mulls) 3460 (m), 3420 (m), 3220 (m), 1680 (s), 1620 (s), 1575 (s), 1510 (s), 1490 (s), 1375 (s), and 1355 cm^{-1} (s); nmr (DMSO-d_6) δ 7.35 (d, 1, J = 10 Hz), 7.45 (s, 2), 7.95 (s, 5), 8.31 (q, 1, J = 10 Hz), 8.87 (d, 1, J = 3 Hz), 10.30 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 265 (50), 183 (46), 38 (37), 36 (100).

Anal. Calcd for $C_8H_{11}ClN_8O_4$: C, 30.15; H, 3.48; N, 35.16; Cl, 11.13. Found: C, 30.34; H, 3.56; N, 34.99; Cl, 11.12

***C*-Azido-1,2,4-triazoles (Table II). General Procedure.** A magnetically stirred solution of the amine (50 mmol), water (500 ml), and 96% sulfuric acid (quantity necessary to give the concentration indicated in Table II) was cooled to 0° by means of an ice–salt water bath. Then, in succession, solutions of sodium nitrite (55 mmol) in water (10 ml) and sodium azide (55 mmol) in water (10 ml) were added such that the temperature remained below 1°. After the second addition, the resulting solution was stirred overnight at 10°. The reaction mixture was neutralized with potassium bicarbonate, saturated with sodium chloride, and extracted with ethyl acetate (10 × 20 ml). The combined extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure.

A. 3-Azido-5-methyl-1,2,4-triazole (15). The solid residue was treated with activated charcoal and recrystallized from benzene to yield feathery, white crystals (76%): mp 144–145° (lit.[55] mp 143–145°); uv max (H_2O) 234 nm (ϵ 4470); ir (fluorolube and Nujol mulls) 3340 (w), 3170 (w), 3040 (m), 2930 (m), 2700 (m, br), 2430 (w), 2140 (s), 1500 (m), 1450 (m, br), 1420 (m), 1400 (m), 1375 (m), 1220 (w), and 1060 cm^{-1} (m); nmr ($CDCl_3$) δ 2.53 (s, 3, CH_3), 13.1 (s, 1, NH).

B. 5-Azido-1,3-dimethyl-1,2,4-triazole (16). The residual oil (0.7 g) was purified by molecular distillation (bath temperature 65–75°, pressure 0.13 Torr) to yield several drops of **16** as a yellow oil: ir (capillary film) 2140 (s), 1540 (s), 1505 (s), 1450 (s), 1410 (s), 1380 (s), 1340 (s), 1250 (s), 700 (m), and 690 cm^{-1} (m); nmr ($CDCl_3$) δ 2.30 (s, 3, CCH_3), 3.56 (s, 3, NCH_3).

Continuous extraction of the aqueous phase with trichloromethane gave 4.7 g of the amine starting material.

C. 3-Azido-5-dimethylamino-1,2,4-triazole (18). The solid residue (4.6 g, mp 153–154° dec) was treated with activated charcoal and recrystallized from benzene to give an analytical sample of yellow crystals: mp 153–154° dec; ir (fluorolube and Nujol mulls) 3330 (w), 2950 (m, br) 2410 (w), 2130 (s), 1640 (s), 1525 (s), 1430 (s), 1405 (s), 1350 (m), 1210 (m), 1045 (m), 930 (m), and 720 cm^{-1} (m); nmr ($CDCl_3$) δ 3.00 (s, 6, NCH_3), 11.7 (s, 1, NH).

Anal. Calcd for $C_4H_7N_7$: C, 31.37; H, 4.61; N, 64.03. Found: C, 31.40; H, 4.50; N, 64.12.

Continuous extraction of the aqueous phase with trichloromethane gave 1.1 g of amine starting material. The overall yield of azide was 72%.

D. 3-Azido-5-methoxy-1,2,4-triazole (19). The solid residue (80%, mp 106–108°) was treated with activated charcoal and recrystallized from benzene to afford an analytical sample of yellow crystals: mp 108–109°; ir (fluorolube and Nujol mulls) 3360 (w), 3200 (m), 3100 (m), 3020 (m), 2900 (m), 2850 (m), 2780 (m), 2720 (m), 2440 (w), 2130 (s), 1600 (s), 1535 (s), 1440 (s), 1395 (s), 1220 (m), and 1070 cm^{-1} (m); nmr ($CDCl_3$) δ 4.07 (s, 3, OCH_3), 11.70 (s, 1, NH).

Anal. Calcd for $C_3H_4N_6O$: C, 25.72; H, 2.88; N, 59.99. Found: C, 25.60; H, 2.87; N, 60.19.

E. 3-Azido-5-methylthio-1,2,4-triazole (21). The solid residue was treated with activated charcoal and recrystallized from benzene to yield an analytical sample of **21** (0.76 g, 70%) as light yellow crystals: mp 108–109°; uv max (H_2O) 238 nm (ϵ 6350); ir (fluorolube and Nujol mulls) 3360 (w), 3150 (m), 2940 (m), 2800 (m), 2440 (w), 2140 (s), 1490 (s), 1340 (m), 1315 (m), 1220 (m), and 1030 cm^{-1} (m); nmr ($CDCl_3$) δ 2.67 (s, 3, SCH_3), 12.50 (s, 1, NH).

Anal. Calcd for $C_3H_4N_6S$: C, 23.07; H, 2.58; N, 53.82. Found: C, 22.92; H, 2.57; N, 53.84.

F. 5-Azido-1-methyl-3-methylthio-1,2,4-triazole (22). After the reaction mixture was stirred overnight at 10°, a precipitate was collected by suction filtration and washed with water to yield 61% of 1,3-bis(1-methyl-3-methylthio-1,2,4-triazol-5-yl)triazene (**23**), mp 181–184° dec. This material was treated with activated charcoal and recrystallized from trichloromethane to afford an analytical sample of tan crystals: mp 191–192° dec; ir (fluorolube and Nujol mulls) 3210 (m), 3110 (m), 3040 (m), 2940 (m), 1590 (s), 1475 (s), 1385 (s), 1360 (s), 1345 (s), and 1215 cm^{-1} (s); nmr (DMSO-d_6) δ 2.74 (s, 6, SCH_3), 3.80 (s, 6, NCH_3), 12.8 (s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 299 (3), 271 (3), 156 (100), 128 (29), 82 (42), 43 (33), 15 (28).

Anal. Calcd for $C_8H_{13}N_9S_2$: C, 32.10; H, 4.38; N, 42.11. Found: C, 31.99; H, 4.43; N, 42.40.

The filtrate was neutralized, saturated, and extracted with trichloromethane (7 × 20 ml). The dark oil obtained by evaporation of the solvent from the dried, combined extracts was distilled to yield 28% of 5-azido-1-methyl-3-methylthio-1,2,4-triazole (**22**), bp 69–71° (0.12 Torr). Molecular distillation gave an analytical sample of yellow oil: ir (capillary film) 3340 (w), 2420 (w), 2120 (s), 1500 (s), 1425 (s), 1350 (s), and 1215 cm^{-1} (m); nmr ($CDCl_3$) δ 2.67 (s, 3, SCH_3), 3.67 (s, 3, NCH_3).

Anal. Calcd for $C_4H_6N_6S$: C, 28.23; H, 3.55; N, 49.38; S, 18.84. Found: C, 28.34; H, 3.62; N, 49.15; S, 18.68.

Consecutive Treatment of 3-Amino-1,5-dimethyl-1,2,4-triazole (7) with Nitrous Acid and Azide Ion. The general procedure for preparing the azides was employed using the following reagents: **7** (90 mg, 0.80 mmol); water (10 ml); 96% sulfuric acid

(78 mg, 0.76 mmol); sodium nitrite (97%, 65 mg, 0.91 mmol) in water (1 ml); and sodium azide (55 mg, 0.85 mmol) in water (1 ml). After the reaction mixture has been stirred overnight at 10°, a precipitate was collected by suction filtration and washed with water to yield 16 mg (17%) of 1,3-bis(1,5-dimethyl-1,2,4-triazol-3-yl)triazene (**29**): mp 226–228° dec; nmr (DMSO-d_6) δ 2.37 (s, 3, CCH_3), 3.74 (s, 3, NCH_3); mass spectrum (70 eV) m/e (rel intensity) 253 (3), 207 (5), 124 (100), 96 (48), 55 (55), 42 (52).

The filtrate was neutralized, saturated, and extracted with trichloromethane (6 × 5 ml). Evaporation of the solvents from the dried, combined extracts gave a yellow semisolid (60 mg). The nmr (DMSO-d_6) spectrum of this material showed peaks due to the triazene as well as the following: δ 2.51 (s, 3), 3.93 (s, 3). The appearance of a strong band at 2140 cm^{-1} in the ir ($CDCl_3$) spectrum indicated the presence of 3-azido-1,5-dimethyl-1,2,4-triazole.

1,3-Dimethyl-1,2,4-triazole (17). To a mechanically stirred solution of **6** (7.22 g, 64.5 mmol), 95% ethanol (400 ml), and 96% sulfuric acid (4.60 ml, 82.8 mmol) was added a solution of sodium nitrite (97%, 7.00 g, 98.5 mmol) and water (15 ml), whereupon a solid precipitated. The reaction mixture was heated at 65° for 15 hr and the resulting solution was concentrated to 30 ml at reduced pressure. The concentrate was diluted with water (150 ml), neutralized with potassium bicarbonate, saturated with sodium chloride, and extracted with trichloromethane (6 × 30 ml). After the combined extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure, the residual brown oil (5.5 g) was distilled to yield **17** (1.85 g, 36%), bp 25–27° (0.12 Torr) [lit.[15] bp 83° (20 Torr)]. Molecular distillation gave an analytical sample of colorless oil: ir (capillary film) 3120 (m), 2950 (m), 1525 (s), 1310 (s), 1195 (s), 740 (m), and 695 cm^{-1} (m); nmr ($CDCl_3$) δ 2.39 (s, 3, CCH_3), 3.86 (s, 3, NCH_3), 7.93 (s, 1, CH) [lit.[15] nmr ($CDCl_3$) δ 2.38 (s, 3, CCH_3), 3.84 (s, 3, NCH_3), 7.94 (s, 1, CH)].

Anal. Calcd for $C_4H_7N_3$: C, 49.47; H, 7.27; N, 43.27. Found: C, 49.26; H, 7.13; N, 43.17.

3-Chloro-5-methylthio-1,2,4-triazole (20). A procedure modeled after that of Reilly and Drumm[28] was used to convert **10** to **20** in 73% yield. Treatment with activated charcoal and recrystallization from ethyl acetate gave an analytical sample of white leaflets: mp 177–178°; uv max (H_2O) 228 nm (ϵ 2820); ir (fluorolube and Nujol mulls) 3090 (s), 2900 (s, br), 2750 (s), 1445 (s), 1305 (s), 1290 (s), 1030 (s), and 705 cm^{-1} (s); nmr (DMSO-d_6) δ 2.64 (s, 3, SCH_3), 14.30 (s, 1, NH).

Anal. Calcd for $C_3H_4ClN_3S$: C, 24.08; H, 2.70; N, 28.09; S, 21.43. Found: C, 24.40; H, 2.78; N, 28.36; S, 21.68.

Procedure for Variable-Temperature Nmr of *C*-Azido-1,2,4-triazoles. Nmr spectra were obtained on a Varian HA-60-EL instrument equipped with a variable-temperature probe. Sample temperatures above 35° were achieved by passing air over heating coils in the probe accessory. Temperatures below 35° were obtained by controlling the vaporization of liquid nitrogen from a Dewar flask by means of an immersed heater. Probe temperatures were monitored by measuring the difference in chemical shifts of the two signals of ethylene glycol for high temperatures (35–175°) and methanol for low temperatures (35 to −82°). For the high-temperature study, the azidotriazoles were dissolved in DMSO-d_6 (10% w/v); for the low-temperature study, solutions of acetone-d_6 (5% w/v) were used.

Registry No.—**1**, 1558-82-3; **2**, 51108-31-7; **3**, 24771-25-3; **4**, 10191-60-3; **5**, 4923-01-7; **6**, 51108-32-8; **7**, 34776-19-7; **8**, 51108-33-9; **9**, 51108-34-0; **10**, 45534-08-5; **11**, 51108-35-1; **12**, 51108-41-9; **13**, 51108-42-0; **14**, 51108-43-1; **15**, 15760-26-6; **16**, 461-58-5; **17**, 51108-36-2; **18**, 21041-86-1; **19**, 51108-37-3; **20**, 16778-76-0; **21**, 51108-38-4; **22**, 51108-39-5; **23**, 51108-40-8; **28**, 51108-44-2; **29**, 51108-45-3; H_2NNH_2, 302-01-2; H_2NNHMe, 60-34-4; 2,4-dinitrophenylhydrazine, 119-26-6.

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Dipole Moments of Some 3- and 4-Substituted Phthalimides and Phthalic Anhydrides. Influence of Steric and Resonance Effects

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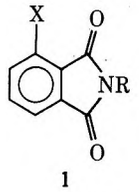
The dipole moments of phthalimide, phthalic anhydride, and 16 derivative compounds in dioxane solution have been measured and compared. The predicted moments of the derivatives have also been calculated from group moments. There is good agreement between the experimental and predicted dipole moments only for 3-methylphthalic anhydride, 3-fluorophthalimide, 4-methylphthalimide, 3-fluorophthalic anhydride, and 4-methylphthalic anhydride. The Zhdanov-Minkin equation for calculating resonance interaction moments has been applied for all of the derivative compounds. Arguments are presented for designating the numerical results of this calculation as *ring polarization moments*. The results of these calculations show that interaction resonance is significant only for 4-chlorophthalic anhydride. Steric and resonance effects are both small or absent as influences upon the dipole moments of 3-fluorophthalic anhydride, 3-fluorophthalimide, and of all methyl derivatives. Steric interaction between ortho substituents appears to be large only in the cases of 3-nitrophthalimide and 3-nitrophthalic anhydride.

The compilation of experimental dipole moments by McClellan[4] records data for a moderate number of cyclic imides, including a portion of the results of two systematic studies of the dipole moments of these compounds. The first of these studies, by Lumbroso and his coworkers,[5-7] dealt primarily with N-substituted succinimides and phthalimides. The second group of studies, by Lee and Kumler,[8-11] was concerned principally with nonaromatic imides, both cyclic and acyclic. The dipole moments of only the most common cyclic anhydrides have been determined, and no comparable systematic examination of these results has been published.

In the course of a series of studies[12-17] of the chemical and spectrophotometric properties of 3-substituted phthalimides **1** and 4-substituted phthalimides **2**, it was of interest to have dipole moment data for these compounds as an aid in the interpretation of the experimental results. Data for only three of these compounds could be found in the literature, namely, the dipole moments measured by Lumbroso and Dabard[5] for 3-chlorophthalimide (**1**, R = H; X = Cl), 4-chlorophthalimide (**2**, R = H; X = Cl), and 4-nitrophthalimide (**2**, R = H; X = NO_2), together with the moments for the *N*-methyl (R = CH_3) and *N*-phenyl (R = C_6H_5) derivatives of these compounds.



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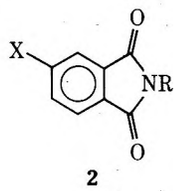

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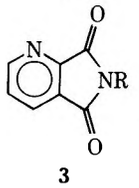

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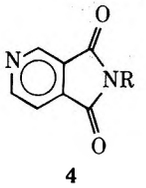
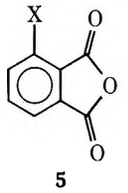


4

We have therefore measured the dipole moments of a more extended series of 3- and 4-substituted phthalimides and also of the pyridine analogs of phthalimide, quinolinimide (**3**), and cinchomeronimide (**4**). Since it was necessary in most cases to prepare the corresponding anhydrides as precursors to the imides, it was convenient to measure also the dipole moments of a number of 3-substituted phthalic anhydrides **5**, 4-substituted phthalic anhydrides **6**, and quinolinic anhydride **7**.



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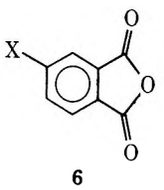

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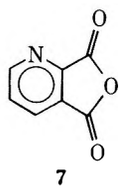

7

The majority of these compounds are sufficiently soluble in only two of the solvents suitable for dipole moment measurements for such measurements to yield useful results. These solvents are benzene and dioxane. Neither of these solvents possesses the inertness desirable in a solvent for dipole moment measurements, since benzene acts as a donor in charge-transfer interactions with phthalic anhydride[18] and a number of its derivatives,[19] while dioxane, in addition to its usual disadvantages,[20] can presumably be hydrogen bonded to the N protons of the imides. Ultimately, dioxane was chosen as the solvent in order to provide the best comparability of the results with those of the previous studies.[5-11]

The method applied for the measurements was that of Guggenheim,[21] as presented by Oehme and Wirth.[22] The rapidity with which the measurements can be made by this method provides a definite advantage for studies involving a highly hygroscopic solvent like dioxane and the moisture-sensitive anhydrides.

Experimental Section

Anhydrides and Imides. The majority of the compounds used in this study were prepared from commercially available 3- and 4-substituted phthalic acids. These acids were converted to the anhydrides either by the action of acetic anhydride or by thermal dehydration in a sublimation apparatus. 3-Fluorophthalic anhydride was prepared by dehydration of 3-fluorophthalic acid with an excess of trifluoroacetic anhydride at room temperature.[23] Phthalimide and the nitrophthalimides were purchased. The remaining imides were prepared from the anhydrides by heating with an equimolar quantity of urea until gas evolution ceased. All of the compounds were purified by recrystallization and sublimation until published melting points or satisfactory microanalyses were obtained. A final purification by sublimation at 1 Torr was always done within 12 hr of the measurements, and the sublimates were kept under vacuum in the sublimator until time for preparation of the solutions.

3-Fluorophthalimide. A mixture of 9 g of 3-fluorophthalic anhydride, 3.6 g of urea, and 50 ml of nitrobenzene was heated 3 hr at 170–180°. The precipitate obtained from the cooled reaction mixture was recrystallized twice from benzene and then sublimed *in vacuo* to give fine, yellowish needles, mp 179.5–180.5°. The yield was 81%. *Anal.* Calcd for $C_8H_4FNO_2$: C, 58.19; H, 2.44; N, 8.48; F, 11.51. Found:[24] C, 58.34; H, 2.28; N, 8.48; F, 11.44.

Table I
Dipole Moments of 3- and 4-Substituted Phthalimides and Phthalic Anhydrides in Dioxane

Compd	Registry no.	Dipole moment, D		Ring polarization moment, D
		Exptl	Predicted	
Phthalimide	85-41-6	2.17[a]		
3-Methylphthalimide	7251-82-3	2.39	2.21	+0.4
3-Fluorophthalimide	51108-29-3	2.60	2.65	−0.1
3-Chlorophthalimide	51108-30-6	2.41[b]	2.72	−0.6
3-Nitrophthalimide	603-62-3	3.90	4.63	*c*
Quinolinimide	4664-00-0	2.97	3.16	*c*
4-Methylphthalimide	40314-06-5	2.53	2.55	<0.0
4-Nitrophthalimide	89-40-7	2.96[d]	2.46	+0.4
Cinchomeronimide	4664-01-1	2.22	1.18	+1.0
Phthalic anhydride	85-44-9	5.34		
3-Methylphthalic anhydride	4792-30-7	5.46	5.36	+0.2
3-Fluorophthalic anhydride	652-39-1	5.44	5.56	−0.3
3-Chlorophthalic anhydride	117-21-5	5.31	5.59	−0.6
3-Nitrophthalic anhydride	641-70-3	5.95	6.73	*c*
Quinolinic anhydride	699-98-9	5.54	5.80	*c*
4-Methylphthalic anhydride	19438-61-0	5.66	5.72	−0.1
4-Chlorophthalic anhydride	118-45-6	4.54	4.00	+0.5
4-Nitrophthalic anhydride	5466-84-2	2.87	2.60	+0.4

[a] Reported values: 2.14 D,[5] 2.91 D.[10] [b] Reported: 2.28 D.[5] [c] Imaginary. [d] Reported: 2.60 D.[5]

Solvents and Apparatus. Spectrophotometric quality 1,4-dioxane[25] was refluxed in contact with sodium metal until the floating globules of molten sodium remained bright.[20] The dioxane was distilled through an 18-in. Vigreux column, and only the middle third of the distillate was used in the measurements. This distillation was always done on the same day on which the measurements were made.

A minimum of five solutions of each of the freshly sublimed compounds in the freshly distilled dioxane was prepared. Weight fractions of solutes fell in the range 10^{-3}–10^{-1}. The refractive indices of the dioxane and of the solutions were measured at 20.00° with either a Bausch and Lomb Type 3L Abbé refractometer or with a Bellingham and Stanley high-precision refractometer. The dielectric constants of dioxane and of the solutions were measured with a WTW Type DM01 dipolmeter,[26] using a Type DFL1 sample holding cell, also at 20.00°.

The dipolmeter was calibrated with spectrophotometric quality cyclohexane, benzene, carbon tetrachloride, and *n*-butyl ether, all of which had been stored over Type 4A molecular sieve for at least 1 week prior to the measurements. Dielectric constants for these liquids at 20° were those quoted by Oehme and Wirth.[22] This calibration was done six times at random intervals during an 8-month period, using new stocks of reference liquids, and found to be reproducible.

Results and Discussion

Calculations. The data from all of the calibration measurements were combined, and the method of least squares was applied to convert these measurements to a calibration equation for translating the dipolmeter readings to dielectric constants. The differences between the dielectric constants of the solutions and the solvent, $\epsilon_2 - \epsilon_1$, and the differences between the squares of the refractive indices, $n_2^2 - n_1^2$, were plotted against weight fraction of solute. If either of these plots showed curvature, sharp breaks, or scatter or failed to go through the origin, the entire set of measurements was repeated with fresh materials.

The slopes, a_n and a_ϵ, of the two plots were determined by the method of least squares. The dipole moment was then calculated from the difference $a_\epsilon - a_n$ by the equation[27]

$$\mu^2 = \frac{27kT}{4\pi N} \cdot \frac{M_2}{d_1(\epsilon_1 + 2)^2} \cdot (a_\epsilon - a_n) \qquad (1)$$

in which μ is the dipole moment in esu cm, k is the Boltzmann constant, T is the absolute temperature, N is Avogadro's number, M_2 is the molecular weight of the solute, d_1 is the density of dioxane at 20°, and ϵ_1 is the dielectric constant of dioxane at 20°.

The precisions of a_ϵ and a_n were calculated from the standard deviations of these slopes and the t factors at the 95% confidence level for the appropriate number of degrees of freedom. These limits were carried through the final calculations, and dipole moment values having precision limits wider than ±0.03 D were discarded. The results of the surviving measurements are presented in Table I.

Sources of Error. Early in this study a few sets of solutions were prepared on the night before the day on which the measurements were to be made. These measurements were later repeated with freshly purified materials and with all of the manipulations being done within 3–4 hr. The redeterminations gave dipole moments which were from 0.1 D larger for imides to as much as 0.7 D larger for anhydrides. The smaller values obtained in the earlier measurements were attributable to the effects of atmospheric oxygen and moisture on the dioxane and subsequent hydrolysis of the anhydrides by the absorbed moisture. It is felt that these effects have been satisfactorily minimized by the use of a short working time.

A source of difficulty inherent in the Guggenheim method lies in the problem of determining refractive indices with a sufficient degree of exactness.[20] The choice of dioxane as solvent has provided an advantage in this respect, since its refractive index is smaller than those of other suitable solvents, thereby giving larger values for $n_2^2 - n_1^2$ than would otherwise have been obtained. The compounds themselves provided a second minimization of this source of error, in that the slope a_ϵ was always one order of magnitude larger than the slope a_n and two orders of magnitude larger in the cases of the anhydrides.

Prediction of Dipole Moments. Predicted dipole moments of the imides and anhydrides were calculated by vectorial addition of group moments. In making these calculations, the assumptions made by Lumbroso and Dabard[5] and by Bakhshiev,[28] for predicting the dipole moments of phthalimides, were adopted and extended to the anhydrides. These assumptions are four in number. (1) The phthalimide and phthalic anhydride molecules are planar. (2) The vectors of the group moments, for the substituents used in this study, lie in the molecular plane. (3) The imide and anhydride moieties are electron withdrawing, and their group moment vectors bisect these groups. (4) The benzene ring is a perfect hexagon and makes no contribution to the total dipole moment. With these assumptions, the dipole moments of the appropriate mono-

substituted benzenes may be taken as the group moments and added vectorially according to the equation[29]

$$\mu^2 = \mu_X^2 + \mu_Y^2 + 2\mu_X\mu_Y \cos\phi \quad (2)$$

in which μ is the predicted moment, μ_X is the group moment for the substituent X, μ_Y is the imide or anhydride group moment, and ϕ is the angle between the vectors of μ_X and μ_Y. On the basis of the assumptions, an angle ϕ must be 90° for **1** and **5**, regardless of the nature of X. In the 4-substituted compounds, **2** and **6**, ϕ is 30° for electron-donating groups (X = CH_3) and 150° for electron-attracting groups (X = F, Cl, NO_2). Since the pyridine ring is not a perfect hexagon, the fourth assumption must be modified slightly for **3**, **4**, and **7**. The geometry of the pyridine ring[30] gives 89° for ϕ in **3** and **7**, and, since the pyridine nitrogen atom is electron-attracting,[31] 149° 10′ for ϕ in **4**.

The dipole moments of phthalimide, 2.17 D, and of phthalic anhydride, 5.34 D, obtained in the current study, were taken as the group moments for the imide and anhydride groups. In order to avoid discrepancies which might be introduced by differing solvent effects, or by differing procedures for evaluating dipole moments, the values for the group moments of the substituent groups were also based on data obtained for dioxane solutions, using the method and apparatus of this study to obtain the dipole moments of the appropriate monosubstituted benzenes. The resulting group moments were F, 1.53 D; Cl, 1.65 D; NO_2, 4.09 D; and the heterocyclic nitrogen of the pyridine ring, 2.27 D. These values are in good agreement with the values obtained by averaging the values listed by McClellan[4] for dioxane solutions of monosubstituted benzenes, which gave the results F, 1.51 D; Cl, 1.65 D; NO_2, 4.05 D; and pyridine, 2.22 D.

The dipole moment of toluene could not be obtained for a dioxane solution by the method and apparatus of this study. Plots of the experimental values of $\epsilon_2 - \epsilon_1$ *vs.* weight fraction for such solutions repeatedly gave sets of random points with no recognizable linearity. Since no published value could be found for the dipole moment of toluene in dioxane, McClellan's[4] "best value" for the dipole moment of toluene, 0.43 D, was taken as the group moment for the methyl group. The difficulty of measuring the dipole moment of toluene in dioxane is apparently the result of the closeness of the dielectric constants of these two liquids, which have been reported[32] to be 2.209 for dioxane and 2.379 for toluene, at 25°. The predicted dipole moments are summarized in Table I for comparison with the experimental values.

Discussion. Earlier studies[5,10] have yielded values of 2.14 D and 2.91 D for the dipole moment of phthalimide in dioxane solution. The current finding of 2.17 D is in satisfactory agreement with the smaller of these values. The paper which reported the higher value also commented upon the tan color of phthalimide, which leads to the suspicion that the material used in that study was not pure, since pure phthalimide is white. The dipole moment of phthalimide in benzene solution has been reported[4] as 2.12 D. There have been no previous measurements of the dipole moment of phthalic anhydride in dioxane solution. Values resulting from measurements with other solvents are 4.71 D in benzene,[18] 5.29 D in benzene,[4] and 5.87 D in carbon tetrachloride.[18]

The dielectric constant data for all of the imides except phthalimide and the methylphthalimides showed changes in the slopes of the plots of $\epsilon_2 - \epsilon_1$ *vs.* weight fraction in the vicinity of 10^{-2} weight fraction, and the measurements for these compounds were not extended to concentrations above this inflection point. This effect was particularly strong in the case of 4-nitrophthalimide, for which the plot of $n_2^2 - n_1^2$ *vs.* weight fraction also curved at the same point. The choice of concentration ranges upon which to base the dipole moment measurement apparently accounts for the differences between the dipole moments obtained in a prior study[5] and those of the current study, for 3-chlorophthalimide and 4-nitrophthalimide. The solutions utilized in the prior study fell in the concentration range 10^{-2}–10^{-1} weight fraction, above the inflection point in the dielectric constant curve.

In the case of 4-chlorophthalimide, the plot of $\epsilon_2 - \epsilon_1$ *vs.* weight fraction failed to go through the origin but was linear, at least up to 2×10^{-2} weight fraction, while the plot of $n_2^2 - n_1^2$ showed slight curvature at the higher concentrations. These results were reproducible. The slopes of the linear portions of the curves gave an apparent dipole moment of 1.01 D for 4-chlorophthalimide, which is smaller than the calculated value of 1.10 D, and appreciably smaller than the previously reported[5] value of 1.43 D, which was obtained from measurements made on more concentrated solutions.

No similar deviations were observed in the measurements made with the anhydrides or with the reference compounds. It is thus probable that the deviations observed with the phthalimide derivatives are the result of hydrogen-bonding interactions, either between the imides and dioxane, or between two imide molecules, or both. In very dilute solution, the predominant H-bonded species must be an association of one imide molecule with one dioxane molecule, and it is actually this species whose dipole moment was measured in this study.

Examination of the results reported in Table I shows that there is good agreement between the experimental and predicted dipole moments only for the 4-methyl compounds and for 3-fluorophthalimide and 3-methylphthalic anhydride. Fair agreement is observed with 3-fluorophthalic anhydride, 3-methylphthalimide, and quinolinimide. At the other extreme, agreement is very poor for 4-nitrophthalimide and 4-chlorophthalic anhydride, and extremely poor for both 3-nitro compounds and for cinchomeronimide. The general lack of agreement between experiment and prediction may indicate errors in the values used in eq 2 or the presence of factors not accounted for by this calculation.

The assumptions, upon which the predictive eq 2 is based, might better be called approximations, and they are not always good ones.[33] The assumptions adequately insert into the calculation the inductive effects of the substituent groups and the contributions to the dipole moment resulting from overlap of the π-electron cloud of the ring with π- or nonbonding electron clouds of individual substituent groups, that is, the mesomeric moments of these groups. The calculation does not allow for the transfer of charge across the π system of the ring from one group to another (the so-called interaction resonance), for any distortions in the geometry of the ring resulting from additional substitutions and probably not adequately for any major reorientations of the π-electron distribution of the ring resulting from the placement of two strongly electron-donating, or two strongly electron-attracting, substituents on the ring at an angle to each other. In the cases of compounds with substituents on adjacent carbon atoms, the calculation should provide adequately for ortho induction, but not for ortho-resonance interaction, for steric or electrostatic interactions through the space between the groups, or for intramolecular hydrogen bonding.

Two of the compounds with best agreement between predicted and experimental values are 4-methylphthalimide and 4-methylphthalic anhydride. For these compounds, all of the neglected factors must be absent, ex-

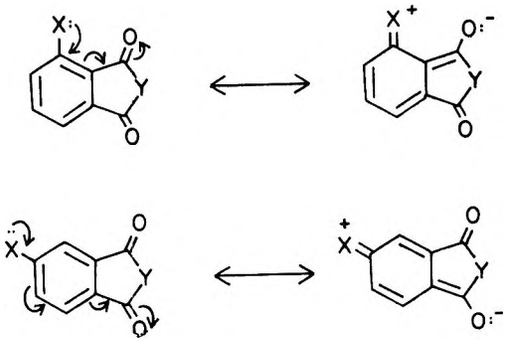

Figure 1. Resonance interactions in substituted phthalic anhydrides and phthalimides.

cept for the possibility of interaction resonance. Such interaction in these cases requires a contribution from $\pi-\sigma$ conjugation or hyperconjugation. This always has an extremely small effect, whose contribution, beyond that already provided for in the group moment of the methyl group, must be less than the experimental error.

The remaining compounds with fair to good agreement between the experimental and calculated values include the 3-methyl and the 3-fluoro derivatives of phthalimide and phthalic anhydride. For these cases, the principal factor not considered in eq 2 is steric interaction between the substituent and the carbonyl group ortho to it. This interaction appears to have only a small effect.

The disagreements between the experimental and predicted moments can be treated quantitatively as an apparent interaction resonance. The interaction effects can be formally represented as depicted in Figure 1, which shows transfer of nonbonding electron charge from the substituent to a specific carbonyl oxygen. The interaction is ortho in the cases of the 3-substituted compounds and para for the 4-substituted compounds. No such formal transfer of charge can be proposed for the nitro compounds or the pyridine derivatives, since there is no basis for supposing electron donation by the nitro group, by the heterocyclic nitrogen, or by the carbonyl group in the electronic ground energy state. The competing attractive forces of these groups for electrons will, however, produce a rearrangement of the electron density distribution in the aromatic ring. There are probably also distortions in the geometries of both rings accompanying all rearrangements in electron distribution, but no estimates of this effect can be made from existing data. Since the three effects considered in this paragraph cannot be separately estimated, we propose to consider them together under the label of *ring polarization effects* and to calculate these effects for all of the compounds under consideration.

Minkin, *et al.*,[33] have proposed a relationship for calculating the interaction moments of para-disubstituted benzenes. For the reasons given above, we will redefine the values provided by this equation as *ring polarization moments*. This equation is

$$\mu_I^2 + 2\mu_I(\mu_X \cos\theta_X + \mu_Y \cos\theta_Y) + \mu_C^2 - \mu_E^2 = 0 \quad (3)$$

where μ_I is the ring polarization moment, μ_C is the predicted dipole moment, μ_E is the experimental dipole moment, μ_X and μ_Y are group moments of the interacting groups X and Y, and θ_X and θ_Y are the angles the vectors of these group moments make with the axis joining the ring carbons to which the interacting groups are bonded.

Since resonance interaction involves only one of the two carbonyls of the imide and anhydride groups, the group moments of these moieties must be resolved into two components to provide suitable values for use in eq 3. Models of the phthalimide and phthalic anhydride molecules showed that the angle between the two legs of the imide or anhydride groups is approximately 30°. Application of eq 2 with this angle and the experimental dipole moments of phthalimide and phthalic anhydride gave a moment of 1.12 D along each leg of the imide group and a moment of 2.76 D along each leg of the anhydride group. These values were defined as μ_Y in eq 3, and the previously defined group moments were defined as μ_X. The angles θ_X and θ_Y, respectively, were estimated as 0 and 15° for the 4-substituted compounds and 60 and 45° for the 3-substituted compounds. The ring polarization moments calculated for these values are listed in the last column of Table I. These results are felt to be meaningful only to the nearest 0.1 D at best, as the result of the uncertainties introduced in the values of θ_X and θ_Y, as well as in the calculation of μ_C.

True interaction moments are positive,[33] since they represent the transfer of charge across the ring from a donor group to an acceptor group, with resulting enhancement of the dipole moment. Among the compounds considered in this study, this effect is certain only in the case of 4-chlorophthalic anhydride but may be a contributor in the cases of the 3-methyl compounds.

One possible interpretation of a negative ring polarization moment is that resonance interaction between a substituent and the ring has been reduced or suppressed. This must be the explanation for the negative ring polarization moments of the 3-fluoro and 3-chloro compounds. Steric interference between the halogen atom and the *o*-carbonyl reduces the interaction between the nonbonding pair and the π cloud. This effect is naturally larger with chlorine than with fluorine, since the larger chlorine atom is more subject to steric hindrance.

The small negative ring polarization moments observed for the 4-methyl compounds, on the other hand, are the result of the lack of a satisfactory group moment for the methyl group. If it is assumed that the ring polarization moments of the 4-methyl compounds are actually zero, then application of eq 2 with the experimental moments gives an average value of 0.39 D as the group moment for the methyl group for measurements made on aromatic compounds in dioxane solution. This is not really a significant change from the value of 0.43 D, since it reduces the calculated moments of the 3-methyl compounds by only 0.01 D.

Application of eq 3 to the data for the 3-nitro compounds and for quinolinimide and quinolinic anhydride gave only imaginary solutions for the ring polarization moments of these compounds. We interpret this to mean that values used for the angles ϕ and θ in eq 2 and 3 for these compounds were in considerable error. Steric effects in the 3-nitro compounds must force the nitro group out of coplanarity with the ring to a sufficient degree as to suppress the resonance interaction of the nitro group with the ring, producing substantially smaller dipole moments than the predicted ones. The group moment of the nitro group in this case also will be smaller than the one assumed in this study. In the cases of the pyridine derivatives, quinolinimide and quinolinic anhydride, the error lies in the assumption that the geometries of these compounds are similar to those of phthalimide and phthalic anhydride. The available data are unfortunately not adequate for the estimation of more accurate angles.

Erroneous geometry is also a contributing factor to the very large positive ring polarization moment of cinchomeromimide. Other factors may be involved, however, with this compound and with the 4-nitro compounds, which also show positive ring polarization moments. All three of these compounds have strongly electron-withdrawing groups acting in opposition to each other, with neither steric effects nor interaction resonance being possible. In

such cases the aromatic ring becomes electron deficient and may act as an acceptor in charge-transfer complexation. Whether or not this effect, with dioxane acting as donor, accounts for the large dipole moments of these molecules is problematical.

Early in this study it was speculated that an enolized form of the imide might be stabilized by intramolecular hydrogen bonding in 3-fluorophthalimide and 3-nitrophthalimide. There is no chemical evidence for such enolization, however, and concurrent ultraviolet and infrared studies by one of us (L. Y. S.) failed to reveal any spectral evidence for it. Construction of models[34] of the enol forms showed that the enol hydrogen cannot be properly oriented to permit hydrogen bonding, either to a fluorine atom or to a nitro group in the 3 position.

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Synthesis of Phosphine Oxides from Phosphorus Esters and Alkyl Halides Using Either Sodium Bis(2-methoxyethoxy)aluminum Hydride or Sodium Aluminum Diethyl Dihydride[1,2]

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Procedures are presented by which phosphorus esters (phosphates, phosphonates, and phosphinates) may be converted to phosphine oxides by reduction with either sodium bis(2-methoxyethoxy)aluminum hydride or sodium aluminum diethyl dihydride followed by addition of an appropriate primary or secondary alkyl halide. Yields are generally comparable to those obtained using a Grignard approach to the same conversions, but the procedures described offer the advantages of greater convenience and experimental simplicity. A number of examples of the synthetic method are presented including the preparations of the phosphorus-containing heterocycles, 1-phenylphospholane 1-oxide, and 1-phenylphosphorinane 1-oxide.

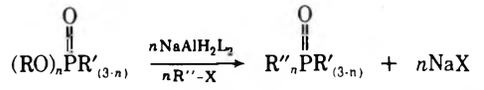
Only a few general approaches to the syntheses of phosphine oxides exist. The Arbuzov reaction of an alkyl halide with an ester of a phosphinous acid,[4] while giving respectable yields of phosphine oxides, is often rendered infeasible by the difficulty in obtaining the necessary phosphinate. Alkaline hydrolysis of quaternary phosphonium salts[5] likewise is only useful if an appropriate phosphonium salt is readily available. The reaction of Grignard reagents with various phosphorus esters[6] is generally more viable than the above methods, but it too has some disadvantages: there is an extra step, the synthesis of the Grignard reagent, and this reagent usually must be employed in large excess in the reaction with the phosphorus ester.[6,7]

We would like to report a new general procedure for the synthesis of phosphine oxides using the aluminum hydride reagents $NaAlH_2(CH_2CH_3)_2$ and $NaAlH_2(OCH_2CH_2OCH_3)_2$. Since some workers have encountered difficulties in attempting to carry out reactions with particular Grignard reagents or particular leaving groups on phosphorus, this new procedure complements the procedure using Grignard reagents. The procedure involves initial reaction of a phosphorus ester (phosphate, phosphonate, or phosphinate) with one of these two aluminum hydride regents to form an intermediate which subsequently reacts with an alkyl halide to form new carbon–phosphorus bonds. In Scheme I, R′ may be alkyl or aryl, and R″ may be a primary or secondary alkyl halide.

Results and Discussion

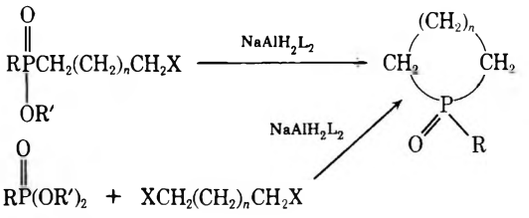
Addition of either $NaAlH_2(CH_2CH_3)_2$ or $NaAlH_2(OCH_2CH_2OCH_3)_2$ to a solution of a phosphinate

Scheme I



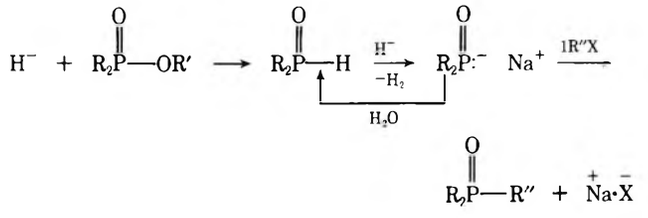
RR′P(O)OR″ in tetrahydrofuran in a 1:1 molar ratio gives the evolution of 1 molar equiv of hydrogen gas. Subsequent addition of an alkyl halide to this solution gives an opaque reaction mixture which, upon hydrolysis, yields a phosphine oxide (Scheme I). A number of examples of such reactions using phosphinates, phosphonates, and phosphates as starting materials are given in the Experimental Section. Yields range from 11 to 52% of isolated products. Additional examples have been reported elsewhere.[8]

Scheme II



The procedure is an especially convenient route to certain types of phosphorus-containing heterocycles, as shown in Scheme II. Both phosphorinanes (n = 3) and phospholanes (n = 2) have been prepared by these approaches.

Scheme III

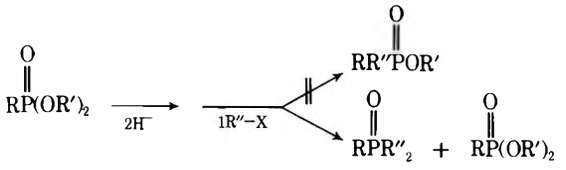


This general behavior is consistent with a mechanism, as shown in Scheme III, involving an intermediate sodium alkylarylphosphine oxide, analogous to the sodium dialkylphosphates used in the Michaelis–Becker reaction.[9] After initial displacement of alkoxide with hydride, a second hydride, acting as a base, removes the new, relatively acidic proton on phosphorus, forming the sodium dialkylphosphine oxide. There is a precedent for both this and the subsequent step in the reaction of R(R′O)P(O)H with R″–X and sodium hydride in dimethylformamide to give R(R′O)P(O)R″.[10] Once formed, the sodium dialkylphosphine oxide would be expected to react with the alkyl halide in a nucleophilic substitution to give phosphine oxide and sodium halide. Reactions involving attack by R(R′O)P(O)Na on alkyl halides to give phosphinates[11] and by RR′P(O)Na to give phosphine oxides,[12] for example, are known.

The mechanism is further supported by the following experiment. Quenching a reaction mixture of $NaAlH_2(OCH_2CH_2OCH_3)_2$ and a phosphinate with H_2O gave secondary phosphine oxide such as that proposed as an intermediate above, and reaction of this secondary phosphine oxide with additional reducing agent, followed by addition of an alkyl halide, gave phosphine oxide (see Scheme III).

The tremendous influence exerted by the cation in the alkylation chemistry of enolates[13] suggests that the sodium cation of these aluminum hydride reagents is necessary for the success of the phosphorus anion alkylation reaction. It is known that phosphorus esters, when treated with $LiAlH_4$, are generally reduced all the way to the phosphine.[14] The reaction can be stopped at the hydrogen phosphine oxide by conducting the reaction at 0°,[15] and treatment at this stage with an aklyl halide gives at least some alkylation as shown by examining a crude reaction mixture by mmr spectroscopy. In our hands this $LiAlH_4$ reaction is impractical as a synthetic route to phosphine oxides. It is because the reaction with sodium aluminum hydride proceeds completely to the sodium phosphorus anion and is stable at that point toward further reduction[16] that the new reaction is synthetically feasible.

Scheme IV



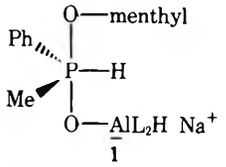
The sequence of events leading to dialkylation of a phosphonate to yield phosphine oxide (Scheme IV) is not so readily apparent. In our hands, many attempts to prepare phosphinates from phosphonates, by controlling stoichiometry and reaction conditions, have led only to a mixture of phosphine oxide (dialkylation) and starting material.[17] Addition of 1 molar equiv of aluminum hydride reagent to a phosphonate gave hydrogen evolution as usual. When bubbling had ceased, 1 molar equiv of alkyl halide was added, and precipitation of sodium halide was immediately noted, but no further evolution of gas was observed. Work-up of the reaction after a reaction time sufficient to give 90% of the theoretical amount of sodium halide gave a 25% yield of the dialkylated product and some starting material but no monoalkylated phosphinate. This evidence suggests that the phosphinate is not even formed as an intermediate, since no hydrogen evolution is observed after addition of the alkyl halide. Attempts to isolate an intermediate, by hydrolyzing the reaction mixture instead of adding alkyl halide, gave no recovery of any organic-soluble phosphorus-containing species.

The chief advantages of the new method are the ready availability and reasonable cost of the starting materials and the experimental simplicity of the one-pot reaction. All the solutions involved in the reaction are homogenous and easily handled. The work-up is simple and fast, and the conditions are very mild. In contrast to the Grignard synthesis, the new reaction generally proceeds with a 1:1 molar ratio of reactants, although reaction time can be cut down by using a 2–3 molar excess of alkyl halide. Yields are similar to those obtained in the Grignard procedure.

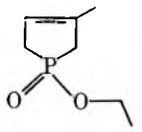
The chief disadvantage of the procedure is the extremely unpleasant odor encountered, presumably due to the presence of some reduced phosphorus species in the reaction mixture. Even with the precaution of conducting all aspects of the reaction in the hood, it is practically impossible to prevent some spread of the odor.

The Grignard procedure remains the method of choice in the preparation of optically active phosphine oxides. Attempts to convert an optically active menthyl phosphinate, prepared following the procedure of Mislow,[7] to an optically active phosphine oxide, led to racemized product. Racemization could be occurring either during the initial reduction, *via* stereomutation of the presumed intermediate phosphorane **1** (analogous to that proposed to explain racemization of recovered starting material in the $LiAlH_4$ reduction of phosphine oxides)[18] or after forma-

tion of the phosphine oxide.[18] The present results cannot distinguish among these possibilities.



1



2

The aluminum hydride reaction failed to give alkylation with *tert*-butyl bromide, giving, after work-up, the phosphinic acid of the starting phosphinate. Attempted alkylation of 1-ethoxy-1-oxo-3-methyl-3-phospholene[19] (2) gave no isolable phosphorus compound. Since several similar saturated phosphorus esters alkylated cleanly, it is likely that the carbon–carbon double bond is interfering in the phospholene reaction.

Attempts to alkylate a cyclic four-membered ring phosphinate were complicated by a great amount of apparent polymerization. It may be that strain in the ring renders the intermediate anion especially unstable. This may also be a factor in the failure of the phospholene reaction, since it appears to be a general rule that a double bond in a phosphorus-containing five-membered ring increases the strain in the ring.[20]

Although most of the examples described in the Experimental Section use $NaAlH_2(OCH_2CH_2OCH_3)_2$ as the reducing agent, the reagent of choice in these reactions seems to be $NaAlH_2(CH_2CH_3)_2$. While it is much more sensitive to air than the $NaAlH_2(OCH_2CH_2OCH_3)_2$, with respectful handling the former presents no danger and bestows the definite advantage of a cleaner hydrolysis mixture. Hydrolysis of $NaAlH_2(OCH_2CH_2OCH_3)_2$ reactions gives high-boiling 2-methoxyethanol, which must generally be removed by vacuum distillation at some point. The hydrolysis of $NaAlH_2(CH_2CH_3)_2$ reactions gives ethane gas, so that removal of volatile solvents after filtration of aluminum salts gives relatively uncontaminated product directly. Yields of final product, whenever direct comparisons have been made, are unaffected by choice of aluminum hydride reagent.

Experimental Section

General Methods. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif. Proton nmr spectra were measured using either a Varian T-60 or A-60A spectrometer, with CCl_4 or $CDCl_3$ as solvent and tetramethylsilane as internal standard, unless otherwise specified. Hydrogen gas was detected using a Consolidated Model 21-103c mass spectrometer. Accurate mass measurements were determined on a Consolidated Model 21-110B double-focusing high-resolution spectrometer. Melting points are uncorrected.

Materials. Sodium bis(2-methoxyethoxy)aluminum hydride, a 70% solution in benzene, was obtained from Eastman. Sodium aluminum diethyl dihydride, a 25% solution in toluene, was purchased from the Ethyl Corp., Baton Rouge, La. Methyl methylphenylphosphinate was the generous gift of Dr. J. A. Virgilio, University of California, Berkeley. Diethyl benzylphosphonate, diethyl phenylphosphonite, and triethyl phosphate were purchased from Aldrich Chemical Co. Diethyl phenylphosphonate was prepared by esterification of phenylphosphonic dichloride (Aldrich) by the method of Kosolopoff and Huber.[21]

Aluminum Hydride Reductions—General Procedures. All the aluminum hydride reactions were run under a nitrogen atmosphere. It most cases no special precautions were taken to dry glassware or solvents, since a slight excess of reducing agent effectively removed water from the reaction. In some of the high-dilution cyclization reactions, however, the tetrahydrofuran (THF) solvent was dried by several hours of heating at reflux over lithium aluminum hydride followed by distillation from $LiAlH_4$ directly into a previously dried flask.

Both aluminum hydride reagents, $NaAlH_2(OCH_2CH_2OCH_3)_2$ and $NaAlH_2(CH_2CH_3)_2$, have a tendency to lose potency over a period of time after they are first opened. Satisfactory results were obtained by assuming freshly opened reagents to be of the strength indicated on the bottle. The strength of old reagent can be determined in a number of ways. Titration with a proton source such as methanol, with collection of evolved hydrogen gas, is one means. In most cases, a convenient alternative is to assume that the reagent is at its maximum strength, and use it in the reaction with the phosphorus ester. After initial addition is complete, but before adding the alkyl halide, a small aliquot of reduced ester can be worked up as discussed below; an nmr spectrum of the crude oil will indicate the amount of unreacted phosphorus ester. Comparison of the integrated area of the remaining ester protons with some other protons in the molecule gives an indication of the amount of unreacted phosphorus ester, and thus the amount of additional reagent necessary. Finally, since neither reagent is very reactive toward alkyl halides[22] or the product phosphine oxides, there is no harm in using more hydride reagent than necessary.

Hydrolysis is generally accomplished by adding water in small increments to the stirring reaction mixture at 25°. In reactions in which $NaAlH_2(CH_2CH_3)_2$ is the reducing agent, precautions should be taken to avoid the consequences of frothing due to the evolution of ethane. A reaction flask two–three times the volume of the solvent used allows plenty of room for frothing. Near the end of hydrolysis the aluminum salts polymerize and the solution becomes very viscous. Addition of a little more water and continued stirring returns the mixture to a lower viscosity. At this point the hydrolyzed mixture is filtered, and the aluminum salts are washed with $CHCl_3$. Occasionally a second filtration is necessary to remove all the aluminum salts.

When $NaAlH_2(OCH_2CH_2OCH_3)$ is used, it is necessary to evaporate the oily residue *in vacuo* to remove the high-boiling hydrolysis product, 2-methoxyethanol. Alternatively, this can be removed as the forerun of a fractional distillation.

Benzylmethylphenylphosphine Oxide. To a stirred solution of 1.60 g (9.4 mmol) of methyl methylphenylphosphinate in 150 ml of THF at 65° was added dropwise over a period of 25 min a solution of 11.3 mmol of $NaAlH_2(OCH_2CH_2OCH_3)_2$ in 50 ml of THF. Vigorous bubbling due to the evolution of hydrogen, detected in one case by a mass spectrometric analysis, occurred throughout the addition. When all the hydride solution had been added, stirring was continued several minutes until bubbling stopped; then a solution of 1.42 g (11.3 mmol) of benzyl chloride in 15 ml of THF was added. The solution, which became cloudy with NaCl after several minutes, was stirred at 65° for 3 hr. Hydrolysis of the stirring reaction mixture at 25° with a minimum amount of water (1–2 ml), followed by filtration (and a wash of the aluminum salts with 50 ml of $CHCl_3$, which was added to the filtrate) and removal of solvent, left an impure white solid which, upon crystallization from hexane–benzene, gave 1.13 g (52% yield based on phosphinate) of benzylmethylphenylphosphine oxide, mp 136–141° (lit.[23] 148–149°). Recrystallization raised the melting point range to 142–144°. In an analogous reaction in which the $NaAlH_2(OCH_2CH_2OCH_3)_2$ was replaced by $NaAlH_2(CH_2CH_3)_2$, virtually the same yield of this product was obtained. The nmr spectrum showed peaks at δ 1.52 (3 H, d, J_{PCH} = 13 Hz), 3.21 (2 H, d, J_{PCH} = 15 Hz), 7.11 (5 H, broad s), and 7.40 (5 H, m).

Ethylmethylphenylphosphine Oxide. Using the same general procedure as in the preparation above, but with toluene as solvent, 6.2 g (0.0365 mol) of methyl methylphenylphosphinate, 12 ml (0.043 mol) of $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution, and 8 ml (0.107 mol) of ethyl bromide were allowed to react; the reaction mixture was heated at 55–60° for 17 hr. Hydrolysis, filtration, and removal of solvent left a crude oil which, upon fractional distillation, gave 2.47 g (40.5% yield) of ethylmethylphenylphosphine oxide, bp 110–112° (0.3 mm). The product was characterized by accurate mass measurement of its parent ion: calcd for $C_9H_{13}OP$, 168.0724; found, 168.0724. The nmr spectrum showed peaks at δ 1.06 (3 H, m), 1.73 (3 H, d, J_{PCH} = 13 Hz), ~1.83 (2 H, m), and 7.64 (5 H, m).

Dibutylbenzylphosphine Oxide. To 10.25 g (0.045 mol) of diethyl benzylphosphonate in THF was added 15.6 g (0.054 mol) of $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution. After bubbling had ceased, 12.3 g (0.09 mol) of *n*-butyl bromide was added, and the cloudy reaction mixture was stirred at 55° under N_2 for 10 hr. The oil obtained on work up was fractionally distilled to give 1.0 g of starting phosphonate, bp 108–111° (0.3 mm), and 1.72 g of dibutylbenzylphosphine oxide, bp 145–154° (0.4 mm). This corresponds to a 17% yield based on unrecovered phosphonate. The phosphine oxide was crystallized from petroleum ether, giving long needles, mp 57–60°. The product was analyzed by accurate mass measurement of its mass spectral parent ion: calcd for $C_{15}H_{25}OP$,

252.1690; found, 252.1693. The nmr spectrum showed peaks at δ 0.91 (6 H, t, J = 6 Hz), 1.53 (12 H, m), 3.14 (2 H, d, J = 15 Hz), and 7.28 (5 H, s).

Dibutylphenylphosphine Oxide. Using 8.0 g (0.037 mol) of diethyl phenylphosphonate, 13 g (0.045 mol) of $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution, and 10.5 g (0.076 mol) of *n*-butyl bromide, 1.25 g of dibutylphenylphosphine oxide was prepared by the same procedure as that used for benzyldibutylphosphine oxide. This corresponds to a 23% yield of phosphine oxide, based on unrecovered phosphonate: bp 147–150° (0.7 mm); mp 50–52°. The product was analyzed by accurate mass measurement of its mass spectral parent ion: calcd for $C_{14}H_{23}OP$, 238.1509; found, 238.1515. The mmr spectrum showed peaks at δ 0.90 (6 H, t, J = 6 Hz), 1.66 (12 H, m), and 7.65 (5 H, m).

1-Phenylphosphorinane 1-Oxide. A 250-ml round-bottom flask containing 100 g (0.43 mol) of 1,5-dibromopentane was fitted with a reflux condenser, on top of which was placed a pressure-equalizing addition funnel containing 21.5 g (0.109 mol) of diethyl phenylphosphonite. With stirring at 150–155° under nitrogen, the phosphonite was added dropwise over a period of 30 min, and stirring at 150° was continued for an additional 15 min. The excess dibromide was removed by vacuum distillation. A solution of the residue in CCl_4 was cooled for 6 hr, giving a clear supernatant over a thick oil. The supernatant was concentrated to give 22 g of 95% pure ethyl (5-bromopentyl)phenylphosphinate, as judged by nmr spectroscopy. The nmr showed peaks at δ 1.29 (3 H, t, J = 7 Hz), 1.73 (8 H, m), 3.39 (2 H, m), 3.97 (2 H, m), and 7.62 (5 H, m).

The phosphinate decomposed with evolution of ethyl bromide on attempted vacuum distillation, but this partially purified oil was sufficiently pure for the subsequent synthesis.

A three-neck, 2-l. round-bottom flask was fitted with two pressure-equalizing addition funnels and a mechanical stirrer. In one funnel was placed a solution of 10.6 g (0.033 mol) of the above-prepared phosphinate in 90 ml of THF, and in the other 10.6 g (0.037 mol) of $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution in 90 ml of THF. These reactants were added simultaneously over a period of 1 hr to 500 ml of refluxing THF. The reaction mixture was heated at reflux for an additional hour, then stirred at room temperature for 6 hr. Work-up gave 7.7 g of oil, which upon fractional distillation started to sublime in the condenser after several forerun fractions were collected. The distillation residue was transferred at this point to a sublimation apparatus, and 1.80 g (28% yield) of 1-phenylphosphorinane 1-oxide was collected: bp 141° (0.2 mm); mp 125–127° [lit. bp 140° (1.0 mm); mp 130°].[21] The nmr spectrum showed peaks at δ 1.92 (10 H, m) and 7.72 (5 H, m).

1-Phenylphospholane 1-Oxide. Using a procedure analogous to the synthesis of ethyl (5-bromopentyl)phenylphosphinate, 35 g of diethyl phenylphosphonite and a fourfold excess of 1,4-dibromobutane were converted to 38 g of 90–95% pure ethyl (4-bromobutyl)phenylphosphinate, a yield of *ca.* 75%. The nmr spectrum showed peaks at δ 1.25 (3 H, t, J = 7 Hz), 1.92 (CH, m), 3.39 (2 H, m), 3.95 (2 H, m), and 7.64 (5 H, m). This ester was not further characterized and was used directly in the next step of the synthesis.

The ester was treated with $NaAlH_2(OCH_2CH_2OCH_3)_2$ as in the above procedure to give a 27% yield of 1-phenylphospholane 1-oxide, bp 140–150° (0.3 mm) [lit. bp 99–100° (0.15 mm)].[22] The nmr spectrum showed peaks at δ 1.95 (8 H, m) and 7.71 (5 H, m).

Ethyl (3-Bromopropyl)phenylphosphinate. Using 50.5 (0.255 mol) of diethyl phenylphosphonite and 250 g (1.24 mol) of 1,3-dibromopropane, 56 g (76% yield based on phosphonite) of ethyl (3-bromopropyl)phenylphosphinate was prepared by a Michaelis–Arbuzov reaction analogous to that used to prepare ethyl (5-bromopentyl)phenylphosphinate. The nmr spectrum showed peaks at δ 1.23 (3 H, t, J = 7 Hz), 2.07 (4 H, m), 3.45 (2 H, m), 3.94 (2 H, m), and 7.83 (5 H, m). The mass spectral parent ion was accurately mass measured: calcd for $C_{11}H_{16}{}^{79}BrO_2P$, 290.0062; found, 290.0048. This product was further characterized as described below.

2-Phenyl-1,2-oxaphospholane 2-Oxide. In order to characterize ethyl (3-bromopropyl)phenylphosphinate, which like similar compounds was too thermally unstable to be purified by distillation, 18 g (0.062 mol) of the slightly impure ester was heated at 200° for 1 hr. The residue was vacuum distilled to give 6.5 g (0.036 mol, 58% yield) of 2-phenyl-1,2-oxaphospholane 2-oxide, bp 157° (0.7 mm). *Anal.* Calcd for $C_9H_{11}O_2P$: C, 59.40; H, 6.05; P, 17.03. Found: C, 59.26: H, 5.98; P, 16.96. The nmr spectrum showed peaks at δ 2.10 (4 H, m), 4.38 (2 H, m), and 7.58 (5 H, m).

Attempted Synthesis of 1-Phenylphosphetane 1-Oxide. This reaction was carried out starting with ethyl (3-bromopropylphenylphosphinate) exactly analogous to the procedure used to prepare 1-phenylphosphorinane 1-oxide, with the exception that the addition time was decreased to 45 min and the period of subsequent reflux was decreased to 45 min. After the usual work-up, a viscous oil was obtained which did not distil at 0.35 mm up to a temperature of 210°.

Isopropylmethylphenylphosphine Oxide. To 3.2 g (0.019 mol) of methyl methylphenylphosphinate in 5 ml of benzene at room temperature was added 18.4 ml of $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution. Isopropyl bromide (7 g, 0.057 mol) was added, after bubbling had ceased, in 5 ml of benzene and the solution was heated at reflux for 3 hr. The standard work-up followed by distillation gave 0.56 g (16.5% yield) of isopropylmethylphenylphosphine oxide, bp 88–91° (0.1 mm). The product was analyzed by accurate mass measurement of its parent ion: calcd for $C_{10}H_{15}OP$, 182.0862; found, 182.0863. The nmr spectrum showed peaks at δ 1.06 (6 H, m), 1.63 (3 H, d, J_{PCH} = 13 Hz), ~1.75 (1 H, m), and 7.67 (5 H, m).

Tribenzylphosphine Oxide. A solution of 3.8 g (0.021 mol) of triethyl phosphate and 13.2 g (0.105 mol) of benzyl chloride in 5 ml of dry benzene was heated at reflux under N_2, and to this stirring solution was added 61 ml of $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution over a period of 2 hr, after which heating at reflux was continued 14 more hr. The cooled reaction mixture was added to 300 ml of ether, and the ether solution was slowly hydrolyzed giving insoluble aluminum salts. The supernatant was reduced to an oil which was crystallized from ether–pentane to give 1.0 g (15.5% yield) of tribenzylphosphine oxide, mp 211–214° [lit. 213°,[24] 214°[25]]. The nmr spectrum showed peaks at δ 3.08 (6 H, d, J_{PCH} = 14 Hz) and 7.28 (15 H, broad s).

Methylphenylphosphine Oxide. To a solution of 3.5 g (0.021 mol) of methyl methylphenylphosphinate in 35 ml of THF at 0° was added dropwise over a 10-min period a solution of 7.4 g of $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution in 10 ml of THF. After bubbling stopped, the mixture was hydrolyzed as usual and distilled, giving 1.38 g (51.5% yield) of methylphenylphosphine oxide, bp 93–102° (0.2 mm). Accurate mass measurement of the mass spectral parent ion confirmed its composition: calcd for C_7H_9OP, 140.0391; found, 140.0395. The proton nmr spectrum showed peaks at δ 1.92 (3 H, d of d, J_{PCH} = 15 Hz, J_{HPCH} = 5 Hz), 7.58 (5 H, m), and 7.72 (1 H, d of q, J_{PH} = 478 Hz, J_{HPCH} = 5 Hz).

Benzylmethylphenylphosphine Oxide from Methylphenylphosphine Oxide. To 1.60 g (0.012 mol) of methylphenylphosphine oxide in 25 ml of THF at 25° was added 2.14 g of $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution in 10 ml of THF. After bubbling had ceased, 3.1 g (0.025 mol) of benzyl chloride was added and the solution was stirred overnight. Work-up as usual gave 1.43 g (51% yield) of benzylmethylphenylphosphine oxide, which had identical spectral properties with those of the previously isolated material.

Attempted Synthesis of Optically Active Benzylmethylphenylphosphine Oxide. (*S*)-(−)-Menthyl methylphenylphosphinate was prepared following the procedure of Mislow and coworkers,[7] $[\alpha]^{23}D$ −98.7° compared to the literature value of −94°. A solution of 1.0 g (0.0034 mol) of this ester in 20 ml of THF was stirred vigorously at 35°, and to this stirring solution was added over a 45-min period a solution of 1.0 g of $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution in 20 ml of THF. Stirring was continued 15 min, after which was added at 30° 0.9 g (0.007 mol) of benzyl chloride. This reaction mixture was stirred at 25° for 43 hr and then worked up as usual. The product was recrystallized from benzene–hexane to give 0.256 g of (44% yield) benzylmethylphenylphosphine oxide, mp 136–140°, $[\alpha]^{23}D$ −3.0°, in MeOH, which should be compared to Mislow's value for (*R*)-(+)-benzylmethylphenylphosphine oxide of +51°. It is concluded that the phosphine oxide obtained was essentially racemized, perhaps completely, since the small optical rotation may be due to contamination by (−)-menthol expected as a side product.

Registry No.—$NaAlH_2(CH_2CH_3)_2$, 17836-88-3; $NaAlH_2(OCH_2CH_2OCH_3)_2$, 21608-56-0; benzylmethylphenylphosphine oxide, 33838-34-5; methyl methylphenylphosphinate, 6389-79-3; ethylmethylphenylphosphine oxide, 7309-49-1; ethyl bromide, 74-96-4; diethyl benzylphosphonate, 1080-32-6; dibutylbenzylphosphine oxide, 4042-81-3; *n*-butyl bromide, 109-65-9; dibutylphenylphosphine oxide, 10557-66-1; diethyl phenylphosphonate, 1754-49-0; 1-phenylphosphorinane 1-oxide, 4963-95-5; 1,5-dibromopentane, 111-24-0; ethyl (5-bromopentyl)phenylphosphinate, 51065-60-2; 1-phenylphospholane 1-oxide, 4963-91-1; 1,4-dibromobutane, 110-52-1; ethyl (4-bromobutyl)phenylphosphinate, 51065-81-7; ethyl (3-bromopropyl)phenylphosphinate, 51065-82-8; 1,3-dibromopro-

pane, 109-64-8; 2-phenyl-1,2-oxaphospholane 2-oxide, 16324-19-9; isopropylmethylphenylphosphine oxide, 36032-81-2; isopropyl bromide, 75-26-3; tribenzylphosphine oxide, 4538-55-0; triethyl phosphate, 78-40-0; benzyl chloride, 100-44-7; methylphenylphosphine oxide, 19315-13-0; (S)-(−)-menthyl methylphenylphosphinate, 16934-92-2; (±)-benzylmethylphenylphosphine oxide, 51153-50-5.

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Two Syntheses of Optically Pure (1*R*,2*R*)-1,2-Dimethylcyclopentane

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Three syntheses of *trans*-1,2-dimethylcyclopentane are described, *viz.*, two syntheses of (1*R*,2*R*)-1,2-dimethylcyclopentane (*trans*-**12** ≡ **20**) and one of the racemic hydrocarbon. In the first synthesis (+)-pulegone was converted into (3*R*)-2,3-dimethylcyclopentanone, whose semicarbazone on Wolff reduction afforded a mixture of *trans*-**12** and *cis*-1,2-dimethylcyclopentane (*cis*-**12**). Formation of *cis*-**12** cannot be prevented because epimerization occurs during Wolff reductions of semicarbazones of α-alkyl ketones. In the second synthesis the title compound (**20**) was prepared from resolved 4-cyclohexene-1,2-dicarboxylic acid. One of the steps in this route was the $LiAlH_4$ reduction of (1*R*,2*R*)-4-cyclohexene-1,2-dimethanol ditosylate. Use of *N*-methylmorpholine instead of THF as a solvent saved labor and increased the yield considerably. **20** was found to have $[\alpha]D$ −51.5° ($CHCl_3$), in disagreement with a literature value of −35.2°. Racemic 2,3-dimethylcyclohexanone was used for the preparation of racemic **1** (and **2**) *via* 2,3-dimethylcyclopentanone.

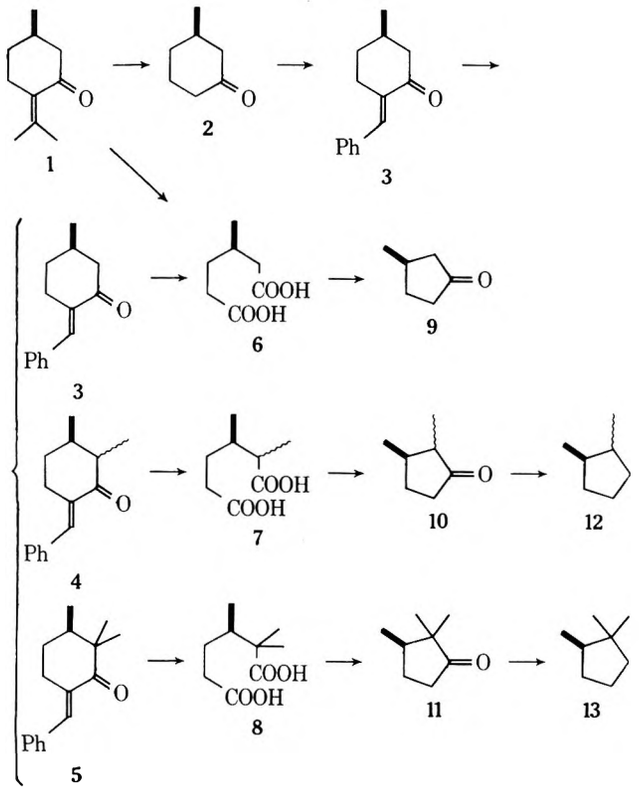
Recently optically active *trans*-1,2-dimethylcyclopentane has been discovered in a crude oil.[1] The specific rotation found was 5.8° but a theoretical estimate made many years ago in this department resulted in a much higher value.[2] Therefore it became of interest to synthesize this substance. When we had completed the synthesis from (+)-pulegone (Scheme I) we became aware of a paper by Hill, *et al.*,[3] which we had overlooked before. In their work on the absolute configuration of the antibiotic sarcomycin they also prepared *trans*-1,2-dimethylcyclopentane from (+)-pulegone, but by a route different from ours. Taking absolute values, the angle of rotation we found was 45% higher than the highest value reported by Hill.[3] Therefore it became of importance to follow a second route to the same substance. The absolute configurations of the compounds are depicted in the schemes.[4]

The route we chose was an obvious extension of a synthesis used by Walborsky, *et al.*,[5] for the determination of the absolute configuration of resolved 4-cyclohexene-1,2-dicarboxylic acid (Scheme II). Both syntheses led to compounds with nearly identical values of the angle of rotation. Therefore it can be stated that the specific rotation of optically pure (1*R*,2*R*)-1,2-dimethylcyclopentane is $[\alpha]D$ −51.5° ($CHCl_3$).

Dimethylcyclopentane from Pulegone (Scheme I). Pulegone was hydrolyzed to give 3-methylcyclohexanone. The 6 position in this ketone was blocked by condensation with benzaldehyde, yielding α-benzylidene ketone.[6] Methylation of this compound gave a mixture of mono- and dimethylated product, together with unreacted α-benzylidene ketone. Oxidation of this mixture and decarboxylation of the acids obtained yielded a mixture of 3-methylcyclopentanone, 2,3-dimethylcyclopentanone, and 2,2,3-trimethylcyclopentanone. The ketones were separated by distillation. The semicarbazone of 2,3-dimethylcyclopentanone gave on Wolff reduction a mixture of optically active and meso dimethylcyclopentane (83.3:16.7). Corrected to chemical purity, *trans*-1,2-dimethylcyclopentane showed $[\alpha]D$ −51.2° ($CHCl_3$). Hill[3] reported $[\alpha]D$ −35.2° ($CHCl_3$). In the course of this investigation it became also of interest to study possible epimerization during Wolff–Kishner reductions. The results are described in the Experimental Section.

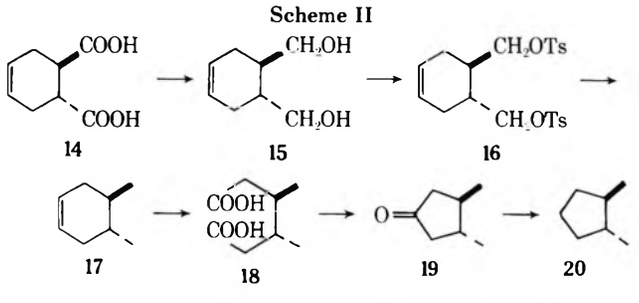
Dimethylcyclopentane from 4-Cyclohexene-1,2-dicar-

Scheme I



boxylic Acid (Scheme II). Two steps in Walborski's synthesis of 3,4-dimethylhexanedioic acid[5] could be improved.

Scheme II



We recommend *N*-methylmorpholine[7] as a solvent for the preparation of low molecular weight hydrocarbons by $LiAlH_4$ reduction of sulfonic esters because the hydrocarbon is easily obtained pure and in high yield when the reaction mixture is worked up by steam distillation.[8]

The resolution of 4-cyclohexene-1,2-dicarboxylic acid was reinvestigated. It was found that the best results are obtained when quinidine is used.

The angle of rotation of 3,4-dimethylcyclopentanone, $[\alpha]_D$ −241° ($CHCl_3$), appeared to be much higher in absolute value than was recorded by Carnmalm,[9] $[\alpha]_D$ −160° ($CHCl_3$); in contrast the angle of rotation of the corresponding semicarbazone was found to be in reasonable agreement with his results.

We also tried to resolve racemic 3,4-dimethylcyclopentanone with the Woodward reagent menthydrazide,[10] but our efforts were not rewarding.

Experimental Section

Melting and boiling points are not corrected. Angles of rotation were determined with a Bendix-NPL photoelectric polarimeter, or with a Perkin-Elmer polarimeter (Model 141) at room temperature. Nmr spectra were recorded with a Jeol 100-MHz nmr spectrometer. The solutions used for the nmr measurements contained 5–15% (by weight) of the solute. Nmr shifts are with respect to TMS. Concentrations are given in grams of solute per 100 ml of solution. New compounds gave satisfactory elemental analyses.

Pulegone (1) was isolated from pennyroyal oil (Dragoco, Holzminden, West Germany) as the sodium bisulfite adduct,[11] prepared at pH 7. After distillation over an efficient column it had $[\alpha]_D$ +23.8° (*c* 2.8, MeOH); $[\alpha]_D$ +24.1° (*c* 1.5, $CHCl_3$) [lit. $[\alpha]_D$ + 22.8° (*c* 20, $CHCl_3$);[12] $[\alpha]_D$ +31.6° (*c* 0.1, $CHCl_3$)].[3] This latter value seems to be erroneous.

(3*R*)-3-Methylcyclohexanone (2), $[\alpha]_D$ +8.60° (*c* 1.9, MeOH), was prepared by hydrolysis of **1** in 65% yield.[13] Nmr data of **2** ($CDCl_3$) include a doublet at δ 1.02 ppm (J = 5.93 Hz, methyl group).

(3*R*)-3-Methyl-6-benzylidenecyclohexanone (3) was prepared by Wallach[14] by condensation of **2** with benzaldehyde in alcohol. To prevent the formation of dibenzylidene ketone it is convenient to use water instead of alcohol.[15] A mixture of **2** (152 g), benzaldehyde (152 g), and 4% KOH solution (1520 g) was vigorously boiled for 3 hr. After neutralization the unreacted ketone and aldehyde were removed by steam distillation. The yellow residue in the steam flask crystallized on cooling in ice. The crude product was distilled and the distillate was recrystallized from petroleum ether to give 208 g (72.5%) of **3**, mp 61.5–63.0° (lit.[14] mp 62°), $[\alpha]_D$ −151.6° (*c* 0.45, MeOH), after recrystallization from THF–hexane. Racemic **3**, prepared in the same manner from racemic **2** (Fluka), had mp 38–41°. Nmr data of **3** ($CDCl_3$) include a quartet at δ 7.48 ppm (J_1 = 2.61 Hz, J_2 = 1.70 Hz, vinylic proton), a multiplet at δ 7.34 ppm (5 aromatic protons), and a doublet at δ 1.00 ppm (J = 6.07 Hz, methyl group).

Methylation of 3. After various attempts on the basis of the procedure of Johnson[16] for the methylation of 2-methyl-6-benzylidenecyclohexanone it was found that the following procedure gave the highest yield of distillable reaction product. In a 2-l. flask, provided with an efficient stirrer,[17] potassium (23.0 g) was dissolved in *tert*-butyl alcohol (1.5 l., dried on sieves) under nitrogen. This solution was placed in an ice–salt mixture, and when it was cooled to 22° a solution of **3** (100 g) in methyl iodide (213 g) was added at once. The temperature then rose to 31–34°. When the mixture was cooled to 25° the bath was removed and the solution was refluxed for 1.5 hr; then the solvent was removed with suction and water and ether were added to the residue. Part of the reaction product crystallized. These crystals had mp 101.0–102.5°, $[\alpha]_D$ −70.5° (*c* 0.4, MeOH), after recrystallization from hexane and ether. It was found to be (mass spectroscopy) almost pure (3*R*)-2,2,3-trimethyl-6-benzylidenecyclohexanone (**5**), the impurity being (3*R*)-2,3-dimethyl-6-benzylidenecyclohexanone (**4**). The part of the reaction product which dissolved in ether was worked up by distillation. Yield (distillate + crystals) 68 g. Mass spectroscopy showed **5** to be the main product; there was more starting material **3** in the mixture than monomethylated product **4**, which was not surprising because Conia[18] has shown an α-alkyl ketone to be more reactive in alkylation than a ketone without an α-alkyl group. Nmr data of **5** ($CDCl_3$) include a multiplet at δ 7.31 ppm (5 aromatic protons + 1 vinylic proton), complex multiplets at δ 2.45–3.13 ppm (2 protons) and at δ 1.37–2.05 ppm (3 protons), singlets at δ 1.20 and 1.03 ppm (methyl groups), and a doublet at δ 0.99 ppm (J = 6.52 Hz, methyl group).

Oxidation of the Methylation Products. The procedure of Johnson[19] for the oxidation of *cis*-2-benzylidene-9-methyldecalone was used. In our case the isolation of the products was simple because the methyl-substituted adipic acids **6**, **7**, and **8** are much more soluble in water than benzoic acid, and most of the latter could be removed by filtration. **3** (450 g) gave after methylation and oxidation a mixture of **6**, **7**, and **8** (175.5 g, a dark brown oil).

A mixture of cyclopentanones 9, 10, and **11** (74.65 g) was prepared by heating the crude mixture of dicarboxylic acids **6**, **7**, and **8** (175.5 g) with $Ba(OH)_2$.[20] The ketones were separated by distillation, using a Nester-Faust spinning band column, to yield **9**, 7.8 g, bp 106° (175 mm); **10**, 3.6 g, bp 115–117° (175 mm); **11**, 20.4 g, bp 124–145° (175 mm).

(3*R*)-3-Methylcyclopentanone (9), bp 144–146°, $[\alpha]_D$ +154.8° (*c* 0.6, MeOH), was prepared by ozonization[21] of **1** to give (3*R*)-3-methylhexanedioic acid (**6**), decarboxylation[20] with $Ba(OH)_2$ and purification *via* the semicarbazone, mp 177.5–178.5° after recrystallization (three times) from alcohol, $[\alpha]_D$ +44.7° (*c* 0.82, $CHCl_3$) (lit.[22] mp 185–186°). Corroborating Tétry's result[6] we found for the methylcyclopentanone fraction of the distillation of the mixture of **9**, **10**, and **11** physical constants in agreement with the data of this reference compound, prepared by ozonization of **1** etc. Nmr data of **9** ($CDCl_3$) include a doublet at δ 1.13

ppm (J = 6.17 Hz, methyl group). Nmr data of **9** semicarbazone (CF_3COOH) include a doublet at δ 1.25 ppm (J = 5.09 Hz, methyl group).

(3R)-2,2,3-Trimethylcyclopentanone (11), bp 162–164°, $[\alpha]_D$ +79.6° (c 0.48, MeOH), which has not been described before, was obtained by purification of the corresponding fraction of the distillation of the mixture of **9**, **10**, and **11** as the semicarbazone, $[\alpha]_D$ +24.1° (c 0.5, $CHCl_3$). This semicarbazone (recrystallized from alcohol) turns yellow at 210°; on rapid heating mp 216–218° is found. Nmr data of **11** ($CDCl_3$) include singlets at δ 0.81 and 1.00 ppm (methyl groups) and a doublet at δ 1.00 ppm (J = 6.45 Hz, methyl group). Nmr data of **11** semicarbazone (CF_3COOH) include singlets at δ 1.46 and 1.26 ppm (methyl groups) and a doublet at δ 1.10 ppm (J = 6.06 Hz, methyl group).

(2R)-1,1,2-Trimethylcyclopentane (13). Using the conditions of Kohlrausch[23] for the reduction of 3-methylcyclopentanone semicarbazone, the semicarbazone of **11** gave **13** on Wolff reduction. We always isolated the reaction products of Wolff reductions by steam distillation. The hydrocarbon layer of the distillate was then shaken with an equal volume of concentrated H_2SO_4, washed with water, dried on sodium, and distilled from sodium. **13** thus prepared was found to be contaminated with 2.32 mol % of (−)-**12** and 0.48 mol % of *meso*-**12** (glc, SE-30 column), yield 66%. **13** was purified by preparative glc (OV-210 column). Pure **13** showed $[\alpha]_D$ −7.74° (c 1.2, $CHCl_3$). Nmr data of **13** ($CDCl_3$) include two singlets at δ 0.72 and 0.94 ppm (methyl groups) and a doublet at δ 0.82 ppm (J = 6.30 Hz, methyl group).

(1R,2R)-1,2-Dimethylcyclopentane [(−)-12]. The semicarbazone of **10**, prepared from the corresponding fraction of the distillation of **9**, **10**, and **11**, after recrystallization from alcohol, had $[\alpha]_D$ +94.1° (c 0.43, $CHCl_3$), mp 200–202°; the crystals turn yellow between 195 and 200°. The chemical purity of this semicarbazone was not 100% because on reduction[23] it gave (−)-**12**, contaminated with 16.3 mol % of *meso*-**12**, 1.52 mol % of **13**, and 0.40 mol % of methylcyclopentane (glc, SE-30 column) in 59% yield. This impure (−)-**12** showed $[\alpha]_D$ −41.9° (c 1.3, $CHCl_3$). Corrected to chemical purity (−)-**12** had $[\alpha]_D$ −51.2° ($CHCl_3$) [lit.[3] $[\alpha]_D$ −35.2° (c 0.2, $CHCl_3$)].

Racemic *trans*-4-Cyclohexene-1,2-dicarboxylic Acid (Racemic 14). In a refrigerator at −15° an autoclave was filled with diethyl fumarate (364 g, Merck) and butadiene (272 ml, excess). The mixture was kept at 140–150° for 24 hr,[24] yield 90% after distillation. This Diels–Alder adduct was saponified[5] to give racemic **14**, mp 166.0–168.5° after recrystallization from water (lit.[25] mp 172°).

Resolution of *trans*-4-Cyclohexene-1,2-dicarboxylic Acid (14). Walborsky's procedure[5] for the resolution of **14** is cumbersome, and that was for us an inducement to reinvestigate the resolution. Bases used were ephedrine, quinine,[26] strychnine, brucine, cinchonidine, cinchonine, and quinidine. The latter gave the best results.

A. Preparation of the Quinidine Salt. In a 1-l. flask were refluxed until homogeneous anhydrous quinidine (Brocades, The Hague, The Netherlands, or Lamers & Indeman, Bois-le-Duc, The Netherlands) (81 g), **14** (21.2 g) (2 mol of base to 1 mol of acid), and alcohol (500 ml). In case the mixture was not homogeneous after 30 min, it was filtered. The alcohol was removed with a rotatory evaporator, and to the residue were added water (500 ml) and alcohol (150 ml); on heating a clear solution was obtained which was left to cool. Every time it became turbid, the turbidity was removed by the addition of some alcohol (about 60 ml of alcohol was necessary). Seeding is recommended. After standing for 2 days at room temperature the crystals were removed by filtration and recrystallized. We used water (6.5 l.) and alcohol (2.5 l.) for the recrystallization of quinidine salt from **14** (292 g) and quinidine (1120 g), seeded the mixture and left it to crystallize for 2 days, and obtained 486.25 g of salt.

B. Regeneration of the Quinidine Salt. Recrystallized quinidine salt (108 g) was stirred with $CHCl_3$ (340 ml) and a solution of NaOH (20 g) in water (120 ml) for 1.5 hr. Then the $CHCl_3$ layer containing the alkaloid was separated from the alkaline layer containing the sodium salt of (1R,2R)-**14**. The latter solution was acidified with concentrated HCl, and the dicarboxylic acid was isolated by ether extraction. From quinidine salt (486.25 g from 292 g of racemic **14**) was thus obtained (1R,2R)-**14** (98.0 g, 67.1% of one antipode), $[\alpha]_D$ −161° (c 0.5, absolute EtOH) [lit.[5] $[\alpha]_D$ −161° (c 2.7, EtOH).

The mother liquor of the resolution of **14** (292 g) with anhydrous quinidine (1120 g) was evaporated to dryness to give an oil, which was treated with NaOH solution and $CHCl_3$, etc., as indicated above to give optically impure (1S,2S)-**14** (166.5 g), $[\alpha]_D$ +90° (c 0.5, absolute EtOH).

Quinidine can be recovered in high yield by evaporating its $CHCl_3$ solution to dryness and recrystallizing the residue from MeOH (~30 g of alkaloid to 1 l. of MeOH).

(1R,2R)-4-Cyclohexene-1,2-dimethanol (15) was prepared by $LiAlH_4$ reduction of (1R,2R)-**14** in THF in 94% yield.

(1R,2R)-4-Cyclohexene-1,2-dimethanol ditosylate (16) was prepared from **15** with A.R. *p*-toluenesulfonyl chloride in A.R. pyridine, yield 84% after recrystallization from alcohol, mp 107–108°, $[\alpha]_D$ −43.7° (c 1.1, $CHCl_3$).

(1R,2R)-1,2-Dimethyl-4-cyclohexene (17). A mixture of *N*-methylmorpholine (Merck or EGA, 1630 ml) and $LiAlH_4$ (77 g) was heated to 60°. Caution: this starting temperature is necessary because **16** is not reduced at room temperature (possibly as a consequence of the low solubility of **16** in cold *N*-methylmorpholine). Then **16** (395 g) was added in few-gram portions at a time at such a rate that the temperature was kept at <75°. Because the mixture became viscous, an efficient stirrer[17] was necessary. After the completion of the addition the mixture was kept at 70° for 1.5 hr, then heated to 100°, left to cool, and worked up by careful addition of water (500 ml) and steam distillation. The upper layer of the distillate was washed with dilute HCl and water, and dried on sodium, yield 83.3 g (84.5%), $[\alpha]_D$ −143.8° (c 0.52, $CHCl_3$) [lit.[5] $[\alpha]_D$ −138° (c 2.58, $CHCl_3$).

Nmr data of **17** ($CDCl_3$) include doublets at δ 5.61 ppm (J = 2.80 Hz, 2 vinylic protons) and at δ 0.93 ppm (J = 5.40 Hz, 2 methyl groups).

(3R,4R)-3,4-Dimethylhexanedioic acid (18) was prepared from **17** using Cope's procedure[27] for the oxidation of bicyclo[6.1.0]nonene. The crude product, obtained in 57.3% yield, was an oil which solidified on standing.

(3R,4R)-3,4-Dimethylcyclopentanone (19). Crude **18** was decarboxylated[20] with $Ba(OH)_2$ to give crude **19** in 88.8% yield. After purification as the semicarbazone, it had mp 205–208° (yellow melt); $[\alpha]_D$ −73.4° (c 0.92, $CHCl_3$) [lit.[9] mp 203.0–204.5°, $[\alpha]_D$ −76° (c 0.74, $CHCl_3$)]. **19** had $[\alpha]_D$ −241° (c 0.46, $CHCl_3$) [lit.[9] $[\alpha]_D$ −160° (c 0.7, $CHCl_3$)], g factor 0.152 (cyclohexane).

Nmr data of **19** ($CDCl_3$) include quartets at δ 2.44 ppm (J_1 = 22.3, J_2 = 11.3 Hz, two protons) and at δ 1.82 ppm (J_1 = 21.3, J_2 = 10.0 Hz, 4 protons) and a doublet at δ 1.13 ppm (J = 5.55 Hz, 2 methyl groups).

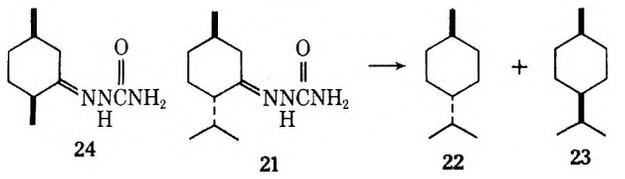
Nmr data of **19** semicarbazone (CF_3COOH) include doublets at δ 1.23 ppm (J = 5.37 Hz, 2 methyl groups) and at δ 3.29 ppm (J = 20.5 Hz, 2 protons), a singlet at δ 1.98 ppm (2 protons), and a quintet at δ 2.59 ppm (J_1 = 19.4, $J_2 = J_3$ = 9.7 Hz, 2 protons).

(1R,2R)-1,2-Dimethylcyclopentane (20) was prepared by reduction[23] of the semicarbazone of **19** in 50% yield: $[\alpha]_D = [\alpha]_{589}$ −51.5°; $[\alpha]_{578}$ −53.6°; $[\alpha]_{546}$ −61.0°; $[\alpha]_{436}$ −102.7°; $[\alpha]_{365}$ −158.0° (c 1.1, $CHCl_3$) [lit.[3] $[\alpha]_D$ −35.2° (c 0.1, $CHCl_3$)]. Nmr data of **20** ($CDCl_3$) include a doublet at δ 0.95 ppm (J = 5.19 Hz, methyl groups).

Attempted Resolution of Racemic 19. Racemic **19**, prepared from racemic **14** in the same manner as (3R,4R)-**19**, was treated with "menthydrazide"[10] under conditions as used for the preparation of the corresponding derivative of α-ionone.[28] The solution was evaporated to dryness, and the residue was recrystallized from *n*-heptane. Neither melting point nor angle of rotation changed on further recrystallization. Regeneration of the derivative, mp 124.5–126.0°, $[\alpha]_D$ −63.0° (c 1.25, MeOH), after the third recrystallization then gave the ketone, small negative Cotton effect around 290 nm, g factor 0.0097 (cyclohexane), *i.e.*, optical purity 6.4%. The semicarbazone of this ketone gave optically impure **20**, $[\alpha]_D$ −3.77° (c 1.25, $CHCl_3$), on reduction.[23]

Epimerization during the Wolff Reduction. As already mentioned, Wolff reduction of the semicarbazone of 2,3-dimethylcyclopentanone yielded a mixture of (−)- and *meso*-dimethylcyclopentane. We found it worthwhile to investigate whether the observed cis–trans ratio was due to careless purification of the semicarbazone, or to epimerization during the reduction, or both. Epimerization during Wolff–Kishner reductions has been frequently observed,[29] but in those cases a hydrazone was decomposed without intermediate purification; so it has not been established whether epimerization occurred during the preparation of the hydrazone or during its decomposition. Epimerization clearly is a limitation of the Wolff reduction, for we found that menthone semicarbazone (**21**), which is easily obtained free from its epimer isomenthone semicarbazone (**24**),[30] gave a 1:1 mixture of *cis*- and *trans*-*p*-menthane (Scheme III) on reduction.[23] After this experiment it was not surprising that the semicarbazone of racemic

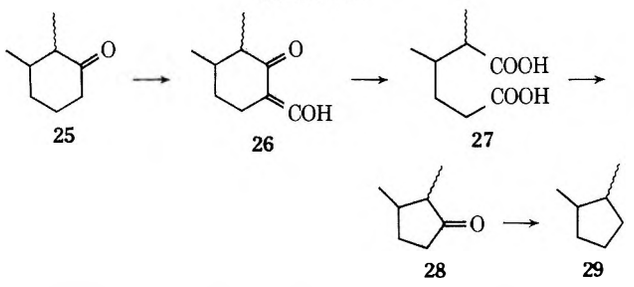
Scheme III



2,3-dimethylcyclopentanone gave on reduction[23] the same cis-trans ratio as was found when working with the corresponding optically active compound.

Racemic 2,3-dimethylcyclopentanone was prepared according to Scheme IV.[31]

Scheme IV



Menthone Semicarbazone (21). Menthone, prepared by oxidation[32] of (−)-menthol (Fluka), was converted into its semicarbazone, mp 186–189° (lit.[30] mp 188°), after two recrystallizations from alcohol. Reduction[23] then gave a 1:1 mixture of two compounds (glc, SE-30 column), which were identified as **22** and **23** because the nmr spectrum of this mixture was a superposition of the nmr spectra of pure **22** and **23**, and because of gas chromatographic identification. Nmr data of **21** (CF_3COOH) include a doublet at δ 1.15 ppm (J = 5.8 Hz, 3 methyl groups). The nmr spectrum produces no evidence for the presence of a large percentage of **24** in **21**.

trans-p-**Menthane (22),** for use as a reference, was made available by Mr. J. C. A. Windhorst in this department. He prepared sterically pure **22** from menthyl tosylate[33] by $LiAlH_4$ reduction in *N*-methylmorpholine.[7] Nmr data of **22** ($CDCl_3$) include a multiplet at δ 1.68 ppm (4 protons), which looks like a doublet (J = 6.4 Hz) under low resolution, and a complex multiplet at δ 0.70–1.05 ppm (16 protons). Two peaks of this latter multiplet have a high intensity, which suggests that these peaks are caused by the three methyl groups of **22** (δ 0.85 ppm. J = 6.70 Hz).

cis-p-**Menthane (23)** was obtained for use as a reference. Redistilled (+)-limonene (Fluka) was hydrogenated [125 g of limonene, 125 g of ethanol or methanol, 1.6 g of Pd/C (10% Pd, Fluka), 150 atm H_2, no external heating (the reaction is exothermic[34])] to give a mixture of three components. Part of this mixture was carefully distilled using a Nester-Faust spinning band column (20 cm/1 ml of distillate per hour). Boiling points of the components were in the order **22** < **23** < unknown compound. The molar ratio of **22** and **23** in the mixture after the hydrogenation was 75:25; about 10% of this mixture (an average of two hydrogenation experiments) consisted of the unknown compound. A comparison of the mass spectrum of this unknown compound with literature data[35] indicated that this compound probably was either *p*- or *m*-cymene. Nmr data supported the *p*-cymene structure: a singlet at δ 7.14 ppm (4 aromatic protons), a quintet at δ 2.78 ppm (J_1 = 13.0 Hz, $J_2 = J_3$ = 6.5 Hz, proton attached to the quaternary carbon atom of the isopropyl group), a singlet at δ 2.30 ppm (methyl group), and a doublet at δ 1.22 ppm (J = 7.20 Hz, two equivalent methyl groups). Note: *p*-cymene was not an impurity of the limonene used for the hydrogenation (glc, Carbowax column). Nmr data of **23** ($CDCl_3$) [freed from **22** and *p*-cymene by preparative glc (SE-30 column)] include a complex multiplet at δ 1.39 ppm (11 protons) and doublets at δ 0.91 ppm (J = 6.63 Hz, 1 methyl group) and at δ 0.86 ppm (J = 6.36 Hz, 2 equivalent methyl groups).

2,3-Dimethylcyclohexanone (25). Chromic acid oxidation[36] of 2,3-dimethylcyclohexanol (Aldrich) gave **25** in 94% yield.

2,3-Dimethyl-6-hydroxymethylenecyclohexanone (26). A procedure for the preparation of hydroxymethylenecyclohexanone[37] was used to give **26** in 70.7% yield.

2,3-Dimethylhexanedioic Acid (27).[31] Because **1** can be ozonized to give **6** in high yield,[21] it was worthwhile trying to prepare **27** from **26** in the same manner. **26** (55.0 g) dissolved in CCl_4 (300 ml) and cooled in ice was ozonized. To the solution of the ozonide, water (300 ml) was added, and while vigorously stirring the CCl_4 was distilled off. The aqueous solution, made alkaline, was extracted with ether, then made acid, and **27** was isolated by ether extraction. From **26** (159.9 g) was obtained in this manner crude **27** (149 g, 82.4%) as an orange-red oil.

2,3-Dimethylcyclopentanone (28). Crude **27** (149 g) was decarboxylated[20] with $Ba(OH)_2$ to give pure **28** (62.0 g, 64.6%) after distillation. It was shown by glc that **28** was an 84:16 mixture of two components. Nmr data of *trans*-**28** (main component of this mixture) include doublets at δ 1.16 ppm (J = 5.28 Hz, methyl group) and at δ 1.05 ppm (J = 6.43 Hz, methyl group). Nmr data of *cis*-**28** (minor component of the mixture) include doublets at δ 0.94 ppm (J = 6.22 Hz, methyl group) and at δ 0.97 ppm (J = 6.62 Hz, methyl group).

1,2-Dimethylcyclopentane (29). **28** was converted into its semicarbazone. Part of the crude semicarbazone was kept; the remainder was recrystallized three times from *n*-butyl alcohol. The purified semicarbazone had mp 210.0–214.5° dec on rapid heating. Reduction[23] of both crude and purified semicarbazone gave a mixture of *cis*-**29** (16.5%) and *trans*-**29** (83.5%). Nmr data of three times recrystallized **28** semicarbazone (CF_3COOH) include doublets at δ 1.25 ppm (J = 6.00 Hz, methyl group), δ 1.46 ppm (J = 6.55 Hz, methyl group) and δ 1.09 ppm (J = 7.0 Hz). The intensity of this latter doublet is ~2% of the intensity of the other doublets, which suggests that the sterical purity of **28** semicarbazone used for the reduction was ~98%.

Acknowledgment. One of the authors (Kokke) is indebted to the Netherlands Organization for the Advancement of Pure Research (Z. W. O.) for the sponsoring of this work. A NATO grant for the purchase of quinidine is gratefully acknowledged. The authors owe their gratitude to Professor L. J. Oosterhoff, who proposed to do the work reported in this paper, and to Professor H. Wynberg (Groningen) for reading and commenting on the manuscript.

Registry No.—**1**, 89-82-7; (3*R*)-**2**, 13368-65-5; (±)-**2**, 625-96-7; (3*R*)-**3**, 7577-00-6; (±)-**3**, 51096-05-0; **5**, 50987-10-5; **6**, 623-82-5; **9**, 6672-30-6; **9** semicarbazone, 50987-11-6; **10**, 51096-06-1; **10** semicarbazone, 50986-97-5; **11**, 50987-12-7; **11** semicarbazone, 50987-13-8; (−)-**12**, 13012-46-9; **13**, 50987-14-9; (±)-**14**, 51096-07-2; (1*R*,2*R*)-**14**, 50987-15-0; (1*S*,2*S*)-**14**, 51096-08-3; **15**, 15679-28-4; **16**, 20246-03-1; **17**, 51025-14-0; **18**, 51063-79-7; (±)-**19**, 50987-16-1; (3*R*,4*R*)-**19**, 51096-09-4; (3*R*,4*R*)-**19** semicarbazone, 50987-17-2; **21**, 51051-09-3; **22**, 1678-82-6; **23**, 6069-98-3; **27**, 50986-96-4; **28**, 14845-37-5; **28** semicarbazone, 50986-97-5.

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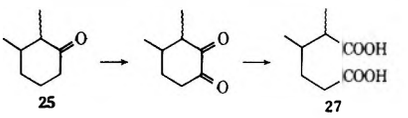

25 27

because cyclohexanedione can be prepared from cyclohexanone by SeO_2 oxidation only in low yield based on ketone: 10.4% [C. C. Hach, C. V. Banks, and H. Diehl, *Org. Syn.*, **32**, 35 (1952)], 19.6% (A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., New York, N. Y., 1957, p 975).
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Unsaturated Organosilicon Heterocycles

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The photolytic addition of H_2S to dimethyldiallylsilane yields 1,1-dimethyl-1-sila-5-thiacyclooctane. Oxidation of the sulfide yields the corresponding sulfone, which can be directly converted *via* a modified Ramberg–Backlund reaction into 1,1-dimethyl-1-sila-4-cycloheptene. This reaction sequence has also been used to prepare 1,1-diphenyl-1-sila-4-cycloheptene from diphenyldiallylsilane. An alternate synthesis of 1,1-dimethyl-1-sila-4-cycloheptene and 1,1-diphenyl-1-sila-4-cycloheptene is also reported.

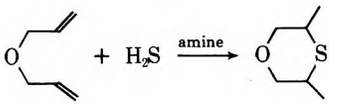
We have been concerned with improving synthetic routes to seven- and eight-membered organosilicon heterocycles.[1] The modified acyloin reaction[2,3] on suitable organosilicon diesters has been the best entry into these ring systems. For instance, dimethyl 4,4-dimethyl-4-sila-1,7-heptanedioate can be cyclized to 1,1-dimethyl-4,5-bis(trimethylsiloxy)-1-sila-4-cycloheptene in good yield.[1] However, two problems remain. One is that the synthesis of suitable organosilicon diester substrates for the acyloin reaction often involves many steps from commercially available dichlorosilanes. The second is that the heterocycle formed after hydrolysis of the trimethylsilyl ether protecting groups contains an α-hydroxy ketone functionality which requires several steps to transform into a carbon–carbon double bond. To solve these problems we have developed a new synthetic entry into these heterocyclic systems.

There are several recent examples of the use of organosulfur compounds to establish both carbon–carbon single[4,5] and carbon–carbon double bonds. The conversion of a sulfide to a carbon–carbon double bond by a double Stevens rearrangement is one example from the latter category.[6,7] The Ramberg–Backlund reaction, which converts an α-chloro sulfone into an alkene, is another.[8-12]

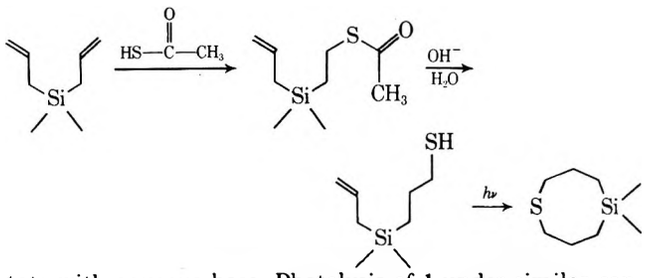
We decided to attempt to prepare cyclic compounds containing silicon and sulfur by addition of H_2S to dimethyldiallylsilane and to diphenyldiallylsilane owing to the ready availability of these organosilicon compounds.[1,13] We find that H_2S adds to dimethyldiallylsilane in a dilute pentane solution at −78° upon irradiation through a quartz photolysis well with a 450-W medium-pressure Hanovia lamp to form 1,1-dimethyl-1-sila-5-thiacyclooctane in 25% isolated yield.[14] Similarly, H_2S adds to diphenyldiallylsilane upon irradiation at −78° to form 1,1-diphenyl-1-sila-5-thiacyclooctane in 10% isolated yield.

This is remarkable considering the problems involved in synthesis of medium-sized ring compounds from alicyclic precursors. For instance, closure of ω-chloro sulfides $RS(CH_2)_nCl$ to form cyclic sulfonium salts fails for n = 6–11.[15] The fact that both C–Si (1.87 Å) and C–S (1.82 Å) bonds are longer than C–C single bonds may make formation of 1,1-dimethyl-1-sila-5-thiacyclooctane more like cyclization of a nine-membered than an eight-membered all-carbon ring system.[16] Ring closure reactions are usually most difficult to accomplish for ring sizes from C_9 to C_{11}. For example, the Ziegler ring closure reaction of α,ω-dinitriles with base fails for rings from C_9 to C_{11} even under high dilution conditions.[17]

Our yields are also remarkable considering the variety of competing pathways open to a thiyl radical intermediate. A thiyl radical must be involved to account for the anti-Markovnikov sense of the addition, since the addition of H_2S to diallyl ether under ionic conditions yields 2,6-dimethyl-1,4-thioxane.[18,19] Clearly the intramolecular



radical addition of the S–H bond of dimethylallyl-3-mercaptopropylsilane (1) to the carbon–carbon double bond of the allyl group is critical to the success of the reaction. To substantiate this point we prepared **1** independently by the photochemical addition of thiolacetic acid to dimethyldiallylsilane followed by hydrolysis of the thiolace-



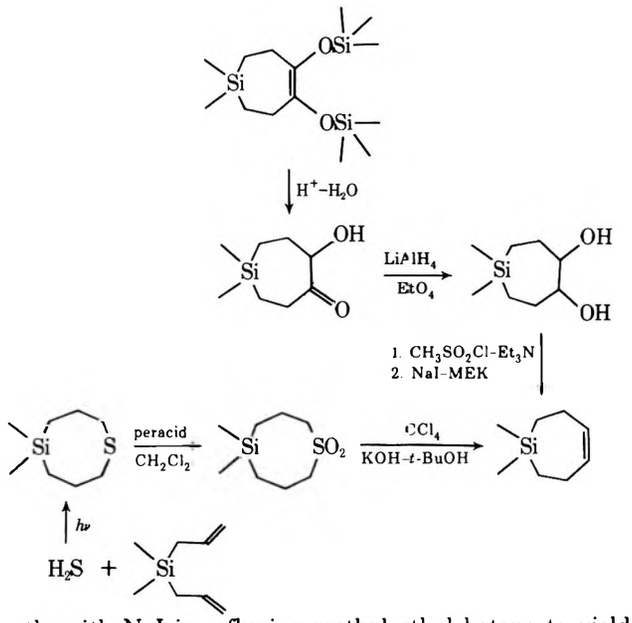
tate with aqueous base. Photolysis of **1** under similar conditions gave comparable yields of 1,1-dimethyl-1-sila-5-thiacyclooctane.

In a related study Surzur has shown that the direction of intramolecular addition of a thiyl radical to a terminal carbon–carbon double bond is strongly influenced by temperature.[20,21] Thus 1-mercapto-5-hexene was cyclized to a mixture of 1-thia-2-methylcyclohexane and 1-thiacycloheptane in which the six-membered ring predominates at high temperature while the seven-membered ring predominates at low temperature (−65°). Surprisingly, in our system in which six-, seven-, and eight-membered rings are all possible the only volatile products detected were the eight-membered rings and uncyclized **1**. Clearly at low temperature formation of the eight-membered ring product must be under irreversible kinetic control.

Successful oxidation of the sulfide to the corresponding sulfone followed by a Ramberg–Backlund reaction afforded 1,1-dimethyl-1-sila-4-cycloheptene in a three-step reaction sequence starting from dimethyldiallylsilane. This is an economical solution to the synthesis of organosilicon heterocycles containing a carbon–carbon double bond.

Thus 1,1-dimethyl-1-sila-5-thiacyclooctane was oxidized to the sulfone by reaction with *m*-chloroperbenzoic acid in dichloromethane at 0° in 95% yield.[22] Treatment of the sulfone with aqueous NaOH in the presence of CCl_4, a modification of the Ramberg–Backlund reaction developed by Meyers,[8,23] led to a 50% yield of 1,1-dimethyl-1-sila-4-cycloheptene. These results are noteworthy, since this reaction usually leads to the corresponding vinylic sulfonic acid when the carbon atoms on either side of the sulfone are primary.[23] Likewise, 1,1-diphenyl-1-sila-5-thiacyclooctane was oxidized to the corresponding sulfone with *m*-chloroperbenzoic acid. The modified Ramberg–Backlund reaction on the sulfone yields 1,1-diphenyl-1-sila-4-cycloheptene in 40% isolated yield.

This reaction permits definitive structure proof that the photoadducts of dimethyldiallylsilane and diphenyldiallylsilane with H_2S are indeed eight-membered rings, since we have prepared both 1,1-dimethyl-1-sila-4-cycloheptene and 1,1-diphenyl-1-sila-4-cycloheptene by independent synthetic routes. Hydrolysis of 1,1-dimethyl-4,5-bis(trimethylsiloxy)-1-sila-4-cycloheptene[1] yields 1,1-dimethyl-5-hydroxy-1-sila-4-cycloheptanone.[24] Reduction of the acyloin with $LiAlH_4$ in ether leads to 1,1-dimethyl-1-sila-4,5-cycloheptanediol in 90% yield. The diol was converted to the dimesylate by reaction with 2 mol of mesyl chloride in the presence of triethylamine.[25] The dimesylate was not purified but was converted directly to the alkene by treatment with NaI in refluxing methyl ethyl ketone in 20% yield.[26,27] The structure of the 1,1-diphenyl-1-sila-5-thiacyclooctane was likewise proved by independent synthesis of the alkene resulting from the Ramberg–Backlund reaction. Dimethyl 4,4-diphenyl-4-sila-1,7-heptanedioate[13] was cyclized using the modified acyloin reaction[2,3] to 1,1-diphenyl-4,5-bis(trimethylsiloxy)-1-sila-4-cycloheptene in 72% yield. The bis silyl enol ether was hydrolyzed to the acyloin in 95% yield. The acyloin was reduced to the diol by treatment with $LiAlH_4$ in THF in high yield. The diol was converted to the dimesylate, which was treated directly with NaI in refluxing methyl ethyl ketone to yield 1,1-diphenyl-1-sila-4-cycloheptene in 37% yield.



Experimental Section

All reactions were carried out under a nitrogen atmosphere. All operations were conducted in an efficient fume hood owing to the toxicity of H_2S and the vile smell of volatile organosulfur compounds. Melting points are uncorrected. Ir spectra were determined as neat liquids or in CCl_4 solution on a Perkin-Elmer 337. They were calibrated against known peaks in a polystyrene film. Nmr spectra were run on a Varian HA-100 using 10% solutions in CS_2. Chloroform, dichloromethane, or tetramethylsilane were used as internal standards. Microanalysis was performed by Elek Microanalytical Laboratory. High-resolution mass spectra were run on an AEI MS-902 instrument. Exact mass determination of the composition of important ions were carried out at resolution of at least 10,000 by peak matching with peaks of known mass of perfluorokerosene: ionizing voltage 70 eV; filament emission 480 μA; source temperature 150°.

1,1-Dimethyl-1-sila-5-thiacyclooctane. A quartz photolysis well was inserted into a 2-l. flask equipped with a Dry Ice–acetone reflux condenser and a fritted gas inlet tube. In this apparatus were placed 50 g (0.36 mol) of dimethyldiallylsilane[28] and 1.5 l. of olefin-free pentane. Purified nitrogen was bubbled through the solution to purge it of air. The solution was cooled to −78° by immersion of the entire apparatus in an isopropyl alcohol–Dry Ice bath. H_2S (10 g, 0.29 mol) was slowly bubbled through the solution while it was being illuminated with a 450-W medium-pressure Hanovia lamp. The addition required 1 hr. Photolysis was continued for an additional 1 hr. The solution was then warmed to room temperature. After removal of pentane, the product was fractionally distilled through a 15-cm Vigreux column. A fraction of bp 115–130° (25 mm) was collected. Final purification was accomplished by glpc on an Apiezon L column (6 ft × 0.25 in.) at 225°. A 25% yield (approximately 6 g) based on recovered starting material was obtained. Ir was characterized by two strong $Si(CH_3)_2$ bands at 1245 and 790 cm^{-1}; nmr s (6 H) δ −0.13, m (4 H) 0.49, m (4 H) 1.61, m (4 H) 2.31. *Anal.* Calcd for $C_8H_{18}SiS$: C, 55.09; H, 10.42. Found: C, 55.09; H, 10.21.

1,1-Dimethyl-1-sila-5-thiacyclooctane 5,5-Dioxide. In a 100-ml three-necked round-bottom flask equipped with a pressure-equalizing addition funnel, a reflux condenser, a magnetic stirring bar, and a thermometer were placed 30 ml of CH_2Cl_2 and 20 g (0.116 mol) of *m*-chloroperbenzoic acid.[22] The solution was cooled to 0° by immersion in a salt–ice bath. 1,1-Dimethyl-1-sila-5-thiacyclooctane (6.5 g, 0.037 mol) dissolved in 5 ml of CH_2Cl_2 was placed in the addition funnel and then added to the well-stirred reaction mixture at a rate such that the temperature did not exceed 5°. After the addition was complete the solution was warmed to room temperature and then heated to reflux for 1 hr. Five grams of Na_2SO_3 was added and stirring was continued for 15 min. The solution was filtered and the CH_2Cl_2 solvent was removed by evaporation under reduced pressure. Final purification was by glpc on an FFAP 2 ft × 0.25 in. column at 215°. Its ir spectrum was characterized by strong SO_2 absorption bands at

1330 and 1140 cm^{-1}; nmr s (6 H) δ 0.02, m (4 H) 0.86, m (4 H) 2.01, m (4 H) 3.04.

1,1-Dimethyl-1-sila-4-cycloheptene. In a dry one-neck 100-ml round-bottom flask equipped with a reflux condenser and a magnetic stirring bar were placed 0.22 g (1.07 mmol) of 1,1-dimethyl-1-sila-5-thiacyclooctane 5,5-dioxide, 3.0 g (0.065 mol) of powdered KOH, 15 ml of dry *tert*-butyl alcohol, and 35 ml of dry CCl_4.[8,23] The mixture was heated for 12 hr at 50° while being stirred. The reaction mixture was transferred to a separatory funnel and 100 ml of ether was added. The organic layer was extracted with three equal volumes of water, dried over anhydrous $MgSO_4$, and filtered, and the solvents were removed by evaporation under reduced pressure. The residue was bulb-to-bulb distilled. Final purification was by glpc on an Apiezon L column (18 ft × 0.25 in.) at 130°. Its ir showed a weak C-C double-bond stretch at 1645 cm^{-1}; nmr (CHF_2Cl solvent) s (6 H) δ 0.06, m (4 H) 0.67, m (4 H) 2.3, m (2 H) 5.8. Its mass spectrum showed a weak parent ion at *m/e* 140, a strong P − 15 ion at *m/e* 125, and a P − 28 ion at *m/e* 112. Calcd for $C_7H_{13}Si$: 125.0786. Found: 125.0756. Calcd for $C_6H_{11}Si$: 112.0708. Found: 112.0697. *Anal.* Calcd for $C_8H_{16}Si$: C, 68.49; H, 11.49. Found: C, 68.54; H, 11.19.

4,4-Dimethyl-4-sila-6-heptene 1-Thiolacetate. In a dry 500-ml round-bottom flask equipped with a reflux condenser and a magnetic stirring bar were placed 167 g (1.15 mol) of dimethyldiallylsilane and 14 g (0.20 mol) of thiolacetic acid. While stirring, the solution was illuminated with a sun lamp for 6 hr. The solution was fractionally distilled through a 15-cm vacuum-jacketed Vigreux column. After removal of unreacted dimethyldiallylsilane, bp 134° (760 mm), the distillation was continued at reduced pressure. A fraction of bp 130–135° (25 mm) was collected. It amounted to 34 g (68%) based on recovered dimethyldiallylsilane. Final purification was accomplished by gplc using an FFAP column (2 ft × 0.25 in.) at 200°. Its ir was characterized by a carbonyl band at 1695 cm^{-1} and a carbon–carbon double-bond stretch at 1640 cm^{-1}; nmr s (6 H) δ −0.17, m (2 H) 0.54, m (4 H) 1.46, s (3 H) 2.19, t (2 H) 2.73, J = 7 Hz, m (2 H) 4.71, m (1 H) 5.65. *Anal.* Calcd for $C_{10}H_{20}SiSO$: C, 55.50; H, 9.31. Found: C, 55.33; H, 9.07.

Dimethylallyl-3-mercaptopropylsilane. In a 500-ml round-bottom flask equipped with a reflux condenser and a magnetic stirring bar were placed 23 g (0.106 mol) of 4,4-dimethyl-4-sila-6-heptene 1-thiolacetate, 2 g (0.037 mol) of KOH, and 30 ml of 1:1 ethanol–water. The solution was refluxed for 3 hr after which it was acidified to pH 4.0 using glacial acetic acid. Pentane was added and the solution was extracted twice with water. The organic layer was dried over anhydrous $MgSO_4$ and filtered and the pentane was removed by distillation through a 15-cm Vigreux column: nmr s (6 H) δ −0.15, m (2 H) 0.55, m (5 H) 0.82, m (2 H) 2.38, m (2 H) 4.66, m (1 H) 5.65.

1,1-Diphenyl-1-sila-5-thiacyclooctane. A quartz photolysis well was inserted in a 2-l. flask equipped with a Dry Ice–acetone reflux condenser and a fritted gas inlet tube at the bottom. In this apparatus were placed 50 g (0.19 mol) of diphenyldiallylsilane[29] and 1.5 l. of olefin-free pentane. Purified nitrogen was bubbled through the solution to purge it of air. The solution was cooled to −78° by immersion of the entire apparatus in an isopropyl alcohol–Dry Ice bath. H_2S (10 g, 0.29 mol) was slowly bubbled through the solution while it was being illuminated with a 450-W medium-pressure Hanovia lamp. The addition required 1 hr. Photolysis was continued for an additional 2 hr. The solution was then warmed to room temperature. After removal of pentane by distillation, the product was fractionally distilled through a 15-cm Vigreux column. A fraction of bp 180–220° (0.1 mm) was collected. This fraction was further purified by chromatography on a 10 × 0.5 in. alumina column. The product was eluted with pentane. A 10% yield (approximately 6 g) based on recovered starting material was obtained: nmr m (4 H) δ 1.27, m (4 H) 1.84, m (4 H) 2.50, m (10 H) 7.24. *Anal.* Calcd for $C_{18}H_{22}SiS$: C, 72.42; H, 7.43. Found: C, 72.71; H, 7.54.

1,1-Diphenyl-1-sila-5-thiacyclooctane 5,5-Dioxide. In a 100-ml three-necked round-bottom flask equipped with a pressure-equalizing addition funnel, a reflux condenser, a magnetic stirring bar, and a thermometer were placed 30 ml of CH_2Cl_2 and 5 g (0.0273 mol) of *m*-chloroperbenzoic acid.[22] The solution was cooled to 0° by immersion in a salt–ice bath. 1,1-Diphenyl-1-sila-5-thiacyclooctane (1.45 g, 4.86 mmol) dissolved in 5 ml of CH_2Cl_2 was placed in the addition funnel and was added to the well-stirred reaction mixture at such a rate that the temperature did not exceed 5°. After the addition was complete, the solution was warmed to room temperature and was then heated to reflux for 1 hr. Five grams of Na_2SO_3 was added to destroy excess peracid. Stirring was continued for 15 min. The solution was filtered, and the CH_2Cl_2 solvent was removed by evaporation under reduced pressure. The residue was chromatographed on a 10 × 0.5 in. alumina column, eluting with $CHCl_3$. Ir was characterized by strong SO_2 absorption bands at 1285 and 1100 cm^{-1}; nmr m (4 H) δ 1.50, m (4 H) 2.14, m (4 H) 2.98, m (10 H) 7.32. *Anal.* Calcd for $C_{18}H_{22}SiSO_2$: C, 65.41; H, 6.71. Found: C, 65.70; H, 6.76.

1,1-Diphenyl-1-sila-4-cycloheptene. In a dry 100-ml round-bottom flask equipped with a reflux condenser were placed 0.49 g (1.5 mmol) of 1,1-diphenyl-1-sila-5-thiacyclooctane 5,5-dioxide, 6.0 g (0.11 mol) of powdered KOH, 30 ml of dry *tert*-butyl alcohol, and 50 ml of dry CCl_4.[8,23] The mixture was heated for 12 hr at 50° while being stirred. The reaction mixture was transferred to a separatory funnel, and 30 ml of CH_2Cl_2 was added. The organic layer was washed with three equal volumes of water, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed by evaporation under reduced pressure. The product was then purified by glpc on an Apiezon L column (18 × 0.25 in.) at 200°, mp 63–63.4°. The ir showed a weak C-C double bond at 1650 cm^{-1}; nmr m (4 H) δ 1.23, m (4 H) 2.35, m (2 H) 5.72, m (10 H) 7.38. The mass spectrum showed a parent ion at *m/e* 264 and an intense P − 28 ion at *m/e* 236. Calcd for $SiC_{18}H_{20}$: 264.1334. Found: 264.1277. Calcd for $SiC_{16}H_{16}$: 236.1021. Found: 236.0997. *Anal.* Calcd for $C_{18}H_{20}Si$: C, 81.76; H, 7.62. Found: C, 81.48; H, 7.54.

1,1-Dimethyl-5-hydroxy-1-sila-4-cycloheptanone.[24] In a 300-ml round-bottom flask equipped with a magnetic stirring bar were placed 19 g (0.06 mol) of 1,1-dimethyl-4,5-bis(trimethylsiloxy)-1-sila-4-cycloheptene,[1] 50 ml of THF, and 40 ml of 2 *N* HCl. The mixture was stirred overnight. The layers were separated. The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated. The yield of crude product was 10 g (97%). The compound was purified by distillation through a 10-cm Vigreux column, bp 130° (25 mm) or 50° (0.2 mm). Ir showed a broad OH band at 3450 cm^{-1} and a carbonyl band at 1710 cm^{-1}; nmr s (3 H) δ −0.01, s (3 H) 0.01, m (4 H) 0.7, m (2 H) 1.9, m (2 H) 2.5, t (1 H) 4.2, J = 5 Hz.

1,1-Dimethyl-1-sila-4,5-cycloheptanediol. In a dry 500-ml round-bottom three-neck flask, equipped with a pressure-equalizing addition funnel, a magnetic stirring bar, and a reflux condenser was placed 2 g (0.53 mol) of $LiAlH_4$ in 100 ml of anhydrous ether. To this was added 12.2 g (0.07 mol) of crude 1,1-dimethyl-5-hydroxy-1-sila-4-cycloheptanone[24] in 50 ml of anhydrous ether. After 2 hr the reaction was quenched by addition of 10 ml of H_2O. The layers were separated. The ether layer was dried over anhydrous $MgSO_4$ and filtered and the solvents were removed under reduced pressure. This reaction yields 11 g (90%) of crude product. The cis isomer was recrystallized from pentane at −20°; mp 48–49°; nmr s (3 H) δ −0.09, s (3 H) −0.07, m (4 H) 0.55, m (4 H) 1.68, m (2 H) 3.59, s (2 H) 4.0. The singlet at δ 4.0 disappeared after treatment with D_2O.

1,1-Dimethyl-1-sila-4-cycloheptene. In a dry 100-ml flask equipped with a magnetic stirring bar were placed 3.7 g (0.02 mol) of 1,1-dimethyl-1-sila-4,5-cycloheptanediol, 8 ml (0.08 mol) of triethylamine, and 4 ml (0.05 mol) of mesyl chloride in 50 ml of CH_2Cl_2.[25] The mixture was stirred at room temperature overnight. The solution was then poured into 50 ml of water. The layers were separated. The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent was removed under reduced pressure. The crude dimesylate (7 g) was dissolved in 100 ml of methyl ethyl ketone, and 11 g (0.8 mol) of NaI was placed in a 250-ml flask equipped with a reflux condenser and a magnetic stirring bar. The reaction was stirred at reflux for 48 hr.[27] The brown solution was cooled, poured into a separatory funnel, and washed with two 50-ml portions of saturated $Na_2S_2O_4$ to remove the I_2 color. The organic layer was then dried over anhydrous $MgSO_4$ and filtered and the solvent was removed by distillation through a 10-cm Vigreux column. A fraction of bp 100–140° was collected (1.6 g). It was further purified by chromatography on a 10 × 0.5 in. alumina column eluted with pentane. In this way 0.63 g (20% yield) was obtained. An analytical sample was purified by gplc on a 15 ft × 0.25 in. Carbowax column at 100°. Its physical and spectral properties were in agreement.

1,1-Diphenyl-4,5-bis(trimethylsiloxy)-1-sila-4-cycloheptene. In a dry 1-l. three-necked round-bottom flask, equipped with a high-speed stirrer, a pressure-equalizing addition funnel, and a reflux condenser were placed 20.0 g (0.9 mol) of Na and 350 ml of dry toluene. The toluene was heated to reflux, at which time stirring was started. To the Na dispersion were added 120 ml (0.9 mol) of trimethylchlorosilane and 64 g (0.2 mol) of dimethyl 4,4-diphenyl-4-sila-1,7-heptanedioate[13] over 2 hr. The reaction mix-

ture was heated at reflux for 2 hr after the addition was complete. The reaction mixture was cooled and filtered under a cone of N_2. The solvent was removed by distillation through a 10-cm Vigreux column at atmospheric pressure. The residue was then distilled. A central fraction of 57 g (72% yield), bp 130° (0.001 mm), was collected. Ir showed a C–C double bond at 1680 cm^{-1}; nmr s (18 H) δ 0.29, m (4 H) 1.4, m (4 H) 2.5, m (10 H) 7.48.

1,1-Diphenyl-5-hydroxy-1-sila-4-cycloheptanone. In a 300-ml round-bottom flask equipped with a magnetic stirring bar were placed 53 g (0.12 mol) of 1,1-diphenyl-4,5-bis(trimethylsiloxy)-1-sila-4-cycloheptene, 75 ml of THF, and 75 ml of 2 *N* HCl. The mixture was stirred overnight. The layers were separated. The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent was evaporated. The yield of crystalline product was 35 g (95%), mp 94–97°. Recrystallization from *n*-hexane gave a white solid, mp 96–98°. Ir showed a broad OH band at 3450 cm^{-1} and a carbonyl band at 1710 cm^{-1}; nmr m (4 H) δ 1.45, m (2 H) 2.1, m (2 H) 2.65, broad s (1 H) 3.8, m (1 H) 4.25, m (10 H) 7.19. *Anal.* Calcd for $SiC_{18}H_{20}O_2$: C, 72.93; H, 6.80. Found: C, 72.73; H, 6.60.

1,1-Diphenyl-4,5-dihydroxy-1-silacycloheptane. In a dry 500-ml round-bottom three-necked flask equipped with a pressure-equalizing addition funnel, a magnetic stirring bar, and a reflux condenser was placed 3 g (0.075 mol) of $LiAlH_4$ in 100 ml of ether. In the addition funnel was placed 35.0 g (0.12 mol) of crude 1,1-diphenyl-5-hydroxy-1-sila-4-cycloheptanone in 100 ml of anhydrous THF. This solution was added to the hydride suspension at a rate to maintain reflux. After 2 hr the reaction was quenched by the addition of water. The layers were separated. The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent was removed at reduced pressure, resulting in 33 g of a thick yellow oil which solidified on standing: nmr m (8 H) δ 1–2, m (4 H) 3.7, m (10 H) 7.3. Its ir showed two OH bands in CCl_4, one at 3300 cm^{-1} and the other at 3550 cm^{-1}.

1,1-Diphenyl-1-sila-4-cycloheptene. In a dry 50-ml flask equipped with a magnetic stirring bar were placed 1 g (3.4 mmol) of 1,1-diphenyl-1-sila-4,5-cycloheptanediol, 1.4 ml (10 mmol) of triethylamine, and 20 ml of CH_2Cl_2. The solution was cooled to 0° and 0.6 ml (7.5 mmol) of mesyl chloride was added.[25] The mixture was stirred for 2 hr and then poured into 50 ml of H_2O. The layers were separated. The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude dimesylate, 3.0 g (20 mmol) of NaI, and 20 ml of methyl ethyl ketone were placed in a 50-ml flask equipped with a reflux condenser and a magnetic stirring bar.[27] The solution was stirred at reflux for 40 hr; 50 ml of ether was added. The reaction mixture was washed with two 50-ml portions of water and once with a saturated solution of $Na_2S_2O_4$ to disperse the I_2 color. It was dried over anhydrous $MgSO_4$ and filtered and the solvents were removed at reduced pressure. The residue, 610 mg, was then chromatographed through a 10 × 0.5 in. alumina column with *n*-hexane. In this way 330 mg (37% yield) of crystalline olefin was collected. It was recrystallized from 95% ethanol, mp 63°.

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Registry No.—1,1-Dimethyl-1-sila-5-thiacyclooctane, 49592-51-0; dimethyldiallylsilane, 1113-12-8; H_2S, 7783-06-4; 1,1-dimethyl-1-sila-5-thiacyclooctane 5,5-dioxide, 51051-56-0; 1,1-dimethyl-1-sila-4-cycloheptene, 51051-57-1; 4,4-dimethyl-4-sila-6-heptene 1-thiolacetate, 51006-76-9; thiolacetic acid, 507-09-5; dimethylallyl-3-mercaptopropylsilane, 49592-52-1; 1,1-diphenyl-1-sila-5-thiacyclooctane, 51051-58-2; diphenyldiallylsilane, 10519-88-7; 1,1-diphenyl-1-sila-5-thiacyclooctane 5,5-dioxide, 51051-59-3; 1,1-diphenyl-1-sila-4-cycloheptene, 51051-60-6; 1,1-dimethyl-5-hydroxy-1-sila-4-cycloheptanone, 10325-25-4; 1,1-dimethyl-4,5-bis(trimethylsiloxy)-1-sila-4-cycloheptene, 32297-03-3; *cis*-1,1-dimethyl-1-sila-4,5-cycloheptanediol, 51051-61-7; 1,1-diphenyl-4,5-bis(trimethylsiloxy)-1-sila-4-cycloheptene, 51051-62-8; dimethyl 4,4-diphenyl-4-sila-1,7-heptanedioate, 34564-74-4; 1,1-diphenyl-5-hydroxy-1-sila-4-cycloheptanone, 51051-63-9; 1,1-diphenyl-4,5-dihydroxy-1-silacycloheptane, 51051-64-0.

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Preparation of New Nitrogen-Bridged Heterocycles. Reaction of Pyridinium *N*-Imines with α-Haloacrylates in the Presence of Alkali

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Pyridinium *N*-imine hydriodides (**1**–**5**) reacted with ethyl and methyl α-chlorocinnamates and methyl α-bromocrotonate in the presence of alkali at room temperature to afford the corresponding 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives (**11**–**17**). Structural elucidation of these compounds was accomplished by physical and spectral means and by the conversion of compounds **11** and **16** to the dehydrogenated 2*H*-pyrido[1,2-*b*]-*as*-triazines **20** and **21**.

Pyridinium *N*-imine is a very useful and versatile precursor for preparations of various nitrogen-bridged heterocycles[1] and N-substituted iminopyridinium ylides[2] as described in many reports. In particular, increased attention

Table I
Nmr Spectral Data of Pyridotriazines

Compd[a]	NH[g]	C-2	C-6	C-7	C-8	C-9	C-9a	R″	R′	
11	2.00	*b*	6.53	*b*	1.72	*b*	*b*	7.16	4.13	1.27
	b		d		s			s	q	t
	$J_{6,7}$ = 7.0, J_{Et} = 7.0									
12	2.15	*c*	6.55	*c*	5.80	*c*	*c*	7.15	4.13	1.25
	b		dd		m			s	q	t
	$J_{6,7}$ = 7.0, $J_{6,8}$ = 1.5, J_{Et} = 7.0									
13	2.10	*d*	2.10	*d*	5.77	*d*	*d*	7.15	4.12	1.22
	b		s		m			s	q	t
	J_{Et} = 7.0									
14	1.96	*e*	6.49	*e*	5.64	*e*	*e*	7.16	4.19	1.27
	b		d		bd			s	q	t
	$J_{6,7}$ = 7.5, $J_{7,8}$ = 6.0, J_{Et} = 7.0									
15	1.80	4.75	6.36	1.68	5.53	1.68	4.85	7.15	4.13	1.28
	b	bd	bs	s	bs	s	bs	s	q	t
	J_{Et} = 7.0									
16	1.90	*f*	6.49	*f*	1.72	*f*		7.12	3.65	
	b		d		s			s	s	
	$J_{6,7}$ = 7.5									
17	1.65	3.65	6.47	4.72	1.77	5.00	5.21	1.26	3.69	
	b	m	d	dd	s	bs	bs	d	s	
	$J_{2,Me}$ = 6.0, $J_{6,7}$ = 7.0, $J_{7,9}$ = 1.5									
20		5.57	6.97	5.50	2.00	6.13		7.10	4.17	1.29
		s	d	dd	s	bs		s	q	t
	$J_{6,7}$ = 7.5, $J_{7,9}$ = 2.0, J_{Et} = 7.0									
21		5.62	7.02	5.56	2.04	6.17		7.15	3.75	
		s	d	dd	s	bs		s	s	
	$J_{6,7}$ = 7.5, $J_{7,9}$ = 2.0									

[a] All compounds were measured in carbon tetrachloride. [b] Overlapped with each other in the range of δ 4.6–5.1. [c] Overlapped with each other in the range of δ 4.6–5.3. [d] Overlapped with each other in the range of δ 4.6–5.3. [e] Overlapped with each other in the range of δ 4.6–5.3. [f] Overlapped with each other in the range of δ 4.6–5.4. [g] Overlapped with each other in the range of δ 4.6–5.1. [g] Exchanged with deuterium oxide.

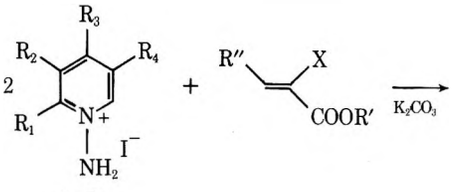
has been paid to the nitrogen-bridged heterocycles in recent years, since their preparations by other methods are difficult.

We recently reported that reactions of pyridinium *N*-imines with β-haloacrylates gave mainly 1,5-dipolar *N*-vinyliminopyridinium ylides, which react intramolecularly to give dihydropyrazolopyridines[3] and intermolecularly with acetylenic compounds to give *N*-dienyliminopyridinium ylide and vinylpyridine derivatives.[4] In continuation of this work, we attempted to carry out the reaction of pyridinium *N*-imines with some α-haloacrylates in the presence of alkali and have found a one-step preparative method for the novel 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazines.

Results and Discussion

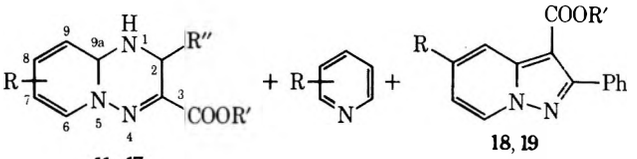
Reactions of Pyridinium *N*-Imine Hydriodides (1–5) with α-Haloacrylates in the Presence of Alkali. A 2:1 mixture of pyridinium *N*-imine hydriodide (**1**) and ethyl α-chlorocinnamate was treated with potassium carbonate in chloroform at room temperature for 4 days to give a yellow, crystalline product (**11**) in 84% yield, together with considerable amounts of γ-picoline. Similar products (**12–15**) were obtained by the reactions of the hydriodides **2–5** with the same reagent in yields of 4–87%. Reactions of the hydriodide **1** with methyl α-chlorocinnamate and methyl α-bromocrotonate gave compounds **16** and **17** in 85 and 36% yields. With hydriodides **1** and **2**, 1,3-dipolar cycloadducts **18** and **19** were also obtained in 5 and 38% yields. In these reactions no ylidic compound could be detected. These results are shown in Scheme I.

Scheme I



1–5

	R_1	R_2	R_3	R_4
1	H	H	Me	H
2	H	H	H	H
3	Me	H	H	H
4	H	Me	H	H
5	H	Me	H	Me



11–17

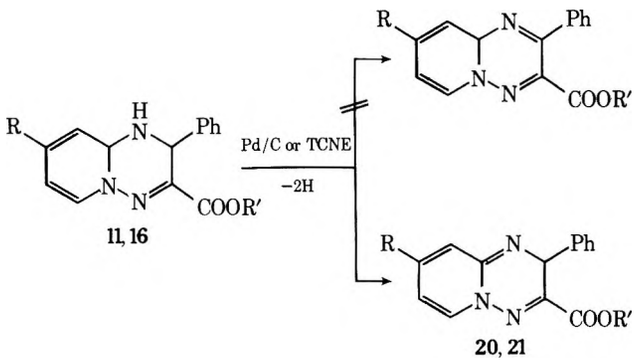
	R′	R″	C_6	C_7	C_8	C_9
11	Et	Ph	H	H	Me	H
12	Et	Ph	H	H	H	H
13	Et	Ph	Me	H	H	H
14	Et	Ph	H	H	H	Me
15	Et	Ph	H	Me	H	Me
16	Me	Ph	H	H	Me	H
17	Me	Me	H	H	Me	H

18, 19

	R	R′
18	Me	Et
19	H	Et

The products **11–17** were very stable under neutral and basic conditions, but were unstable in acid. The ir spectra showed characteristic absorption bands of a secondary amino group at 3290–3330 cm^{-1} and of an α,β-unsaturated carbonyl group at 1695–1713 cm^{-1}, respectively. The nmr spectrum (Table I) of compound **17**, for example, exhibited signals[6] at δ 6.47 (1 H, d), 5.21 (1 H, bs), 5.00 (1 H, bs), 4.72 (1 H, dd), and 1.77 (3 H, s) due to a dihydropyridine moiety and at δ 3.65 (1 H, m), 1.26 (3 H, d), 3.69 (3 H, S), and 1.65 (1 H, b) attributable to the residual skeleton. The signal at δ 1.65 (1 H, b) was exchanged with deuterium oxide (active amino proton) and the signals at δ

Scheme II



R R′
11 Me Et 20
16 Me Me 21

5.21 (1 H, bs) and 3.65 (1 H, m) were sharpened, indicative of their adjacent situation with the amino group. From these data the compounds **11–17** were assigned to be 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives.

To obtain further evidence for the proposed structure, we attempted the dehydrogenation of the compounds **11** and **16** to the corresponding pyridotriazine derivatives. Treatment of compounds **11** and **16** with lead tetraacetate gave intractable, tarry materials, but with palladium on carbon or tetracyanoethylene, the expected pyrido[1,2-*b*]-*as*-triazines **20** and **21** were obtained in low yields (Scheme II).

The ir spectrum of the compound **20** showed no absorption at the amino absorption region but a new band at 1660 cm^{-1} due to an unsaturated bond was present, and the nmr signals attributable to a bridgehead proton and an amino proton were absent. The large downfield shifts of the protons on the pyridine ring suggested that these compounds were not the 9a*H*-pyrido[1,2-*b*]-*as*-triazine derivatives but the alternative 2*H* isomers. Similar correlation of the chemical shifts was observed between 3,3a-dihydropyrazolopyridines[3,4] and 2,3-dihydroindolizines[7] described in our previous papers. The nmr data of pyridotriazine derivatives **11–17**, **20** and **21** are summarized in Table I.

In contrast with the stability of the dihydro compounds **11–17**, the pyridotriazines **20** and **21** were unstable and decomposed gradually even at room temperature.[5]

Reaction Mechanism. Tentative mechanisms for these reactions are shown in Scheme III.

The reactions may be initiated by Michael addition of pyridinium *N*-imine to the α-haloacrylate followed by elimination of pyridine derivative. Nucleophilic substitution of another molecule of the *N*-imine to the resulting haloaziridine **23** (path a) or nucleophilic addition to the azirine **24** (path b) would lead to the *N*-(2-aziridinyl)iminopyridinium ylide **25**, which rearranges to dihydropyridotriazine *via* the 1,6-dipolar intermediate **26**. The alternative course (path c) was negligible, since the product expected from the reaction *via* the 1,3-dipolar species **27** is a different type of dihydropyridotriazine (**29** and/or **30**). Nucleophilic substitution of haloaziridine has been reported by Deyrup and Greenwald[8] but the addition of pyridinium *N*-imidine to the carbon–nitrogen double bond is unknown. Pyridinium *N*-imine also reacted with dimethyl maleate to give dimethyl aminofumarate; this reaction should proceed *via* Michael addition of the *N*-imine to the α,β-unsaturated ester.[9] An attempt to obtain a pyridopyridazine from pyridinium *N*-imine and halocyclopropane[10] was unsuccessful.[11]

Experimental Section

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 Elemental Analyzer. The nmr spectra were determined with a JEOL JNM-4H-100 spectrometer in carbon tetrachloride with tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values. The ir spectra were taken with a JASCO DS-301 spectrophotometer.

Reactions of Pyridinium *N*-Imine Hydriodides (1–5) with α-Haloacrylates in the Presence of Alkali. General Method. A mixture of pyridinium *N*-imine hydriodide (2 mmol) and α-haloacrylate (1 mmol) was treated with potassium carbonate (10 g) in chloroform at room temperature for 4–8 days. The reaction mix-

Scheme III

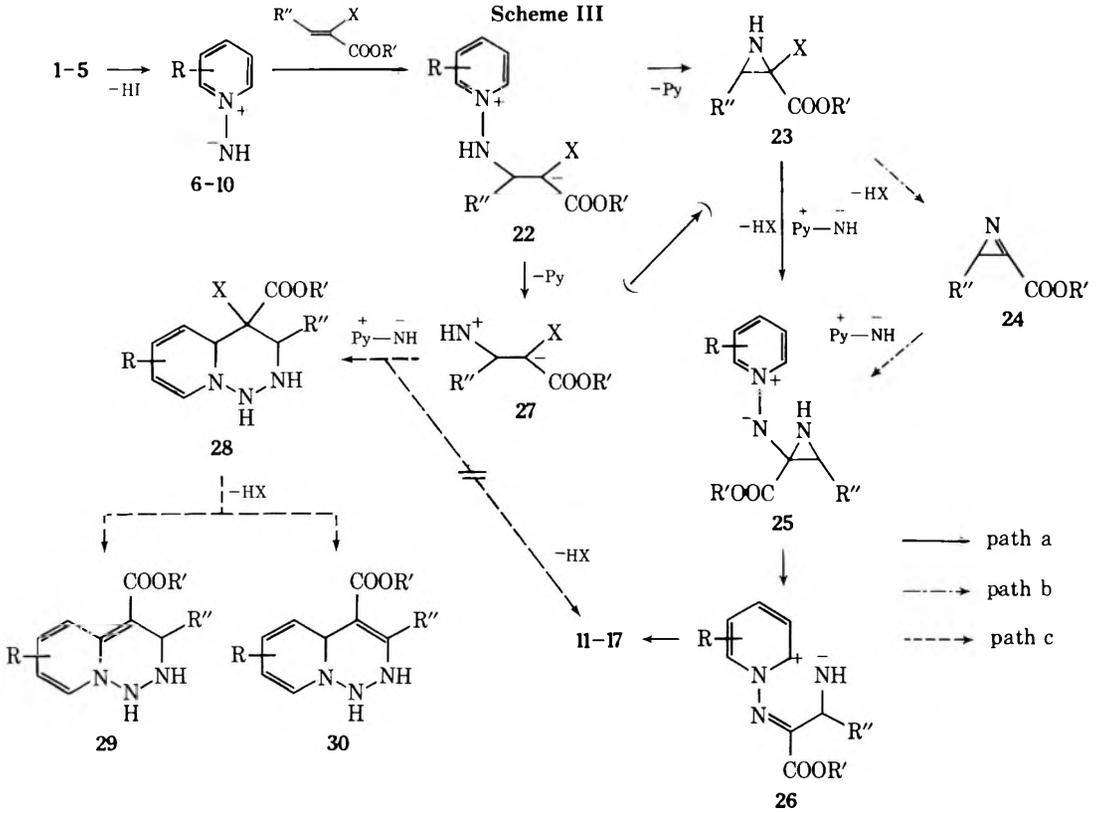


Table II
Results and Some Properties of Dihydropyridotriazines

Compd[b]	Reactant: *N*-Imine	Reactant: α-Haloacrylate[a]	Yield, %	Mp, °C	Ir (KBr), cm⁻¹: C=O	Ir (KBr), cm⁻¹: NH
11	**1**	ECC	84	112–115	1710	3330
12	**2**	ECC	4	125–127	1700	3310
13	**3**	ECC	27	91–93	1713	3290
14[c]	**4**	ECC	64	136–139	1695	3320
15	**5**	ECC	87	106–109	1695	3290
16	**1**	MCC	85	143–145	1717	3320
17	**1**	MBC	36	74–76	1708	3290

[a] ECC, ethyl chlorocinnamate; MCC, methyl chlorocinnamate; MBC, methyl bromocrotonate. [b] **11.** *Anal.* Calcd for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.92; H, 6.45; N, 13.92. **12.** Calcd for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.75; H, 6.15; N, 14.70. **13.** Calcd for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.89; H, 6.55; N, 13.79. **14.** Calcd for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.62; H, 6.53; N, 13.87. **15.** Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50. Found: C, 69.39; H, 6.91; N, 13.20. **16.** Calcd for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.99; H, 6.17; N, 14.83. **17.** Calcd for $C_{11}H_{15}N_3O_2$: C,59.71; H, 6.83; N, 18.99. Found: C, 59.90; H, 6.85, N, 18.81. [c] The 7-methyl isomer could not be detected.

ture was filtered to remove insoluble inorganic substances and the filtrate was concentrated under reduced pressure. The residual oil was separated by column chromatography (alumina) using ether as an eluent. Recrystallization from ether–*n*-hexane gave the corresponding 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives as yellow crystals. In these reactions considerable amounts of the corresponding pyridine derivatives were formed, which could be detected by thin layer chromatography and their odor. In the cases of the hydriodides **1** and **2** with ethyl α-chlorocinnamate the corresponding pyrazolo[1,5-*a*]pyridine derivatives **18** and **19** were also obtained in 5 and 38% yields. The structures of these compounds (**18** and **19**) were determined by the spectral comparisons with the methyl ester derivatives prepared by the reactions of pyridinium *N*-imines **6** and **7** with methyl phenylpropiolate. These results and some properties of these dihydropyridotriazine derivatives (**11**–**17**) are listed in Table II.

3-Ethoxycarbonyl-5-methyl-2-phenylpyrazolo[1,5-*a*]pyridine (**18**) was obtained as colorless needles (from ether–*n*-hexane): mp 88–90°; $\nu_{C=O}$ (KBr) 1719 cm⁻¹; nmr (CCl_4) δ 1.22 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 2.41 (3 H, s, C_5 CH_3), 4.17 (2 H, q, J = 7.0 Hz, OCH_2CH_3), 6.55 (1 H, dd, J = 7.5, 1.0 Hz, C_6 H), 7.25 (3 H, m, meta and para protons of C_2 phenyl), 7.62 (2 H, m, ortho protons of C_2 phenyl), 7.84 (1 H, bs, C_4 H), and 8.20 (1 H, d, J = 7.5 Hz, C_7 H).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.84; H, 5.78; N, 9.68.

3-Ethoxycarbonyl-2-phenylpyrazolo[1,5-*a*]pyridine (**19**) was obtained as colorless needles (from ether–*n*-hexane): mp 73–75°; $\nu_{C=O}$ (KBr) 1718 cm⁻¹; nmr (CCl_4) δ 1.25 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 4.19 (2 H, q, J = 7.0 Hz, OCH_2CH_3), 6.73 (1 H, t, J = 7.0, 7.0 Hz, C_6 H), 7.20 (1 H, bt, J = 7.0, 8.0 Hz, C_5 H), 7.29 (3 H, m, meta and para protons of C_2 phenyl), 7.67 (2 H, m, ortho protons of C_2 phenyl), 8.10 (1 H, dd, J = 8.0, 1.0 Hz, C_4 H), and 8.37 (1 H, d, J = 7.0 Hz, C_7 H).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.40; H, 5.33; N, 10.30.

Dehydrogenation of Dihydropyridotriazines (11 and 16). General Method. A. A mixture of dihydropyridotriazine (200 mg) and palladium on carbon (5%, 1.0 g) was stirred in dry benzene (30 ml) at room temperature for 4 days. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was separated by column chromatography (alumina) using methylene chloride as an eluent. From this procedure 2*H*-pyridotriazine derivatives **20** and **21** were obtained in 30 and 25% yields, respectively.

B. A equimolar mixture of dihydropyridotriazine and tetracyanoethylene was stirred in dry benzene at room temperature for 1 day. Similar treatment of the reaction solution gave 2*H*-pyridotriazine derivative. The yields of the compounds **20** and **21** were 50 and 45%.

3-Ethoxycarbonyl-8-methyl-2-phenyl-2*H*-pyrido[1,2-*b*]-*as*-triazine (**20**) was obtained as orange crystals (from chloroform–*n*-hexane), mp 108–110°, ν (KBr) 1713 (C=O) and 1660 cm⁻¹ (C=N); its picrate, yellow crystals (from ethanol), had mp 178–181° dec, $\nu_{C=O}$ (KBr) 1736 cm⁻¹.

Anal. Calcd for $C_{23}H_{20}N_6O_9$: C, 52.67; H, 3.84; N, 16.03. Found: C, 52.88; H, 3.82; N, 15.74.

3-Methoxycarbonyl-8-methyl-2-phenyl-2*H*-pyrido[1,2-*b*]-*as*-triazine (**21**) was an amorphous substance; its picrate, yellow crystals (from ethanol), had mp 189–192° dec, $\nu_{C=O}$ (KBr) 1740 cm⁻¹.

Anal. Calcd for $C_{22}H_{18}N_6O_9$: C, 51.77; H, 3.55; N, 16.47. Found: C, 51.65; H, 3.50; N, 16.40.

Reaction of Pyridinium *N*-Imine (6) with Dimethyl Maleate. A mixture of pyridinium *N*-imine hydriodide (**1**, 0.24 g, 1 mmol) and dimethyl maleate (0.14 g, 1 mmol) was treated with potassium carbonate (5 g) in chloroform at room temperature for 4 days. The reaction mixture was worked up by the procedure described above to give dimethyl aminofumarate in 35% yield as a colorless oil. The structure of this product was determined by comparison with an authentic specimen.[9] The reaction of the hydriodide **1** with ethyl cinnamate was unsuccessful.

Registry No.—**1**, 7583-92-8; **2**, 6295-87-0; **3**, 7583-90-6; **4**, 7583-91-7; **5**, 7585-71-9; **11**, 51065-68-0; **12**, 51065-69-1; **13**, 51065-70-4; **14**, 51065-71-5; **15**, 51065-72-6; **16**, 51065-73-7; **17**, 51065-74-8; **18**, 51065-75-9; **19**, 51065-76-0; **20**, 51065-77-1; **20** picrate, 51065-78-2; **21**, 51065-79-3; **21** picrate, 51065-80-6; ECC, 26880-33-1; MCC, 4519-51-1; MBC, 17642-18-1; dimethyl maleate, 624-48-6.

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(6) Abbreviations of the spectral patterns are follows: s, singlet; b, broad; bs, broad singlet; d, doublet; m, multiplet; t, triplet; q, quartet; dd, double doublet.

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Synthesis of Pharmacologically Active Nitrogen Analogs of the Tetrahydrocannabinols

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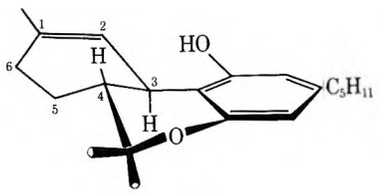
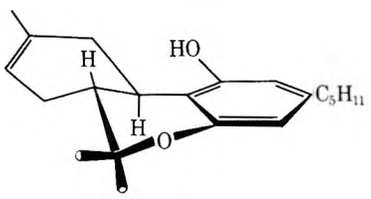
Received October 19, 1973

The synthesis of a nitrogen analog of $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol, a psychoactive component of *Cannabis sativa* L, is described. The condensation of 2,6-dimethoxy-4-*n*-amylbenzylidenemethylamine (**9**) with glutaric anhydride in refluxing xylene provided *trans*-1-methyl-5-carboxy-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (**11**). Subsequent transformations yielded the desired tricyclic system **27** in which the C-2 methylene of $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol is replaced by an *N*-methyl moiety. Configurational and conformational assignments of the intermediates were made by nmr spectroscopy. The diastereomeric mixture of amines **4** and **5** **5** obtained on catalytic reduction of **27** possesses both antidepressant and anticonvulsant activity.

Two psychoactive constituents of Cannabis have been shown, Δ^1-*trans*-tetrahydrocannabinol (Δ^1-THC, **1**)[2] and $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol ($\Delta^{1(6)}$-THC, **2**).[3] We recently reported the synthesis of a series of model nitrogen analogs of the THC's, including **3**.[4] Since a phenolic group and an alkyl side chain have been demonstrated to be structural requirements for pharmacologic activity,[5,6] our model compounds did not appear to be promising candidates for biologic evaluation. We now wish to report the successful extension of our studies to the preparation of the nitrogen analog of $\Delta^{1(6)}$-THC, compound **27**. Catalytic reduction of **27** gave a diastereomeric mixture of amines **4** and **5**. Preliminary pharmacologic tests[7] indicate that this mixture possesses both antidepressant (modified dopa test in mice; marked activity at 5 mg/kg) and anticonvulsant (audiogenic seizure in mice; 60% protection at 30 mg/kg) activity.



1



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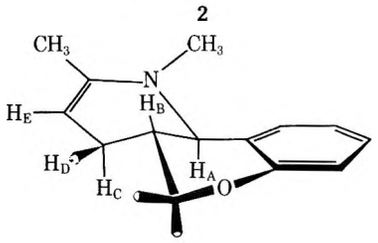

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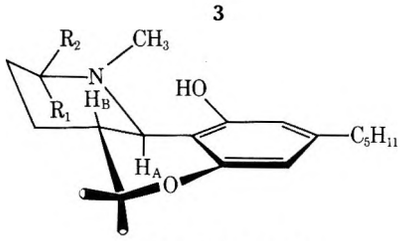
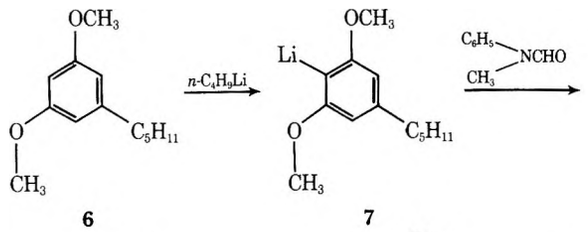
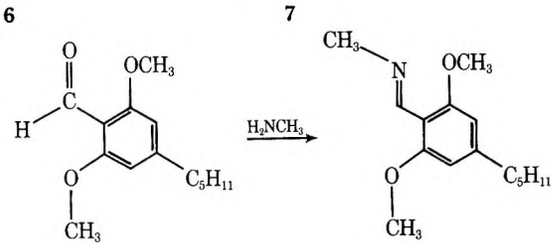


4, $R_1 = CH_3$; $R_2 = H$
5, $R_1 = H$; $R_2 = CH_3$

Metalation of olivetol dimethyl ether (**6**) with *n*-butyllithium provided the phenyllithium intermediate **7**, which was converted to 2,6-dimethoxy-4-*n*-amylbenzaldehyde (**8**) with *N*-methylformanilide.[8] The Schiff base **9** was obtained by stirring a solution of the aldehyde **8** and methylamine in benzene over molecular sieves.



6 **7**

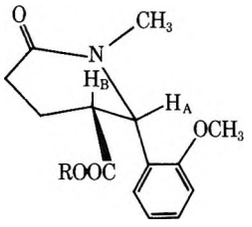


8 **9**

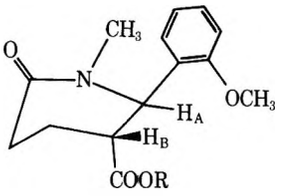
Condensation of the Schiff base **9** with glutaric anhydride in refluxing xylene gave an 86% yield of the diastereomeric mixture of piperidones **10** and **11**, which was separated by fractional crystallization. The minor cis diastereomer **10** produced the expected axial-equatorial coupling constant J_{AB} = 5 Hz, which is identical with that of the model cis diastereomer **12**. The major diastereomer was isolated in 45% yield and displayed an nmr coupling constant J_{AB} = 7 Hz. Since vicinal diaxial protons show coupling constants of 8–13 Hz and vicinal diequatorial protons 1–5 Hz in six-membered rings,[9] evidently the trans diastereomer **11** spends more time in the diequatorial conformation than the model trans compound **13** (J = 2.5 Hz), which appears to exist largely in the diaxial conformation. This change in conformational equilibrium of the trans diastereomer **11** relative to **13** is also reflected in the chemical shift value for the methoxycarbonyl proton signal of the trans ester **14** (δ 3.61 ppm) relative to the model trans ester **15** (δ 3.75 ppm). This is expected, since the methoxycarbonyl protons can experience the shielding effect of the aromatic π cloud in the diequatorial conformation but cannot in the diaxial conformation. The corresponding values in the cis methyl ester **16** and cis model methyl ester **17** were δ 3.51 and 3.56, respectively.

Finally, the trans dimethyl ether **11** was demethylated to the diphenol **18** with boron tribromide in methylene chloride.[10] Subsequent cyclodehydration to the rigid di-

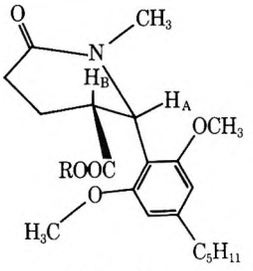
equatorial lactone **19** (J_{AB} = 13 Hz) was accomplished with dicyclohexylcarbodiimide in tetrahydrofuran.



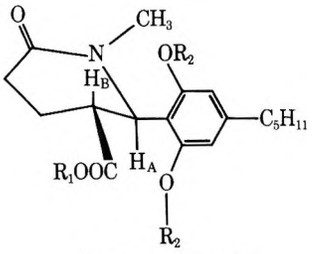
12, R = H
17, R = CH_3



13, R = H
15, R = CH_3



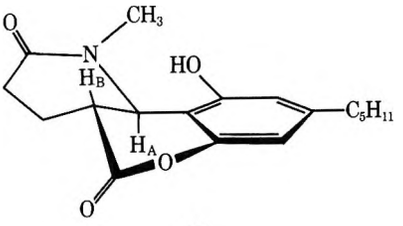
10, R = H
16, R = CH_3



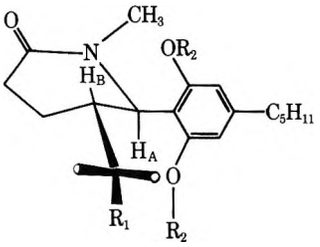
11, R_1 = H; R_2 = CH_3
14, R_1 = R_2 = CH_3
18, R_1 = R_2 = H

Methylation of the trans ester **14** with methylmagnesium bromide in ether gave the corresponding tertiary alcohol **20** in 83% yield, which was demethylated with boron tribromide in methylene chloride to form the tertiary bromide **21**. The crude bromide was dehydrohalogenated in boiling ethanol solution to form the terminal olefin **22**, which was obtained as a glass.[11] Although **22** could be isolated as a crystalline solid in 29% yield from **20**, higher overall yields of the desired tricyclic lactam **25** were realized when the glass was used without further purification.

We anticipated from our model studies that the terminal olefin **22** could be cyclized to the trans tricyclic compound **25** in the presence of trifluoroacetic acid. However,

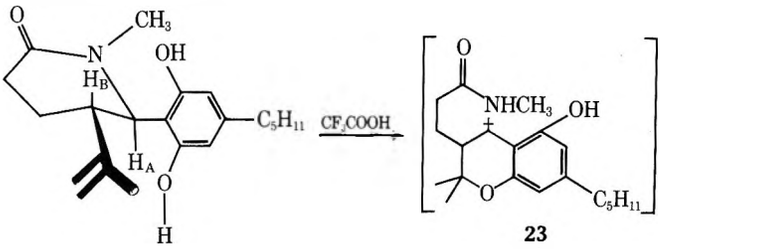


19



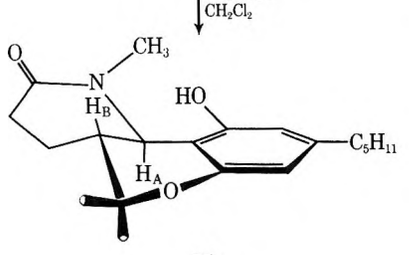
20, R_1 = OH; R_2 = CH_3
21, R_1 = Br; R_2 = H

treatment of **22** with trifluoroacetic acid at reflux for 1 hr gave exclusively the cis diastereomer **24** (J_{AB} = 5 Hz) and none of the trans isomer **25** could be detected when the reaction was followed by nmr. From our model studies it was apparent that the transformation of **22** to the cis tricyclic system **24** proceeds *via* the resonance-stabilized benzylic carbonium ion species **23**. The much greater rate of isomerization of **22** to **24** relative to the case of the corresponding model compounds must reflect the stabilization of species **23** by the electron-donating phenolic and alkyl substituents, and supports our earlier view that the principal pathway for the trans to cis conversion in this series involves epimerization at the benzylic carbon atom rather than at the allylic center.[4] It seemed reasonable to anticipate that the formation of charged species **23** would be discouraged by employing a less polar solvent. Therefore, in an attempt to promote formation of the desired trans lactam **25**, cyclization of the terminal olefin was ef-

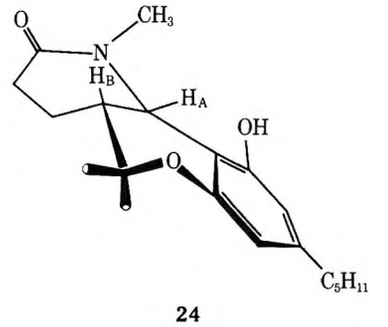


22

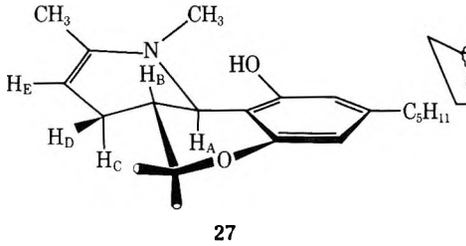
23



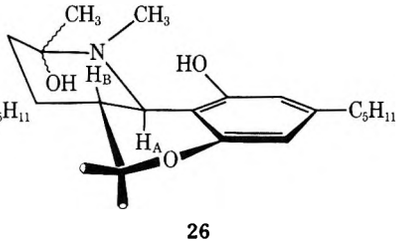
25



24



27



26

fected in methylene chloride containing boron trifluoride etherate. Overall yields of the trans lactam **25** (J_{AB} = 10 Hz) of 25% from **20** were thus realized.

The nmr signal for proton H_A of **22** in $CDCl_3$ appears as a doublet at δ 5.00 ppm, whereas for **24** it appears at δ 4.63 and for **25** at δ 4.45. Proton H_A of the bicyclic system **22** is forced into the plane of the aromatic ring owing to steric interactions between the two phenolic substituents and the *N*-methyl and isopropenyl groups, and is therefore deshielded relative to the tricyclic systems **24** and **25** in which H_A cannot be in the plane of the ring. Similar variations in field effects were observed in the cyclization of cannabidiol to Δ^1-THC.[2]

Methylation of the trans lactam **25** with methylmagnesium bromide in tetrahydrofuran led to a mixture of the carbinolamine **26** and enamine **27**. The carbinolamine **26** could be isolated in 14% yield. The corresponding amino aldehyde and "enamine plus water" structures were ruled out owing to the absence of aldehyde or enamine double-bond absorbance in the solid-state ir spectrum. The spontaneous dehydration of **26** in $CDCl_3$ to give **27** could be followed by nmr. This facile dehydration was also evident in the electron impact mass spectrum of **26**, which was essentially identical with that of the enamine **27**. Pure **27** in practice was obtained by stirring the mixture of **26** and **27** in methylene chloride over molecular sieves. In this way, the enamine **27** was prepared in 81% yield. Addition of D_2O to $CDCl_3$ solutions of **27** resulted in the disappearance of the olefinic proton H_E and olefinic methyl group in the nmr spectrum.

The enamine **27** was subjected to catalytic hydrogenation in acetic acid over 5% palladium on carbon. The nmr spectrum, high-resolution chemical ionization mass spectrum, and combined gas chromatography–electron impact mass spectrum indicated that the isolated oil was a 3:1 mixture of diastereomeric amines **4** and **5**. The signals for the *C*-methyl, *N*-methyl, and H_A protons of the major diastereomer appeared upfield in the nmr spectrum relative to the minor diastereomer. However, the relative configurations of the major and minor diastereomers were not assigned. The ratio of the major to minor diastereomer increased after crystallization from methanol, but complete separation was not attempted.

Experimental Section

All reactions were performed under a nitrogen atmosphere, and solvents were evaporated on a rotary evaporater under vacuum. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nmr spectra were recorded on a JEOL JNM-4H-100 100-MHz instrument and, except where noted, in $CDCl_3$ solvent. Chemical shift values are reported in parts per million relative to TMS as internal standard. Ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Glpc analyses were performed on a Varian Aerograph Model 2100 gas chromatograph equipped with a flame ionization detector using a 6 ft × 0.125 in. column of 3% SE-30 on Chromosorb W, 100–120 mesh. The electron impact mass spectra were recorded on an AEI MS-12 instrument at 70 eV and the chemical ionization mass spectrum was recorded on an AEI MS-901 spectrometer modified for chemical ionization. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

Olivetol Dimethyl Ether (6). A solution of CH_2N_2 (*ca.* 12 g, 0.29 mol) in EtOH–Et_2O (800 ml) was added to a solution of olivetol (18.02 g, 0.10 mol) in Et_2O (50 ml). After standing at room temperature overnight, additional CH_2N_2 (*ca.* 6 g, 0.14 mol) in EtOH–Et_2O (400 ml) was added to the solution. The reaction progress could be followed by glpc analysis (3% SE-30 on Chromosorb W, 100–120 mesh, 150°, 37 ml/min) of the solution, which gave the following retention times: olivetol dimethyl ether, 1 min 59 sec; olivetol monomethyl ether, 2 min 34 sec; olivetol, 3 min 13 sec. The solution was allowed to stand for 3 days before it was concentrated to 100 ml by evaporation of solvent and unreacted CH_2N_2. The solution was washed with 5% NaOH (100 ml) and the aqueous layer was extracted with Et_2O (50 ml). The combined organic layers were washed with H_2O (50 ml) and dried ($MgSO_4$) and the solvent was evaporated. The residue was distilled at 103° (0.05 mm)–105° (0.06 mm) to yield olivetol dimethyl ether (15.16 g, 73%): ir ($CDCl_3$) 2920, 1605 (shoulder), 1595, 1460, 1200, 1148, 1067 cm^{-1}; nmr ($CDCl_3$) δ 6.30 (m, 3 aromatics), 3.71 (s, 2 OCH_3), 2.52 (br t, benzylic CH_2), 1.72–1.15 (m, 6 methylene), 0.88 (br t, terminal CH_3).

2,6-Dimethoxy-4-*n*-amylbenzaldehyde (8).[8] *n*-Butyllithium (9 ml of a 9.7 *M* solution in hydrocarbon, 87 mmol) was added dropwise to an ice-cold, stirred solution of olivetol dimethyl ether (13.54 g, 65 mmol) in Et_2O (45 ml). After stirring at room temperature for 16 hr a solution of *N*-methylformanilide (14.87 g, 110 mmol) in Et_2O (45 ml) was added dropwise to the ice-cold reaction mixture. The mixture was stirred at room temperature for 2 hr before dropwise addition of 3% aqueous H_2SO_4 (45 ml) to the suspension. The organic phase was separated and the aqueous phase was washed with Et_2O (2 × 45 ml). The solvent was evaporated from the combined, dried (Na_2SO_4) organic layers and the residue was distilled. The aldehyde was collected at 149–153° (0.2 mm) [lit.[8] bp 148–152° (0.3 mm)] as a yellow oil (12.78 g, 83%): ir ($CDCl_3$) 2950, 1675 cm^{-1} (C=O); nmr δ 10.44 (s, CHO), 6.39 (s, 2 aromatics), 3.87 (s, 2 OCH_3), 2.60 (br t, benzylic CH_2), 1.80–1.10 (m, 6 H, amyl methylene), 0.92 (br t, terminal CH_3).

2,6-Dimethoxy-4-*n*-amylbenzylidenemethylamine (9). Methylamine (4.29 g, 0.138 mol) was dissolved in a solution of the aldehyde **8** 29.48 g, 0.125 mol) in benzene (50 ml) in the presence of molecular sieves (3A, 20 g) with occasional stirring. After 30 min, the sieves were filtered off and washed with benzene (2 × 50 ml). Evaporation of solvent from the filtrate left the imine (31.07 g, 100%) as a pale yellow oil. The analytical sample was prepared by evaporative distillation at 80° (3 μ): ir (thin film) 2915, 1645 cm^{-1} (C=N); nmr δ 8.58 (q, J = 1.5 Hz, imino H), 6.38 (s, 2 aromatics), 3.82 (s, 2 OCH_3), 2.58 (br t, benzylic CH_2), 2.52 (d, J = 1.5 Hz, NCH_3), 1.80–1.10 (m, 6 H, amyl methylene), 0.90 (br t, terminal CH_3).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 71.99; H, 9.16; N, 5.53.

***trans*-1-Methyl-5-carboxy-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (11).** The imine **9** (15.91 g, 63.8 mmol) and glutaric anhydride (7.28 g, 63.8 mmol) were heated in refluxing xylene (15 ml) for 30 min. The reaction mixture was cooled to room temperature and extracted with 5% aqueous $NaHCO_3$ (200 + 100 ml). The combined aqueous layers were acidifed to pH 1 with concentrated H_2SO_4 and the resulting suspension was extracted with Et_2O (2 × 100 ml). The combined, dried ($MgSO_4$) Et_2O layers were concentrated to 100 ml and the suspension was stored at 1° overnight before filtration of the colorless solid (11.20 g, 48%). The only detectible (by nmr) impurity proved to be a trace of Et_2O which could not be completely removed at 25° (0.04 mm) overnight. The analytical sample was prepared by heating a sample (36.5 mg) at 98° for 10 min, during which time the sample melted, Et_2O vapor evolved, and the pure solid (34.8 mg) crystallized from the melt: mp 144–145°; ir ($CDCl_3$) 2925, 1710 (carboxyl C=O) 1610 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 9.68 (s, COOH, exchangeable with D_2O), 6.36 (s, 2 aromatics), 5.44 (d, J = 7 Hz, H_A), 3.76 (s, 2 OCH_3), 3,13 (m, H_B), 2.67 (s, NCH_3), 2.58 (m, benzylic CH_2 and $COCH_2$), 2.13 (m, $COCH_2CH_2$), 1.80–1.16 (m, 6 H, amyl methylene), 0.91 (br t, terminal CH_3); electron impact mass spectrum *m/e* (rel intensity) 363 (19), 318 (12), 307 (28), 261 (14), 260 (58), 250 (22), 249 (20), 248 (100), 234 (10), 219 (16).

Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.89; H, 7.94; N, 3.81.

***cis*-1-Methyl-5-carboxy-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (10).** The solvent was evaporated from the solution left after filtration of the trans diastereomer **11** and the residue was recrystallized four times from Me_2CO–Et_2O to yield the pure cis diastereomer (0.12 g, 0.5%): mp 155–155.5°; ir (KBr) 2910, 1735 (carboxylic acid C=O), 1625 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 10.28 (s, COOH, exchangeable with D_2O), 6.32 (s, 2 aromatics), 5.40 (d, J = 5 Hz, H_A), 3.68 (s, 2 OCH_3), 3.18 (m, H_B), 2.74 (s, NCH_3), 2.70–2.02 (m, benzylic CH_2 and $COOCH_2CH_2$), 1.90–1.20 (m, 6 H, amyl methylene), 0.91 (br t, terminal CH_3); electron impact mass spectrum *m/e* (rel intensity) 363 (20), 307 (28). 261 (21), 260 (83), 250 (24), 249 (25), 248 (100), 234 (10), 219 (14).

Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8,04; N, 3.85. Found: C, 66.27; H, 7.88; N, 3.95.

***trans*-1-Methyl-5-methoxycarbonyl-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (14).** An excess of CH_2N_2 in EtOH–Et_2O was added to the trans acid **11** (3.64 g, 10 mmol). Evapora-

tion of solvent from the solution left the ester as a viscous oil (3.78 g, 100%). The analytical sample was prepared by evaporative distillation at 110° (75 μ): ir ($CDCl_3$) 2945, 1735 (ester C=O), 1625 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 6.38 (s, 2 aromatics), 5.36 (d, J = 8 Hz, H_A), 3.78 (s, 2 OCH_3), 3.61 (s, $COOCH_3$), 3.13 (m, H_B), 2.63 (s, NCH_3), 2.49 (m, benzylic CH_2 and $COCH_2$), 2.09 (m, $COCH_2CH_2$), 1.82–1.29 (m, 6 H, amyl methylene), 0.91 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 377 (30), 321 (24), 318 (14), 260 (35), 250 (21), 249 (18), 248 (100), 192 (23).

Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.77; H, 8.22; N, 3.49.

***cis*-1-Methyl-5-methoxycarbonyl-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (16).** An excess of CH_2N_2 in EtOH–Et_2O was added to the cis acid **10** (727 mg, 2 mmol). Evaporation of solvent from the filtered solution left the cis ester as a colorless, viscous oil (640 mg, 85%). The analytical sample was obtained by evaporative distillation at 110° (10 μ): ir ($CDCl_3$) 2915, 1735 (ester C=O), 1650 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 6.36 (s, 2 aromatics), 5.35 (d, J = 5 Hz, H_A), 3.74 (s, 2 OCH_3), 3.51 (s, $COOCH_3$), 3.19 (m, H_B), 2.73 (s, NCH_3), 2.53 (m, benzylic CH_2 and $COCH_2CH_2$), 1.92–1.20 (m, 6 H, amyl methylene), 0.92 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 377 (30), 321 (25), 318 (10), 261 (14), 260 (63), 250 (28), 249 (19), 248 (100), 235 (10), 219 (15), 192 (35).

Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.52; H, 8.26; N, 3.78.

***trans*-1-Methyl-5-carboxy-6-(2,6-dihydroxy-4-*n*-amylphenyl)-2-piperidone (18).** A solution of the trans acid **11** (6.00 g, 16.5 mmol) in CH_2Cl_2 (60 ml) was added dropwise to a stirred solution of BBr_3 (25.10 g, 100 mmol) in CH_2Cl_2 (80 ml) at 0°. After stirring for 48 hr at room temperature, H_2O (250 ml) and Et_2O (600 ml) were added slowly to the solution at 0°. The organic phase was separated and dried (Na_2SO_4) and the solvent was evaporated. The residue (6.24 g) was dissolved in acetone (10 ml), and Et_2O (20 ml) was added to the filtered solution. The diphenol **18** crystallized from the solution as a colorless solid (2.10 g, 38%), mp 195° dec. The analytical sample was recrystallized from aqueous EtOH: mp 203° dec; ir (KBr) 2910, 1700 (carboxyl C=O), 1585 cm^{-1} (lactam C=O); nmr ($CDCl_3$–pyridine-d_5, 3:1) δ 6.41 (s, 2 aromatics), 5.64 (d, J = 7 Hz, H_A), 3.55 (m, H_B), 2.88 (s, NCH_3), 3.20–2.00 (m, $COCH_2CH_2$), 2.40 (br t, benzylic CH_2), 1.85–1.10 (m, 6 H, amyl methylene), 0.80 (br t, terminal methyl); electron impact mass spectrum m/e (rel intensity) 335 (15), 317 (20), 291 (22), 260 (14), 259 (38), 258 (100), 235 (10), 232 (14), 230 (14), 219 (20), 218 (18), 217 (26), 204 (21), 202 (42), 124 (88).

Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.53; H, 7.50; N, 4.24.

1-Methyl-2,5-dioxo-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-10-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (19). A mixture of the diphenol **18** (1585 mg, 4.73 mmol) and DCC (976 mg, 4.73 mmol) was heated in refluxing THF (20 ml) with stirring for 2.5 hr. The suspension was stirred under nitrogen for an additional 24 hr before filtration of the DCU. Evaporation of the solvent from the filtrate left the lactone as a colorless solid (1343 mg, 89%), mp 177–180°. The analytical sample was recrystallized once from benzene and twice from Me_2CO: mp 174–175°; ir ($CDCl_3$) 2920, 1775 (lactone C=O), 1620 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 8.66 (br, OH), 6.65 (d, J = 1.5 Hz, 1 aromatic), 6.51 (d, J = 1.5 Hz, 1 aromatic), 4.60 (d, J = 13 Hz, H_A), 3.25 (m, H_B), 3.20 (s, NCH_3), 3.05–2.10 (m, $COCH_2$), 2.55 (t, benzylic CH_2), 1.92 (m, $COCH_2CH_2$), 1.80–1.12 (m, 6 H, amyl methylene), 0.91 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 317 (31), 259 (34), 258 (100), 202 (35), 201 (11), 188 (24).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.35; H, 7.24; N, 4.62.

***trans*-1-Methyl-5-(2-hydroxyisopropyl)-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (20).** A solution of the trans ester **14** (7.28 g, 19.3 mmol) in Et_2O (100 ml) was added dropwise to a stirred solution of CH_3MgBr (26 ml of a 3 M solution, 78 mmol) in Et_2O at 0°. The mixture was allowed to stand at room temperature for 2 hr before it was again cooled in an ice bath, following which saturated aqueous NH_4Cl (100 ml) was added to the suspension. The white solid was filtered from the organic layer, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 100 ml). The white solid was added to the combined organic layers and the volume of the suspension was reduced to 25 ml. The suspension was stored at 0° overnight before filtration of the tertiary alcohol **20**, obtained as a colorless solid (6.07 g, 83%), mp 111–113°. The analytical sample was recrystallized from Me_2CO–Et_2O: mp 114–114.5°; ir ($CDCl_3$) 2930, 1625 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 6.38 (s, 2 aromatics), 4.97 (d, J = 8 Hz, H_A), 3.81 (s, 2 OCH_3), 2.90–2.38 (m, benzylic CH_2 and $COCH_2$), 2.55 (s, NCH_3), 2.27 (s, OH, exchangeable with D_2O, 2.05 (m, $COCH_2CH_2$), 1.80–1.15 (m, 6 H, amyl methylene), 1.20 (s, *gem*-dimethyl), 0.90 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 377 (15), 349 (20), 344 (39), 330 (99), 328 (79), 323 (16), 321 (19), 318 (29), 316 (15), 274 (20), 261 (22), 260 (100), 250 (32), 248 (58), 219 (18), 200 (19).

Anal. Calcd for $C_{22}H_{35}NO_4$: C, 69.99; H, 9.34; N, 3.71. Found: C, 69.84; H, 9.12; N, 3.76.

***trans*-1-Methyl-5-isopropenyl-6-(2,6-dihydroxy-4-*n*-amylphenyl)-2-piperidone (22).** A solution of BBr_3 (12.53 g, 50 mmol) in CH_2Cl_2 (40 ml) was added dropwise to a stirred solution of the trans dimethyl ether **20** (3.77 g, 10 mmol) in CH_2Cl_2 (40 ml) at 0°. After stirring for 2 days at room temperature, H_2O (150 ml) was added dropwise followed by Et_2O (300 ml). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 150 ml). The solvent was evaporated from the combined, dried ($MgSO_4$) organic layers to leave a glassy residue (4.52 g) containing the tertiary bromide **21**. This residue was boiled in EtOH (50 ml) for 30 min. The solution was cooled to room temperature before addition of H_2O (50 ml) and Et_2O (50 ml). The organic layer was separated and the aqueous layer was extracted with Et_2O (50 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic layers left the crude olefin **22** as a glassy residue (3.05 g). Crystallization from Et_2O–pentane (15 + 5 ml) afforded a solid (0.96 g, 29%), mp 177–183°. The analytical sample was recrystallized from aqueous EtOH: mp 193–194°; nmr ($CDCl_3$–pyridine-d_5, 1:1) δ 9.58 (br, 2 OH, exchangeable with D_2O), 6.45 (s, 2 aromatics), 5.31 (d, J = 9 Hz, H_A), 4.83 (s, 1 olefinic H), 4.73 (s, 1 olefinic H), 3.41 (m, H_B), 2.93 (s, NCH_3), 2.64 (m, $COCH_2$), 2.41 (br t, benzylic CH_2), 1.95 (m, $COCH_2OH_2$), 1.83 (s, olefinic CH_3), 1.72–1.10 (m, 6 H, amyl CH_2), 0.79 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 331 (65), 317 (12), 316 (50), 259 (18), 258 (10), 246 (29), 245 (14), 231 (20), 222 (100), 221 (62), 220 (19).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.32; H, 8.44; N, 4.10.

1,5,5-Trimethyl-2-oxo-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-10-hydroxy-*cis*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (24). A solution of the olefin **22** (332 mg, 1 mmol) in CF_3COOH (5 ml) was heated at reflux for 1.5 hr. Evaporation of solvent left an orange oil which was dissolved in Et_2O (20 ml). The solution was washed with 5% aqueous $NaHCO_3$ (20 ml). Evaporation of solvent from the dried ($MgSO_4$) organic layer left a glass, which crystallized on trituration with Et_2O (2 ml) as a colorless solid (113 mg, 34%), mp 158–160°. Recrystallization from MeOH (1 ml) provided the analytical sample as colorless needles: mp 169–170°; ir (KBr) 2920, 1625 cm^{-1} (lactam C=O); nmr δ 8.88 (s, OH), 6.37 (d, J = 1.5 Hz, 1 aromatic), 6.22 (d, J = 1.5 Hz, 1 aromatic), 4.63 (d, J = 5 Hz, H_A), 3.00 (s, NCH_3), 2.62–1.90 (m, benzylic CH_2 + $COCH_2CH_2$), 1.80–1.15 (m, 6 H, amyl methylene), 1.33 (s, CH_3), 1.19 (s, CH_3), 0.87 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 331 (14), 317 (22), 316 (100).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.43; H, 8.73; N, 4.42.

1,5,5-Trimethyl-2-oxo-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-10-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (25). To a solution of the crude, glassy olefin **22** [3.05 g, prepared from 3.77 g (10 mmol) of **20**] in CH_2Cl_2 (150 ml) was added BF_3–Et_2O (30 ml). The solution was left standing in a sealed flask for 21 hr before addition of H_2O (150 ml). The organic layer was separated, washed with 5% aqueous $NaHCO_3$ (150 ml), and then dried ($MgSO_4$). Evaporation of solvent left a solid residue (3.00 g), mp 157–168°, containing **22** and **25** in a 1:4 ratio, respectively. The solid was dissolved in 5% aqueous NaOH (150 ml) and the purple solution was added to Et_2O (150 ml) in a separatory funnel. The mixture separated into three phases. The deep purple, oily middle layer was separated and dissolved in H_2O (50 ml), and the solution was acidified (pH 1) with concentrated H_2SO_4. The solid precipitate was filtered off and recrystallized from MeOH (8 ml) to yield analytically pure product (0.82 g, 25% from **20**): mp 227–228°; ir (KBr) 2910, 1625 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 9.27 (s, OH, exchangeable with D_2O), 6.38 (d, J = 1.5 Hz, 1 aromatic), 6.29 (d, J = 1.5 Hz, 1 aromatic), 4.45 (d, J = 10 Hz, H_A), 2.86 (s, NCH_3), 2.68 (m, H_B, $COCH_2$), 2.47 (br t, benzylic CH_2), 1.96 (m, $COCH_2CH_2$), 1.78–1.10 (m, 6 H, amyl methylene), 1.36 (s, CH_3), 0.88 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 331 (13), 317 (22), 316 (100); high resolution chemical ionization mass spectrum, 332.2219 (calcd for $C_2OH_{30}NO_3$, 332.2226).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.61; H, 9.02; N, 4.21.

1,2,5,5-Tetramethyl-2,10-dihydroxy-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (26). Methylmagnesium bromide (2 ml of a 3 *M* solution in Et_2O, 6 mmol) was added slowly to a solution of **25** (332 mg, 1 mmol) in THF (10 ml). The solution was heated at reflux for 24 hr. The solution was cooled to 0° before addition of saturated aqueous NH_4Cl (10 ml). The organic phase was separated and the aqueous phase was washed with Et_2O (2 × 10 ml). Evaporation of solvent from the combined organic layers left a semisolid residue which was triturated with Et_2O (2 ml). The colorless carbinolamine (49 mg, 14%) was filtered and washed with H_2O (2 × 1 ml) and Et_2O (1 ml): mp 101° dec; nmr ($CDCl_3$) δ 6.23 (d, *J* = 1 Hz, 1 aromatic), 6.18 (d, *J* = 1 Hz, 1 aromatic), 4.67 (br, H_A), 2.47 (br t, benzylic CH_2), 2.25 (s, NCH_3), 2.15–1.05 (br, H_B, $COCH_2CH_2$, 6 amyl methylene), 1.58 (s, C-2 CH_3), 1.38 (s, C-5 CH_3), 1.17 (s, C-5 CH_3), 0.88 (br t, terminal CH_3); electron impact mass spectrum *m/e* (rel intensity) 329 ($M^+ - H_2O$, 98), 328 (12), 315 (23), 314 (88), 301 (19), 283 (18), 259 (13), 243 (15), 232 (12), 231 (69), 174 (19), 150 (22), 84 (100).

Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.85; H, 9.81; N, 4.24.

Evaporation of solvent from the filtrate left the crude enamine **27** (199 mg, 60%) as a light amber oil.

1,2,5,5-Tetramethyl-1,4,4a,10b-tetrahydro-8-*n*-amyl-10-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (27). Methylmagnesium bromide (10 ml of a 3 *M* solution in Et_2O, 30 mmol) was added slowly to a solution of **25** (1.66 g, 5 mmol) in THF (50 ml). The solution was heated at reflux for 24 hr. The clear solution was cooled to 0° before addition of saturated aqueous NH_4Cl (50 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 50 ml). Evaporation of solvent from the combined, dried (Na_2SO_4) organic phases left a semisolid residue (1.65 g), which was dissolved in CH_2Cl_2 (50 ml). The solution was stirred over molecular sieves (3A, 10 g), for 4 hr. The sieves were filtered off and washed with CH_2Cl_2 (10 ml). Evaporation of solvent from the filtrate left the enamine as a light amber oil (1.34 g, 81%). The analytical sample was evaporatively distilled at 108° (0.1 mm): $n^{24}D$ 1.5379; ir (thin film) 1660 cm^{-1} (enamine C=C); nmr ($CDCl_3$) δ 6.28 (d, *J* = 1.5 Hz, 1 aromatic), 6.23 (d, *J* = 1.5 Hz, 1 aromatic), 5.05 (m, H_E, $t_{1/2}$ for D_2O exchange *ca.* 11 hr), 3.92 (d, *J* = 10 Hz, H_A), 2.49 (br t, benzylic CH_2), 2.25 (s, NCH_3), 1.99 (m, $H_{B,C,D}$), 1.84 (s, C-2 CH_3, $t_{1/2}$ for D_2O exchange *ca.* 40 min), 1.72–1.17 (m, 6 H, amyl methylene), 1.40 (s, C-5 CH_3), 1.13 (s, C-5 CH_3), 0.89 (br t, terminal CH_3); electron impact mass spectrum *m/e* (rel intensity) 329 (88), 328 (13), 315 (19), 314 (70), 301 (10), 300 (22), 283 (14), 259 (15), 243 (13), 232 (12), 231 (68), 174 (19), 150 (22), 84 (100).

Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.64; H, 9.34; N, 4.26.

1,2,5,5-Tetramethyl-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-1-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (4 and 5). A solution of the enamine **27** (637 mg, 1.93 mmol) in acetic acid (90 ml) was hydrogenated over 5% Pd/C (150 mg) at 35 psi for 24 hr. The catalyst was filtered off and the solvent was sublimed at 16° (0.1 mm) from the frozen solution; aqueous 5% NaOH (30 ml) and Et_2O were added to the residue. The organic layer was separated and the aqueous layer was extracted with Et_2O (30 ml). Evaporation of solvent from the combined, dried (Na_2SO_4) organic layers left a diastereomeric mixture of amines **4** and **5** as an oil (537 mg, 84%). The ratio of major to minor diastereomer was 3:1 (by nmr). Recrystallization from MeOH (2 ml) gave a solid (380 mg, mp 72–81°). The ratio of major to minor diastereomer in the solid was 6:1 (by nmr). On glpc analysis (3% SE-30 on Chromosorb W, 155°, 37 ml/min), the solid produced two peaks with retention times of 42.5 (minor) and 45.0 min (major). When subjected to glpc–mass spectrum, these glpc peaks corresponded to the following mass spectra: minor diastereomer *m/e* (rel intensity) 331 (100), 316 (38), 314 (19), 285 (19), 275 (35), 260 (19), 259 (92), 245 (37), 231 (67); major diastereomer *m/e* (rel intensity) 331 (99), 316 (38), 314 (22), 285 (22), 275 (27), 260 (22), 259 (100), 245 (36), 231 (60); high resolution chemical ionization mass spectrum, 322.2581 (calcd for $C_{21}H_{34}NO_2$, 322.2589).

Registry No.—**4**, 51014-90-5; **5**, 51064-86-9; **6**, 22976-40-5; **8**, 3410-84-2; **9**, 51015-16-8; **10**, 51014-91-6; **11**, 51014-92-7; **14**, 51014-93-8; **16**, 51014-94-9; **18**, 51014-95-0; **19**, 51014-96-1; **20**, 51014-97-2; **22**, 51014-98-3; **24**, 51014-99-4; **25**, 51015-00-0; **26**, 51015-17-9; **27**, 51015-01-1; olivetol, 500-66-3.

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D-Homoandrostanes. I. Preparation and Properties of *D*-Homo-5α-androstan-1-, -2-, -3-, and -4-ones[1a]

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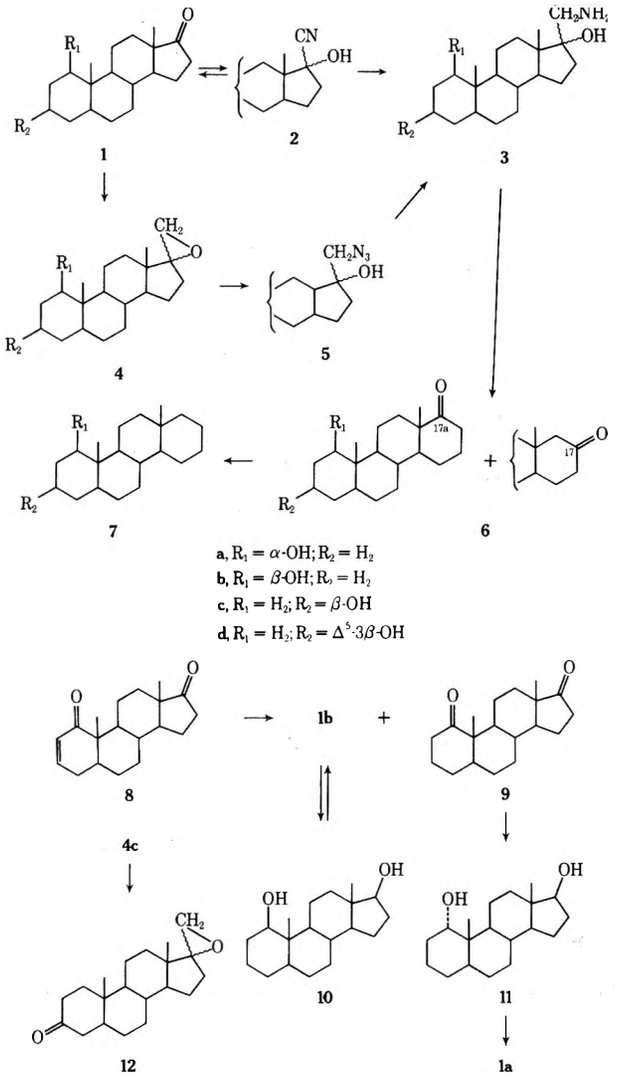
The synthesis of the four *D*-homo ketones from commercially available 17-oxo steroids is described. A key step in an alternate synthesis of the 1-ketone is a selective silver carbonate oxidation of a 17β-hydroxyl group in the presence of 1-hydroxyl groups in the 5α-androstane series. Sodium borohydride reduction of the ketones gives similar results to the analogs, while the almost exclusive 1α-alcohol formation can be explained in terms of "steric intermediate control."

Previous studies on monofunctional *D*-homoandrostanes have been concerned with those possessing functional groups in the expanded terminal ring.[2] In connection with other work we required the title compounds, thus excluding many *D*-homo rearrangements[3] as potential synthetic methods, as the products contain undesired groupings, such as alkyl groups, in the D ring. The earlier method[4] of expanding androstan-17-ones (**1**) has several disadvantages, discussed previously,[5] such as the reversible formation of cyanohydrins **2**, using potentially hazardous cya-

Scheme I



nides, and the difficulties encountered in their reduction to hydroxyamines **3**. Kirk and Wilson[5] also reported a more convenient synthesis *via* C(17)-spirooxiranes **4** and hydroxy azides **5**, which we have adopted in our preparation of the desired ketones.

Although the spirooxiranes **4**, formed from the 17-keto compounds **1**, were used directly for the subsequent step, an attempt was made to determine the epimeric composition of the oxiranes **4c** spectrographically, but overlapping of the methyl signals in the nmr necessitated an oxidation of the 3β-hydroxyl group under basic conditions[6] to the epoxy ketone **12**, in which it was estimated that the β-spirooxirane predominated in the ratio 3:1. The conversion of the 1-hydroxy 17-ketones **1a** and **b** could not be achieved even by prolonged contact with an excess of reagents. The reasons for this are not clear; in other work[7] we found that 5α-androstan-17-one could not be converted completely. The most reproducible method of reducing the hydroxy-azides **5** utilized zinc–hydrochloric acid, but, in one case of extended reaction time with zinc–acetic acid and **5d**, copious amounts of *D*-homo ketones were obtained together with hydroxyamine **3d** (Scheme I).

Huang-Minlon reduction and subsequent oxidation of 3β-hydroxy-*D*-homo-5α-androstan-17A- and -17-one (**6c**) gave *D*-homo-5α-androstan-3-one (**13**).

Like the 3-ketone, *D*-homo-5α-androstan-1-one (**18**) was obtained by the same process from the ring expanded products, **6a** and **b**, derived from 1α- (**1a**) or 1β-hydroxy-5α-androstan-17-one (**1b**), the preparation of which we described in an earlier communication.[8] The ease of selective oxidation[9] of the 17-hydroxyl group in 5α-androstane-1α,17β-diol (**11**), prompted us to test it on the 1β,17β-diol (**10**) where it proceeded smoothly.[10]

At the same time we considered obtaining the 1-ketone from the 3-ketone by the established procedures[11] (**7c** → **18**). We were unable to convert the Δ²-1α-ol **16** directly into the desired ketone by hydrogenation with 10% palladium on charcoal; the Δ²-1,17-dione **8** likewise was unchanged under the same conditions. As in the androstane series (**8** → **1b** + **9**),[8] the oxidation product **17** of the Δ²-1α-ol was hydrogenated, forming a 1:1 mixture of *D*-homo-5α-androstan-1-one (**18**) and the corresponding 1β-alcohol **7b** (Scheme II). Although variation in quantity of catalyst and reaction time did not lead to increased alcohol formation, it appears to be one of the few methods of obtaining reasonable amounts of 1β-orientated alcohols.

The available methods of converting 3- to 2-keto steroids have been summarized recently by authors[12] interested in the transposition of oxo groups with adjacent methylene groups. The intermediates were not purified until the final stages of the synthesis (**19** → **23**), which is an alternative to that previously reported,[13] where the 3-acetoxy 2-ketone **22** was obtained directly from 2α-acetoxy-*D*-homo-5α-androstan-3-one.

The first objective in the synthesis of *D*-homo-5α-androstan-4-one (**29b**) was *D*-homoandrost-4-ene (**27**), and, although lithium aluminum hydride–aluminum chloride has been used for the reduction of androst-4-en-3-one,[14] conversion to the thioketal **26** and desulfurization with sodamide in liquid ammonia was more effective. Hydroboration of **27** gave an alcohol mixture **28**, which was oxidized directly to a mixture of **29b** and the 5β-epimer **29a**, the former predominating as in the normal series.[15]

Scheme II

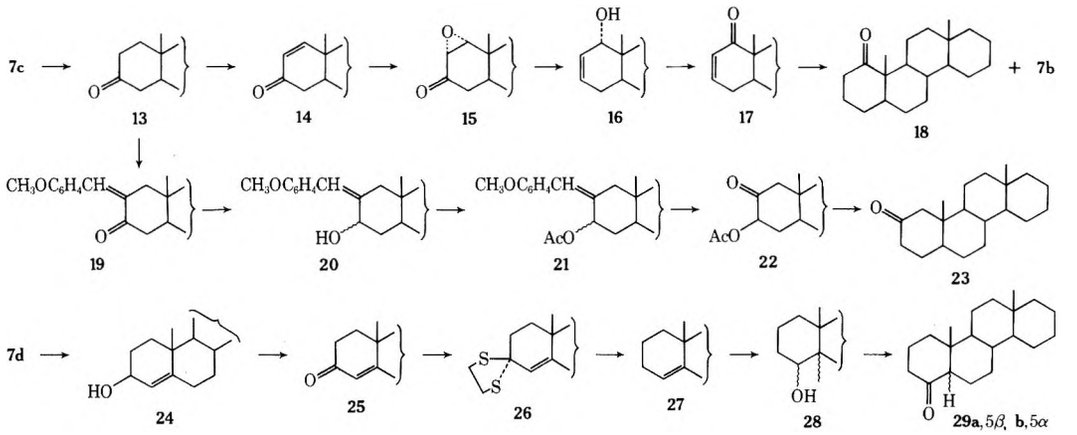


Table I
Borohydride Reduction Products (%) from *D*-Homo Ketones: Comparison with Normal Series

Ketone position	*D*-Homo alcohol		Androstane series		Ref
	Axial	Equatorial	Axial	Equatorial	
1	*ca.* 100	None detected	*ca.* 100	None detected	
2	66	34	68	32	*a*
3	20	80	14	86	*b*
4	83	17	90	10	*a*

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Reduction of the Title Ketones. The results of borohydride reduction are presented in Table I; those for the 2-, 3-, and 4-ketones are very similar to the values for the normal series. It is interesting to compare the metal hydride reduction of 1-ketones with the similarly situated *D*-homo 17A-ketones which yield the more stable 17Aβ-alcohol as the major product.[2b] Inspection of models indicates that the only appreciable difference between the surroundings of the two carbonyl groups is the close proximity of C(11) to C(1). Since reagent approach occurs from the α side of the molecule in the 17A-ketone, then it should approach from that side in the 1-ketone, as access is even more limited on the β side by the C(11) hydrogens. That the reagent evidently attacks from the β face must be due to steric compression between the 11α hydrogen and any bulky borohydride–carbonyl complex as it is forced into the 1β position. Hence a less desirable approach from the β direction is aided by the relative ease with which the intermediate complex can assume the 1α configuration. Thus the 1-ketone is a special case, in which the controlling factor is not "steric approach control"[16] but rather what we term "steric intermediate control."

Experimental Section[17]

Melting points determined with a Reichert apparatus are uncorrected. Infrared spectra were obtained as chloroform solutions with a Perkin-Elmer 257. Nmr spectra were run on a Varian S-60T, as deuteriochloroform solutions containing tetramethylsilane. Singlets are undesignated but the notation d = doublet, t = triplet, q = quartet, sx = sextet, m = multiplet is used to describe the multiplicity of more complex signals, and $W_{1/2}$ = width at half peak height. Thin layer chromatography, tlc, and preparative layer chromatography, plc, employed Camag silica gel type D, in thicknesses of 0.25 and 1 mm, respectively. In plc the samples were applied by an automatic applicator,[18] in amounts of 50 to 80 mg per 20 × 20 cm plate, and developed with mixtures of acetone–petroleum ether or ethyl acetate–benzene. The products isolated are described in order of increasing polarity. The elemental analyses were obtained with a Hewlett-Packard 185B, or determined by Dr. F. B. Strauss, Oxford. "Extraction" indicates chloroform extraction, followed by washing with sodium carbonate solution where appropriate, drying, etc., unless otherwise indicated.

5α-Androstane-1α,17β-diol (11) and 5α-Androstane-1β,17β-diol (10). 5α-Androstane-1,17-dione (**9**,[19] 174 mg) was stirred with 150 mg of sodium borohydride in 10 ml of methanol for 1 hr. Addition of water and extraction gave the diol **11** (163 mg): nmr τ 9.25 (CH_3-18), 9.18 (CH_3-19), 6.30 (m, $W_{1/2}$ = 12 Hz, H-1, H-17 overlapped).

The 1β-hydroxy 17-ketone[8] **1b** (50 mg) was treated similarly with 42 mg of sodium borohydride in 3 ml of methanol giving the 1β,17β-diol (47 mg): mp 186–188° from acetone–hexane; ν_{max} 3610 cm^{-1}; nmr τ 9.25 (CH_3-18), 9.14 (CH_3-19), 6.63 (q, *J* = 10, 5 Hz, H-1), and 6.37 (t, *J* = 8, 8 Hz, H-17) overlapped.

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.0; H, 11.0. Found: C, 78.2; H, 11.1.

1α-Hydroxy-5α-androstan-17-one (1a) and 1β-Hydroxy-5α-androstan-17-one (1b). The crude diol **11** (160 mg) was refluxed with 8.5 g of silver carbonate on Celite[9] in 25 ml of dry toluene for 1 hr, the reaction being monitored by tlc. Filtration of insoluble material, which was washed with acetone, and evaporation gave an oil which was separated by plc into the diketone **9** (10 mg), and hydroxy ketone **1a** (112 mg), mp[8] 152–153°.

Similarly the diol **10** (30 mg) was refluxed with 1.5 g of silver carbonate on Celite in 10 ml of toluene for 30 min giving the hydroxy ketone **1b** (22 mg), mp 168°, undepressed on admixture with the hydrogenation product of the endione 8.[8]

Ring A Hydroxy-*D*-homoandrostan-17A- and -17-ones 6. Sodium hydride (50% in oil, 12 g) was washed with dry benzene, and added in portions to a stirred suspension of 25 g of trimethyloxosulfonium iodide in 120 ml of dimethylformamide under nitrogen. After hydrogen evolution, 10 g of 3β-hydroxy-5α-androstan-17-one (**1c**) was added and stirring continued until tlc analysis by green spot formation in iodine vapor, and the lack of carbonyl absorption in the ir, indicated completion of the reaction. Addition of water and extraction with ethyl acetate gave a quantitative yield of solid spirooxiranes **4c:** ν_{max} 3600, 3420, 1023 cm^{-1}; nmr τ 9.16 (CH_3-19 and CH_3-18 of 17α-oxirane), 9.11 (CH_3-18 of 17β-oxirane), 7.43 and 7.13 (2d, *J* = 5 Hz, H-20), 6.45 (m, $W_{1/2}$ = 24 Hz, H-3).

Spirooxirane **4d** was similarly prepared in ca. 98% yield, from 10 g of **1d,** while conversions of 132 mg of **1a** and 167 mg of **1b** resulted in yields of *ca.* 70%, due to incomplete reaction, subsequent separation of product from starting material by plc, and recyclization. **4a:** nmr τ 9.16 (CH_3-19 and CH_3-18 of 17α-epoxide), 9.10 (CH_3-18, β-epoxide), 7.40 and 7.10 (2d, *J* = 5 Hz, H-20), 6.30 (m, $W_{1/2}$ = 7 Hz, H-1). **4b:** nmr τ 9.17 (CH_3-18, α-epoxide), 9.14 (CH_3-19), 9.10 (CH_3-18, β-epoxide), 7.43 and 7.10 (2d, *J* = 5 Hz, H-20), 6.61 (m, $W_{1/2}$ = 18 Hz, H-1). **4d:** ν_{max} 3600, 1615, 1050 cm^{-1}; nmr τ 9.09 (CH_3-19), 8.95 (CH_3-18), 7.30 and 6.90 (2d, *J* = 5 Hz, H-20), 6.50 (m, $W_{1/2}$ = 20 Hz, H-3), 4.63 (m, $W_{1/2}$ = Hz, H-6).

The spirooxiranes **4c** (10 g) were heated at reflux temperature with 10 g of sodium azide and 10 g of boric acid for 4.5 hr. Dilution with water and extraction with ethyl acetate gave a 98% yield of hydroxy azide **5c.** The hydroxy azides **5a, b,** and **d** were similarly prepared. All showed the characteristic azide absorption ν_{max} 2100 cm^{-1}.

The crude hydroxy azide **5c** obtained in the above reaction was dissolved in 150 ml of acetone and 50 ml of concentrated hydrochloric acid, and zinc powder was added in small portions until nitrogen evolution had ceased. The remaining zinc was filtered out and washed with acetone. The combined filtrate and washings were diluted with 500 ml of water and extracted with ether to remove neutral components. The stirred layer was cooled to below 5° and 24 g of sodium nitrite added in portions. The solution was kept at this temperature overnight, before extraction gave 7.3 g of 3β-hydroxy-*D*-homo-5α-androstan-17A- and -17-ones (**6c**): ν_{max} 3600, 1700 cm^{-1}; nmr τ 9.19 (CH_3-19), 8.90 (CH_3-18), 6.42 (m, $W_{1/2}$ = 22 Hz, H-3). Similarly obtained, with corresponding quantities, were 3β-hydroxy-*D*-homoandrost-5-en-17A- and -17-ones (**6d**) [ν_{max} 3600, 1695, 1615 cm^{-1}; nmr τ 8.99 (CH_3-19), 8.87 (CH_3-18), 6.42 (m, $W_{1/2}$ = 19 Hz, H-3), 4.67 (m, $W_{1/2}$ = 8 Hz, H-6) in comparable yield to **6c**], 1β-hydroxy-*D*-homo-5α-androstan-17A- and -17-ones (**6b,** 26 mg) [ν_{max} 1710 cm^{-1}; nmr τ 8.93 (CH_3-18), 9.15 (CH_3-19), 6.53 (m, $W_{1/2}$ = 16 Hz, H-1)], and 1α-hydroxy-*D*-homo-5α-androstan-17A- and -17-ones (**6a,** 29 mg) [ν_{max} 1712 cm^{-1}; nmr τ 9.15 (CH_3-18), 9.01 (CH_3-19), 6.30 (m, $W_{1/2}$ = 5 Hz, H-1)].

17,20-Epoxy-21-nor-17-norpregnan-3-ones (12). A standard Sarrett reaction converted **4c** (1 g) into the epoxy ketones **12** (870 mg): ν_{max} 1710, 1050 cm^{-1}; nmr τ 9.14 (CH_3-18 of α-epoxide), 9.07 (CH_3-18 of β-epoxide), 8.94 (CH_3-19), 7.37 and 7.13 (2d, *J* = 5 Hz, H-20).

Huang-Minlon Reduction of Hydroxy Ketones 6. The usual reaction conditions were used to convert hydroxy ketone **6a** (24 mg) to *D*-homo-5α-androstan-1α-ol (**7a,** 16 mg), hydroxy ketone **6b** (24 mg) to *D*-homo-5α-androstan-1β-ol (**7b,** 17 mg), and hydroxy ketone **6c** (4 g) to *D*-homo-5α-androstan-3β-ol (2.3 g). (See Table II for properties.) Similarly the enol **7d,** recrystallized from methanol (1.8 g), mp 137–138° (lit.[5] 137–139°), was obtained from hydroxy ketone **6d** (2.2 g).

***D*-Homo-5α-androstan-3-one (13).** Oxidation of the 3β-alcohol **7c** (2.2 g) by Jones reagent gave 2.15 g **13,** recrystallized from methanol: mp 167–168° (lit.[20] 168.5–170°); ν_{max} 1700 cm^{-1}; nmr τ 9.14 (CH_3-18), 8.98 (CH_3-19).

***D*-Homoandrost-1-en-3-one (14).** Bromine (284 mg) dissolved in 2 ml of glacial acetic acid was added dropwise to a stirred solution of 445 mg of 3-ketone **13** in 6 ml of acetic acid and 3 drops of

Table II[a]

Registry no.		Anal. found, % C	Anal. found, % H	Mp, °C	C-19	C-18	Nmr, τ, H–C–OH	$W_{1/2}$, Hz
				Alcohol				
51056-93-0	1α	83.0	11.6	128–129	9.22	9.18	6.30	6
51056-94-1	1β	82.7	11.6	109–112	9.18	9.17	6.60	13
51064-96-1	2α	82.6	12.0	145–148	9.21	9.19	6.33	22
51056-95-2	2β	82.9	11.8	153–154	8.98	9.17	5.84	8
51056-96-3	3α			171–174[b]	9.17	9.22	5.97	7
51056-97-4	3β			141–144[c]	9.19	9.19	6.40	24
51056-98-5	4α	82.6	11.9	167–169	9.20	9.19	6.60	18
51056-99-6	4β	82.4	11.5	123	8.95	9.20	6.20	6
				Acetate				
51108-11-3	1α	79.7	10.7	65–67	9.16	9.19	5.16	5
51057-00-2	1β	79.7	10.7	51–52	9.07	9.21	5.40	10
51057-01-3	2α	79.6	11.0	89–91	9.18	9.18	5.16	18
51057-02-4	2β	79.7	11.0	80–81	9.07	9.19	4.93	9
51057-03-5	3α	79.8	11.0	98–104	9.21	9.17	5.00	7
51064-97-2	3β	79.8	10.9	113–117	9.18	9.18	5.31	24
51057-04-6	4α	79.7	10.7	150–153	9.16	9.18	5.24	22
51057-05-7	4β	79.5	10.9	133–135	8.98	9.19	5.10	4

[a] Calcd for $C_{20}H_{34}O$: C, 82.7; H, 11.8, and $C_{22}H_{36}O_2$: C, 79.5; H, 10.9. Acetate protons appear at *ca.* τ 8.0. [b] Lit.[20] mp 168–169°. [c] Lit.[20] mp 143.5°.

48% hydrobromic acid; dilution with water and extraction left 481 mg of a gum which was refluxed in 10 ml of dimethylformamide with 300 mg of lithium carbonate–lithium bromide. Addition of water and extraction gave a gum. Purification by plc yielded **14** (210 mg), recrystallized from methanol: mp 135–138°; ν_{max} 1670 cm^{-1}; nmr τ 9.13 (CH_3-18), 8.97 (CH_3-19), 4.18 (d, J = 10 Hz, H-1), 2.99 (d, J = 10 Hz, H-2).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.9; H, 10.6. Found: C, 83.8; H, 10.6.

1α,2α-Oxido-*D*-homo-5α-androstan-3-one (15). The Δ^1-3-ketone (200 mg), in 5 ml of dioxane was treated with 5 ml of 5% sodium hydroxide solution, and 3 ml of 35% hydrogen peroxide. After 3 hr the solution was diluted with water and extracted continuously giving after plc, 191 mg of white solid, recrystallized from methanol: mp 132–135°; ν_{max} 1710, 875 cm^{-1}; nmr τ 9.14 (CH_3-18 and -19 superimposed), 6.80 (d, J = 4 Hz, H-2), 6.47 (d, J = 4 Hz, H-1).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.2; H, 9.9.

***D*-Homo-5α-androst-2-en-1α-ol (16).** A mixture of 156 mg of epoxide **15** in 3 ml of hydrazine hydrate was heated at 135° for 35 min. Dilution with water and extraction gave 152 mg of solid recrystallized from methanol: mp 96–97°; ν_{max} 3605, 1610 cm^{-1}; nmr τ 9.29 (CH_3-19), 9.17 (CH_3-18), 6.30 (m, $W_{1/2}$ = 7 Hz, H-1), 4.20 (2d superimposed, J = 3 Hz, H-2, and H-3).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.6; H, 10.9.

***D*-Homo-5α-androst-2-en-1-one (17).** Oxidation of allylic alcohol **16** (130 mg) with Jones reagent gave the enone **17**, recrystallized from methanol (123 mg): mp 106–108°; ν_{max} 1673 cm^{-1}; nmr τ 9.15 (CH_3-18), 8.93 (CH_3-19), 4.25 (sx, J = 11, 2, 2 Hz, H-2), 3.35 (m, one coupling of 11 Hz discernible, H-3).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.9; H, 10.6. Found: C, 83.6; H, 10.9.

Catalytic Hydrogenation of Enone 17. The enone (103 mg) was hydrogenated in 8 ml of glacial acetic acid containing 40 mg of Adams catalyst. Filtration and solvent evaporation gave a gum which was separated by plc into the 1β-alcohol **7b** (39 mg), identical with that obtained previously, and *D*-homo-5α-androstan-1-one (**18**, 37 mg): mp 100–102°; ν_{max} 1697 cm^{-1}; nmr τ 9.17 (CH_3-18), 8.84 (CH_3-19).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.3; H, 11.2. Found: C, 83.3; H, 11.0.

2-*p*-Methoxybenzylidene-*D*-homo-5α-androstan-3-yl Acetates (21). The anisylidene alcohols **20** (1.6 g) were acetylated with dehyde, and 5 g of potassium hydroxide in 3 ml of water with 10 ml of ethanol was stirred for 6 hr at room temperature in the dark. Filtration and recrystallization from ethanol gave **19** (1.8 g): mp 206–207°; ν_{max} 1670 cm^{-1}; nmr τ 9.24 (CH_3-19), 9.20 (CH_3-18), 7.20 (CH_3O–), 6.88 (d, J = 15 Hz, H-1), 2.86 (4 H, symmetrical m, C_6H_4–), 2.40 (m, H-olefinic).

Anal. Calcd for $C_{28}H_{38}O_2$: C, 82.7; H, 9.4. Found: C, 82.8; H, 9.4.

2-*p*-Methoxybenzylidene-*D*-homo-5α-androstan-3-ols (20). The anisylidene ketone **19** (1.8 g) was reduced with sodium borohydride as in the first experiment to the anisylidene alcohols (**20** (1.6 g): ν_{max} 3570 cm^{-1}; nmr τ 9.33 (CH_3-19), 9.22 (CH_3-18), 7.03 (d, J = 13 Hz, H-1), 6.21 (s, CH_3O–), 5.83 (m, $W_{1/2}$ = 18 Hz, H-3), 3.43 (m, $W_{1/2}$ = 8 Hz, H-olefinic), 3.06 (4 H, symmetrical m, C_6H_4–).

2-*p*-Methoxybenzylidene-*D*-homo-5α-androstan-3-yl Acetates (21). The anisylidene alcohols **20** (1.6 g) were acetylated with acetic anhydride–pyridine under the usual conditions producing the acetates **21** (1.6 g), ν_{max} 1730 cm^{-1}.

3β-Acetoxy-*D*-homo-5α-androstan-2-one (22). Ozone was passed through a solution of 0.5 g of anisylidene acetate **21** in 34 ml of methanol and 27 ml of ethyl acetate at −70° until a blue color persisted, followed by nitrogen. Glacial acetic acid was added, and after warming to 30°, 10 g of zinc dust was added carefully. The zinc was filtered off and washed with ethyl acetate. Plc of the concentrated filtrate and washings gave the 3β-acetoxy-2-one **22** (186 mg), mp[13] 188–191°.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.5; H, 9.8.

***D*-Homo-5α-androstan-2-one (23).** The acetoxy ketone **22** (80 mg) was refluxed for 3 hr with 6 g of activated zinc in 17 ml of glacial acetic acid. The solution was filtered and the zinc washed with acetic acid. After dilution with water, the combined filtrate and washings were extracted. Separation by plc yielded material of low polarity, probably hydrocarbons, starting material (11 mg), and the ketone **23** (52 mg), mp[13] 160–163°.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.4; H, 11.3.

***D*-Homoandrost-4-en-3-one (25).** Solvent (40 ml) was distilled from a solution of 1.64 g of 3β-hydroxy-*D*-homoandrost-5-ene in 100 ml of dry toluene, using a Dean–Stark apparatus. Cyclohexanone (18 ml) was added and another 15 ml of solvent distilled off, followed by the dropwise addition of 900 mg of aluminum isopropoxide in 20 ml of dry toluene, while simultaneously distilling off 20 ml of solvent. The mixture was cooled and treated with 20 ml of saturated solution of sodium potassium tartrate. The resulting yellow residue was steam distilled and extracted, leaving 1.42 g Δ^4-3-one **25**, recrystallized from methanol: mp 145°; ν_{max} 1670, 1610 cm^{-1}; nmr τ 9.12 (CH_3-18), 8.79 (CH_3-19), 4.34 (H-4).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.9; H, 10.6. Found: C, 83.8; H, 10.5.

Ethylene Thioketal of *D*-Homoandrost-4-en-3-one 26. Boron trifluoride etherate (1 ml) and 2 ml of ethylene thioglycol were added to 1.5 g of enone **25** in 40 ml of glacial acetic acid. After 30 min the precipitate was collected, washed with 80% acetic acid, and dried under vacuum, giving **26** (1.75 g): mp 151° from methanol; ν_{max} 1640, 635 cm^{-1}; nmr τ 9.15 (CH_3-18), 8.97 (CH_3-19), 6.66 [t, J = 2, 2 Hz, (SCH_2–)], 4.53 (H-4).

Anal. Calcd for $C_{22}H_{34}S_2$: C, 72.5; H, 10.0. Found: C, 72.4; H, 9.8.

***D*-Homoandrost-4-ene (27).** The thioketal **26** (730 mg) in 25 ml of dry tetrahydrofuran was added to a stirred solution of sodamide in liquid ammonia during 1 hr at −70°. The usual work-up gave 596 mg of alkene **27** recrystallized from methanol: mp 80–82°; ν_{max} 1640 cm^{-1}; nmr τ 9.17 (CH_3-18), 8.97 (CH_3-19), 4.72

(m, $W_{1/2}$ = 8 Hz, H-4).

Anal. Calcd for $C_{20}H_{32}$: C, 88.2; H, 11.8. Found: C, 88.3; H, 11.7.

Hydroboration of *D*-Homoandrost-4-ene and Subsequent Oxidation. Diborane was bubbled into a solution of 500 mg of alkene in 15 ml of tetrahydrofuran during 1.5 hr. After the excess reagent was destroyed with ice, oxidation (as of **7c**) produced 480 mg of oil separated by plc into *D*-homo-5β-androstan-4-one (**29a**, 78 mg): mp 154–159° from methanol; ν_{max} 1700 cm^{-1}; nmr τ 9.18 (CH_3-18), 8.88 (CH_3-19); a portion sublimed for analysis had mp 166–167° (*Anal.* Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: 83.0; H, 11.2) and *D*-homo-5α-androstan-4-one (**29b**, 105 mg), recrystallized from methanol: mp 122–124°; nmr τ 9.27 (CH_3-19), 9.18 (CH_3-18); ν_{max} 1710 cm^{-1} (*Anal.* Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.5; H, 11.2).

Borohydride Reduction of the Title Ketones and Acetylation of the Alcohols. Similar reduction conditions to those of the first experiment were employed. Except for the 1-ketone which yielded the 1α-alcohol **7a**, all gave mixtures, separated by plc into the components shown in Table I. The acetates were formed under standard conditions, and their properties together with those of the alcohols are presented in Table II. All were recrystallized from methanol.

Registry No.—**1a**, 29220-43-7; **1b**, 42548-29-8; **1c**, 481-29-8; **1d**, 53-43-0; **4a** isomer A, 51057-06-8; **4a** isomer B, 51057-07-9; **4b** isomer A, 51057-08-0; **4b** isomer B, 51057-09-1; **4c** isomer A, 51057-10-4; **4c** isomer B, 4503-01-9; **4d** isomer A, 847-74-5; **4d** isomer B, 847-75-6; **6a** 17-one, 51057-11-5; **6a** 17A-one, 51057-12-6; **6b** 17-one, 51057-13-7; **6b** 17A-one, 51057-14-8; **6c** 17-one, 51057-15-9; **6c** 17A-one, 26729-16-8; **6d** 17-one, 3278-90-8; **6d** 17A-one, 3278-99-7; **9**, 10455-05-7; **10**, 51153-08-3; **11**, 7417-23-4; **12** isomer A, 51057-16-0; **12** isomer B, 51057-17-1; **13**, 39851-65-5; **14**, 51057-18-2; **15**, 51057-19-3; **16**, 51057-20-6; **17**, 51057-21-7; **18**, 51057-22-8; **19**, 51057-23-9; **3α-20**, 51057-24-0; **3β-20**, 51057-25-1; **3α-21**, 51057-26-2; **3β-21**, 51057-27-3; **22**, 39851-67-7; **23**, 39851-68-8; **24**, 51057-28-4; **25**, 51057-29-5; **26**, 51057-30-8; **27**, 51057-31-9; **29a**, 51057-32-0; **29b**, 51057-33-1.

References and Notes

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3-Acyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxides. I. Alkylation, Amination, and Ethoxycarbonylation

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Preparation of ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**2c**) is described. Treatment of **2c** with ammonia gave carboxamide **8**, whose reactions with ethyl chloroformate could be directed to afford either 3-(ethoxycarbonyl)carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**22**), ethyl 3-(ethoxycarbonyl)-carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine-2-carboxylate 1,1-dioxide (**25**), or 2*H*,5*H*-1,3-oxazino[5,6-c][1,2]benzothiazine-2,4(3*H*)-dione 6,6-dioxide (**24a**). Alkylation reactions of **2c** with methyl iodide and 1,2-dibromoethane are compared with those of 3-acetyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2b**). Mass spectral evidence is presented for the assignment of structure **13** to the products of **2b** with ammonia and primary amines.

In 1956, Abe, Yamamoto, and Matsui[1] reported the base-induced rearrangement of *N*-phenacylsaccharin **1a** to 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2a**) (Scheme I). Since then, rearrangements of a wide variety of *N*-β-keto-substituted saccharins have been studied.[2a,b]

Our interest in the chemistry of ring system **2** was stimulated by its apparent polydentate character, which offered potential versatility for preparation of a variety of novel derivatives for pharmacological testing.

We wish to report here and in an accompanying paper[3] our findings with some alkylation and amination reactions carried out on the known 3-acetyl derivative **2b** and the previously unreported ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**2c**).[4]

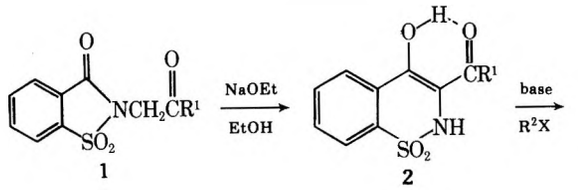
Results and Discussion

Synthesis of ester **2c** was carried out analogously to that reported for ketones **2a**[1] and **2b**;[2a] however, higher base concentration and longer reaction times were required to achieve satisfactory yields.[5]

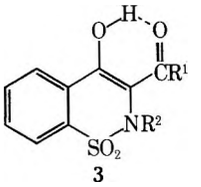
Conventional alkylation reactions of **2a** and **2b** have been shown to occur preferentially at sulfonamide nitrogen.[2a] Ester **2c** behaves similarly, providing alkylated products **3c** and **3d**[6] upon treatment with methyl iodide and ethyl bromoacetate, respectively (Scheme I).

Ketone **2b** and ester **2c** both undergo cycloalkylation when treated with 1,2-dibromoethane. However, the course of these reactions differs, as illustrated in Scheme II. Formation of oxazine **4** from **2b** and azetidine **6** from **2c**

Scheme I



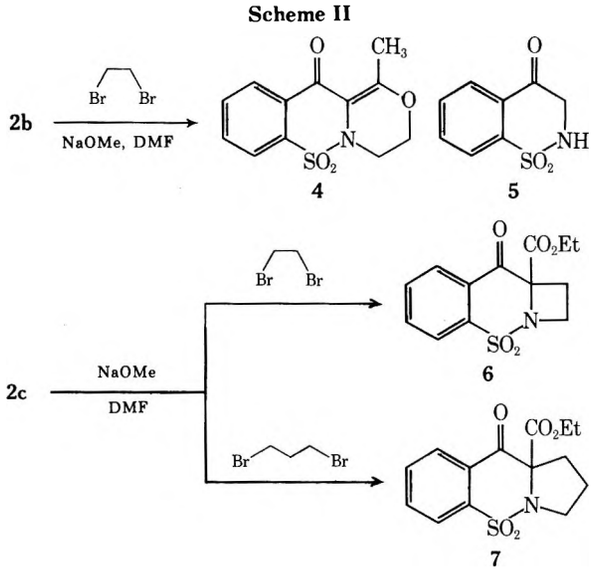
1, 2 R¹
a Ph
b Me
c OEt



3 R¹ R²
a Ph Me
b Me Me
c OEt Me
d OEt CH_2CO_2Et

reflects the enhanced nucleophilic character of the 3-keto oxygen atom as compared to that of the ester carbonyl. When **2c** was allowed to react with 1,3-dibromopropane, pyrrolidine **7**, analogous to **6**, was obtained. Both products **6** and **7** gave negative ferric chloride tests and their uv spectra, unlike that of **4** (Table II), were virtually identical with the published spectrum of 2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide (**5**).[7]

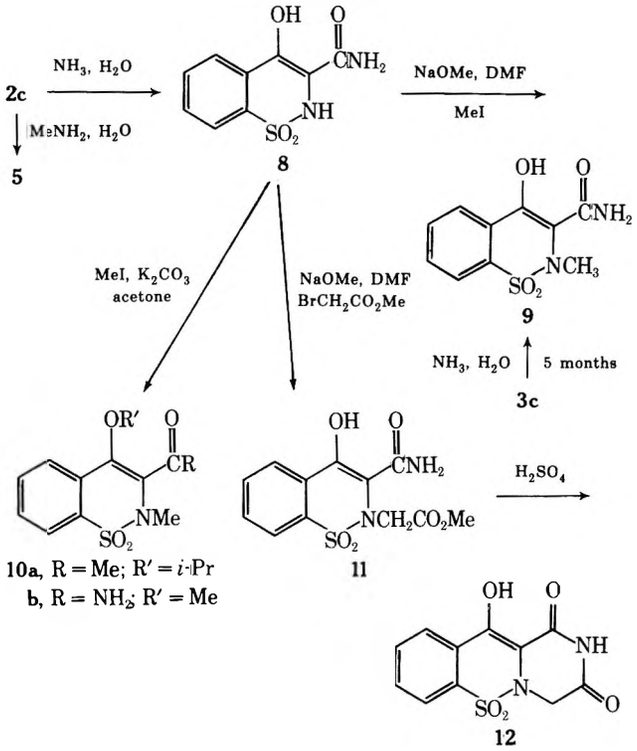
Scheme II



Reaction of ester **2c** with aqueous ammonia gave 3-carboxamide **8** in 90% yield (Scheme III). Treatment of **8** with methyl iodide gave in 56% yield 2-methyl derivative **9**, whose structure was confirmed by ammonolysis of 2-methyl-3-carboxylate **3c**. Reaction of **3c** with ammonia was largely incomplete after 5 months, indicating severe steric hindrance caused by the 2-methyl substituent. When allowed to stand in the presence of excess aqueous methylamine, ester **2c** gave only ketone **5**[7] in poor yield along with unchanged starting material.

Employing the conditions of Zinnes[2a] for the conversion of **2b** to isopropyl ether **10a**, amide **8** gave, in 35% yield, methoxyamide **10b** (negative ferric chloride test). Treatment of **8** in 1,2-dimethoxyethane with 2 equiv of diazomethane gave amide **9** in 20% yield. No enol ether **10b** was isolated.

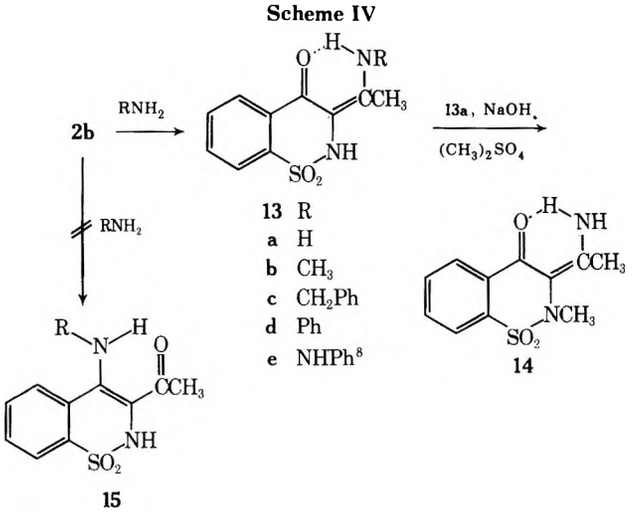
Scheme III



Alkylation of amide **8** with methyl bromoacetate afforded 2-acetate **11**, whose cyclization to imide **12** was effected in warm sulfuric acid.

Aqueous solutions of ammonia, methylamine, and benzylamine were found to react with **2b** in excellent yields, affording vinylogous amides **13a–c**. Aniline failed to react with **2b** under aqueous conditions; however, **13d** was obtained in 60% yield upon warming **2b** neat with excess amine (Scheme IV). Compounds **13a–d** were intensely yellow, generally retained solubility in dilute aqueous alkali, and gave negative ferric chloride tests.

Scheme IV

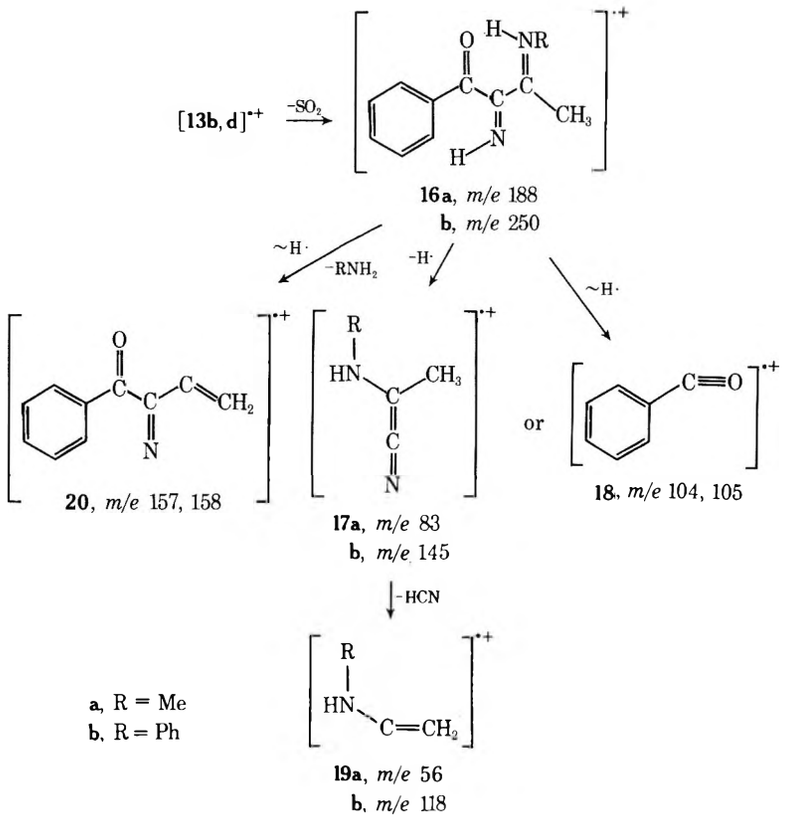


13 R
a H
b CH_3
c CH_2Ph
d Ph
e NHPh[8]

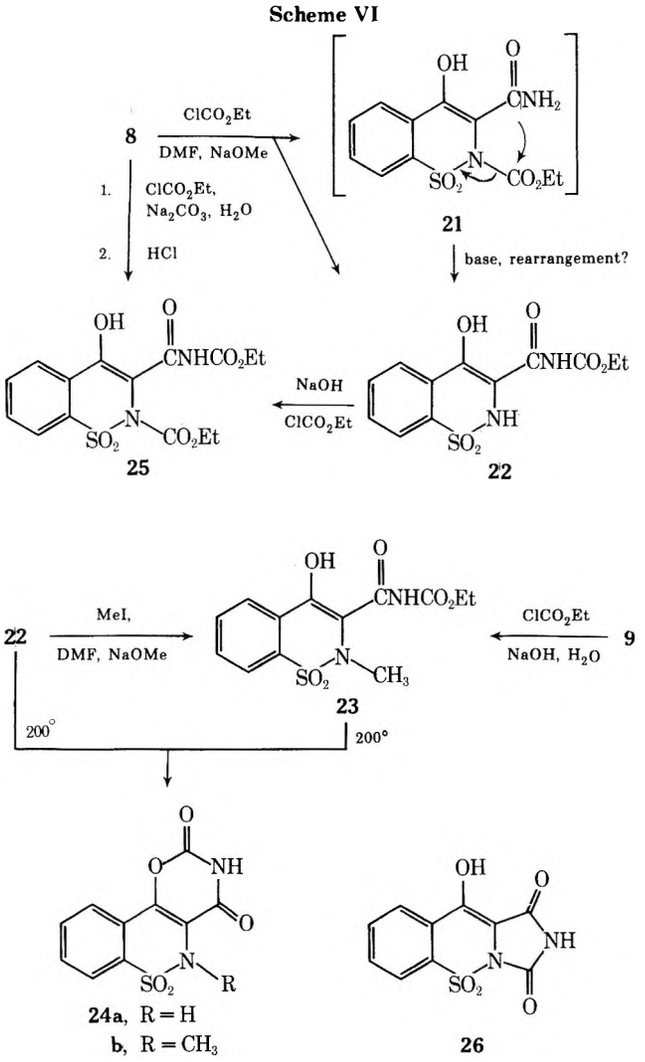
Phenylhydrazone **13e** has been reported[8] but no structure proof was given. Published uv data for **13e** are compared with those of **13a–d** and 2-methyl derivative **14** in Table I.

Alternate structure **15**, which could have conceivably arisen from the reaction of **2b** with primary amines, was ruled out by mass spectroscopic examination of represen-

Scheme V



Scheme VI



tative compounds **13b** and **13d**. The salient features of these results are shown in Scheme V and Table II.

Relatively abundant ions common to both **13b** and **13d** were observed at *m/e* 157 and 158, indicating structural similarity. In accordance with Spiteller's observations,[9] **13b** and **13d** primarily undergo loss of SO_2.

We, therefore, favor structure **13** over **15** because (1) ions assigned structures **17a** and **17b** are base and 89% of base peaks, respectively, and (2) no significant peak at *m/e* 43, corresponding to loss of CH_3CO^+, was observed in either spectrum. It is expected that such a fragment would be relatively abundant if **15** were the correct structure.[10]

Ethoxycarbonylation of amide **8** was carried out in DMF containing 1 equiv of sodium methoxide in an attempt to obtain 2-ethoxycarbonyl-3-carboxamide **21** (Scheme VI). The only product isolated from this reaction in poor yield was the 3-*N*-ethoxycarbonylamide **22**. The structure of **22** was confirmed by the transformations **9** → **23** and **22** → **23**.

At temperatures near 200°, **22** and **23** decomposed to give new compounds. These decomposition products were assigned oxazinedione structures **24a** and **24b** on the basis of negative ferric chloride tests, solubility in aqueous alkali, uv spectra, and elemental analyses. Imide **26**, which could have conceivably arisen from **23**, was ruled out because of the negative ferric chloride test.[5]

Treatment of aqueous alkaline solutions of either **8** or **22** with excess ethyl chloroformate gave the *N,N'*-diethoxycarbonyl derivative **25** as a sodium salt which separated from the reaction medium at pH values of *ca.* 8–10. Similarly, 2-methylamide **9** afforded **23** as a sodium salt. Excess chloroformate and concentrated sodium hydroxide effected direct conversion of **8** to **24a** in 70% yield.

Although occurring in the presence of substituted sulfonamide nitrogen (**9** → **23**), ethoxycarbonylation of 2-unsubstituted amide **8** may, like alkylation, take place at the 2 position, affording intermediate **21**. Under basic

Table I[e]
Physical Data of Vinylogs 4, 13a–e, and 14

Compd	Mp, °C[a]	R	Yield, %	ν NH, cm^{-1}[b]	ν C=O, cm^{-1}	λ_{max} (MeOH), nm (ε)	Formula
4	157.5–158.5		35		1660	256 (8,450) 330 (6,100)	$C_{12}H_{11}NO_4S$
13a	259–261 dec	H	91	3380, 3140 (KBr)	1615 (KBr)	249 (9,800) 358 (11,300)	$C_{10}H_{10}N_2O_3S$
14	199–201		42	3475, 3400	1610	245 (10,500) 351 (11,000)	$C_{11}H_{12}N_2O_3S$
13b	235–236 dec	CH_3	81	3300	1605	252 (9,800) 370 (13,700)	$C_{11}H_{12}N_2O_3S$
13c	196–199	CH_2Ph	73	3305, 3220	1602	253 (11,100) 372 (15,000)	$C_{17}H_{16}N_2O_3S$
13d	163–165	Ph	63	3350	1608	256 (13,600) 382 (17,100)	$C_{16}H_{14}N_2O_3S$
13e	175–170[c]	NHPh				239 (12,000)[d] 387 (13,500)	

[a] Uncorrected. [b] Chloroform unless otherwise specified. [c] Data taken from ref 8. [d] EtOH (95%). [e] Satisfactory analytical values (±0.3% for C, H, N, S) were reported for all compounds in table: Ed.

Table II
Fragmentation of 3-[(1-Methylamino)- and -(1-anilino)ethylidene]-2*H*-1,2-benzothiazine-4(3*H*)-one 1,1-Dioxides at 70 eV

Assignment	13b *m/e* (intensity)[a]		13d *m/e* (intensity)[a]	
M^+	252 (31)		314 (100)	
13 − HCN	225 (3)	m* 140.3[b]		m* 199.0[b]
13 − CH_2N	224 (2)			
16 (**13** − SO_2)	188 (13)		250 (38)	
16 − H	187 (<5)	m* 155.5[b]	249 (24)	m* 217.2[b]
16 − CH_3 and/or NH	173 (16)		235 (12)	
16 − NH_3	171 (8)		233 (18)	
16 − RNH	158 (11)		158 (11)	
20	157 (26)		157 (45)	
20 − CH_3	132 (15)		132 (<5)	
17	83 (100)	m* 83.5[b]	145 (89)	
19	56 (51)		118 (46)	
18 + C_7H_7N	105 (75)		105 (51)	
18 − H + C_7H_6N + C_7H_4O	104 (8)		104 (12)	
$PhNH_2$			93 (33)	
Ph	77 (22)		77 (59)	
19 − CH_2 + **18** − H	42 (31)		104 (12)	
CH_3CO	43 (1.4)[c]		43 (1.7)[c]	

[a] Expressed as per cent of base peak. [b] Metastable peaks were observed for the transitions indicated. [c] See discussion.

conditions, rearrangement of the 2-ethoxycarbonyl group to the 3-carboxamide nitrogen atom as a contributing pathway leading to the formation of **22** can be envisioned. Several unsuccessful experiments avoiding excess base were carried out in an effort to obtain **21**. Thin layer chromatograms of the reaction mixtures indicated materials other than those attributable to **8**, **22**, and **25**. The presence of **21** in these mixtures remains speculative.

Experimental Section

Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 521 grating instrument. Uv spectra were obtained from a Cary 14 spectrophotometer. Nmr spectra were recorded on a modified Varian A-60. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane as internal standard. Mass spectra were obtained at 70 eV from Morgan-Shaffer Corp., Montreal, Canada, and from a Perkin-Elmer Hitachi RMU-6E. Elemental analyses were obtained from Scandinavian Microanalytical Laboratories, Herlev, Denmark. Thin layer chromatograms were generally carried out on silica gel GF plates with benzene–acetone mixtures as developing solvents.

Starting Materials. 1b. This compound was prepared according to the method of Eckenroth and Klein in 82% yield, mp 142–144° (lit.[11] mp 143°).

1c. The preparation was carried out according to the method of Eckenroth and Koerppen[12a] in 82% yield, mp 104–106° (lit.[12a] mp 104°, lit.[12b] mp 107°).

2b. Synthesis of **2b** was carried out essentially as reported in 92% yield, mp (155) 157–158.5° (lit.[2a] mp 158–159°).

Ethyl 4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (2c). To a solution of 57.5 g (2.5 g-atoms) of sodium in 1 l. of absolute EtOH was added 271 g (1.01 mol) of **1c**. The rapidly stirred mixture was warmed to 57–62° and maintained at these temperatures for 2 hr. The orange slurry was poured onto ice–concentrated HCl (260 ml). Extraction with methylene chloride (5 × 1 l.), drying (Na_2SO_4), solvent removal *in vacuo*, and trituration of the residue with benzene gave 188 g (69%) of product (two crops). Recrystallization from acetone–benzene afforded the analytical sample: mp 139.5–141°; ir ($CHCl_3$) 3350, 3240 (OH, NH), 1660, 1608 cm^{-1} (HOC=CC=O); nmr ($CDCl_3$) δ 11.45 (s, enol, OH or NH), 6.67 (broad singlet, NH or OH), 4.40 (q, J = 7 Hz, $-OCH_2-$), 1.38 (t, J = 7 Hz, CH_2CH_3); uv max (MeOH)[13] 241 nm (ε 4800), 284 (inflection, 3700), 301 (shoulder, 4800), 322 (6600).

Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20; S, 11.91. Found: C, 49.12; H, 4.18; N, 4.88; S, 11.89.

Conventional alkylation procedures gave the following derivatives of **2c**.

Ethyl 4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (3c). Reaction of **2c** with methyl iodide in DMF containing NaOMe gave, after recrystallization from EtOH (95%)–H_2O, pure **3c** in 71% yield, mp 136–138°.

Ethyl 3-Ethoxycarbonyl-4-hydroxy-2*H*-1,2-benzothiazine-2-acetate 1,1-Dioxide (3d).[6] This compound was prepared in 72% yield by reaction of ethyl bromoacetate with **2c** in ethanolic NaOEt. After recrystallization from EtOH (95%), the melting point was 97–98°.

Anal. Calcd for $C_{15}H_{17}NO_7S$: C, 50.70; H, 4.82; N, 3.94. Found: C, 50.50; H, 4.61; N, 4.09.

3,4-Dihydro-1-methyl-11*H*-1,4-oxazino[4,3-*b*][1,2]benzothiazin-11-one 6,6-Dioxide (4). To a solution of 2.3 g (0.1 g-atom) of

sodium in MeOH (150 ml) was added 23.9 g (0.1 mol) of **2b** and 60 ml of DMF. Most of the MeOH was removed *in vacuo*. To the residue was added 75.2 g (0.4 mol) of ethylene dibromide and the mixture was warmed on the steam bath for 2 hr. Addition of H_2O threw down the crude product, which was treated with aqueous NaOH (10%) to remove base-soluble materials. Recrystallization of the base-insoluble residue from acetone–MeOH gave 9.36 g (35%) of pure **4**, nmr ($CDCl_3$) A_2B_2 pattern at δ 4.38 (m, 2, $-OCH_2-$) and 3.87 (m, 2, $-CH_2N$) and 2.51 (s, 3, CH_3). See Table II for the other physical data.

Since this reaction was run only once, it is assumed that use of 2 equiv of base would substantially improve the yield.

Ethyl 9,9a-Dihydro-9-oxoazetidino[1,2-*b*][2*H*]-1,2-benzothiazine-9a-carboxylate 4,4-Dioxide (6). To a solution of 5.75 g (0.25 g-atom) of sodium in 100 ml of MeOH was added 100 ml of DMF. The mixture was concentrated *in vacuo* to *ca.* 75 ml. A solution of **2c** in 100 ml of DMF was then added and the orange solution was cooled to 10°. 1,2-Dibromoethane (23.5 g, 0.125 mol) was added in one portion with swirling. After heating on the steam bath for 2 hr, most of the solvent was removed *in vacuo*. After addition of 500 ml of H_2O, the brown oil was extracted into ether (4 × 250 ml). The combined extracts were washed with aqueous Na_2CO_3 (10%, 5 × 50 ml) and aqueous NaOH (1 *N*, 2 × 50 ml). Drying ($MgSO_4$) and solvent removal *in vacuo* gave 15.3 g (52%) of a syrup. Fresh ether (100 ml) was added to the residue. Cooling and scratching gave crystals contaminated with yellow oil. Several recrystallizations from ether gave 7.6 g (26%) of pure **6**: mp 86.5–88.5°; uv max (MeOH) 251 nm (ϵ 9660), 289 (1800), and 295 (inflection, 1540); ir ($CHCl_3$) 1736 (ester C=O) and 1684 cm^{-1} (aromatic C=O); nmr ($CDCl_3$) δ 4.35 (q, 2, J = 7 Hz, $-OCH_2-$), 4.0 (m, 2, NCH_2), 3.4 (m, 1, H_b),[14] 2.28 (m, 1, H_a), and 1.30 (t, 3, J = 7 Hz, $-CH_2CH_3$).

Anal. Calcd for $C_{13}H_{13}NO_5S$: C, 52.87; H, 4.44; N, 4.74; S, 10.86. Found: C, 53.07; H, 4.41; N, 4.89; S, 10.88.

Ethyl 10,10a-Dihydro-10-oxopyrrolidino[1,2-*b*][2*H*]-1,2-benzothiazine-10a-carboxylate 5,5-Dioxide (7). The preparation was carried out on a 0.05-mol scale in a manner analogous to that described for **6**. Several recrystallizations from ether gave 5.3 g (34%) of pure **7**: mp 80.5–83°; uv max (MeOH) 246 nm (ϵ 9250), 288 (1880), and 296 (shoulder, 1540); ir ($CHCl_3$) 1735 (ester C=O) and 1690 cm^{-1} (aromatic C=O); nmr ($CDCl_3$) δ 4.28 (q, 2, J = 7 Hz, OCH_2), 4.0–3.3 (m, 2, NCH_2), 2.72 (m, 2, H_a, H_b),[14] 2.5–1.6 (m, 2, $CH_2CH_2CH_2$), 1.25 (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{14}H_{15}NO_5S$: C, 54.36; H, 4.89. Found: C, 54.24; H, 4.93.

4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (8). A solution of 53.85 g (0.2 mol) of **2c** in 2 pints of aqueous NH_3 (58%) was allowed to stand at room temperature for 2 days. Removal of most of the excess NH_3 *in vacuo*, pouring into ice–HCl, and recrystallization of the resulting solid from acetone–MeOH gave 43 g (90%) of **8**: mp 244–247° dec; uv max (MeOH) 226 nm (ϵ 8000), 297 (shoulder, 6100), 313 (7300), and 361 (shoulder, 1450); ir (KBr) 3485 (NH), 1653 and 1645 cm^{-1} (HOC=CCONH$_2$).

Anal. Calcd for $C_9H_8N_2O_4S$: C, 45.00; H, 3.36; N, 11.66; S, 13.35. Found: C, 45.10; H, 3.32; N, 11.64; S, 13.35.

4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (9). Method A. The preparation was carried out by reaction of methyl iodide (7.8 g, 0.055 mol) with 12.0 g (0.055 mol) of amide **8** in the presence of NaOMe (0.055 mol) in DMF. Conventional work-up and recrystallization from acetone gave 7.1 g (56%) of pure product, mp 240–245° dec.

Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96. Found: C, 47.22; H, 4.08.

Method B. Ester **3c** (2.82 g, 0.01 mol) was dissolved in 100 ml of aqueous NH_3 (28%), tightly stoppered, and allowed to stand for 5 months. Acidic work-up and recrystallization from acetone gave **9** identical in all respects with that obtained from method **A**.

4-Methoxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (10). A solution of 12.0 g (0.05 mol) of **8** and 71 g (0.5 mol) of methyl iodide in 500 ml of acetone was allowed to reflux for 6 hr in the presence of 85 g of anhydrous K_2CO_3. After standing overnight, filtration and solvent removal *in vacuo* gave a semi-solid gum. Trituration with H_2O followed by MeOH gave 6.2 g (46%) of crystals (two crops). Recrystallization from acetone gave 4.7 g (35%) of pure **10**: mp 208–218°; ir (KBr) 3445, 3335, 3260 (NH), 1675–1670 ($CONH_2$), and 1590 cm^{-1} (C=C); uv max (MeOH) 230 nm (inflection, ϵ 8450), 281 (shoulder 9000), 287 (9300), and 306 (8800); nmr (DMSO-d_6) δ 3.75 (s, 3, OCH_3) and 2.97 (s, 3, NCH_3).

Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.31; H, 4.59; N, 10.20; S, 11.92.

Methyl 3-Carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine-2-acetate 1,1-Dioxide (11). A solution of 1.55 g (0.067 g-atom) of sodium in absolute MeOH was evaporated to near dryness *in vacuo*. To the residue was added 60 ml of dry DMF followed by 16.05 g (0.067 mol) of amide **8**. To the resulting solution was added, with stirring, 10.4 g (0.067 mol) of methyl bromoacetate over 5 min. After stirring overnight at ambient temperature, the solvent was removed *in vacuo* and the residue was treated with H_2O. Recrystallization of the resulting solid from acetone gave 15.5 g (74%) of pure **11** as colorless crystals: mp 223–225° dec; ir (KBr) 1750 (CH_2CO_2Me), 1655 and 1607 cm^{-1} (HOC=CCONH$_2$).

Anal. Calcd for $C_{12}H_{12}N_2O_6S$: C, 46.12; H, 3.87; N, 8.97; S, 10.27. Found: C, 46.30; H, 4.00; N, 8.88; S, 10.23.

1,2,3,4-Tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]benzothiazine-1,3-dione 6,6-Dioxide (12). A mixture of 13.08 g (0.042 mol) of **11** and *ca.* 8 ml of concentrated H_2SO_4 (98%) was warmed on the steam bath with stirring until solution was complete. Heating was continued for 1 hr, during which time the mixture crystallized (sometimes scratching with a glass rod was necessary). The reaction was quenched by pouring into ice water. Recrystallization from acetone gave 6.6 g (56%) of pure product: mp 234–238° dec; uv max (MeOH) 242 nm (ϵ 7950), 254 (shoulder, 6600), and 350 (10,800); ir (KBr) 3450 (broad), 3225, 1755 (shoulder), 1728, and 1650 cm^{-1}; nmr (DMSO-d_6) δ 12.3–11.6 (broad, *ca.* 1, OH and/or NH) and 4.47 ppm (s, 2, NCH_2). A dilute ethanolic solution of **12** gave a deep green ferric chloride test.

Anal. Calcd for $C_{11}H_8N_2O_5S$: C, 47.14; H, 2.88; N, 10.00. Found: C, 47.06; H, 3.00; N, 9.85.

Preparation of 13a–d. The physical data for these compounds are shown in Table I. Reaction conditions, work-up, and the solvents used for recrystallization are described below.

3-[(1-Amino)ethylidene]-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide (13a). A solution of 10.7 g (0.045 mol) of **2b** in 110 ml of concentrated aqueous NH_3 was allowed to stand for 2 days at room temperature, during which time amber crystals formed. Removal of most of the excess NH_3 and H_2O *in vacuo* gave the crude solid, which was collected, dried, and recrystallized from acetone.

The 2-methyl derivative **14** was prepared by the action of dimethyl sulfate in aqueous NaOH (10%). The alkali-insoluble product was recrystallized from acetone–EtOH.

3-[(1-Methylamino)ethylidene]-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide (13b). A solution of 2.39 g (0.01 mol) of **2b** in 11 ml of aqueous $MeNH_2$ (30%) was allowed to stand for 1 day at room temperature. The work-up was essentially the same as for **13a** except that aqueous HCl was employed to remove the remaining $MeNH_2$. The solid which was obtained after trituration with MeOH was recrystallized from acetone.

3-[(1-Benzylamino)ethylidene]-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide (13c). A mixture of 2.39 g (0.01 mol) of ketone **2b** and 3.21 g (0.03 mol) of benzylamine in 10 ml of H_2O was stirred until **2b** dissolved. The resulting mixture was allowed to stand for 1 day at room temperature. Work-up was identical with that described for **13b**. Recrystallization from acetone–MeOH gave pure **13c**.

3-[(1-Anilino)ethylidene]-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide (13d). A mixture of 12.0 g (0.05 mol) of **2b** and 14.0 g (0.15 mol) of aniline was heated on the steam bath overnight. Excess aniline was removed *in vacuo*. Trituration of the red oil with EtOH and recrystallization from acetone gave pure **13d**.

3-(Ethoxycarbonyl)carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide (22). A solution of 2.76 g (0.12 g-atom) of sodium in 50 ml of absolute EtOH was evaporated to near dryness *in vacuo*; then 75 ml of DMF was added followed by 24.0 g (0.1 mol) of amide **8**. When solution had occurred, 12.96 g (0.12 mol) of ethyl chloroformate was added dropwise with stirring and cooling. The color of the solution changed to light yellow. After stirring at room temp for 1 hr, most of the DMF was removed *in vacuo*. The oily residue was treated with H_2O and allowed to stand until crystallization occurred. Recrystallization from acetone–H_2O gave the pure product: mp 192–193° dec (dependent on rate of heating); ir (KBr) 3350, 3120, 1745, and 1640 cm^{-1}; uv (MeOH, freshly prepared) 234 nm (shoulder, ϵ 9150), 236 (9200), and 325 (10,000); uv (MeOH, standing overnight) 251 nm (ϵ 5600), 252 (shoulder, 5600), and 285 (shoulder 2000) (see footnote 13). This preparation gave erratic yields of **22**.

Anal. Calcd for $C_{12}H_{12}N_2O_6S$: C, 46.15; H, 3.87; N, 8.97; S, 10.27. Found: C, 46.00; H, 3.88; N, 8.57, 9.11; S, 10.19.

3-(Ethoxycarbonyl)carbamoyl-4-hydroxy-2-methyl-2*H*-1,2-

benzothiazine 1,1-Dioxide (23). A. To a vigorously stirred solution of 7.62 g (0.03 mol) of amide **9** in 25 ml of aqueous NaOH (10%) was added 6 ml of ethyl chloroformate. Repeated additions of ethyl chloroformate and NaOH solution were carried out maintaining the pH at 8–9 (pH paper) until solid no longer appeared to be forming. Addition of brine (saturated), filtration, and washing with brine gave the crude sodium salt, which was taken up in warm H_2O and acidified with HCl. Recrystallization of the resulting solid from dioxane gave 5.0 g (39%) of pure product: mp (195) 196–197° dec (dependent on rate of heating); uv (MeOH, freshly prepared) 235 nm (ϵ 10,900) and 325 (10,900); ir (KBr) 3330, 1770–1760, 1730 (shoulder), 1650 (shoulder), and 1644–1640 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}N_2O_6S$: C, 47.85; H, 4.32. Found: C, 47.87; H, 4.49.

B. *Via* **22.** To a solution of 0.34 g (0.005 mol) of NaOEt in 10 ml of DMF was added 1.2 g (3.84 mmol) of **22**. After solution was complete, 2 ml of methyl iodide was added and the reaction mixture was allowed to stir for 1 hr at room temperature. Addition of H_2O threw down a solid which was recrystallized as above, mp 201–202° dec (dependent on rate of heating). The ir and uv spectra of the product indicated identity with **23** prepared *via* procedure A. A mixture decomposition point of both products was undepressed.

2*H*,5*H*-1,3-Oxazino[5,6-*c*][1,2]benzothiazine-2,4(3*H*)-dione 6,6-Dioxide (24a). A. A test tube containing 1 g (3.2 mmol) of **22** was heated in an oil bath (preheated to *ca.* 200°) until gas evolution ceased. Trituration with acetone gave 0.4 g (47%) of crude product. Recrystallization from acetone gave the analytical sample: mp 292–294° dec (dependent on rate of heating); uv (MeOH) 255 nm (broad, ϵ 6000) and 360 (7600); uv (MeOH + 1 drop of 0.1 *N* HCl) 237 nm (ϵ 9000), 300 (shoulder, 8200), and 320 (11,200) (traces of acid sometimes present in MeOH gave uv spectra which appeared to be mixtures of both protonated and unprotonated **24a**); ir (KBr) 3410, 3240, 1740, 1710 (shoulder), 1700, and 1630 cm^{-1}.

Anal. Calcd for $C_{10}H_6N_2O_5S$: C, 45.12; H, 2.27; S, 12.04. Found: C, 45.28; H, 2.50; S, 11.96.

B. *Via* **8.** A solution of 12.0 g (0.05 mol) of amide **8** in 100 ml of aqueous NaOH was treated with excess ethyl chloroformate (*ca.* 2–3 ml added at 5–10-min intervals over 1 hr). The solution became warm and some cooling was necessary (H_2O bath). Aqueous NaOH (50%) was added as needed [in order to maintain a pH >10 (pH paper)]. Two crops of sodium salt were removed by filtration. The mother liquors were poured into excess ice–HCl. The combined crops of sodium salt were dissolved in H_2O and acidified. The resulting solid was combined with that obtained by acidification of the alkaline filtrate, taken up in hot THF–dioxane (1:1, *ca.* 200 ml), filtered through a pad of Filter-aid, and concentrated *in vacuo* to *ca.* 100 ml. Addition of acetone (100 ml) followed by 500 ml of H_2O gave 9.35 g (70%) of pure **24a** which was identical with that prepared by procedure A by melting point, ir, and uv.

5-Methyl-2*H*,5*H*-1,3-oxazino[5,6-*c*][1,2]benzothiazine-2,4(3*H*)-dione 6,6-Dioxide (24b). Fusion of 8.4 g (0.026 mol) of **23** at 195–205° in the manner described for **24a** (method A) gave 3.64 g (50.5%) of pure product (from acetone): mp (262) 264–267°; uv 231 nm (shoulder, ϵ 7700), 241 (shoulder, 7100) 284 (shoulder 7000), 292 (7950), and 314 (9100) (the uv solutions of **24b** did not undergo significant change in the 314-nm region upon either acidification or basification); ir (KBr) 3230, 3180, 1781 (shoulder), 1779, 1744, 1705 (shoulder), 1700, 1692, and 1610 cm^{-1}.

Anal. Calcd for $C_{11}H_8N_2O_5S$: C, 47.14; H, 2.88; N, 10.00; S, 11.44. Found: C, 47.15; H, 2.92; N, 9.82; S, 11.55.

Ethyl 3-(Ethoxycarbonyl)carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine-2-carboxylate 1,1-Dioxide (25). A solution of 4.8 g (0.02 mol) of amide **8** in 25 ml of aqueous Na_2CO_3 (10%) was treated with excess ethyl chloroformate (*ca.* 2-ml portions added at intervals of 10–15 min over 1 hr). Aqueous NaOH (10%) was added in sufficient amounts to maintain a pH of *ca.* 8–10 (pH paper). Brine (saturated) was added and the resulting sodium salt was collected, washed with brine, and recrystallized from acetone–EtOH (95%): mp 182.5–184° dec; uv (MeOH) 240 nm (shoulder, ϵ 9900), 266 (shoulder, 3600), and 350 (8900).

Anal. Calcd for $C_{15}H_{15}NaN_2O_8S \cdot H_2O$: C, 42.45; H, 4.05; N, 6.61; S, 7.55. Found: C, 42.43; H, 4.08; N, 6.45; S, 7.30.

The above sodium salt was dissolved in warm water and acidified with a slight excess of concentrated HCl. The resulting oil crystallized upon scratching and cooling. Recrystallization from acetone–MeOH gave 4.5 g (59%) of pure product: mp 159–160°; uv (MeOH) 232 nm (broad, ϵ 11,500), 266 (shoulder, 4000), and 337 (9000); ir ($CHCl_3$) 3415, 1775–1770, 1750 (shoulder), 1660–1650, and 1606 cm^{-1}. The nmr spectra of the sodium salt (*vide supra*) and the conjugate acid **25** (DMSO-d_6) indicated the presence of two nonequivalent ethyl groups.

Anal. Calcd for $C_{15}H_{16}N_2O_8S$: C, 46.87; H, 4.20. Found: C, 46.72; H, 4.27.

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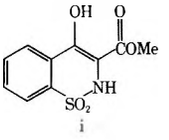
Registry No.—**1c,** 24683-20-3; **2b,** 51015-24-8; **2c,** 24683-21-4; **3c,** 24683-26-9; **3d,** 20566-30-7; **4,** 51015-25-9; **6,** 24802-31-1; **7,** 24802-32-2; **8,** 24683-22-5; **9,** 24683-25-8; **10b,** 27222-93-1; **11,** 27321-37-5; **12,** 51015-26-0; **13a,** 24196-95-0; **13b,** 24196-96-1; **13c,** 24196-97-2; **13d,** 24196-98-3; **14,** 24196-99-4; **22,** 24683-23-6; **23,** 24683-24-7; **24a,** 24683-27-0; **24b,** 24683-28-1; **25,** 27222-95-3; **25** Na salt, 51015-27-1.

References and Notes

(1) K. Abe, S. Yamamoto, and K. Matsui, *Yakugaku Zasshi*, **76**, 1058 (1956); *Chem. Abstr.*, **51**, 3499 (1957).
(2) (a) H. Zinnes, R. A. Comes, F. R. Zuleski, A. N. Caro, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 2241 (1965); (b) A. Kraaijeveld and M. Akkerman, U. S. Patent 3,284,450 (1966).
(3) C. R. Rasmussen and D. L. Shaw, *J. Org. Chem.*, **39**, 1560 (1974).
(4) During preparation of this paper, synthesis of methyl ester i in DMSO solution was published: J. G. Lombardino, E. H. Wiseman, and W. M. McLamore, *J. Med. Chem.*, **14**, 1171 (1971). Ester i could not be obtained in satisfactory yield under methanolic sodium methoxide conditions. We verify this observation.



i

(5) All enolizable dicarbonyl compounds of this and our subsequent paper appear to be completely enolic by nmr. Each of these enolic compounds shows a positive ferric chloride test. We prefer the "4-hydroxy" of Abe[1] rather than the "4(3*H*)-one" nomenclature of Zinnes *et al.*[2a] A. R. Katritzky, *Chem. Ind.* (*London*), 334 (1965).
(6) Diester **3d** has been found to be a potent inducer of ventricular fibrillation. The potential use of this compound as a pharmacological tool is reported elsewhere: T. P. Pruss, *Toxicol. Appl. Pharmacol.*, **14**, 1 (1969).
(7) H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 162 (1966).
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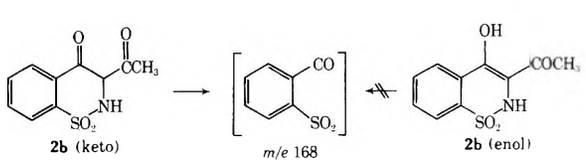
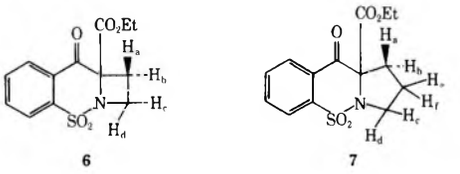
(9) G. Spiteller, *Advan. Heterocycl. Chem.*, **7**, 373 (1966).
(10) F. W. McLafferty, *Advan. Chem. Ser.*, **40**, 8 (1963). We have also recorded the mass spectrum of **2b** at 70 eV and have found an abundant *m/e* 43 peak.
(11) H. Eckenroth and K. Klein, *Chem. Ber.*, 29, 329 (1896).
(12) (a) H. Eckenroth and G. Koerppen, *Chem. Ber.*, **30**, 1267 (1897); (b) O. J. Magidson and S. W. Gorbatshaw, *ibid.*, **56**, 1816 (1923).
(13) Freshly prepared alcoholic solutions of **2a**, **2b**, and **2c** were found to be mandatory for consistent uv spectra. The uv characteristics of these solutions underwent marked deterioration above 300 nm upon standing. Acetonitrile solutions of these compounds were stable. In an effort to understand these observations, a methanolic solution of **2b** (50 mg/100 ml), which had been allowed to stand for 1 week, was evaporated in the cold (N_2). This residue (negative ferric chloride test) and untreated **2b** were examined by mass spectroscopy at 70 eV. The methanol-treated sample showed a significant *m/e* 168 peak (structure ii) while untreated **2b** did not. Both samples gave identical molecular ions. We interpret these results as differences in the fragmentation patterns of enol **2b** and keto **2b**, since it is known that polar solvents favor the keto form of β-dicarbonyl compounds: E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 380.



ii

(14) It was not clear from molecular Dreiding models why the proton we

ascribe to be H_b in **6** appears at such low field (δ 3.4). Protons which we assign to H_a and H_b in **7** appear as a two-proton multiplet centered at δ 2.72. Protons assigned H_c and H_d in both molecules are observed at δ 4.0–3.5, which appears to be consistent with adjacency to the electronegative nitrogen atom. It seems difficult to invoke primary deshielding effects on H_b in **6** by the aromatic carbonyl group (H_b in **6** and H_b in **7** both approach coplanarity with the aromatic carbonyl group) because the same large effect (deshielding of H_b) is not observed in **7**. If our analysis of the molecular models is correct, H_b in **6** is about 0.8 Å closer to the nearest sulfonamide oxygen than H_b in **7** which may account for its appearance at lower field. Because the conformational preferences of **6** and **7** are not known, these chemical shift assignments should be regarded as tentative.



6 **7**

3-Acyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxides. II.[1] Reaction with Aziridines. Nucleophilic Displacements on (1,2,3,4-Tetrahydro-11-hydroxy-1-oxopyrazino[1,2-*b*][1,2]benzothiazin-2-yl)ethyl Methanesulfonate 6,6-Dioxide

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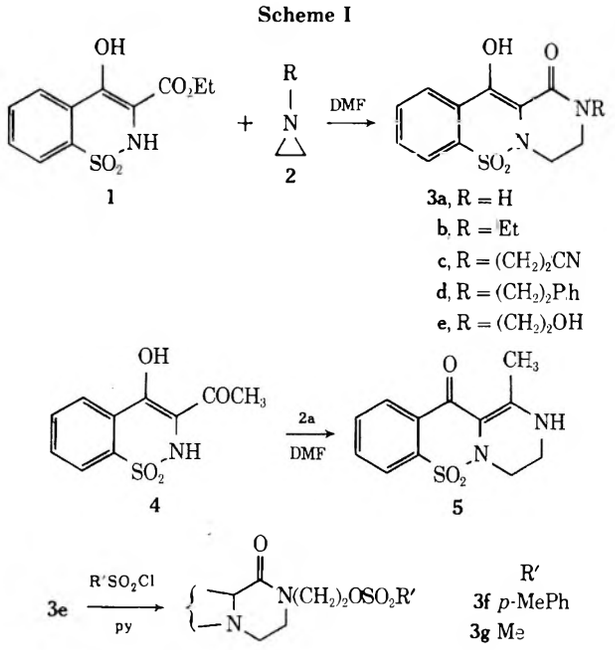
Ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**1**) reacts with aziridines **2** to give 1,2,3,4-tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-dioxides (**3**) in 60–95% yields. Reactions of 2-ethyl methanesulfonate **3g** with various sulfur and nitrogen nucleophiles have been shown to proceed *via* the intermediate 2,3,5,6-tetrahydro-13*H*-oxazolo[2′,3′:3,4]pyrazino[1,2-*b*][1,2]benzothiazin-13-one 8,8-dioxide (**6**). The different reaction pathways taken by either **3g** or **6** with primary and secondary amines are described in terms of a postulated mechanism.

Aziridines (ethylenimines) are known to undergo autocatalytic ring-opening reactions with a variety of acidic nucleophiles.[2] The availability of carboxylate **1** in these laboratories prompted us to explore the apparently little-investigated reactions of acidic sulfonamides[3,4] with ethylenimines **2**.

Scheme I

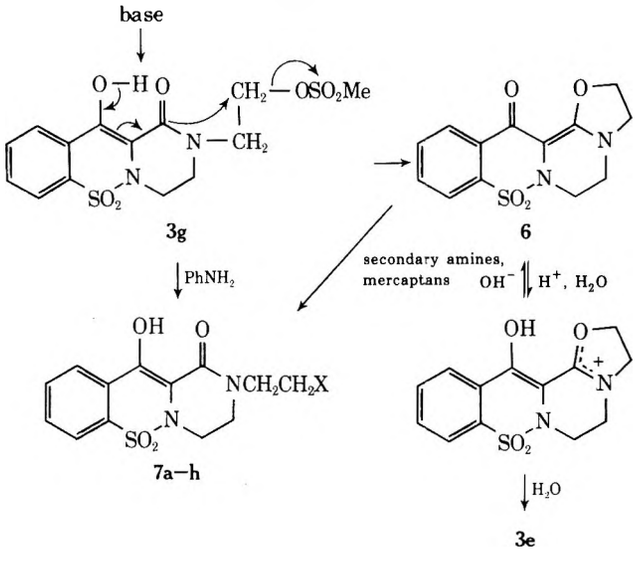


Treatment of ester **1** in DMF solution with **2** gave novel piperazines **3** in 60–90% yields (Scheme I, Table I). These compounds were acidic and completely enolic (nmr). Reaction of 3-acetylbenzothiazine **4**[5] with ethylenimine (**2a**) afforded piperazine **5** in only 8% yield. Treatment of **4** with other aziridines was not attempted.

Further work was centered on reactions of ethanol **3e** and its sulfonate esters **3f**[6] and **3g**.

Treatment of **3g** with either dimethylamine or sodium methyl mercaptide led to isolation of a bright yellow product which was assigned structure **6**. The latter reaction also afforded the expected product **7f** in 28% yield. Methanolic triethylamine, used preparatively, gave **6** in 83% yield. The uv spectrum of **6** showed a reversible 21-nm hypsochromic shift in acid, indicating oxazolinium ion formation (Scheme II). Dilute aqueous hydrochloric acid converted **6** to alcohol **3e**.

Scheme II



Formation of **7f** in the reaction of **3g** with methyl mercaptide led us to investigate the possibility that **6** might

Table I
Preparation of 1,2,3,4-Tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-Dioxides (3)[a,b]

Compd	R	Method	Yield, %	Mp, °C	Uv_{max} (MeOH), nm (ϵ)	Formula
3a	H	A	60	(260) 262–264[c]	246 (7,600)	$C_{11}H_{10}N_2O_4S$
		C	22		339 (10,700)	
3b	Et	C	41	(155) 156–159	249 (7,660)	$C_{13}H_{14}N_2O_4S$
					342 (11,700)	
3c	$(CH_2)_2CN$	B	95	190–191	248 (8,100)	$C_{14}H_{13}N_3O_4S$
		C	60		343 (11,200)	
3d	$(CH_2)_2Ph$	C	43	163.5–165.5	250 (8,250)	$C_{19}H_{18}N_2O_4S$
					343 (12,600)	
3e	$(CH_2)_2OH$	B	83	158–161	249 (8,000)	$C_{13}H_{14}N_2O_5S$
					343 (12,300)	

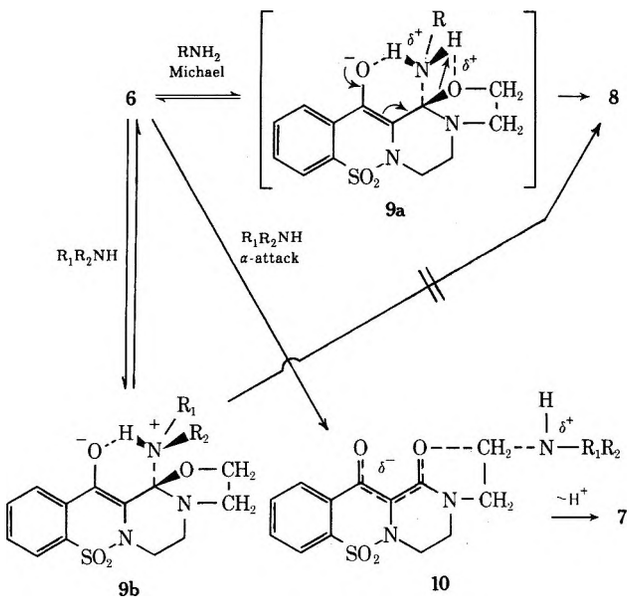
[a] For other physical data, see Experimental Section. [b] Satisfactory analytical values (±0.30% for C, H, N, S) were reported for all compounds in table: Ed. [c] With slight decomposition.

be a reaction intermediate capable of undergoing ring-opening reactions in the presence of nucleophiles. Indeed, when either **6** or **3g** was allowed to react with secondary amines and mercaptide ions, products assigned structure **7** were obtained in good yield (Scheme II, Table II). Evidence (tlc) supporting the intermediacy of **6** was obtained from those reactions in which **3g** was employed as starting material. The reaction of **3g** with aniline, however, does not proceed *via* **6** (*vide infra*).

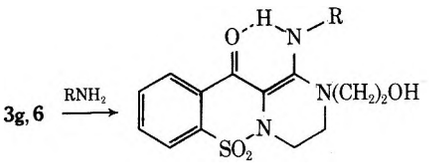
Reactions of **3g** with ammonia and primary amines were also found to proceed *via* intermediate **6**, affording brilliant yellow products which were assigned eneamidine structure **8** (Scheme III). These compounds, in contrast with those of structure **7**, failed to show positive ferric chloride tests, and their uv spectra underwent marked hypsochromic shifts (40–66 nm) in acidified methanol. These shifts indicated amidinium cation formation analogous to the ion derived from **6**. No evidence was obtained for any products of structure **7** in these reactions.

As previously stated, **3g**, when heated with aniline, does not proceed through **6** to **7e** (tlc). Treatment of **6**, however, with aniline under the same conditions resulted in a sluggish reaction which was incomplete after 72 hr. A new yellow product, **7e**, **6**, and at least five minor components were present in the reaction mixture. Preparative tlc, carried out on a portion of this mixture, allowed isolation of the yellow substance, which was assigned structure **8d** on the basis of uv (neutral and acid) and mass spectroscopy.

Apparently, **6** operates as a remarkably selective substrate in its reactions with nucleophiles. To account for these observations, we propose the following mechanism.



Scheme III



8a, R = $(CH_2)_2Ph$
b, R = H
c, R = Me
d, R = Ph

3g + $PhNH_2$ ⟶ **7e**

6 + $PhNH_2$ ⟶ **7e** + **8d**

Inspection of the structures of final products **7** and **8** clearly shows that strongly H-bonded compounds are formed in all cases. Formation of **7** results from displacement of the ring oxygen atom of **6** as a resonance-stabilized anion of the β-ketoamide type **10**. On the other hand, products of structure **8** are derived from a Michael addition. A postulated transition state for the reactions of **6** with ammonia and primary amines is represented by **9a**. Ammonia and primary amines have a proton in addition to that required for H-bond formation. This additional proton is available for transfer to the oxazolidine oxygen atom, allowing its conversion to an oxonium-type leaving group. Thus, **9a** can collapse to **8**.

Secondary amines may react reversibly *via* the Michael pathway **9b**. However, in this case, only one proton is available and that, apparently, is utilized for incipient H-bond formation. Since no additional proton is available for transfer to ring oxygen, the only plausible route to **8** is by expulsion of the relatively poor leaving group alkoxide ion. Amine nitrogen, being more basic than oxygen, simply retains the only available proton and is rejected, permitting reaction by the α route.

The reaction of aniline with **6** mainly by the α route can be explained by steric factors and its lower basicity.

Experimental Section[7]

The following procedures are illustrative of the methods used for the preparations of **3** (Table I).

Method A. Low-Boiling (<100°) Aziridines in DMF. 1,2,3,4-Tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-Dioxide (3a). A solution of 13.46 g (0.05 mol) of **1**[1] in 100 ml of DMF was cooled with stirring to 5° and then 2.32 g (0.054 mol) of **2a** was added dropwise. The reaction mixture was allowed to stir at 3–5° for 1.5 hr and then overnight at room temperature. Most of the solvent was removed *in vacuo* and to the residue was added a solution of 20 ml of aqueous HCl (10%) in 100 ml of H_2O. The resulting gummy solid was triturated with acetone–MeOH, affording 8.0 g of **3a**. Recrystallization from ace-

Table II
Physical Data for 2-(2-Substituted)ethyl Derivatives 7[a]

Compd	X	Mp, °C	Yield (method)		Uv_{max} (MeOH), nm (ϵ)	Formula
7a		(181) 184–186	53	(A)[b]	248 (7,800)	$C_{18}H_{23}N_3O_4S$
			78	(B)[c]	342 (12,100)	
7b	NMe_2	105–107	53	(C)[d]	243 (6,900)	$C_{15}H_{19}N_3O_4S$
					343 (8,700)	
7c		165–166	41	(C)	248 (7,700)	$C_{18}H_{24}N_4O_4S$
					342 (12,700)	
7d		152–153	80	(C)	248 (7,400)	$C_{17}H_{21}N_3O_5S$
					347 (10,800)	
7e	NHPh	144–145	66.5	(C)	248 (19,600)	$C_{19}H_{19}N_3O_4S$
			47	(B)	300 (5,300)	
					347 (12,400)	
7f	SMe	122–123	65	(C)	250 (8,000)	$C_{14}H_{16}N_2O_4S_2$
					345 (12,000)	
7g	SCH_2Ph	113–115	70	(C)	250 (7,900)	$C_{20}H_{20}N_2O_4S_2$
					345 (10,900)	
7h	SPh	141–142	80	(C)	251 (14,600)	$C_{19}H_{18}N_2O_4S_2$
					344 (9,200)	

[a] Satisfactory analytical data were reported for all compounds in table: Ed. [b] Tosylate **3f**. [c] Intermediate **6**. [d] Mesylate **3g**.

tone gave the analytical sample: ir (KBr) 3290, 3180, 1650, and 1598 cm^{-1}; nmr (DMF–NaOD) δ 3.60 (m, 4, NCH_2CH_2N).

Method B. High-Boiling (>100°) Aziridines in DMF. 1,2,3,4-Tetrahydro-11-hydroxy-2-(2-hydroxy)ethylpyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-Dioxide (3e). To a warm (steam bath), well-stirred solution of 73.5 g (0.273 mol) of **1** in 120 ml of DMF was added dropwise over 1 hr 31.7 g (0.364 mol) of 1-(2-hydroxy)ethylaziridine (**2e**) in 50 ml of DMF. Five minutes after completion of the addition, the reaction mixture was poured onto crushed ice. The resulting crystals were collected, dried, and recrystallized from acetone–MeOH, affording 70.1 g of **3e**: ir ($CHCl_3$) 3620, 3440, and 1620 cm^{-1}; nmr (DMSO-d_6) δ 13.60 (s, 1, enol H), 7.92 (m, 4, aromatic), 3.75 (~9 H, NCH_2CH_2N + NCH_2CH_2O + OH).

2-(2-Cyano)ethyl-1,2,3,4-tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2,]benzothiazin-1(2*H*)-one 6,6-Dioxide (3c). This preparation was carried out in a manner analogous to that described for **3e** using a 1:1.5 molar ratio of **1** to **2c**. The yield was 30.5 g, ir ($CHCl_3$) 2245 (CN), 1623 and 1600 cm^{-1} (shoulder).

Method C. Refluxing EtOH. 1,2,3,4-Tetrahydro-11-hydroxy-2-phenethylpyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-Dioxide (3d). A solution of 13.46 g (0.05 mol) of **1** and 11.04 g (0.075 mol) of 1-phenethylaziridine (**2d**) in 60 ml of absolute EtOH was heated under reflux overnight. The resulting solid, after recrystallization from acetone–EtOH (95%), gave 7.89 g of pure **3d**: ir ($CHCl_3$) 1622 and 1600 cm^{-1} (shoulder); nmr ($CDCl_3$) δ 13.28 (s, 1, enol H), 8.2–7.5 (m, 4, aromatic, 7.25 (s, 5, Ph), 3.82–3.28 (m, 6, NCH_2CH_2Ph + NCH_2CH_2N), 2.92 (t, 2, J = 7 Hz, $-CH_2CH_2Ph$).

2-Ethyl-1,2,3,4-tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]-benzothiazin-1(2*H*)-one 6,6-Dioxide (3b). This preparation, carried out on the same scale as that described for **3d**, afforded 6.12 g of pure product: ir ($CHCl_3$) 1623 cm^{-1}; nmr ($CDCl_3$) δ 13.31 (s, 1, enol H), 3.80 (m, 4, NCH_2CH_2N), 3.50 (q, 2, NCH_2CH_3, J = 7 Hz, overlapping part of the A_2B_2 system), 1.21 (t, 3, CH_2CH_3, J = 7 Hz).

3,4-Dihydro-1-methylpyrazino[1,2-*b*][1,2]benzothiazin-11(2*H*)-one 6,6-Dioxide (5). A solution of 23.9 g (0.1 mol) of 4[5] in 100 ml of DMF was stirred while 4.3 g (0.1 mol) of **2a** was added dropwise. Following the addition the mixture was heated for 1 hr on the steam bath, after which time most of the DMF was removed *in vacuo*. The resulting dark tar was triturated with acetone and allowed to remain overnight. The solid was recrystallized twice from DMSO–H_2O to give 2.2 g (8.3%) of **5** as a yellow solid: mp 285° dec; ir (KBr) 3270, 3240 (shoulder), 3220 (shoulder), 1620 (shoulder), 1595, and 1580 cm^{-1}; uv max (CH_3CN) 255 nm (ϵ 9100) and 383 (10,700).

Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.09; H, 4.79; N, 10.41; S, 12.16.

(1,2,3,4-Tetrahydro-11-hydroxy-1-oxopyrazino[1,2-*b*][1,2]-benzothiazin-2-yl)ethyl Methanesulfonate 6,6-Dioxide (3g). A solution of 27.93 g (0.09 mol) of **3e** in 100 ml of dry (KOH) pyridine was cooled to −5° in an ice–salt water bath. Methanesulfonyl chloride (20.54 g, 0.18 mol) was added such that the temperature did not rise above 0°. A heavy slurry of pyridinium chloride formed. The reaction mixture was poured onto ice containing excess HCl. The resulting solid was filtered, washed well with H_2O, and dried, yield 34.9 g (99%). Recrystallization from dioxane–MeOH gave pure **3g**: mp 172–174°; ir (KBr) 1622, 1600 cm^{-1} (shoulder); uv max (MeOH) 250 nm (ϵ 7500) and 350 (8250); nmr (DMF-d_7) δ 13.42 (s, broad, enol H), 8.2-7.8 (m, 4, aromatic), 4.62 (t, J = 5.5 Hz, 2, $NCH_2CH_2OSO_2$), 3.98 (m, 6, NCH_2CH_2N + NCH_2CH_2O–), 1.98 (s, 3, SO_2CH_3).

Anal. Calcd for $C_{14}H_{16}N_2O_7S_2$: C, 43.29; H, 4.15; N, 7.21. Found: C, 43.28; H, 4.15; N, 7.16.

3f. The toluenesulfonate ester was prepared in a manner analogous to that described for **3g**. Following acidic work-up, the oily ester was extracted into methylene chloride, washed successively with brine and brine (100 ml)–$NaHCO_3$ (20 ml, saturated), and dried (Na_2SO_4). After solvent removal *in vacuo*, the oil was dissolved in sufficient dioxane–ethanol (*ca.* 1:1) to make 300 ml of a stock solution. Aliquots of this solution were used for reactions with piperidine and phenethylamine.

2,3,5,6-Tetrahydro-13*H*-oxazolo[2′,3′:3,4]pyrazino[1,2-*b*][1,2]benzothiazin-13-one 8,8-Dioxide (6). A. A suspension of 7.77 g (0.02 mol) of **3g** in 150 ml of MeOH was treated with 4.05 g (0.04 mol) of triethylamine. After heating under reflux for 20 min, tlc indicated complete reaction. Solvent removal *in vacuo* and trituration with ice water gave crude **6**. Recrystallization from EtOH (95%) gave 5.15 g (83.1%) of pure **6**: mp 196–198° dec; ir ($CHCl_3$) 1640, 1590, 1570, 1549–1542 cm^{-1}; uv max (MeOH) 252 nm (ϵ 11,300) and 377 (12,700); uv max (MeOH–HCl) 255 nm (ϵ 8500) and 356 (14,700); nmr ($CDCl_3$) δ 8.3–8.1 (m, 1, aromatic), 7.9–7.6 (m, 3, aromatic), 4.75 (t, 2, J = 8.5 Hz, OCH_2CH_2N), 4.0–3.45 (m, 6, NCH_2CH_2N + OCH_2CH_2N).

Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.43; H, 4.14; N, 9.59. Found: C, 53.30; H, 4.18; N, 9.59.

B. From 3g and Dimethylamine. To a solution of 4.5 g (0.1 mol) of dimethylamine in MeOH was added 3.88 g (0.01 mol) of **3g**. After stirring at ambient temperature for 1 hr, no **3g** remained as shown by tlc [silica gel GF: benzene–acetone (1.5:1)]. Removal of solvent and excess amine *in vacuo* followed by trituration with water gave **6** identical in all respects with that obtained by procedures A and C. No **7b** was detected under these conditions.

C. From 3g and Sodium Methyl Mercaptide. Methanol (25 ml) containing 0.9 g (0.04 g-atom) of dissolved sodium was concentrated *in vacuo* to a thick syrup which was taken up in DMF (50 ml) and saturated with MeSH. To this solution was added 15 g (0.039 mol) of **3g**. After stirring for 2 hr, the solvent was removed *in vacuo*. Fractional crystallization of the residual solid from MeOH–H_2O and acetone–H_2O combinations gave 3.5 g (28%) of **7f** (*vide infra*) and sufficient **6** (*ca.* 100 mg) for characterization (ir, uv, nmr, tlc, melting point). Physical data for compounds **7a–h** are shown in Table II.

1,2,3,4-Tetrahydro-11-hydroxy-2-[2-(1-piperidino)]ethylpyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-Dioxide (7a). Method A. To a 75-ml aliquot of the dioxane–EtOH stock solution con-

taining *ca.* 0.025 mol of tosylate ester **3f** was added a solution of 6.4 g (0.075 mol) of piperidine in 20 ml of absolute EtOH. The reaction mixture was stirred at ambient temperature overnight. The solvent was removed *in vacuo* and to the residue was added dilute aqueous $NaHCO_3$ (5%) which threw down a gummy solid. Recrystallization from acetone–MeOH gave 5.05 g of **7a** as a light yellow solid, ir ($CHCl_3$) 1619 cm^{-1}.

Method B. A solution of **6** (6 g, 0.02 mol) and piperidine (2.13 g, 0.025 mol) in 40 ml of DMF was heated for 1.5 hr on the steam bath. Solvent removal *in vacuo* followed by treatment with aqueous $NaHCO_3$ (5%) and recrystallization above gave 5.91 g of **7a** identical in all respects with that obtained by method A.

Method C. 2-(2-Dimethylamino)ethyl-1,2,3,4-tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-Dioxide (7b). To a saturated solution of anhydrous dimethylamine in 50 ml of DMF was added 20.0 g (0.0515 mol) of **3g**. After stirring for 15 min, additional dimethylamine was passed into the solution until saturated. Heating for 1 hr on the steam bath followed successively by removal of solvent *in vacuo*, dissolution of the residue in dilute HCl (1.3 *N*), and precipitation of the free base by aqueous $NaHCO_3$ (5%) and recrystallization as above gave 5.91 g of **7a** acetone–H_2O gave 9.1 g of pure **7b**, ir ($CHCl_3$) 1620 cm^{-1}.

Preparations of **7c**, **7d** and **7e** were analogous to those described above. DMF solutions of **3g** (1 mol) were treated with 2.2–3.0 molar equiv of the corresponding amine with warming (steam bath). Each compound was recrystallized from acetone–H_2O.

Reaction of 6 with Aniline (7e and 8d). A solution of 2.92 g (0.01 mol) of **6** and 5.59 g (0.06 mol) of aniline was heated on the steam bath for 72 hr, after which time most of the DMF was removed *in vacuo*. Dilution of the residue with 50 ml of MeOH and cooling afforded 2.5 g of a solid comprised mostly of **7e** containing lesser amounts of **6**, **8d**, and unidentified materials. Recrystallization from acetone–MeOH gave 1.8 g (47%) of pure **7e** identical with that obtained previously (melting point, tlc, ir).

The methanolic mother liquors from which **7e** was obtained were reconcentrated *in vacuo* and to this residue was added *ca.* 200 ml of ether. A small amount of dark solid (mostly **7e** by tlc) was discarded. The ether solution was washed successively with H_2O, dilute HCl (10%) (to remove aniline and residual **6**), and saturated $NaHCO_3$. After drying over anhydrous K_2CO_3, a portion of this solution was applied to 1000-μ silica gel GF preparative tlc plates (Analtech). Development with benzene–acetone (2:1), scraping the prominent yellow band (R_f 0.7), extraction with acetone, filtration (diatomaceous earth), and solvent removal *in vacuo* gave a yellow oil which was redissolved in fresh ether (100 ml) and refiltered as before. Concentration to *ca.* 5 ml, cooling, and scratching gave 10 mg of homogeneous **8d**: mp 174–175°; uv max (MeOH) 235 nm (ϵ 11,600), 248–260 (broad shoulder, ϵ 10,900), and 404 (14,600); uv max (MeOH–HCl) 236 nm (ϵ 12,900), 247 (shoulder, 11,700), and 338 (10,800); mass spectrum (70 eV) M^+ *m/e* 385.

2-(2-Benzylthio)ethyl-1,2,3,4-tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-Dioxide (7g). This procedure is illustrative of the reactions of sodium mercaptides with **3g** (Table II). Two equivalents each of sodium methyl and benzyl mercaptide and 1 equiv of thiophenolate were used. These reactions generated **6**, which was also independently shown to undergo ring-opening reactions with thiophenolate and methyl mercaptide anions.

To 20 ml of MeOH was added 0.69 g (0.027 g-atom) of sodium. After the sodium had dissolved, excess MeOH was removed *in vacuo*; 20 ml of DMF was added followed by 3.41 g (0.027 mol) of benzyl mercaptan. To this solution was added with stirring 5.0 g (0.013 mol) of **3g** followed by 50 ml of DMF. Tlc indicated rapid conversion to **6**. Heating was employed to complete conversion of **6** to **7g**. An aqueous work-up followed by recrystallization from acetone–H_2O gave 3.75 g of pure **7g**, ir ($CHCl_3$) 1625 and 1595 cm^{-1}.

3,4-Dihydro-2-(2-hydroxy)ethyl-1-phenethylaminopyrazino-[1,2-*b*][1,2]benzothiazin-11(2*H*)-one 6,6-Dioxide (8a). To 20 ml of absolute EtOH containing 9.1 g (0.075 mol) of phenethylamine was added 75 ml of the dioxane–EtOH solution of **3h** (*ca.* 0.025 mol). The reaction mixture was allowed to stir overnight at ambient temperatures. After removal of solvent *in vacuo* the residue was triturated with water–dilute aqueous $NaHCO_3$ (5%) and the aqueous layer was discarded. The resulting gummy solid was taken up in MeOH. Cooling and scratching gave crystals which were recrystallized from acetone–MeOH, affording 2.5 g (24%) of pure **8a**: mp 144–146°; uv max (MeOH) 252 nm (ϵ 10,300) and 388 (12,000); uv max (MeOH–HCl) 247 nm (ϵ 10,800), 275–300 (broad shoulder, ~7000), and 329 (10,700); ir (KBr) 1573, 1550 (shoulder), and 1540 cm^{-1}.

Anal. Calcd for $C_{21}H_{23}N_3O_4S$: C, 61.00; H, 5.61; N, 10.16; S, 7.76. Found: C, 60.97; H, 5.66; N, 10.17; S, 7.75.

Compound **8a** was also prepared from (1) **3g** (1 mol) and phenethylamine (3 mol) in DMF, and (2) from **6** (1 mol) and phenethylamine (3 mol) in DMF. The product from each of these reactions was identical in all respects with **9a** prepared from **3h**.

1-Amino-3,4-dihydro-2-(2-hydroxy)ethylpyrazino[1,2-*b*][1,2]benzothiazin-11(2*H*)-one 6,6-Dioxide (8b). To 2 pints of rapidly stirred aqueous NH_3 (28%) was added 58.26 g (0.15 mol) of **3g**. The starting material dissolved, and upon continued stirring yellow crystals separated. Tlc indicated the presence of **6** in the mixture. Stirring was continued until **6** disappeared. Filtration and recrystallization from $CHCl_3$–EtOH (95%) gave pure **8b**: mp 204–206° dec; uv max (MeOH) 246–252 nm (broad shoulder, ϵ 9360), 254 (9450), and 379 (12,300); uv max (MeOH–HCl) 253 nm (ϵ 9700), 294 (shoulder, 5400), and 340 (12,600); ir (KBr) 1592 (shoulder), 1580, 1560, and 1540 cm^{-1}; nmr (DMSO-d_6) δ 9.25 (broad, enol OH), 8.25–8.0 (m, 1, aromatic), 7.85–7.6 (m, 3, aromatic), 5.13 (t, 1, CH_2OH), 3.9–3.3 (m, 8, two A_2B_2 patterns).

Anal. Calcd for $C_{13}H_{15}N_3O_4S$: C, 50.47; H, 4.89; N, 13.58; S, 10.37. Found: C, 50.32; H, 4.99; N, 13.53; S, 10.35.

3,4-Dihydro-2-(2-hydroxy)ethyl-1-methylaminopyrazino[1,2-*b*][1,2]benzothiazin-11(2*H*)-one 6,6-Dioxide (8c). This preparation was carried out in DMF saturated with methylamine (anhydrous) using 20.0 g (0.052 mol) of **3g**. After solvent removal *in vacuo*, treatment with H_2O threw down a solid which was recrystallized from acetone–H_2O, affording 9.5 g (59%) of pure **8c**: mp 174–175°; uv max (MeOH) 252 nm (ϵ 9500) and 385 (12,600); uv max (MeOH–HCl) 248 nm (ϵ 9900) and 328 (10,400); ir (KBr) 1600, 1590, and 1550 cm^{-1}; nmr (DMSO-d_6) δ 10.47 (broad, enol H), 8.2–7.9 (m, 1, aromatic), 7.85–7.5 (m, 3, aromatic), 5.08 (poorly resolved triplet, 1, CH_2OH), 3.8–3.4 (m, 8, two A_2B_2 patterns), 3.05 (d, 3, $NHCH_3$). The addition of DCl to the nmr solution caused collapse of the NHMe signal to a singlet.

Anal. Calcd for $C_{14}H_{17}N_3O_4S$: C, 52.00; H, 5.30; N, 12.99. Found: C, 51.93; H, 5.33; N, 13.32.

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Registry No.—**1**, 24683-21-4; **2a**, 151-56-4; **2c**, 1072-66-8; **2d**, 3164-46-3; **2e**, 1072-52-2; **3a**, 51016-24-1; **3b**, 51016-25-2; **3c**, 51016-28-5; **3d**, 51016-27-4; **3e**, 51016-26-3; **3f**, 51016-29-6; **3g**, 51016-30-9; **4**, 51015-24-8; **5**, 5016-31-0; **6**, 51016-32-1; **7a**, 51016-33-2; **7b**, 51016-34-3; **7c**, 51016-35-4; **7d**, 51016-36-5; **7e**, 51016-37-6; **7f**, 51016-38-7; **7g**, 51016-39-8; **7h**, 51016-40-1; **8a**, 51016-41-2; **8b**, 51016-42-3; **8c**, 51016-43-4; **8d**, 51016-44-5.

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(6) Oily tosylate ester **3f** was prepared initially and employed as a dioxane–ethanol solution in reactions with piperidine and phenethylamine. Since its reactions were later shown to be essentially identical with those of mesylate **3g**, discussion has been limited to **3g**.
(7) See paper I for instrumentation.

Nucleic Acid Related Compounds. 11. Adenosine 2′,3′-*ribo*-Epoxide. Synthesis, Intramolecular Degradation, and Transformation into 3′-Substituted Xylofuranosyl Nucleosides and the *lyxo*-Epoxide[1,2]

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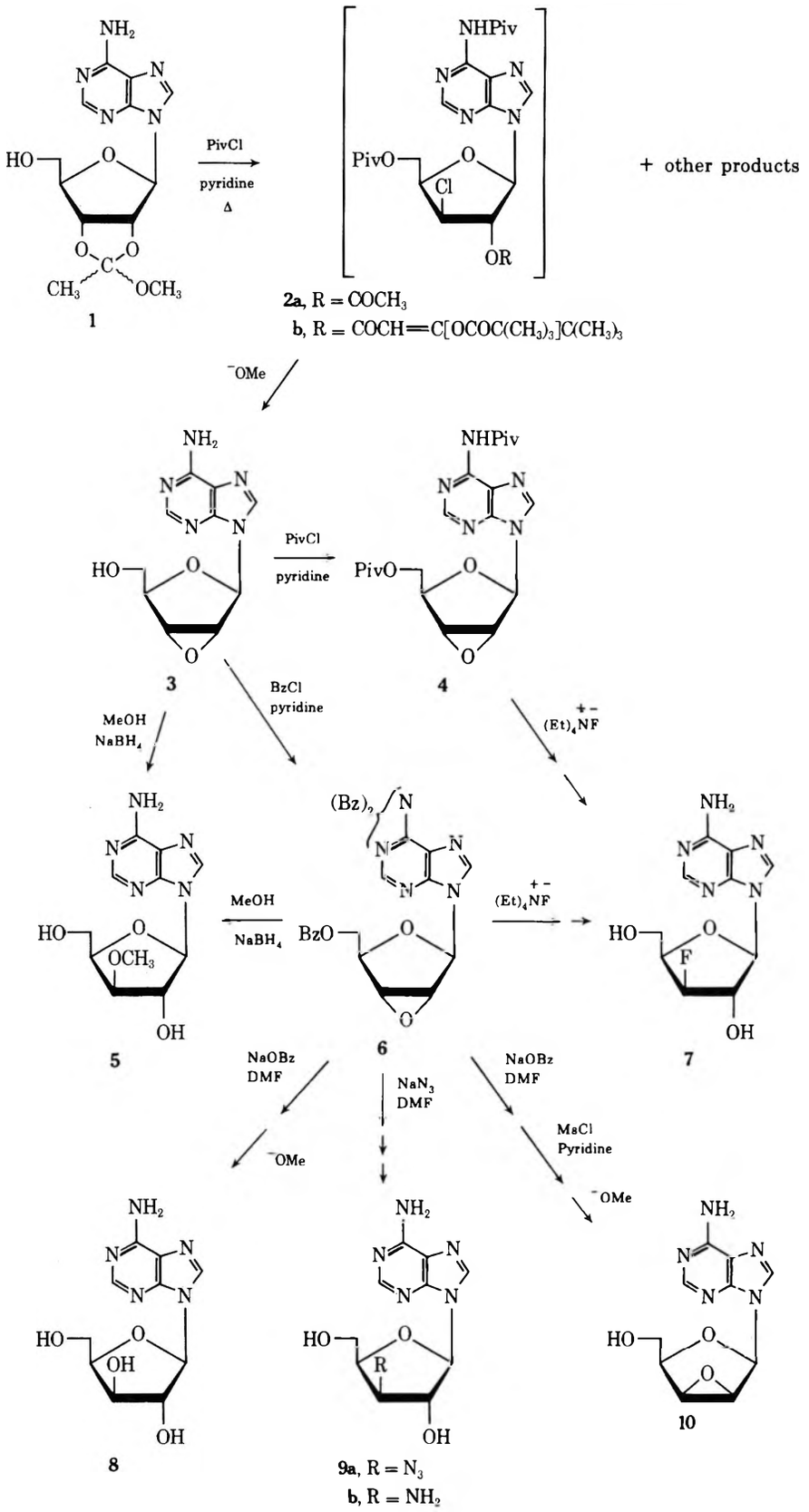
Treatment of 2′,3′-*O*-methoxyethylideneadenosine (**1**) with excess pivalic acid chloride in refluxing pyridine gave a mixture composed primarily of 6-*N*-pivalamido-9-(3-chloro-3-deoxy-2-*O*-acetyl-5-*O*-pivalyl-β-D-xylofuranosyl)purine (**2a**) and 6-*N*-pivalamido-9-(3-chloro-3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivalyloxypent-2-enoyl]-β-D-xylofuranosyl)purine (**2b**) in high combined yield. Methanolic sodium methoxide converted this mixture to 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (adenosine *ribo*-epoxide) (**3**) in greater than 60% overall yield from starting adenosine. The epoxide **3** was found to spontaneously decompose (presumably *via* the $N^3 \rightarrow 3'$-*xylo*-cyclonucleoside, i) to the ring-opened aminoimidazole carboxamidine cyclonucleoside ii in water. Sodium hydroxide smoothly effected transformation of ii to the corresponding carboxamide, iii. Pivalylation and benzoylation of **3** in pyridine with the appropriate acid chloride gave 6-*N*-pivalamido-9-(5-*O*-pivalyl-2,3-anhydro-β-D-ribofuranosyl)purine (**4**) and the corresponding $N,N,O^{5'}$-tribenzoate, **6**, respectively. Tetraethylammonium fluoride in refluxing acetonitrile followed by methoxide deblocking converted **4** or **6** into 9-(3-fluoro-3-deoxy-β-D-xylofuranosyl)adenine (**7**). Reaction of **6** with sodium benzoate in moist DMF followed by deblocking gave 9-β-D-xylofuranosyladenine (adenine xyloside) (**8**) in high yield. Treatment of **6** with sodium azide in hot DMF gave 9-(3-azido-3-deoxy-β-D-xylofuranosyl)adenine (**9a**) in excellent yield after removal of protecting groups. Hydrogenation of **9a** gave 9-(3-amino-3-deoxy-β-D-xylofuranosyl)adenine (**9b**). Treatment of the crude product [presumably a mixture of N-benzoylated 9-(3,5-di-*O*-benzoyl-β-D-xylofuranosyl)adenines] from sodium benzoate reaction with **6** with methanesulfonyl chloride in pyridine gave a monomesyl ester. This material was converted into 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (**10**) upon stirring with methanolic sodium methoxide. Sodium borohydride in methanol effected epoxide ring opening of **6** by methoxide. Treatment of the unblocked epoxide **3** with sodium borohydride in refluxing methanol gave high yields of 9-(3-*O*-methyl-β-D-xylofuranosyl)adenine (**5**) directly with no apparent formation of cyclonucleoside products.

Epoxides are useful intermediates for the introduction of trans β-hydroxy functionality, and various anhydro ring openings have been explored in carbohydrate and nucleoside chemistry.[4] However, adenine nucleoside epoxides had previously been somewhat difficultly accessible by coupling of suitably substituted and stereochemically oriented sugar derivatives with the base followed by subsequent anhydro-forming transformations.[5-8] Certain attempted nucleophilic openings of such *ribo*-epoxides have been unsuccessful owing to N^3 intramolecular attack leading to presumed $N^3 \rightarrow 3'$-cyclonucleosides[7,9] (however, see ref 5, 6, and 9 for successful displacements). We wish to report a convenient and direct synthetic route to *ribo*-epoxides from the corresponding ribonucleosides, preliminary results on their intramolecular degradation, and their transformation into 3′-substituted *xylo*-nucleosides.

Treatment of 2′,3′-*O*-methoxyethylideneadenosine[10,11] (**1**) with excess pivalic acid chloride in refluxing pyridine gave a mixture composed primarily of 6-*N*-pivalamido-9-(3-chloro-3-deoxy-2-*O*-acetyl-5-*O*-pivalyl-β-D-xylofuranosyl)purine[11,12] (**2a**) and 6-*N*-pivalamido-9-(3-chloro-3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivalyloxypent-2-enoyl]-β-D-xylofuranosyl)purine[11,12] (**2b**). The crude mixture was treated with methanolic sodium methoxide at room temperature to give 9-(2,3-anhydro-β-D-ribofuranosyl)adenine[5,6,13,14] (**3**) in 63% overall yield from **1**. A small amount of contaminating 9-(2-chloro-2-deoxy-β-D-arabinofuranosyl)adenine[11,13,14] was separated from **3** using the useful Dowex 1-X2 (OH^-) column procedure devised by Dekker.[15] This compound is converted into **3** upon more vigorous treatment with base[13,14] than required for the 3′-chloro isomer.

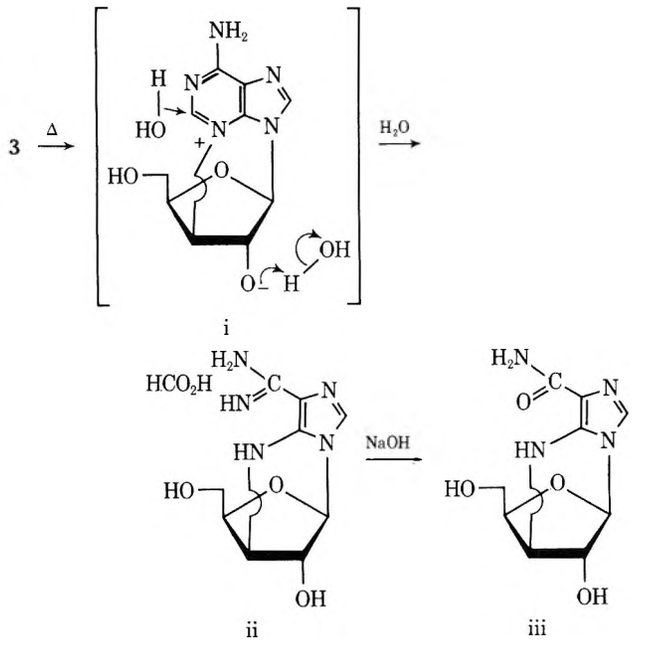
Epoxide **3**, which has been prepared from adenosine by a recently reported[14] alternative procedure, had properties generally consistent with recorded values.[5,6,14] Its melting–decomposition range depends on the rate of heating and its ^1H nmr spectrum has $J_{1'-2'}$ and $J_{3'-4'} \cong 0$.[14] However, it is susceptible to purine ring opening, presumably *via* the $N^3 \rightarrow 3'$-cyclonucleoside i, especially in aqueous solution. In water at room temperature, degradation occurs slowly, but at 80° decomposition is essentially complete after 4 hr (see Figure 1 for a uv absorption *vs.* time study at pH 7). Goodman and coworkers have noted the formation of water-soluble products in reactions of adenine nucleosides involving 2′,3′-*ribo*-epoxides[7,9] and episulfonium[16] intermediates. They postulated $N^3 \rightarrow 3'$-cyclonucleoside structures analogous to i on the basis of salt-like properties and a bathochromic shift in the uv absorption maximum. It should be noted, however, that the shift observed in going from the nucleoside (~260 nm) to the postulated $N^3 \rightarrow 3'$-cyclonucleosides[7,9,16] (~293 nm) is 33 nm, whereas a shift of about 12 nm to ~272 nm is ordinarily found with known adenine $N^3 \rightarrow 5'$-cyclonucleosides.[17] The uv maxima of the postulated $N^3 \rightarrow 3'$-cyclonucleosides[7,9,16] at ~293 nm is in reasonable agreement with that of a $N^3 \rightarrow 5'$-cyclonucleoside in the puromycin aminonucleoside series (288 nm).[18] However, the 6-*N*,*N*-dimethylaminopurine nucleoside precursor in that case[18] had its uv maximum at 275 nm, which again corresponds to a 13-nm shift. Uv absorption in the 280–290-nm range has been reported for 5-aminoimidazole-4-carboxamidine.[19,20] It is also of interest that, whereas the $N^3 \rightarrow 5'$-cyclonucleoside of the puromycin aminonucleoside derivative had a negative optical rotation,[18] the derived product of pyrimidine ring opening, 5-amino-1-(3-amino-3-deoxy-2, 3-carbonyl-β-D-ribofuranosyl)imidazole-4-carboxamide $N^5 \rightarrow 5'$-cyclonucleoside[18,20] had a large positive rotation.

The initial product *isolated* from the decomposition of **3** in boiling water had spectral properties in accord with the long-wavelength material of Figure 1. The compound was finally crystallized using ether diffusion into methanol (see Experimental Section) and had elemental analyses compatible with **3** plus two molecules of water. It was strongly basic (spectrophotometrically estimated $pK_a \cong 11.5$), migrated toward the cathode during electrophoresis, had a large positive optical rotation and circular di-



chroism spectrum similar to that of the carboxamide iii, and gave a mass spectral peak at m/e 239 as the highest mass peak. These properties are in accord with the structure ii, 5-amino-1-3-deoxy-β-D-xylofuranosyl)imidazole-4-carboxamidine $N^5 \rightarrow 3'$-cyclonucleoside hydroformate salt,[20a] which would be expected to vaporize as the free base in the mass spectrometer. Attack of water on the positively polarized C^2 of the initially formed $N^3 \rightarrow 3'$-cyclonucleoside intermediate, i, followed by hydrolysis of the resulting ring-opened N^5-formyl derivative in the hot aqueous solution, could lead to ii.

Treatment of this solution with sodium hydroxide resulted in a uv spectral shift to 274 nm, which is compatible[18-20] with conversion of ii into 5-amino-1-(3-deoxy-β-D-xylofuranosyl)imidazole-4-carboxamide $N^5 \rightarrow 3'$-cyclonucleoside (iii). Structure iii is supported by elemental analysis, mass spectroscopy (M^+ m/e 240), spectrophotometrically estimated pK_a = 2.76, uv absorption,[18,19] and ^1H



i ii iii

nmr spectroscopy. Irradiation of the peak corresponding to H_3' caused the H_2' multiplet to collapse into a doublet ($J_{2'-2'\text{-OH}}$ = 3.2, $J_{2'-1'} \cong 0$ Hz) and the N^5-H doublet to collapse into a singlet. Further double-resonance experiments verified the peak assignments and thus, C3′-N5 D-xylofuranosyl)imidazole-4-carboxamide $N^5 \rightarrow 3'$-cyclonucleosides is now placed on a firm experimental basis.[21a] A detailed study of the intramolecular decomposition of various nucleoside epoxides and investigation of products formed will be reported separately.[21b]

An additional point concerning the epoxide **3** *per se* is its optical activity. Goodman and coworkers reported $[\alpha]^{26}D$ −18.3° (*c* 0.6, 20% aqueous pyridine) for a solid which had "several trace spots as contaminants."[6] They recorded $[\alpha]^{26}D$ −17.5° (c 0.4, 20% aqueous pyridine) and $[\alpha]^{26}D$ −35.2° (c 0.33, H_2O) for an analytical sample (see footnote 11 in ref 6). Moffatt and coworkers[14] report $[\alpha]^{23}D$ −21.8° (*c* 0.2, H_2O) and quoted the $[\alpha]D$ −18.3° value, with no concentration nor solvent specified, from ref 6. A carefully purified and dried sample of **3**, which had no observable cyclonucleoside breakdown products nor other impurities when applied heavily to a tlc plate, had $[\alpha]^{24}D$ −35.4° (c 0.22, H_2O) and −20.4° (c 0.4, 20% aqueous pyridine) in close agreement with Goodman's values.[6] Considerable care must be exercised in working with **3**, especially in aqueous solutions, since decomposition to highly dextrorotatory products occurs.

Owing to the instability observed with **3**, adenine ring-acylated derivatives were prepared. Jahn[22] has reported that such N-acylated adenosine 5′-tosylates were effective substrates for nucleophilic displacement reactions whereas the unprotected nucleoside readily forms $N^3 \rightarrow 5'$-cyclonucleoside under those conditions. Treatment of **3** with pivalic acid chloride in pyridine at room temperature gave 6-*N*-pivalamido-9-(5-*O*-pivalyl-2,3-anhydro-β-D-ribofuranosyl)purine (**4**) in essentially quantitative yield. Benzoylation similarly afforded an *N,N,O*5-tribenzoyl derivative, **6**. Bis-N-benzoylation has usually been assigned N^1,N^6-dibenzoyl structures[23] after the suggestion of Khorana;[23a] however, the N^6,N^6-dibenzoyl isomer was postulated recently.[24]

Treatment of either **4** or **6** with tetraethylammonium fluoride in dry acetonitrile at reflux for an extended period effected epoxide ring opening by fluoride. After deblocking and purification on a Dekker column,[15] 9-(3-fluoro-3-deoxy-β-D-xylofuranosyl)adenine (**7**) was obtained in over 60% yield. Physical properties of **7** were generally in agreement with values reported[25] for a sample prepared by coupling of 2,5-di-*O*-benzoyl-3-fluoro-3-deoxy-α,β-D-xylofuranosyl bromide and 6-benzamidopurine mercury salts. No 2′-fluoro isomer[26] was observed in our sequence of **6** → **7**, although a small amount of 9-β-D-xylofuranosyladenine (**8**) was formed. Tolman and coworkers[27] recently reported obtaining only the product of 3′ attack upon reaction of 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine with KHF_2 in refluxing ethylene glycol.

Sodium benzoate in hot DMF containing some water[28] converted **6** into a presumed mixture of mono- and di-N-benzoylated 9-(3,5-di-*O*-benzoyl-β-D-xylofuranosyl)adenine intermediates which were deblocked to give almost quantitative yields of 9-β-D-xylofuranosyladenine[29] (**8**). Previously recorded physical constants for **8** are rather ill defined.[29] Acid hydrolysis of **8** and paper chromatography[30] of the sugar *vs.* the four aldopentoses showed only xylose present. The ^1H nmr spectrum was in agreement with reported values.[29b,31] The mass spectrum agreed with the tabulation of McCloskey and coworkers.[32] The melting point, ~185° with decomposition, is dependent on how it is heated and previous values[29] differ. The $[\alpha]^{25}D$ −67° (c 1.14, H_2O) of **8** is significantly more strongly levorotatory than recorded for other preparations.[29b-d] All of those, however, involved coupling procedures and anomer contamination was possible. This sequence of reactions represents the transformation of a naturally occurring ribonucleoside to its xylo epimer. Such schemes should be applicable to nucleoside antibiotics which are readily accessible by fermentation but which are not practically amenable to base-sugar (or fraudulent sugar) coupling procedures.[33]

Treatment of **6** with sodium azide in hot DMF[34] followed by deblocking gave high yields of 9-(3-azido-3-deoxy-β-D-xylofuranosyl)adenine (**9a**). A trace of presumed 2′-azido isomer was separated by column chromatography[15] and its structure was suggested by the absence of ion d[32] in its mass spectrum, which is characteristic for nucleosides with a 2′-hydroxyl function, as well as other fragmentation effects compatible with the 2′-azido structure. Catalytic hydrogenation of **9a** to give 9-(3-amino-3-deoxy-β-D-xylofuranosyl)adenine (**9b**) proceeded smoothly. This product is seen to be the 3′ epimer of N^6-bis(demethyl)puromycin aminonucleoside.

Treatment of the crude product of reaction of **6** with sodium benzoate-DMF with methanesulfonyl chloride in cold pyridine gave a monomesylate, which was converted to 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine[8] (**10**) by methanolic sodium methoxide. Direct access to this useful[8,35] *lyxo*-epoxide type from naturally occurring ribonucleosides is thus provided.

Reaction of **6** with a large excess of sodium borohydride in methanol proceeded slowly at room temperature to give 9-(3-*O*-methyl-β-D-xylofuranosyl)adenine (**5**) after deblocking. Alternatively, heating **3** in methanol at reflux with sodium borohydride proceeded to give **5** without apparent cyclonucleoside formation. An analogous reaction has been reported very recently[36] in the steroid series. Interestingly, heating a methanolic sodium methoxide solution of **3** at reflux gives but a trace of product migrating (tlc) with **5** plus material not moving from the origin. Inhibitory biological activity of 9-β-D-xylofuranosyladenine (**8**) has been reported[29c,e,37] and the investigation of *O*-methyl ethers of biochemically important nucleosides is of current interest.[38]

The mass spectra of these compounds in general followed trends outlined by McCloskey and coworkers.[32] Certain characteristic fragment ions are listed in Table I. An interesting fragmentation of the epoxides **3** and **10** was

Table I
Characteristic Mass Spectral Ions[a]

Compd	Temp, °C	*m/e* (rel intensity) M	c	d	h	f	b + H	b + 2H	Other selected ions
3	190	249 (4.5)	219 (4.5)		164 (100)	148 (7.5)	135 (85)	136 (48)	202 (2, c − 17), 190 (4.5, j)
5	200	281 (5)	251 (5)	178 (9)	164 (100)	148 (15)	135 (85)	136 (60)	250 (3, M − 31), 220 (7.5, c − 31), 194 (3, i)
7	155	269 (4)	239 (5)	178 (6)	164 (80)	148 (6)	135 (100)	136 (62)	219 (5, c − 20)
8	170	267 (6)	237 (3)	178 (36)	164 (65)	148 (12)	135 (100)	136 (95)	220 (5, c − 17), 194 (6, i), 190 (1.5, j)
9a	120	292 (6)		178 (20)	164 (50)	148 (20)	135 (100)	136 (50)	264 [2, M − 28 (N_2)], 250 [10, M − 42 (N_3)], 220 [30, c − 42 (N_3)]
9b	210	266 (1.5)	236 (4.5)	178 (15)	164 (15)	148 (7.5)	135 (50)	136 (100)	220 (3, c − 16), 194 (32, i)
10	190	249 (5)	219 (6)		164 (100)	148 (10)	135 (45)	136 (45)	202 (1, c − 17), 190 (3, j)

[a] Ions named by letters as in ref 32.

observed, giving an ion corresponding to the loss of 17 mass units (presumably the epoxide oxygen plus a hydrogen) from ion c (M − 30, loss of $C^{5'}$ as formaldehyde)[32] at *m/e* 202.0721 (calcd for $C_9H_8N_5O$, 202.0729). Neither **3** nor **10** gave a measurable ion d (protonated base plus $C^{1'}$, $C^{2'}$, and group attached to $C^{2'}$)[32] nor ion i (involves transfer of active hydrogen from a heteroatom on $C^{3'}$). Since ions e and f were postulated[32] to arise from ion d, the reasonably high abundance of ion f in the spectra of **3** and **10** would demand alternate routes. Ion h (protonated adenine plus a formyl group derived from $C^{1'}$, $H^{1'}$, and $O^{4'}$)[32] is seen to be the mass spectral base peak for the two epoxides **3** and **10**. This is of interest since the major pathway previously postulated[32] involves transfer of a hydrogen from the 2′-hydroxyl group in most nucleosides, and ion h was of low intensity in 2′-deoxy derivatives studied where proton transfer from carbon was assumed.[32] The azido nucleoside **9a** undergoes facile loss of the azide function. In fact, no peak corresponding to loss of $C^{5'}$ as formaldehyde (ion c[32]) was measurable, although a large peak was present at *m/e* 220 (c − N_3). A peak corresponding to loss of the 3′ substitutent (and also a proton in the cases of **3**, **7**, and **10**) from ion c was observed with each of the free nucleosides.

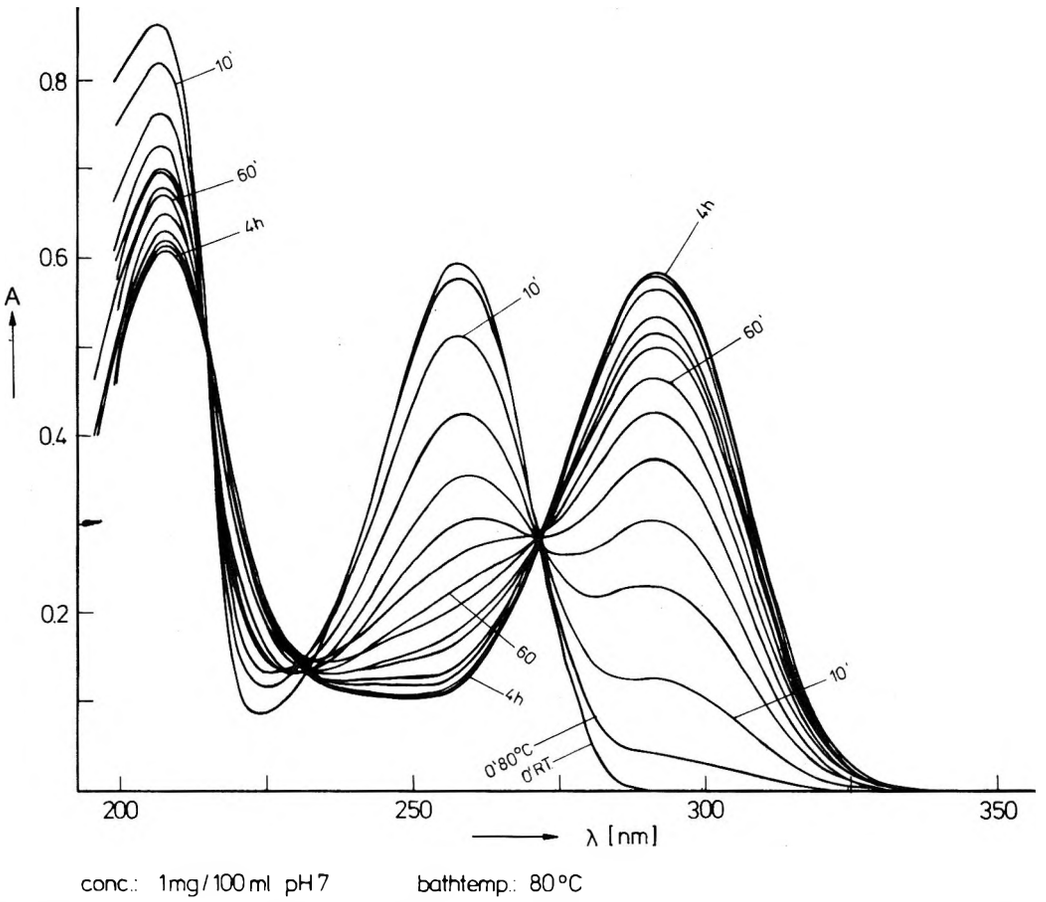


Figure 1. Ultraviolet absorption *vs.* wavelength of a solution of **3** in aqueous solution measured at various times up to 4 hr. No further significant change occurs over at least 10 hr.

This study demonstrates an example of a facile direct conversion of ribonucleosides into their 2′,3′-anhydro derivatives and the first generally successful transformation of acylated[39] *ribo*-epoxides into a selected series of xylofuranosyl products and the *lyxo*-epoxide **10**. Studies on other nucleoside epoxides, 2′,3′-anhydronucleoside degradations,[21] and further useful synthetic transformations employing nucleoside 2′,3′-ortho esters[11,12] will be reported in detail.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Nmr spectra were recorded on Varian 56/60, HA-100, and Bruker 90 spectrometers with TMS or DSS as reference for proton spectra. Uv spectra were recorded on Cary 14 and 15 spectrometers. CD spectra were obtained on a Cary Model 60 instrument. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter using a 10-cm 1-ml microcell. Mass spectra were determined by the mass spectroscopy laboratory of this department on AEI MS-2 and MS-9 instruments at 70 eV using a direct probe for sample introduction. Elemental analyses were determined by the microanalytical laboratory of this department and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Evaporations were effected using Büchler rotating evaporators under aspirator or mechanical oil pump vacuum at 40° or lower. Thin layer chromatography (tlc) was performed on Eastman Kodak chromatogram sheets (silica gel 13181). Column chromatography was effected using J. T. Baker 3405 silica gel.

9-(2,3-Anhydro-β-D-ribofuranosyl)adenine[5,6,13,14] (3). To a solution of 2.9 g (0.009 mol) of **1**[10,11] in 60 ml of dry pyridine was added 12 ml (0.1 mol) of pivalic acid chloride dropwise with stirring and exclusion of moisture. The solution was then slowly (1 hr) heated to reflux and refluxed for 1 hr. The resulting yellow solution was allowed to cool to room temperature and 20 ml of MeOH was added dropwise with stirring. This solution was evaporated until precipitation of solid began. Dry Et_2O (100 ml) was added and the mixture was filtered. The filtrate was washed with 2 × 100 ml of 10% $NaHCO_3$ solution and 2 × 100 ml of H_2O, dried over Na_2SO_4, filtered, and evaporated to give a yellow solid foam. This material (composed primarily of **2a** and **2b**)[11,12] was dissolved in 300 ml of MeOH and 3.2 g (0.059 mol) of $NaOCH_3$ was added. The resulting solution was stirred for 17 hr at room temperature, neutralized with HOAc–H_2O (1:9), and evaporated to give a yellow powder. Residual pyridine was removed by codistillation with 3 × 60 ml of dry toluene. The product mixture was partitioned between Et_2O–H_2O (50:20 ml) and the aqueous layer was applied to a column (4 × 40 cm) of Dowex 1-X2 (OH^-) resin packed in MeOH–H_2O (3:7).[15] The column was *rapidly* developed with the same solvent mixture and the appropriate fractions containing pure **3** (tlc) were combined and evaporated to give 1.42 g (63%) of solid **3** after drying. This material had mp ~180° dec (when rapidly heated); $[\alpha]^{24}D$ −35.4° (*c* 0.22, H_2O); uv (H_2O) max 258 nm (ε 14,900), min 225 (2200); uv (0.1 *N* HCl) max 255 nm (ε 14,600), min 228 (3400); uv (0.1 *N* NaOH) max 258 nm (ε 15,000), min 228 (4000); $pK_a \cong 3.55$; nmr (DMSO-d_6) δ 3.58 (m, 2, $H_{5',5''}$), 4.2 ("t", $J_{4'-5',5''} \cong 5$ Hz, 1, $H_{4'}$), 4.25 (d, $J_{3'-2'} = 2.5$ Hz, 1, $H_{3'}$), 4.45 (d, $J_{2'-3'} = 2.5$ Hz, 1, $H_{2'}$), 5.1 (t, 1, 5′-OH), 6.22 (s, 1, $H_{1'}$), 7.26 (s, 2, 6-NH_2), 8.18 (s, 1, H_2), and 8.35 (s, 1, H_8). (See discussion and ref 6 and 14 for literature comparisons.)

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N. 28.10. Found: C, 48.43; H, 4.62; N, 28.05.

6-*N*-Pivalamido-9-(5-*O*-pivalyl-2,3-anhydro-β-D-ribofuranosyl)adenine (4). To a suspension of 0.13 g (0.0005 mol) of **3** in 5 ml of dry pyridine was added 0.5 ml (0.004 mol) of freshly distilled pivalic acid chloride and the resulting clear solution was stirred for 28 hr at room temperature. Ice chips were added and the solution was poured slowly with stirring into 150 ml of ice and water. This mixture was extracted with 2 × 150 ml of $CHCl_3$ and the combined organic phase was washed with 2 × 100 ml of 10% aqueous $NaHCO_3$ solution and 2 × 100 ml of H_2O and dried over Na_2SO_4. Drying agent was removed by filtration and the filtrate was evaporated to give 0.21 g (100%) of a pale yellow powder. A more rapidly migrating (tlc) contaminant was readily removed by recrystallization from 95% EtOH to give 0.19 g (92%) of **4**: mp 176–179° dec; uv (MeOH) max 270 nm (ε 18,500), min 230 (3800); nmr (DMSO-d_6) δ 1.0 [s, 9, 5′-OCOC(CH_3)$_3$], 1.28 [s, 9, 6-NHCOC(CH_3)$_3$], 4.0–4.4 (m, 4, $H_{4'}$, $H_{5',5''}$, $H_{3'}$), 4.58 (d, $J_{2'-3'} = 2.5$ Hz, 1, $H_{2'}$), 6.36 (s, 1, $H_{1'}$), 8.60, 8.71 (s, s; 1, 1; H_2, H_8), 10.16 (s, 1, 6-N**H**-Piv); mass spectrum (175°) *m/e* (rel intensity, ion) 417 (4, M), 332 [16, M − COC(CH_3)$_3$], 316 [4, M − OCOC(CH_3)$_3$], 220 (16, b + 2), 199 (28, sugar).

Anal. Calcd for $C_{20}H_{27}N_5O_5$: C, 57.53; H, 6.52; N, 16.77. Found: C, 57.35; H, 6.45; N, 16.58.

***N*,*N*-Dibenzoyl-9-(5-*O*-benzoyl-2,3-anhydro-β-D-ribofuranosyl)adenine (6).** To a suspension of 1.46 g (0.0059 mol) of **3** in 36 ml of dry pyridine was added 3.6 ml (0.031 mol) of freshly distilled benzoyl chloride and the resulting clear solution was stirred for 8 hr at room temperature. Ice chips were added and the solution was poured slowly into 1000 ml of ice and water with vigorous stirring. The resulting white precipitate was filtered, washed with 1000 ml of cold water, and dried (finally *in vacuo* at 78°) to give 2.7 g (82%) of **6**. Recrystallization of 0.2 g of this product from 16 ml of EtOH gave 0.15 g of pure **6**: mp 167–168°; uv (MeOH) max 273, 230 nm (ε 22,600, 35,000), shoulder 250 (27,800); nmr (DMSO-d_6) δ 4.45 (br s, 2, $H_{5',5''}$), 4.6 (m, 2, $H_{3'}$, $H_{4'}$), 4.7 (d, $J_{2'-3'} \cong 3$ Hz, 1, $H_{2'}$), 6.42 (s, 1, $H_{1'}$), 7.3–7.8 (m, 15, aromatic), 8.72, 8.78 (s, s; 1, 1; H_2, H_8); mass spectrum (210°) *m/e* (rel intensity, ion) 561 (25, M), 456 (100, M − COC_6H_5), 440 (37, M − $OCOC_6H_5$), 219 (30, sugar).

Anal. Calcd for $C_{31}H_{23}N_5O_6$: C, 66.30; H, 4.13; N, 12.47. Found: C, 66.08; H, 3.85; N, 12.25.

9-(3-Fluoro-3-deoxy-β-D-xylofuranosyl)adenine[25] (7). To a solution of 0.28 g (0.0005 mol) of **6** in 25 of dry, freshly distilled CH_3CN was added 0.45 g (0.003 mol) of dried tetraethylammonium fluoride. The yellow solution was heated at reflux for 5 days while protected from moisture by a Drierite drying tube and then evaporated. The resulting gum was dissolved in 100 ml of MeOH, 1.0 g (0.019 mol) of sodium methoxide was added, and the solution was stirred for 15 hr at room temperature. This mixture was neutralized with HOAc–H_2O (1:9) and evaporated. The resulting residue was partitioned between 20 ml of Et_2O and 10 ml of H_2O. The aqueous phase was applied to a column (2.2 × 17 cm) of Dowex 1-X2 (OH^-) resin packed in MeOH–H_2O (3:7) and elution was begun with the same solvent mixture. A small quantity (27 mg) of material indistinguishable from 9-β-D-xylofuranosyladenine (**8**) by nmr and mass spectroscopy was obtained, and after changing to MeOH–H_2O (6:4), the desired product, **7**, was eluted. Evaporation of appropriate fractions and crystallization of the residue from 95% EtOH gave 0.085 g (63%) of **7**: mp 212–214°; $[\alpha]^{24}D$ −30.4° (*c* 0.64, DMF) [lit. mp 218–220°; $[\alpha]^{21}D$ −40.1° (*c* 0.5, H_2O); our product was insoluble in H_2O at half this attempted concentration]; uv (0.1 *N* HCl) max 256 nm (ε 14,100), min 228 (4300); uv (H_2O) max 258 nm (ε 14,100), min 223 (2800); uv (0.1 *N* NaOH) max 258 nm (ε 14,300), min 228 (4000); ^1H nmr (DMSO-d_6) δ 3.85 ("d," 2, $H_{5',5''}$), 4.36 (d of sextets, $J_{4'-3'-F} = 28$ Hz, $J_{4'-5',5''} \cong 5.5$ Hz, $J_{4'-3'} \cong 2.5$ Hz, 1, $H_{4'}$), 4.78 (d of t, $J_{2'-3'-F} = 16$, $J_{2'-3'} \cong J_{2'-1} = 2.3$ Hz, 1, $H_{2'}$), 5.1 ("t," $J_{5'-OH-5',5''} \cong 6$ Hz, 1, 5′-OH, 5.13 (d of "t," $J_{3'-3'-F(gem)} = 54$, $J_{3'-2'} \cong 2.3$, $J_{3'-4'} \cong 2.5$ Hz, 1, $H_{3'}$), 6.04 (d, $J_{1'-2'} = 2.3$ Hz, 1, $H_{1'}$), 6.25 (br s, 1, 2′-OH), 7.36 (s, 2, 6-NH_2), 8.14, 8.22 (s, s; 1, 1; H_2, H_8); ^{19}F nmr (DMSO-d_6, ppm upfield, CCl_3F external) δ 200.8 ["octet" (d of d of d), $J_{3'-F-3'(gem)} = 55$, $J_{3'-F-4'} = 28.5$, $J_{3'-F-2'} = 15.5$ Hz, 1, $F_{3'}$].

Anal. Calcd for $C_{10}H_{12}FN_5O_3$: C, 44.61; H, 4.45; F, 7.06; N, 26.01. Found: C, 44.68; H, 4.52; F, 7.03; N, 26.20.

9-β-D-Xylofuranosyladenine[29] (8). To a solution of 0.56 g (0.001 mol) of **6** in 50 ml of DMF containing 2 ml of water was added 0.3 g (0.002 mol) of sodium benzoate. This mixture was heated at 100° for 22 hr with stirring and then evaporated *in vacuo*. The resulting gum was partitioned between 100 ml of $CHCl_3$ and 50 ml of H_2O. The aqueous phase was extracted with 2 × 50 ml of $CHCl_3$ and the combined organic phase was washed with 2 × 100 ml of H_2O, dried over Na_2SO_4, filtered, and evaporated to give a pale yellow, solid foam.

This foam was dissolved in 100 ml of MeOH and 1 g (0.019 mol) of NaOMe was added. The solution was stirred for 16 hr at room temperature, neutralized with HOAc–H_2O (1:9), and evaporated. The residue was partitioned between 20 ml of H_2O and 50 ml of Et_2O and the aqueous phase was applied to a column (2.2 × 20 cm) of Dowex 1-X2 (OH^-) resin packed in MeOH–H_2O (3:7). Elution with the same solvent mixture and evaporation of appropriate fractions gave 0.26 g (100%) of **8**, which could be recrystallized from 95% EtOH to give 0.21 g (80%) of **8**: mp 185–187° dec; $[\alpha]^{25}D$ −67° (*c* 1.14, H_2O) [lit. mp 125–140°,[29a] 225–230°,[29b] 100–130°;[29c] $[\alpha]^{24}D$ −22.5° (*c* 1.22, H_2O),[29f] −16.4° (*c* 1.10, H_2O),[29b] −30.1° (*c* 1.2, H_2O),[29c] −19° (*c* 1.2, H_2O)[29d]]; uv (0.1 *N* HCl) max 255 nm (ε 15,000), min 228 (4000); uv (H_2O) max 258 nm (ε 15,100), min 225 (2400); uv (0.1 *N* NaOH) max 258 nm (ε 15,700), min 225 (3600); nmr (DMSO-d_6) δ 3.7 (m, 2, $H_{5',5''}$), 4.15 (m, 2, $H_{3'}$, $H_{4'}$), 4.35 (m, 1, $H_{2'}$), 4.72 (t, $J_{5'-OH-5',5''} = 6$ Hz, 1, 5′-OH), 5.78 (br s, 1, 3′-OH), 5.83 (br s, 1, 2′-OH), 5.85 [d, $J_{1'-2'} = 2$ Hz

(by D_2O exchange), 1, $H_{1'}$], 7.3 (s, 2, 6-NH_2), 8.15 (s, 1, H_2), 8.3 (s, 1, H_8).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.20. Found: C, 44.95; H, 4.96; N, 26.33.

9-(2,3-Anhydro-β-D-lyxofuranosyl)adenine[8,40] (10). The procedure given above for the preparation of 8 was followed to the end of the first paragraph. The resulting pale yellow solid foam was dissolved in 50 ml of dry, freshly distilled pyridine and cooled to 0°. Freshly distilled methanesulfonyl chloride (0.1 ml, 0.0013 mol) was added and the solution was stirred for 3 days at 0°. Ice chips were added and the solution was poured into 100 ml of ice water. This mixture was extracted with 150 ml of $CHCl_3$. The organic phase was washed with 100 ml of 10% aqueous $NaHCO_3$ solution and 100 ml of H_2O, dried over Na_2SO_4, filtered, and evaporated. The resulting residue was dissolved in 70 ml of MeOH and the solution was stirred with 0.4 g (0.0075 mol) of NaOMe for 16 hr at room temperature. This solution was neutralized with HOAc-H_2O (1:9) and 2.3 g of neutral silica gel was added. The mixture was evaporated to dryness and the impregnated powder was added to a column (2 × 28 cm, 47 g) of silica gel. The column was washed with EtOAc and the wash was discarded. The product was eluted using EtOAc–MeOH (8:2) and evaporation of appropriate fractions gave a yellow powder, which was crystallized from a mixture of 95% EtOH and *n*-pentane to give 0.126 g (50%) of **10**: mp 208–210° dec; $[\alpha]^{25}D$ −17.5° (c 0.19, H_2O) [lit.[40] mp 210–211°; $[\alpha]^{22}D$ −14° (c 1, H_2O)]; uv (0.1 *N* HCl) max 258 nm (ε 14,700), min 228 (2600); uv (H_2O) max 258 nm (ε 14,800), min 225 (2000); uv (0.1 *N* NaOH) max 258 nm (ε 14,600), min 225 (2500); nmr (DMSO-d_6) δ 3.6 (m, 2, $H_{5',5''}$), 4.14 (m, 2, $H_{3'}$, $H_{4'}$), 4.25 (d, $J_{2'-3'} \cong 3$ Hz, 1, $H_{2'}$), 5.0 (br s, 1, 5′-OH), 6.26 (s, 1, $H_{1'}$), 7.32 (s, 2, 6-NH_2), 8.18, 8.22 (s, s; 1, 1; H_2, H_8).

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 47.95; H, 4.76; N, 28.19.

9-(3-Azido-3-deoxy-β-D-xylofuranosyl)adenine (9a). To a solution of 1.11 g (0.002 mol) of **6** in 100 ml of dry, distilled DMF was added 1 g (0.015 mol) of sodium azide. The mixture was heated for 10 hr at 100° with stirring and then evaporated *in vacuo*. The resulting pale yellow gum was partitioned between 100 ml of $CHCl_3$ and 50 ml of H_2O and the aqueous layer was extracted with 2 × 25 ml of $CHCl_3$. The combined organic phase was washed with 2 × 50 ml of H_2O, dried over Na_2SO_4, filtered, and evaporated to give a pale yellow solid foam. This material was dissolved in 100 ml of MeOH and stirred for 21 hr at room temperature with 1 g (0.019 mol) of NaOMe. The solution was neutralized with HOAc-H_2O (1:9) and evaporated. The residue was partitioned between 50 ml of Et_2O and 20 ml of H_2O and the aqueous layer was evaporated to dryness. The residue was crystallized from H_2O to give 0.54 g (92%) of a pale yellow solid. This material was recrystallized from EtOH to give 0.49 g (83%) of **9a**: mp 177–178°; $[\alpha]^{24}D$ −128° (*c* 0.94, MeOH); uv (H_2O) max 260 nm (ε 15,100) min 232 (3000); nmr (DMSO-d_6) δ 3.65 (br s, 2, $H_{5',5''}$), 4.32 (m, 2, $H_{3'}$, $H_{4'}$), 4.8 ("t," $J_{2'-1'} = 6$, $J_{2'-3'} \cong 6$ Hz, 1, $H_{2'}$), 5.4 (br s, 1, 5′-OH), 5.85 (d, $J_{1'-2'} = 6$ Hz, 1, $H_{1'}$), 6.25 (br s, 1, 2′-OH), 7.35 (s, 2, 6-NH_2), 8.18 (s, 1, H_2), 8.3 (s, 1, H_8).

Anal. Calcd for $C_{10}H_{12}N_8O_3$: C, 41.09; H, 4.14, N, 38.34. Found: C, 41.35; H, 4.27; N, 38.54.

9-(3-Amino-3-deoxy-β-D-xylofuranosyl)adenine (9b). A solution of 0.37 g (0.0013 mol) of **9a** in 100 ml of 95% EtOH was hydrogenated at 45 psi (gauge pressure) for 48 hr at ambient temperature over 0.19 g of 5% Pd/C catalyst. The mixture was filtered, the filter cake was washed with 20 ml of hot EtOH, and the combined filtrate was evaporated to give a white solid which was recrystallized from 95% EtOH to give 0.27 g (81%) of **9b**: mp 250–251°; $[\alpha]^{24}D$ −30.1° (*c* 0.5, H_2O); uv (0.1 *N* HCl) max 255 nm (ε 14,500), min 225 (2500); uv (H_2O) max 258 nm (ε 14,300), min 225 (2000); uv (0.1 *N* NaOH) max 258 nm (ε 14,000), min 228 (3000); nmr (DMSO-d_6) δ 1.1 (t, J = 7 Hz, 3, CH_3CH_2OH), 1.8 (br s, 2, 3′-NH_2), 3.3–3.5 (m, 2, $H_{3'}$ and OH), 3.5 (q, J = 7 Hz, 2, CH_3CH_2OH), 3.7 (m, 2, $H_{5',5''}$), 4.16 (m, 1, $H_{4'}$), 4.39 ("t," $J_{2'-1'} \cong J_{2'-3'} \cong 6$ Hz, 1, $H_{2'}$), 5.6–5.74 (br d, $J_{1'-2'} \cong 6$ Hz, 2, $H_{1'}$ and OH), 7.3 (br s, 2, 6-NH_2), 8.16 (s, 1, H_2), 8.48 (s, 1, H_8).

Anal. Calcd for $C_{10}H_{14}N_6O_3 \cdot C_2H_5OH$: C, 46.13; H, 6.45; N, 26.91. Found: C, 45.93; H, 6.32; N, 27.00.

9-(3-*O*-Methyl-β-D-xylofuranosyl)adenine (5). To a suspension of 0.25 g (0.001 mol) of **3** in 50 ml of MeOH was added 1.15 g (0.03 mol) of $NaBH_4$. The mixture was heated for 12 hr at reflux with three further additions of 0.25-g portions of $NaBH_4$ after heating for 1, 4, and 6 hr. The solution was evaporated and the white residue was dissolved in 30 ml of H_2O. This solution was continuously extracted with 100 ml of CH_2Cl_2 for 24 hr and the organic phase was evaporated to give 0.28 g (~100%) of white product. A sample of this material (0.28 g) was purified by chromatography on Dowex 1-X2 (OH^-) using MeOH-H_2O (3:7) as the elution solvent mixture followed by evaporation and recrystallization of the residue from MeOH to give 0.24 g (85%) of **5**: mp 167–168°; $[\alpha]^{24}D$ −60.5° (c 0.3, MeOH); uv (0.1 *N* HCl) max 258 nm (ε 14,100), min 230 (3000); uv (H_2O) max 258 nm (ε 14,200), min 225 (2500); uv (0.1 *N* NaOH) max 259 nm (ε 14,400), min 230 (3700); nmr (DMSO-d_6) δ 3.3 (s, 3, 3′-OCH_3), 3.72 (br s, 2, $H_{5',5''}$), 3.80 (m, 1, $H_{3'}$), 4.28 (m, 1, $H_{4'}$), 4.56 ("t," $J_{2'-3'} = 2.5$, $J_{2'-1'} = 2.7$ Hz, $H_{2'}$), 4.86 (br s, 1, 5′-OH), 5.90 (br d, 2, $J_{1'-2'} = 2.7$ Hz, $H_{1'}$, 2′-OH), 7.26 (s, 1, 6 NH_2), 8.12 (s, 1, H_2), 8.18 (s, 1, H_8). The mass spectrum of this product had peaks corresponding to that of 3′-*O*-methyladenosine (with significant intensity variations) and different from that of 2′-*O*-methyladenosine.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.37; N, 24.90. Found: C, 46.98; H, 5.66; N, 24.70.

5-Amino-1-(3-deoxy-β-D-xylofuranosyl)imidazole-4-carboxamidine-$N^5 \rightarrow$3′-cyclonucleoside Hydroformate (ii). A solution of 0.5 g (0.002 mol) of **3** in 50 ml of H_2O was heated for 1 hr at reflux, cooled, and evaporated to dryness. The colorless residue was dissolved in 55 ml of hot MeOH and this solution was filtered. The flask containing the cooled filtrate was sealed in a desiccator containing 250 ml of Et_2O and allowed to stand at room temperature. After 2 days the resulting crystals were filtered and dried at 100° (0.1 mm) over P_2O_5 for 18 hr to give 0.45 g (79%) of colorless needles of ii: mp 230–232°; $[\alpha]^{23}D$ 155° (*c* 1.1, H_2O); $pK_a \cong 11.5$; uv (1 *N* HCl) max 292 nm (ε 13,100), min 237 (2500); uv (pH 7) max 293 nm (ε 14,500), min 252 (2300); uv (pH 13) max 278, 222 nm (ε 9600, 8400), min 243 (5000); acidification of the pH 13 solution back to pH 6 gave essential reproduction of the pH 7 spectrum, indicating that no hydrolysis of the amidine function had occurred; nmr (DMSO-d_6) δ 3.54 (d, $J_{5',5''-4'} \cong 6.7$ Hz; 2, $H_{5',5''}$), 3.81 (d, $J_{3'-4'} = 2.5$, $J_{3'-2'} < 1$ Hz, 1, $H_{3'}$), 4.35 (sextet, $J_{4'-3'} = 2.5$, $J_{4'-5',5''} \cong 6.7$ Hz, 1, $H_{4'}$), 4.52 (d, $J_{2'-3'} < 1$ Hz, 1, $H_{2'}$), 5.63 (s, 1, $H_{1'}$), 7.42 (s, 1, H_2), 8.45 (s, 1, formate), the NH and OH protons gave broad, integrated absorption with no distinct signals.

Anal. Calcd for $C_9H_{13}N_5O_3 \cdot HCO_2H$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.04; H, 5.38; N, 24.42.

5-Amino-1-(3-deoxy-β-D-xylofuranosyl)imidazole-4-carboxamide-$N^5 \rightarrow$3′-cyclonucleoside (iii). A solution of 2.0 g (0.008 mol) of 3 in 400 ml of H_2O was heated for 40 min at reflux and 20 ml of 1 *N* NaOH was added. Refluxing was continued for 2 hr and the solution was cooled. Dowex 50 (H^+) resin was added, the mixture was stirred until neutral and filtered, and the filtrate was evaporated to dryness. The residue was dissolved in 200 ml of hot MeOH, the solution was filtered, and methanolic HCl was added. The resulting precipitate was filtered and dried over P_2O_5 at room temperature to give 1.92 g (81%) of iii hydrochloride hydrate, mp ~180° dec.

Anal. Calcd for $C_9H_{12}N_4O_4 \cdot HCl \cdot H_2O$: C, 36.68; H, 5.13; N, 19.01. Found: C, 36.85; H, 4.60; N, 19.18.

A solution of 1 g (0.0034 mol) of this salt in 50 ml of H_2O was neutralized with Dowex 1-X8 (OH^-). The resin was filtered and the filtrate was evaporated to give 0.8 g (95%) of colorless iii. This product was recrystallized from 40 ml of H_2O–EtOH (1:10) to give 0.5 g (60%) of needles which were dried over P_2O_5 at 120° (0.1 mm) for 18 hr to provide iii: mp 234–235°; $[\alpha]^{23}D$ 140° (*c* 1, H_2O); $pK_a \cong 2.76$; uv (1 *N* HCl) max 274; 257 nm (ε 10,600, 10,100), min 263, 223 nm (ε 10,000, 2100); uv (pH 7) max 275 nm (ε 13,800), min 221 (2200); uv (pH 13) max 279 nm (ε 13,400), min 230 nm (3200); nmr (DMSO-d_6–Me_2CO-d_6, 4:1) δ 3.56 (m, 2, $H_{5',5''}$), 3.75 (m, 1, $H_{3'}$), 4.31 ("sextet" $J_{4'-3'} \cong 3.2$, $J_{4'-5',5''} \cong 6.6$ Hz, 1, $H_{4'}$), 4.52 (m, 1, $H_{2'}$), 4.76 ("t," $J_{5'-OH-5',5''} \cong 6.2$ Hz, 1, 5′-OH), 5.60 (s, 1, H_1), 5.98 (d, $J_{2'-OH-2'} = 3.2$ Hz, 1, 2′-OH), 6.48 (d, $J_{5-NH-3'} = 4.4$ Hz, 1, 5-NH), 6.73 (s, 2, $-NH_2$), 7.13 (s, 1, H_2). Irradiation at δ 3.56 ($H_{5',5''}$), caused the exchangeable "triplet" at δ 4.76 (5′-OH) to collapse to a singlet and the "sextet" at δ 4.31 ($H_{4'}$) to collapse to a doublet. Irradiation of the multiplet at δ 3.75 ($H_{3'}$) caused the multiplet at δ 4.52 ($H_{2'}$) to collapse to a clean doublet and the doublet at δ 6.48 (5-NH) to collapse to a singlet. Irradiation at δ 4.52 ($H_{2'}$) caused the multiplet at δ 3.75 ($H_{3'}$) to collapse to a "triplet" and the doublet at δ 5.98 (2′-OH) to collapse to a singlet. These experiments verified the peak assignments and also allowed the determination of $J_{2'-2'OH} = 3.2$, $J_{2'-3'} \cong 1.2$, and $J_{1'-2'} < 0.7$ Hz.

Anal. Calcd for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.32. Found: C, 44.93; H, 5.25; N, 23.46.

Acknowledgment. We wish to thank Mrs. M. Bischler (Universität Konstanz) for pK_a measurements and certain

uv spectral determinations and Miss Walia Halim (The University of Alberta) for excellent technical assistance.

Registry No.—ii, 51022-59-4; iii, 51022-60-7; iii hydrochloride, 51096-70-9; **1**, 16667-61-1; **3**, 2627-64-7; **4**, 51014-72-3; **5**, 51014-73-4; **6**, 51014-74-5; **7**, 20535-16-4; **8**, 524-69-6; **9a**, 51014-75-6; **9b**, 51014-76-7; **10**, 40110-98-3.

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(3) University of Alberta Postdoctoral Fellow, 1969–1971. Present address: Fachbereich Chemie der Universität Konstanz, D-7750 Konstanz, Postfach 733, West Germany.
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(20a) Note Added in Proof. An X-ray crystallographic analysis of this product is in agreement with the assigned structure. The formic acid molecule is associated with the basic amidine function as would be expected. (Dr. M. N. G. James, Department of Biochemistry, private communication.)
(21) (a) Intermediate formation of the corresponding $N^3 \rightarrow 2'$-arabinocyclonucleoside from **3**, which would have been ring opened to give 5-amino-1-(2-deoxy-β-D-arabinofuranosyl)imidazole-4-carboxamide-$N^5 \rightarrow 2'$-cyclonucleoside instead of iii, was suggested by a referee on the basis of inspection of models. This possibility is precluded by the absence of coupling ($J_{1'-2'} < 0.7$ Hz) of the anomeric proton of iii (and ii), which demands a trans 1′,2′-proton geometry (see ref 31, pp 330–331), as well as by the double-irradiation experiments (*i.e.*, triplet and doublet patterns for the 3′ and 2′ protons upon irradiation of the 2′ and 3′ frequencies, respectively) outlined in the Experimental Section. (b) R. Mengel *et al.*, in preparation.
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A Solvolytic Investigation of Cyclobutylcarbinyl and Related *p*-Bromobenzenesulfonates

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The solvolysis rates of cyclobutylcarbinyl (4-OBs), cyclopentylcarbinyl (5-OBs), cyclohexylcarbinyl (6-OBs), and 1-adamantylcarbinyl (AC-OBs) brosylates have been determined in a series of solvents. The extent of rearrangement of 5-OBs is sensitive to reaction conditions, including buffer. The kinetic and product distribution data indicate that solvent capture of a carbon-bridged species accounts for 99% of the acetolysis product of 4-OBs, 91% of 5-OBs, and 0% of 6-OBs.

The occurrence of Wagner–Meerwein type rearrangements in solvolysis reactions of cycloalkylcarbinyl derivatives has been well demonstrated.[2] To the extent that the current view of solvolysis reactions[3] is correct, the observation of Wagner–Meerwein type rearrangement products in the solvolysis of cycloalkylcarbinyl arenesulfonates is evidence for neighboring group participation in the ionization step *via* σ-bond delocalization of charge into the cycloalkane ring.

Although the study of the nature of σ-bond participation by the cyclopropane ring in solvolysis reactions has been the subject of considerable experimental and theo-

Table I
First-Order Solvolysis Rates

Brosylate	Registry no.	Solvent	Temp, °C	k_t, 10^6 sec^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
4-OBs	51108-24-8	EtOH[a]	45	1.3		
		AcOH	45	3.4	24.9 ± 0.1[b]	−5.6 ± 0.3[b]
			55	11.7		
			65	35.9		
			75	111		
		CF_3CH_2OH	30	13.3	19.7 ± 0.1	−15.9 ± 0.3
			35	24.4		
			45	70.8		
			55	186.0		
		HCO_2H	35	210	20.3 ± 0.1	−9.6 ± 0.4
			45	630		
			55	1665		
5-OBs	38806-24-5	EtOH	45	0.21		
		AcOH	55	0.42	25.4 ± 0.1	−10.7 ± 0.4
			65	1.36		
			75	4.20		
		CF_3CH_2OH	35	0.64	23.6 ± 0.2	−10.4 ± 0.5
			45	2.22		
			55	7.30		
		HCO_2H	35	9.75	23.1 ± 0.1	−6.5 ± 0.4
			45	34.5		
			55	103.7		
6-OBs	51108-25-9	AcOH	55	0.053	27.8 ± 0.1	−7.2 ± 0.5
			65	0.200		
			75	0.675		
		CF_3CH_2OH	35	0.039	23.6 ± 0.2	−16 ± 0.8
			45	0.131		
			55	0.444		
		HCO_2H	35	0.51	25.3 ± 0.1	−5.3 ± 0.3
			45	1.96		
			55	6.78		
AC-OBs	51108-26-0	EtOH	45	0.0047		
		AcOH	55	0.033	29.6 ± 0.6	−3 ± 2
			65	0.111		
			75	0.488		
			100	7.44		
		CF_3CH_2OH	35	0.25	23.6 ± 0.2	−12.4 ± 0.6
			45	0.89		
			55	2.67		
		HCO_2H	55	24.1	24 ± 0.1	−6 ± 0.3
			75	219		
Neophyl	24517-38-2	CF_3CH_2OH	45[c]	40		

[a] Initial concentration 0.015–0.030 *M*. [b] One standard deviation unit from mean. [c] Average of two runs with standard deviation ±0.1.

retical work,[4] comparatively few such investigations have been carried out to elucidate the nature of σ-bond participation by the cyclobutane ring or the related cyclopentane and cyclohexane rings.

Neighboring group participation involving ring expansion has been postulated for the solvolysis of cyclobutylcarbinyl and cyclopentylcarbinyl derivatives,[5,6] and

$(CH_2)_nCHCH_2OBs$
$n + 1 = 4$, **4-OBs**
$n + 1 = 5$, **5-OBs**
$n + 1 = 6$, **6-OBs**

neighboring group participation by hydrogen has been postulated for the solvolysis of cyclohexylcarbinyl derivatives;[7] however, these studies were either carried out prior to development of current solvolysis reaction theory and/or with little attention given to the nature of the σ-bond participation, particularly in the case of the cyclobutane ring.

For these reasons, we undertook the present investigation of the solvolytic behavior of the following cycloalkylcarbinyl brosylates. This paper reports the analysis of both the reaction kinetics and product distribution data in an effort to gain further insight into the nature of the σ-bond participation by the cycloalkane rings in the ionization process. During the course of this investigation some related points of interest were developed and are included in this report.

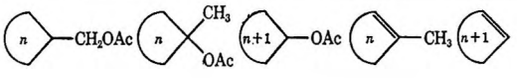
The data indicate that with *urea buffer* solvent capture of a carbon-bridged species accounts for 99% of the acetolysis product of **4**-OBs, 91% of the acetolysis product of **5**-OBs, and 0% of the acetolysis product of **6**-OBs.

The first-order rate constants for solvolysis of the cycloalkylcarbinyl brosylates and related substrates are summarized in Table I. The reaction progress was followed by titrating the liberated *p*-bromobenzenesulfonic acid and the reaction followed strictly first-order kinetic law up to at least 75% conversion furnishing, within experimental error,[8] 100% of the theoretical amount of acid present.

The product distribution data are collected in Table II. The vapor-phase chromatographic separations and characterizations of products were carried out on a Carbowax 20M silver nitrate column. Urea was used as a buffer to avoid an S_N2 displacement reaction by sodium acetate,[9] and the product studies were conducted at the same temperature (75°) as the kinetic investigations. Previously reported[5a,6,7,10a] stability studies have established that the reported products are indeed the initially formed products and not those of subsequent isomerization reactions.[10b]

On the basis[3] that primary solvolysis occurs by two discrete pathways—k_s, solvent assisted which leads to only

Table II
Summary of Product Runs, Acetalysis at 75° [a]



Brosylate	n[b]	A	B	C	D	E
4-OBs[c]	4	1		99[h]		
5-OBs	5	4.5	2.7	90.8[i]	0.8	1.2
6-OBs	6	47.5[f]	12.5[g]		40.0[j]	
c-C_5H_9OBs[e]	5[d]			80		20[k]

[a] Initial ester concentration 0.20 *M*; initial urea concentration 0.30 *M*. [b] The initial ring size of the cycloalkyl group. [c] The average of three runs. [d] Cyclopentyl brosylate. [e] Registry no.: 4596-40-1; [f] 937-55-3; [g] 16737-30-7; [h] 933-05-1; [i] 622-45-7; [j] 591-49-1; [k] 110-83-8.

Table III
Per Cent k_s Reaction for the Acetolysis of Selected Substrates at 75°

Substrate	% k_s This study	% k_s Lit. value	Ref
1-Adamantylcarbinyl OBs		0	3c
c-$C_4H_7CH_2OBs$	1[a]	1[b]	5c
c-$C_5H_9CH_2OBs$	4.5[a]	61[c]	7
c-$C_6H_{11}CH_2OBs$	47.5[a]	49[c]	7

[a] Buffered with urea. [b] At 100° without buffer. [c] At 120° with NaOAc.

Table IV
Variation in the *E*/*S* Ratio with Reaction Conditions for Acetolysis of Selected Substrates

Substrate	Temp, °C, buffer	% alkene	% acetate
c-$C_4H_7CH_2OBs$	100, none	nd	100[a]
	75, urea	nd	100[b]
c-C_5H_9OBs	50, KOAc	39	61[c]
	75, urea	20	80[b]
c-$C_5H_9CH_2OBs$	75, urea	2	98[b]
	80, NaOAc	78	23[d]
	80, NaOAc	74	25[e]
	120, NaOAc	11	89[f]
c-$C_6H_{11}OSO_2Ar$[h]	50, KOAc	85	15[c]
	100, NaOAc	81	19
	100, urea	80	20
c-$C_6H_{11}CH_2OBs$	75, urea	40	60[b]
	120, NaOAc	46	54[b]
	115, NaOAc	23	77[g]

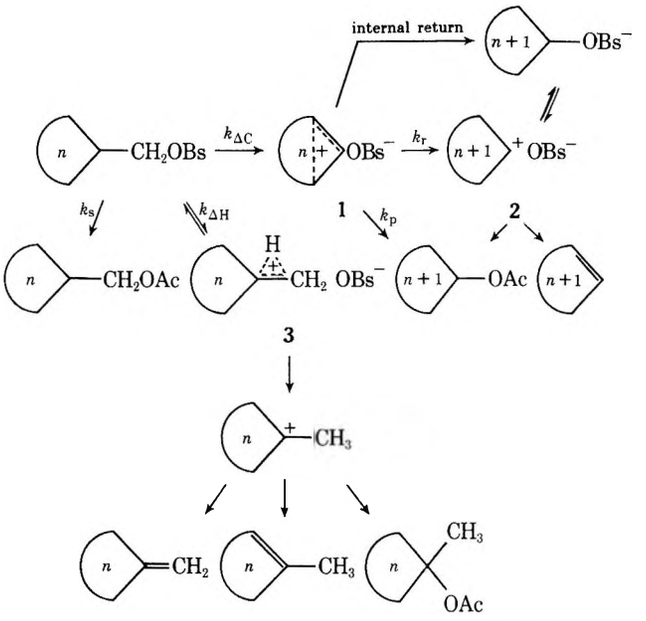
[a] Reference 5c. [b] This work. [b] Tosylate: J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, **73**, 5034 (1951). [d] Nasylate, ref 6. [e] Reference 12. [f] Tosylate, ref 7. [g] Tosylate: R. Kotani and S. Satoh, *J. Org. Chem.*, **30**, 3245 (1965). [h] Registry no. 953-91-3.

unrearranged products; and k_Δ, neighboring group assisted which leads to only rearranged products[11]—the data in Table III are readily obtained.

Not unexpectedly, the fraction of 5-OBs solvolyzing *via* the k_s pathway (approximated by the fraction of cyclopentylcarbinyl acetate in the product mixture) is significantly lower than the literature value. Both Bartlett[6] and LeNy[12] reported yields of cyclopentylcarbinyl acetate (5.1 and 9.0%, respectively) substantially in agreement with that found in the present study. This result emphasizes that the extent of rearrangement (and the subsequent dissection of k_t into k_Δ and k_s) is sensitive to reaction conditions and, therefore, care should be taken that the kinetic and product data are obtained under the same reaction conditions.[13]

The data presented in Table IV provide further evidence for product sensitivity to reaction conditions. For

Scheme I



example, in the acetolysis of 5-OBs the replacement of sodium acetate by urea as a buffer results in a dramatic increase in the yield of substitution product or the elevation of the reaction temperature for 80–120° produces a similar dramatic increase in the substitution product.

Since Bartlett, *et al.*,[9] have shown that urea is as effective as sodium acetate in stabilizing cyclohexene against conversion to cyclohexyl acetate under the reaction conditions, it is unlikely that the increased substitution product observed with urea is due to an enhanced acid-catalyzed addition of acetic acid to cyclohexene. On the other hand, the increased substitution product observed at higher temperature may be attributed, at least in part, to an enhanced displacement reaction by acetate ion; that is, in the acetolysis of 5-OBs the rate constant temperature profiles could be favorable for $k_2(AcO^-)$ at elevated temperatures.

Insight concerning this somewhat complicated product distribution picture is provided by Scheme I. A minimum of four product pathways are necessary to accommodate the product data: (1) k_s, a solvent-assisted pathway leading to unrearranged acetate;[14] (2) $k_{\Delta H}$, a neighboring hydrogen assisted pathway leading to non-ring-expanded olefins and tertiary acetates; (3) $k_{\Delta C}{}^1$, a σ-bond participation pathway, leading to bridged intermediate **1** which is attacked by solvent yielding ring-expanded acetates;[17] and (4) $k_{\Delta C}{}^2$, a σ-bond participation pathway leading to classical ion **2** which is attacked by solvent leading to both ring-expanded acetates and olefins. A fifth pathway, $k_{\Delta C}{}^3$, internal return isomerization to a secondary brosylate, has been proposed[6] for the acetolysis of 5-OBs in the presence of sodium acetate buffer. Although this pathway cannot be ruled out in the present study, it is unfavored for two reasons: (1) the products of acetolysis of cyclohexyl arenesulfonates (see Table IV) are very rich in cyclohexene, just the opposite of that observed for the acetolysis of 5-OBs, and (2) the acetolysis products of cyclopentyl brosylate (see Table IV) include at least 20% cyclopentene while none was detected in the acetolysis products of 4-OBs.

Additional insight into the mechanistic details of the $k_{\Delta C}$ pathway proposed for the ring-expanded products observed in the acetolysis of 4-OBs and 5-OBs is provided by the relative rate data collected in Table V. The most striking feature of these data is the small effect of the methyl and phenyl substituents upon the acetolysis rates

Table V
Relative Rates of Acetolysis of 1-X-Cycloalkylcarbinyl Brosylates and the Relative Rates of Solvolysis of the Corresponding 1-X-Cycloalkyl Derivatives

Compound	X	Rel rate, 75°	Compound	X	Rel rate
c-$C_4H_6XCH_2OBs$	H	1.0	c-C_5H_8XCl[a]	H	1.0
	CH_3[b]	10		CH_3	1.75×10^5
	Ph[c]	1.9		Ph	6.6×10^8
c-$C_5H_8XCH_2OBs$	H	1	c-$C_6H_{10}XCl$[a]	H	1.0
	CH_3[b]	1		CH_3	3.33×10^4
	Ph[d]	34		Ph[a]	6.3×10^7

[a] H. C. Brown and M.-H. Rei, *J. Amer. Chem. Soc.*, **86**, 5008 (1964), at 25° in EtOH. [b] Reference 16. [c] Registry no.: 50978-05-7; [d] 51108-27-1.

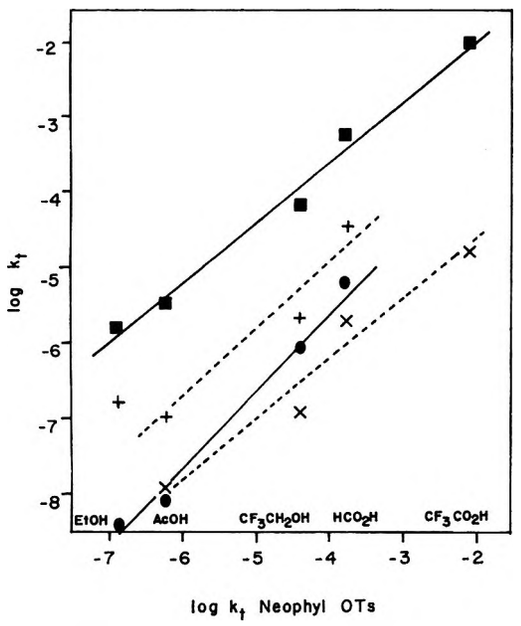


Figure 1. Plot of log k_t for 4-OBs (■), 5-OBs (+), 6-OBs (×), and AC-OBs (●) *vs.* log k_t for neophyl tosylate at 45°.

of 4-OBs and 5-OBs. This result clearly establishes that, in the conversion of 4-OBs or 5-OBs to ring-expanded products, the charge distribution in the transition state has little similarity to **2**, the localized charge species, but instead argues in favor of a delocalized structure similar to **1**.[18] Furthermore, the high yields of ring-expanded substitution products observed in the acetolysis of 4-OBs and 5-OBs (about 99% in each case) suggest[17] that **1**, instead of the rearranged, localized species **2**, is the intermediate attacked by solvent leading to the ring-expanded substitution products.

Such is not the case, of course, in the acetolysis of 6-OBs which does not produce any ring-expanded product. In this case the $k_{\Delta C}$ pathway is noncompetitive with both the k_s and $k_{\Delta H}$ pathways. It is of interest to note that, in the acetolysis of 6-OBs, $k_{\Delta H}$ makes a contribution to k_t approximately equal to that of k_s and therefore precludes the use of this substrate as a model for k_s solvolysis.

Winstein has provided a useful diagnostic test for the presence of a $k_{\Delta C}$ pathway by establishing the linearity of plots of log $k_{\Delta C}$ for *n*-propyl,[20] 2-phenylethyl,[3a] and 1-phenyl-2-propyl[21] tosylates *vs.* log k_t for neophyl tosylate as the solvent is varied.[22] Accordingly, the data for the solvolysis of 4-OBs, 5-OBs, 6-OBs, and AC-OBs were submitted to a similar analysis which produced the curves illustrated in Figure 1. The rate constant for the trifluoroacetolysis of 4-OBs at 45° (1×10^{-2} sec^{-1}) was derived from a log k_t *vs.* *Y* plot of carboxylic acid solvents where the *Y* value for trifluoroacetic acid (4.4), in turn, was derived from a plot of log k_t for neophyl tosylate *vs.* *Y* for carboxylic acids. The rate constant for the trifluoroacetolysis of 6-OBs was taken from the work of Krapcho and Johanson.[7]

Table VI
Some Slope Values for Correlation of Log k_Δ^R (RCH_2OTs) with Log k_t^N (Neophyl Tosylate) as Solvent is Varied

R	Temp, °C	Slope values	Ref
Et	75	0.85	20
$PhCH_2$	75	1.02	3a
t-Bu	75	0.83	20
c-C_4H_9	45	0.82[a]	This work
1-Adamantyl	45	1.02[a]	This work

[a] Brosylate k_Δ is equated with k_t.

The correlation coefficients for linearity of the various curves in Figure 1 are 0.99 (30° of freedom) for 4-OBs, 0.94 (20° of freedom) for 5-OBs, 0.94 (17° of freedom) for 6-OBs, and 0.99 (18° of freedom) for AC-OBs.

The good correlation between log k_t for 4-OBs and log k_t for neophyl tosylate is consistent with the nearly exclusive $k_{\Delta C}$ pathway proposed for the solvolysis of 4-OBs throughout the entire solvent series. It is interesting to note that the correlation coefficient for 4-OBs is identical with the value determined for AC-OBs, a compound that reportedly[3c] solvolyzes *via* an exclusively $k_{\Delta C}$ pathway involving a carbon-bridged intermediate due to steric inhibition of the k_s pathway.

The poor correlation between log k_t for 6-OBs and log k_t for neophyl tosylate is accountable by the significant contribution that k_s makes to k_t for the solvolysis of 6-OBs in solvents of low ionizing strength, while the poor correlation between log k_t for 5-OBs and log k_t for neophyl tosylate is attributed to the enhancement of k_t by k_s for the solvolysis of 5-OBs in the relatively nucleophilic solvent, ethanol.

The slope values for representative log k_Δ^R *vs.* log k_t^N (neophyl tosylate) correlations are listed in Table VI. Interestingly, the magnitude of these slopes varies only slightly from a mean value of 0.91 which reveals the change in log (k_Δ^R/k_t^N) with variable solvent is nearly insensitive to change in neighboring group (H, Me, cyclobutyl, or 1-adamantyl).

It is tempting to speculate that this slope insensitivity to neighboring group effect (δ_R) reflects a similar participation response, $\delta_m(k_\Delta/k_C)^R$, to medium effect (δ_m) by the various neighboring groups.[23] Because there is no suitable model for evaluating the unassisted ionization rates (k_C) of primary substrates, additional slope values will be determined in future studies to assess the validity of the assumption[23] $\delta_m\,(k_\Delta/k_C)_R/\delta_m(k_\Delta/k_C)^N \sim$ constant.

Another factor inherent in the estimate of extent of participation is the accompanying change in strain energy. For example, release of strain energy in going from starting material to transition state complex is expected[2,5c,24] to accompany σ-bond participation by the cyclobutane

ring. However, its magnitude is small compared to the change expected in going from starting material to the ring-expanded product,[25] and, more significantly, there appears to be a linear relationship[24b] between ring strain changes (either relief or increase) and extent of participation in solvolysis reactions which is nonfactorable

Primary alkyl arenesulfonates which suffer acetolysis *via* the k_Δ pathway are characterized by values of ΔS^* that fall in the 0 to −10 eu range,[27a] while the acetolysis of simple, unbranched primary alkyl arenesulfonates is characterized by values of ΔS^* that fall in the range −19 ± 2 eu.[27b] The ΔS^* values reported in Table I for both the acetolysis and formolysis of **4**-OBs, **5**-OBs, and AC-OBs are consistent with the $k_{\Delta C}$ solvolysis pathway as outlined in Scheme I. A word of caution, however, is in order. The ΔS^* values for both the acetolysis and formolysis of **6**-OBs also fall in the range 0 to −10 eu, apparently due to a fortuitous blend of ΔS^* values for the competing k_Δ and k_s pathways.

It is of interest to note that the ΔS^* values for trifluoroethanolysis are *ca.* 10 eu more negative than the corresponding acetolysis values for **4**-OBs, **6**-OBs, and AC-OBs. This same phenomenon has been observed in the solvolysis of 1-arylcyclobutylcarbinyl brosylates[28] and can be attributed to greater hydrogen bonding solvation of the anion in the looser ion pair generated in trifluoroethanol.[29]

Experimental Section

Melting points were not corrected for stem exposure and were taken on a Mel-Temp apparatus. Infrared spectra were recorded on a Bausch and Lomb 1R 270 spectrophotometer and the nmr spectra were obtained on a Hitachi Perkin-Elmer R-24 instrument with tetramethylsilane as internal reference standard. A Beckman GC-4 chromatographic instrument equipped with a thermal conductivity detector and a 24 ft × 0.25 in. column of 20% Carbowax 20M, 2% $AgNO_3$ on Chromosorb W, AW-DMCS (45–60 mesh), was used for analytical gc work. All microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Cyclobutylcarbinyl Brosylate (4-OBs). To a stirred solution of 2.6 g (30 mmol) of cyclobutylcarbinol [56% from cyclobutanecarboxylic acid (Aldrich Chemical Co.) and borane-tetrohydrofuran, bp 141° (750 mm) (lit.[30] bp 142–143° (750 mm)), ir spectrum consistent with assigned structure] in 40 ml of dry pyridine cooled to 0° was added 8.9 g (35 mmol) of *p*-bromobenzenesulfonyl chloride. After standing 17 hr at 5°, the mixture was carefully hydrolyzed by the slow addition of 20 ml of cold water (reaction temperature maintained between 0 and 5°) followed by the rapid addition of sufficient cold, dilute HCl to acidify the mixture. The precipitated ester was separated on a Büchner funnel (packed in cracked ice to prevent ester from melting) and washed several times with cold, dilute HCl, several times with cold water, and then with cold petroleum ether (bp 30–60°) and after air drying yielded 4.2 g (46%) of white needles (mp 20–25°). Recrystallization from petroleum ether (bp 30–60°)–ethyl acetate (50:5) gave 3.0 g (33%) of white crystals, mp 25° (lit.[5a] ~25°).

Cyclopentylcarbinyl brosylate (5-OBs) was prepared from *p*-bromobenzenesulfonyl chloride and cyclopentylcarbinol (Aldrich Chemical Co.) as described above in 65% yield: mp [after one recrystallization from petroleum ether (bp 30–60°)] 49.5–50° (lit.[31] mp 49.5–50°).

Cyclohexylcarbinyl brosylate (6-OBs) was prepared from cyclohexylcarbinol (Aldrich Chemical Co.) and *p*-bromobenzenesulfonyl chloride as described above in 70% yield: mp [after two recrystallizations from petroleum ether (bp 30–60°)] 41.5–42° (lit.[31] mp 42.5–43°).

1-Adamantylcarbinyl brosylate (AC-OBs) was prepared from 1-adamantylcarbinol [39% from 1-adamantylcarbonyl chloride (Aldrich Chemical Co.) and a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (Aldrich Chemical Co.), mp 114.5–115.5° (lit.[16] mp 115–116°)] and *p*-bromobenzenesulfonyl chloride as described above in 72% yield: mp [after two recrystallizations from petroleum ether (bp 30–60°)] 103–104°. *Anal.* Calcd for $C_{17}H_{21}BrO_3S$: C, 53.00; H, 5.49; Br, 20.74. Found: C, 53.03; H, 5.45; Br, 20.98.

Preparation of Reference Olefins and Esters. Cyclopentene, cyclohexene, cycloheptene, and 1-methycyclohexene were purchased from Aldrich Chemical Co. and used as received. 1-Methylcyclopentene was prepared *via* acid-catalyzed dehydration of 1-methylcyclopentanol and the structure assignment confirmed by nmr. Cyclobutylcarbinyl acetate, cyclopentyl acetate, cyclopentylcarbinyl acetate, 1-methylcyclopentyl acetate, cyclohexyl acetate, cyclohexylcarbinyl acetate, 1-methylcyclohexyl acetate, and cycloheptyl acetate were prepared by published procedure[5,6] and their purity and structure assignment confirmed by comparison with recorded nmr data.[6]

Solvents. Absolute ethanol was prepared according to the method of Fieser.[32] Acetic acid solvent was prepared from 994.9 ml of glacial acetic acid (Matheson Scientific, 99.8%) and 5.1 ml of acetic anhydride. 2,2,2-Trifluoroethanol (Aldrich Chemical Co.) was redistilled prior to use.

Acetolysis Product Studies. Solutions (25 ml, 0.2 *M*) of the sulfonates **4**-OBs, **5**-OBs, and **6**-OBs in acetic acid (0.3 *M* in urea) were sealed in ampoules under N_2 and immersed in a constant temperature bath at 75 ± 0.1°. After 10 half-lives each solution was diluted with 150 ml of water and continuously extracted with ether for 48 hr. The ether extract was neutralized with $NaHCO_3$ and dried (Na_2SO_4), and most of the solvent was removed by controlled distillation with a Nester-Faust NFA-200 annular still. The composition (see Table II) of each residue was established by gc (using authentic reference olefins and esters) and confirmed by nmr analysis.

Rote measurements were accomplished by usual ampoule technique.[19] The titrating solutions were, for ethanolysis and 2,2,2-trifluoroethanolysis, 0.020 *N* sodium methoxide in anhydrous methanol[33] and, for acetolysis, 0.050 *N* sodium acetate in acetic acid. The indicators used were Bromthymol Blue (in water), Bromphenol Blue (in 20% aqueous EtOH), and Bromphenol Blue (in acetic acid), respectively.

Treatment of Kinetic Data. The thermodynamic activation parameters were obtained by IBM 1620 computer regression analysis. The linear correlations, slope values, and correlation coefficients were also obtained by IBM 1620 computer regression analysis.

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(6) P. D. Bartlett, W. D. Closson, and T. J. Cogdell, *J. Amer. Chem. Soc.*, **87**, 1308 (1965).
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(13) See ref 3b for a similar finding for the acetolysis of 2-phenylethyl tosylate.
(14) The possibility that solvent attack on **1** could yield unrearranged acetate with retained configuration has not been excluded in this or previous studies[5c,6,7,15] but, based on recent solvolytic studies with neopentyl[16] and 1-adamantylcarbinyl[3c] tosylates, this pathway is poorly favored.
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(17) Bridged intermediate **1** is considered a geometrically unfavorable precursor for cyclohexene.[6]
(18) This substituent effect behavior is very similar to that of 1-*p*-X-phenylcyclopropylcarbinyl derivatives[19] where it is agreed[4] that ionization is anchimerically assisted by the cyclopropane ring.
(19) (a) D. D. Roberts, *J. Org. Chem.*, **29**, 294 (1964); (b) *ibid.*, **31**, 2000 (1966); (c) *ibid.*, **33**, 2712 (1968); (d) *ibid.*, **34**, 285 (1969).

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(21) A. F. Diaz and S. Winstein, *J. Amer. Chem. Soc.*, **91**, 4300 (1969).
(22) Where it is generally agreed[3a] that neophyl tosylate ionizes with phenyl participation at a rate equal to k_t and dependent on solvent ionizing power but not nucleophilicity.
(23) This speculation is based on the following assumption: $\delta_m(k_\Delta/k_C)^R/\delta_m(k_\Delta/k_C)^N \sim$ constant where $\delta_m(k_\Delta/k_C)^R$ is defined in the text and $\delta_m(k_\Delta/k_C)^N$ is the participation response to medium effect by the phenyl group in neophyl tosylate.
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(25) The calculated strain release[26a] in going from starting material to the ring-expanded product is 19.5 kcal/mol which is equivalent to a log ($k_{4\text{-OBs}}/k_{5\text{-OBs}}$) value of 13; the measured value[26b] is −1.
(26) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 193; (b) H. Duivila and W. Masterson, *J. Amer. Chem. Soc.*, **74**, 4953 (1952).
(27) (a) S. Winstein and R. Heck, *J. Amer. Chem. Soc.*, **78**, 4801 (1956); (b) W. Pritzkow and K. H. Schoppler, *Chem. Ber.*, **95**, 834 (1962).
(28) D. D. Roberts, *J. Org. Chem.*, in press.
(29) The nearly identical ΔS^* value observed for acetolysis and trifluoroethanolysis of 5-OBs is an interesting exception to this general phenomenon. This anomolous behavior of ΔS^* is suggestive that more than a change in solvotion effects is involved in the acetolysis and trifluoroethanolysis of 5-OBs.
(30) N. J. Demjanow, *Ber.*, **40**, 4959 (1907).
(31) H. Felkin and G. LeNy, *Bull. Soc. Chim. Fr.*, 1169 (1957).
(32) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 285.
(33) Near the end of this series of experiments it was found that dilution of the 2-ml aliquots with 5 ml of acetic acid solvent followed by titration as with acetolysis samples gives much sharper end points.

Mechanism of the Catalyzed Thio-Claisen Reaction. Triggering of Concerted Rearrangement Processes

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Evidence is presented substantiating a thiophenolic intermediate in the thio-Claisen rearrangement of allylic phenyl sulfides under conditions (amine or carboxylic acid solvents at temperatures in the range 220–300°) only recently found to propitiate this reaction. This includes synthesis of the allyl thiophenol intermediate in relatively pure form, and converting it under normal reaction conditions to the same product distribution observed to form directly from the allyl phenyl sulfide substrate. The intermediate thiophenol is found to resist cyclization when present in its anionic form, and this is a basis for trapping it and preventing formation of the normal cyclization products. The intermediate anion is also shown to generate o-allyl side products as a result of nucleophilic displacement on the allylic carbon of the substrate. A number of anionic bases, but not their conjugate acids, are also found to catalyze the thio-Claisen, including phenoxide, acetate, and thiophenolate. Unlike the oxy-Claisen, where electrophilic agents are known to be exclusively catalytic, the thio-Claisen appears to be susceptible only to nucleophilic catalysis. This is confirmed by kinetic studies of the concentration rate dependencies (first order in substrate and catalyst) and reactivity as a function of structure among a series of amine catalysts. The relative catalytic efficiencies of the members of this series show no correlation with their base strengths, but do give evidence of a rough parallel with nucleophilicity. However, the scale of nucleophilic activities is very compressed compared to the range of rate variation in normal SN2 displacements, where a considerable degree of nucleophilic bonding is being created in the activation process. These and a number of other observations can be accounted by the proposal of a pericyclic transition state of thio-Claisen rearrangement which has been triggered by a nucleophilic attack at the allylic carbon of the substrate. The effect of the nucleophile is to bring about a small amount of displacement in the electron density of the C–S bond, and formation of a p orbital on the allylic carbon to accommodate the orbital requirements and the geometry of the [3,3] sigmatropic transition state.

The thermolysis of allylic phenyl sulfides[1] stands in contrast to that of their oxygen analogs in experiencing Claisen rearrangements. They exhibit extraordinary thermal stability and undergo propenylization and subsequent cleavage reactions[2,3] only at temperatures approaching 300°. In fact, the possibility of a thio-Claisen rearrangement to compete with degradative side reactions was established only recently (1962).[1,4-6] It was found that in solutions of carboxylic acid[5] or amine[1,4,6,7] solvents a facile rearrangement of Claisen character can be observed. This reaction has now been widely applied and is recognized to be of general preparative interest.[8-11]

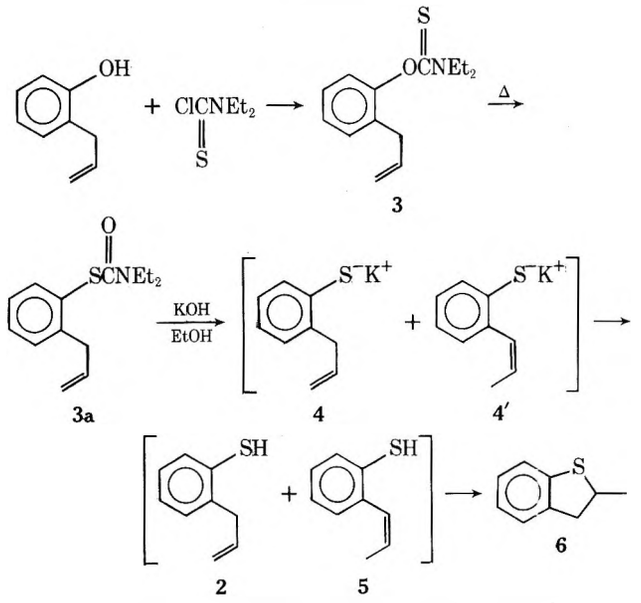
The activation energy[12] for this "catalyzed" thio-Claisen is somewhat greater than for the oxy-Claisen and the products realized are thiocoumarans and thiochromanes which could have arisen from presumed o-allylthiophenyl intermediates. In an earlier communication[13] preliminary evidence for this presumption has been described. This is based on trapping some of the intermediate as the o-allylmethylthiophenyl ether and preventing cyclic product formation when the reacting mixture is quenched with KOH and CH_3I.

This report is intended to provide full documentation of the evidence bearing on the occurrence of an o-allylthiophenol intermediate corroborating the thio-Claisen nature of the catalyzed, thermal rearrangement of allylic phenyl sulfides. Additional lines of experimentation will also be discussed which were directed toward elucidating the role of catalytic agents which are often indispensable to obtaining a thio-Claisen reaction.

Results and Discussion

I. Evidence Substantiating a Thiophenolic Intermediate in the Thio-Claisen Rearrangement of Allyl Phenyl Sulfide (1). A. Cyclization of o-Allylthiophenol (2) under Typical Thio-Claisen Reaction Conditions. Independent synthesis of the intermediate 2 was achieved earlier[3] through a two-step reaction involving gas-phase pyrolysis of the o-allylthiocarbonate or o-allylthiocarbamate, 3. Hydrolysis of the product, **3a**, in alkaline medium followed by acidification gave rise to **2**. The o-allylthiophenol had to be separated from propenylization (5) and cyclization (6) products, which could not be completely avoided even

Scheme I



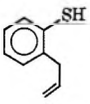
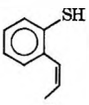
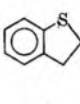
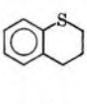
under the mildest conditions. This work has now been reviewed; see Scheme I. It is found that the cyclization process, from both thiols **2** and **5**, occurs with great readiness, and is exothermic at room temperature. Acid catalysis of the cyclization reaction is also evident from the fact that neutralization of the potassium thiolates, **4** and **4′**, had to be carried out with the weakest acids to get any significant yield of **2**. However, the thiophenolate anion as its sodio or potassium salt is extremely stable by comparison, and its formation could be quantitatively estimated by admixing with CH_3I and conversion to the unreactive thiomethyl ether. Using $NaOCH_3$ in CH_3OH as the hydrolysis medium and refluxing for 36 hr gives the stable sodio salt **4** in about 90% yield, with the remainder consisting of **4′** and **6**. After the latter are separated by extraction, working in the cold, neutralization is accomplished with dilute acetic acid and the free thiol **2** is obtained for storage at −30° until required.

In earlier experiments when the thiol **2** was heated in quinoline solution from room temperature to reflux, the ratio of thiochroman (**7**) to thiocoumaran (**6**) product was observed to be 4:1. The high tendency of **2** to cyclize (even at ambient) would suggest that this procedure would lead to product compositions which were not strictly comparable to what would form from **2** at the normal temperatures of the thio-Claisen reaction in quinoline (*ca.* 230°). Injecting the thiol **2** into refluxing quinoline, however, would be a more likely way of determining how the putative intermediate behaves on cyclization under the actual thio-Claisen conditions. Table I presents a summary of the results obtained when operating in this fashion. The ratio of **7** to **6** observed (*ca.* 1.44) is very close to the experimental ratio of 1.47 realized from thio-Claisen rearrangement of **1** in refluxing quinoline.

B. Trapping *o*-Allylthiophenol (2).[14-17] To intercept formation of **2** in the course of rearrangement of **1**, two approaches were successfully employed. Both made use of the fact that an aqueous solution of potassium *o*-allylthiophenolate strongly resists the cyclization reaction which takes place so readily in the case of the free thiol.

In the first instance, the reaction in refluxing quinoline was carried out for 1 hr, a time considerably shorter than that required for completion; the mixture was then quenched by addition to 3 *N* aqueous KOH. Neutral and water-insoluble compounds were removed and methyl iodide was added to the basic solution. An immediate reaction occurred to give a small amount of o-allylphenyl methyl sulfide as a pale yellow liquid; this accounted for about 5% of the product. In the second approach, **2** was captured as formed *in situ* by adding a strong inorganic base as a trapping agent directly to the quinoline reaction medium; this must inhibit cyclization. Lithium methoxide was chosen, since earlier work with this base had shown that it also produced the least amount of undesirable isomerization of the allyl double bond. The substrate **1** was heated under reflux in the presence of an equivalent amount of lithium methoxide in quinoline. The mixture was quenched and treated as above with methyl iodide. The thiomethyl ether obtained in this reaction accounted for *ca.* 50% of the total thio-Claisen product. These results coupled with the earlier characterization of the cyclization pattern under normal reaction conditions of thiol **2** would seem to substantiate the previous conclusion that o-allylthiophenol is formed in the course of rearrangement of allyl phenyl sulfide.

Table I
Cyclization Products Derived from Reaction of Mixtures of 2 and 5 in Refluxing Quinoline[a]

Reactant compositions[b]		Product compositions[b]			
				Ratio 7/6	
2	**5**	**6**	**7**	Uncorrected	Corrected[c]
94.9	5.1	44.4	55.6	1.25	1.41
90.0	10.0	46.7	53.3	1.14	1.45
85.5	14.5	49.4	50.6	1.02	1.45
22.6	77.4	86.7	13.3	0.15	1.43

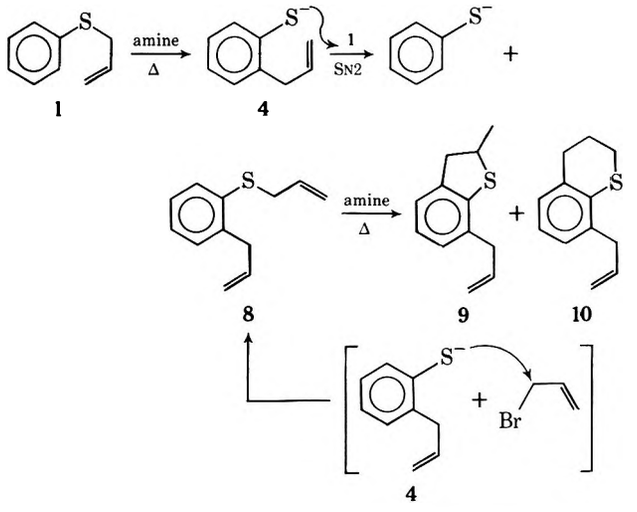
[a] Concentration of reactants 0.8 *M*. [b] Relative concentrations determined by glc analysis of the corresponding thiomethyl ethers. [c] Assumes that **5** cyclizes exclusively to **6**.

II. Isolation and Identification of Side-Reaction Products and Their Significance. Several experiments in which reaction was deliberately terminated prematurely gave indication of an additional product boiling in the range of the normal products **6** and **7**. It became evident that the unknown material, which was formed during the progress of rearrangement of **1**, was accumulated up to a point, but then slowly disappeared as heating continued. It was also evident that the reaction products of this unknown (intermediate) material **8** comprised the series of peaks of higher boiling substances following it in the glc spectrum and accounting for up to 10% of the total product composition. A sufficient quantity of **8** was then isolated for spectroscopic examination and identified as *o*-allylphenyl allyl sulfide. Confirmatory evidence was obtained by its independent synthesis through addition of allyl bromide to aqueous *o*-allylthiophenolate **4**.

A sufficient quantity of the first product peak following **8** was isolated for analytical purposes. The nmr spectrum (see Experimental Section) of this material corresponds to that which would be predicted for 7-allyl-2-methyl-1-thiocoumaran (**9**). It is reasonable to assume that 8-allyl-1-thiochroman (**10**) is one of the constituents of the cluster of four peaks following **8**. Others highly likely to be present are the ortho propenyl isomers of **9** and **10**. The reaction pathways delineated by all these observations are outlined in Scheme II.

It also seems logical to attribute the formation of **8** to a simple S_N2 displacement by intermediate thiolate on the starting sulfide (**1**). This bimolecular reaction accounts for the observed, early accumulation of **8** and its subsequent demise through ultimate thio-Claisen rearrangement to cyclic products. Support for this proposal was found by examining the *neutral* products of thio-Claisen rearrange-

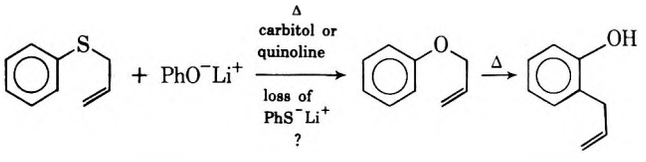
Scheme II



confirming synthesis

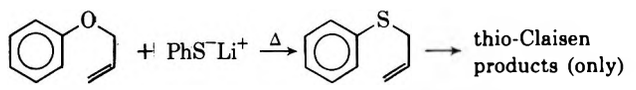
ment under conditions whereby the thiol intermediate **2** was long lived. In the second trapping experiment previously cited, where lithium methoxide was added to the quinoline solution of sulfide, greater than 30% of the extracted neutral products could be accounted for by formation of diallyl derivative **8**. The cyclic products **9** and **10**, identified by glc retention times, were further observed independently when an authentic sample of 8 was thermolyzed under the usual thio-Claisen conditions (refluxing quinoline).

To further test this interesting SN2 behavior the effect of heating **1** in the presence of lithium phenoxide was examined. Two solvents were chosen: the first, quinoline, to simulate the reaction medium in which displacement was first discovered; the second, diethyl carbitol, a neutral inert solvent in which Claisen rearrangement of allyl phenyl(oxy) ether (as and if it formed) is known to occur readily. The results of these studies are compiled in Table II.



The product compositions from these reactions (shown in Table II) demonstrate that SN2 displacement by phenoxide forming allyl phenyl ether is never realized. A bimolecular side reaction (SN2) involving displacement of thiophenolate anion from the allyl carbon by *thiophenolate anions* in solution has been implicated as the source of diallyl side-reaction products. Yet phenoxide ion is incapable of effecting displacement of the allyl chain. If it had, the products of oxy-Claisen rearrangement would have been readily visible in the glc, since this reaction has a much lower activation energy than the thio-Claisen. Clearly, the bimolecular displacement side reaction occurs only in the presence of very powerful nucleophiles in the medium.

A final experiment illustrates the competition of bimolecular displacement and Claisen rearrangement steps occurring at normal reaction temperatures. Here the effect of heating allyl phenyl *ether* in the presence of lithium thiophenolate in diethyl carbitol at 230° was examined. In sharp contrast to the case cited earlier for phenoxide, thiophenoxide readily displaced the allyl side chain to such an extent that only thio-Claisen products were observed; little or no oxy-Claisen products could be detected. These results and their mechanistic implications will receive further consideration in a subsequent section of this report.



III. Role of the Medium. Several alternatives can be considered. (1) A special solvent effect could be operating to complex the double bond in such a way as to inhibit or prevent irreversible isomerization to propenyl and simultaneously to maintain the structural, intramolecular relationships necessary for rearrangement to occur. (2) Basicity of the amine may produce the proper circumstances for rearrangement *via* a proton-transfer mechanism involving the substrate or a reactive equivalent thereof. (3) The nucleophilic character of the amine could be brought to bear to accelerate rearrangement at the expense of isomerization in some as yet undetermined manner.

In the final analysis it was concluded that nucleophilicity was the key parameter. This conclusion was generalized by verifying that rearrangement could be carried out in a neutral, inert solvent so long as the required presence of a nucleophilic agent was satisfied. In the following sections the basis for reaching this conclusion is discussed.

A. Complexation Effect of the Medium. Two alternative ways in which amine could complex with the substrate **1** have been considered previously.[2,3] Both of these visualize an interaction that serves to retain the allylic sulfide configuration and thus promotes rearrangement at the expense of propenylization; *i.e.*, the nature of the substrate–amine complex inhibits propenylization.[18] Evidence is at hand to indicate that very specific effects are involved in promoting and/or preventing propenylization of allylic sulfides.[19,20] Thus, it has been demonstrated that the proper choice of conditions for the hydrolysis of **3a** results in the prevention of extensive propenylization of the carbamate prior to cleavage of the ester link. For example, a reaction medium consisting of ethanolic potassium hydroxide at reflux reduces the purity of the desired o-allylthiophenolate anion **4** to only 20%, whereas treatment with sodium methoxide in anhydrous methanol affords 90% of pure **4** after hydrolysis is complete in the same period of time. The limited ability of sodium methoxide in methanol to promote isomerization was corroborated by the observation that heating o-allylphenyl methyl sulfide or *o*-allylphenyl methyl ether with

Table II
Reaction of Allyl Phenyl Sulfide and Lithium Phenoxide in Equimolar Amounts (0.8 *M*) at 240° for 3 Hr

	Product distribution, %				
Solvent	Allylic substrate **1**	Propenylized substrate **1′**	Thiocoumaran **6**	Thiochroman **7**	Higher boiling products **9** + **10**
Quinoline	Trace	4	48	33	10
Diethyl carbitol	5.4	4.6	50.6	24.7	9.9
Quinoline[a]	2	2	33	49	8
Diethyl carbitol[a]	67.2	29.7	Trace	Trace	Trace

[a] Control reaction—no phenoxide added.

Table III
Influence of Equimolar Concentrations of Various Acids on the Isomerization of a 0.1 *M* Solution of Allyl Phenyl Sulfide in Diethyl Carbitol at 240° for 3 Hr

Proton source	Substrate, % Unreacted	Substrate, % Propenylized	Cyclic products[a]
Phenol	70.7	29.3	Trace
Octanoic acid	73.5	26.5	Trace
Thiophenol	50.4	49.6	Trace
Methanesulfonic acid	71.2	28.8	Trace
None	68.9	31.1	Trace

[a] These cyclic materials are the normal thio-Claisen products—thiochromans, thiocoumarans, etc.

quinoline had no effect on these materials. After 6 hr at 240°, circumstances sufficient to complete the rearrangement of allyl phenyl sulfide, analysis of the isolated reaction products by gas chromatography failed to detect the presence of propenyl isomer in each case.

The diminished ability of the amine (as opposed to other bases) to promote the competing propenylization only explains part of its role. It is possible that in the absence of amine solvent propenylization is much faster than rearrangement, so that inhibiting propenylization may make rearrangement a more visible reaction. However, this does not account for the fact that other bases, such as $LiOCH_3$ in quinoline and $LiOC_6H_5$ in carbitol, which promote propenylization, can catalyze rearrangement to the extent that it is the predominant product-forming reaction. In all likelihood, therefore, amine solvents also exert an accelerating effect on the rearrangement reaction while affording no catalysis of propenylization; thus, nearly total conversion to thio-Claisen product is found.

B. Effect of Acids and Their Conjugate Bases in the Medium. It is well known that proton sources influence the kinetic pattern and increase the rate of the oxy-Claisen rearrangement. Kincaid and Tarbell[21] have observed that the rate of rearrangement of allyl *p*-tolyl ether in the absence of solvent gradually increased to about four times the initial rate as the medium changed from ether to phenol. Goering and Jacobson[22] have studied the relative rates of rearrangement of allyl *p*-cresyl ether in various solvents and report a 22-fold difference in the rate in phenol compared with diphenyl ether. Whether the greater rate in phenolic solvent might in some way be connected with hydrogen bonding between the solvent and substrate[22] or be a consequence of acid catalysis[21] is a matter of controversy, but, regardless of the reason, the fact that proton sources influence the oxy-Claisen rearrangement has been established. On the other hand, base catalysis of the oxy-Claisen rearrangement cannot be confirmed.

The possibility of general acid–base catalysis of the thio-Claisen must be considered in view of the fact that the reaction is known to take place readily in both (weakly acid) carboxylic and in (weakly basic) amine media, but is too slow to compete with propenylization in the absence of either of these medium components. Moreover, it has also been shown (above) that bases such as phenoxide anion increase the rate of the thio-Claisen *vs.* propenylization even in neutral media such as diethyl carbitol. However, the data in Table III show that when equimolar amounts of acids of widely varying strength are heated with substrate 1 in a 0.1 *M* solution of diethyl carbitol only propenylization takes place to all intents and purposes. In contrast to these results the conjugate bases of the same acids formed in quinoline, when the quinoline solution was heated under the same reaction conditions (time and temperature), allow nearly total thio-Claisen reaction accompanied by only minor amounts of propenylization.

Table IV
Influence of Various Lithium Salts on Thio-Claisen Rearrangement of Allyl Phenyl Sulfide (1) in Diethyl Carbitol Solution

Products	Lithium salt: Acetate[a]	Lithium salt: Phenoxide[b]	Lithium salt: Thiophenoxide[c]
Recovered substrate, %	55	5.4	15
Propenylized substrate, %	25	4.6	12
Thio-Claisen product, %	20	90	73

[a] 230°, 6 days. [b] 240°, 3 hr. [c] 230°, 6 hr.

The catalytic influence of the anions of these weak acids on the thio-Claisen, independent of the quinoline solvent, was confirmed by allowing 1 to react in the presence of their lithium salts in diethyl carbitol solution, as summarized by Table IV.

It must be emphasized that these lithium salts were only partially soluble in the diethyl carbitol. Since the amount of undissolved salt in each case could not be determined, the data in Table IV cannot be applied for comparison of the catalytic efficiencies of the respective anions. They can be cited, however, to support the conclusion that only the conjugate bases and not the weak acid themselves possess the ability to accelerate thio-Claisen rearrangement *vs.* the competing propenylization.

As noted previously,[2] thiophenol exerts a specific effect in promoting propenylization in both the carbitol and quinoline solutions. Nonetheless, the rearrangement with thiophenol is still considerably faster than propenylization in quinoline, while occurring only to a trace extent in the carbitol. As mentioned above, the phenoxide promotes the rearrangement even in the carbitol. Since the acid phenol does *not* have a catalytic effect in this solvent (Table III), the role of catalyst must be distinctively different from in the oxy-Claisen, where phenolic acids afford significant acceleration in direct proportion to their concentration.[21]

In connection with catalysis by octanoic acid and other carboxylic acids it should be recognized that somewhat forcing conditions (300°) were required to bring about the thio-Claisen. Moreover, a large amount (54%) of propenylization was observed under these conditions. Most probably this reflects the exceedingly low concentration of octanoate anion, which is the actual catalytic species in the presence of an enormous dilution of octanoic acid. The latter is capable of promoting only the degradative propenylization side reaction.

C. Kinetic Factors. In the course of studies establishing the intermediacy of o-allylthiophenol in the thio-Claisen rearrangement of allyl phenyl sulfide, it was demonstrated that rearrangement could be effected in a solvent of choice so long as an amine or the conjugate base of an acid was included. This constituted an approach in studying the kinetic influence of a wide variety of organic bases and inorganic bases. The kinetic technique consisted, in general, of subjecting diethyl carbitol solutions, 0.8 *M* in sulfide and 0.8 *M* in amine, to heating at some specified temperature. The reaction mixtures, sealed into small glass tubes, were placed in a suitably controlled constant-temperature bath for a prescribed period of time. At appropriate intervals the tubes were pulled, cooled to room temperature, and analyzed directly using gas chromatographic peak area ratios of sulfide and products compared to an internal standard, 1,3,5- or 1,2,4-trichlorobenzene. Chromatographic columns which afforded complete resolution of solvent, amine, standard, sulfide, and products were selected.

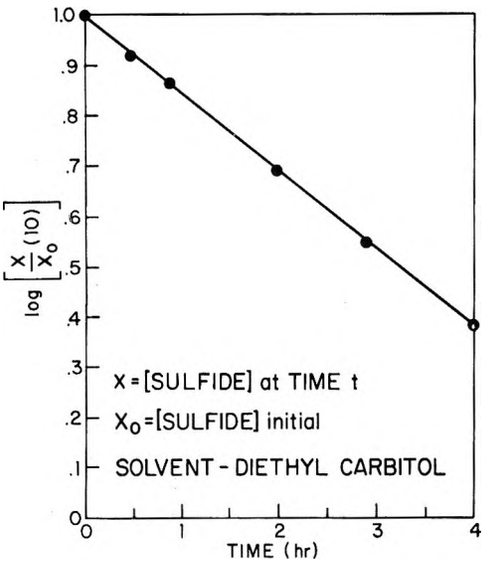


Figure 1. First-order kinetic behavior of allyl phenyl sulfide at 228.7° in the presence of an equimolar amount of pyridine (0.8 mol/l.).

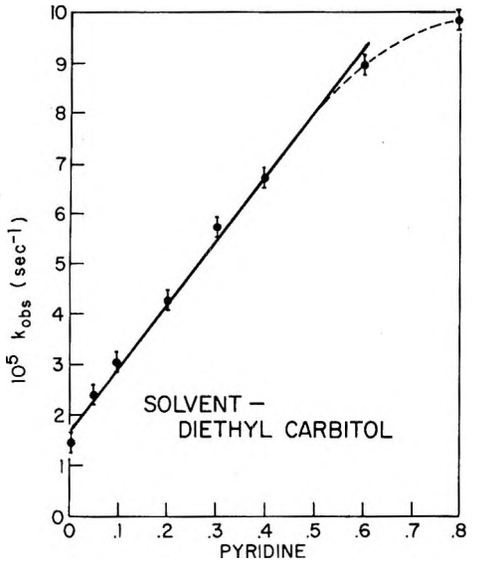


Figure 2. First-order kinetic behavior of allyl phenyl sulfide at 228.7° in the presence of various amounts of pyridine.

In view of earlier studies by Tarbell and Kincaid[21] of the oxy-Claisen rearrangement, first-order kinetics were anticipated. The approach, therefore, was to make this assumption and examine a first-order plot of the disappearance of sulfide. The data for reaction between pyridine and allyl phenyl sulfide are tabulated in Table V and plotted according to a first-order relationship (see Figure 1) in which x_0 is the initial concentration of allyl phenyl sulfide and x is the concentration of sulfide remaining at time t (in seconds). The results show that the reaction is strictly first order over the range studied. It is recognized, however, that the linear (first order) rate of disappearance of 1 represented by the plot in Figure 1 is the sum of two first-order rates, the propenylization rate being only a minor component of the total.

The dependence of rearrangement rate on the concentration of pyridine can be perceived from data summarized in Table VI and plotted in Figure 2. Within a concentration span in which the activity (basicity or nucleophilicity) of the pyridine may be assumed to be relatively constant, the rate depends on the first power of the amine. Furthermore, it remains at constant concentration effectiveness throughout the course of reaction. Only at

Table V
Kinetics of Allyl Phenyl Sulfide Reaction at 228.7°, 0.8 mol/l. in Diethyl Carbitol, in the Presence of 0.8 mol/l. of Pyridine (Calculated as a First-Order Rate)

Time, sec	% reaction	$k_{obsd} \times 10^5$, sec^{-1}
1,800	17.6	10.8
3,000	27.8	10.9
7,200	50.8	9.9
10,200	65.4	10.4
14,400	75.8	9.9
		10.4 av

Table VI
First-Order Rates Determined at Various Pyridine Concentrations in Thio-Claisen Reaction of 1 in Diethyl Carbitol Solvent at 228.7°

[Pyridine], mol/l.	$10^5 k_{obsd}$, sec^{-1}
0.050	2.42
0.100	3.06
0.200	4.33
0.301	5.75
0.401	6.71
0.602	8.90
0.802	9.85
0.000	1.45

the higher amine concentrations, which begin to alter the nature of the medium, and perhaps to produce a somewhat greater degree of propenylization, or both of these influences, can the relative catalyst efficiency be seen (Figure 2) to depart from the linear relationship. Moreover, since a function of the rate of disappearance of substrate is being considered in the plot, there is some significance to be associated with the fact that the intercept ([pyridine] = 0) nearly coincides with the experimental rate of thermal propenylization determined in the absence of catalyst. This result confirms the deduction (made in an earlier section) that within a limited range of concentrations the amine only influences the rearrangement to occur faster than the competing propenylization. Thus, in the absence of amine, propenylization occurs some 10–20 times faster than rearrangement at *ca.* 230° and only a trace of thio-Claisen can be noted. In the presence of moderate amine concentrations rearrangement is accelerated to the point where it is more than ten times faster than propenylization. For practical purposes it can be said that the ability to isolate a better than 90% yield of thio-Claisen products depends on catalysis which accelerates rearrangement by factors of about 20. The difference between being able to realize a practical preparation and failure to achieve the desired reaction is due only to comparatively small catalytic effects.

D. Structure–Rate Relationships among Amine Catalysts. Basicity *vs.* Nucleophilicity as the Rate-Controlling Factor. The effect on rate of eight amines differing in their basicity (in water) by 11 orders of magnitude has been examined. The results are tabulated in Table VII. Apparently there is a complete lack of correlation of rate and basicity. In view of all the evidence presented above and in previous sections of this report, it is reasonable to conclude that basicity is not a significant consideration in understanding the catalytic activity of amines.

On the other hand, reactivity appears roughly to parallel the order of nucleophilicity[23] of the amines listed in Table VII. Two distinct classes of amine nucleophiles have been examined: those (the first five entries) which might be called "normal" and those (the last three entries) which could be classified as "facilitated." Among the latter, the most active catalysts are α nucleophiles

Table VII
Rates of Thio-Claisen Rearrangement of Allyl Phenyl Sulfide in the Presence of Various Amines in Equimolar Concentration (0.8 mol/l.) in Diethyl Carbitol at 228.7°

pK_a	Amine	$10^5 k_{obsd}$, sec^{-1}
4.63	Aniline	2.52
5.15	*N,N*-Dimethylaniline	3.42
4.90	Quinoline	7.26
11.0	Triethylamine	9.41
5.25	Pyridine	9.85
0.75	α-Pyridone	14.2
6.95	Imidazole	18.4
8.86	Dabco[a]	19.5

[a] 1,4-Diazabicyclooctane; Dabco is the commercial product of Houdry Co.

possessing an enhanced degree of effectiveness in displacement reactions which is independent of the basicity of the attacking atom.[24] In terms of their relative catalytic activities in the thio-Claisen reaction the facilitated nucleophiles are two to six times more effective than the normal. The fact that relative rate is directly correlated with the nucleophilicity of the catalyst is also evident for anionic nucleophiles, as summarized in Table VIII.

However, the reactivity order does not reflect the full range of nucleophilic "power" available for use if the transition state of the thio-Claisen involved the bond-making step of a normal SN2 displacement reaction. In the classical SN2 reaction[24b] the bond between the advancing nucleophile and the reaction seat is at least half complete in the transition state and this bond-forming step is completed in the product. However, in the thio-Claisen the nucleophilic catalyst never completes a bond to carbon. The very small range of reactivites displayed by catalysts, which as nucleophiles in ordinary SN2 displacements show enormously greater reactivity differences, suggests that in the activation step of the thio-Claisen only a very small degree of bonding between the nucleophilic catalyst and the seat of displacement is ever achieved. That is to say, only a small degree of the nucleophilic capabilities of the amine reagents is exerted in the activation step of the thio-Claisen. Consequently, only a small fraction of the rate differences that distinguish these nucleophiles in ordinary SN2 reactions is actually realized. This assumption accounts for the severely compressed scale of catalytic activities as well as the rough parallel with nucleophilicity. Further evidence in support of this conclusion is considered in connection with identifying the seat of nucleophilic attack in the thio-Claisen substrate.

E. Relative Reactivities among Nucleophilic Catalysts of Widely Varying Nature. A series of experiments, designed to estimate the full range of nucleophilic activities available to catalyze the thio-Claisen, involved measurement of the relative rates of rearrangement, each in the presence of known quantities of various catalytic anions. A solution was prepared consisting of diethyl carbitol containing 0.4 mol/l. of allyl phenyl sulfide and 0.4 mol/l. of triethylamine. Aliquots of this solution were made up to 0.4 mol/l., respectively, with acetic acid, phenol, or thiophenol and each was allowed to react in sealed tubes at 227°. The equilibrium concentrations of the anionic nucleophiles and free triethylamine in these reaction mixtures were calculated assuming the following relationships to hold in the neutral solvent.

$$R_3N + HA \rightleftharpoons R_3\overset{+}{N}H + A^-$$

$$K_{eq} = \frac{[R_3NH^+][A^-]}{[R_3N][HA]} = K_a^{HA} / K_a^{R_3\overset{+}{N}H}$$

Table VIII
Relative Reactivity of Allyl Phenyl Sulfide in the Presence of Various Catalysts

Nucleophile	Catalytic[a] relative rate	Displacement[b] relative rate
$C_6H_5S^-$	1.43	16,000
$C_6H_5O^-$	1.33	13.3
CH_3COO^-	1.02	0.67
$(C_2H_5)_3N$:	1.00	1.00[c]

[a] Determined for thio-Claisen rearrangement. [b] Streitweiser's average relative rate of displacement for the nucleophile in a typical displacement process. [c] This value is for trimethylamine.

Table IX
Effect of Methyl Substitution on Reactivity in the Thio-Claisen Rearrangement (0.25 mol/l. Substrate, 0.25 mol/l. Pyridine in Diethyl Carbitol Solvent at 227.8°)

Sulfide substrate	$10^5 k_{obsd}$, sec^{-1}	Rel rate
Allyl phenyl[a]	3.40	2.1
1,3-Dimethylallyl phenyl[b]	1.65	1.0

[a] Registry no., 5296-64-0. [b] Registry no., 17417-79-7.

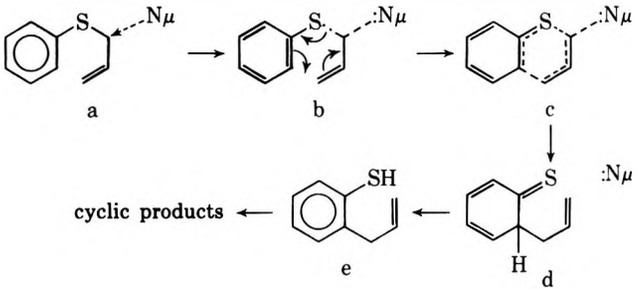
The K_a values used were those reported for pure water.[25] It was considered unlikely that the relative acidities of the three uncharged acids, in relation to the acidity of the triethylammonium ion, would be greatly affected by the carbitol solvent.

The comparative rates were determined by heating the sealed reaction tubes for a specified period of time and determining the relative extent of thio-Claisen rearrangement. Under the chosen reaction conditions it was shown that only an insignificant amount of propenylization was produced. The results are given in Table VIII.

Streitweiser[25] has compiled the list of relative nucleophilic activities by reviewing a multitude of displacement reactions. Included in Table VIII are his values for the "average relative displacements rates" of the nucleophiles examined. Although the catalytic activities of the nucleophiles in the thio-Claisen are in more or less the same order as their nucleophilic activities in the SN2, the range of relative activities is enormously compressed compared to their inherent bond-making capabilities. Thus, the relative activity of thiophenolate and acetate anions in the thio-Claisen is only 1.4, whereas in normal SN2 reactivity this ratio is more than 15,000. This confirms the suggestion that only a small degree of nucleophilic bonding between catalyst and substrate exists in the transition state of the thio-Claisen.

F. The Seat of Nucleophilic Susceptibility. It will be recalled that "diallyl" products such as 8 and 9 can be isolated from thio-Claisen rearrangement. These are most reasonably accounted for on the basis of an act of SN2 displacement on the starting sulfide by the rearrangement intermediate, o-allylthiophenol, in the form of its anion. Moreover, when allyl phenyl(oxy) ether was treated with lithium thiophenoxide, a quantitative SN2 displacement, ultimately giving thio-Claisen products, was observed. On the other hand, phenoxide ion was found to be incapable of effecting displacement, but, instead, was shown to be a functioning catalyst for thio-Claisen rearrangement. Both of these observations establish the allyl side chain as the position susceptible to attack. However, this may not be unrelated to the question (previously noted) as to why thiophenolate produces both bimolecular reaction as well as catalysis, whereas somewhat weaker nucleophiles produce only catalysis.

Scheme III
A Proposal for the Mechanism of Thio-Claisen Catalysis



Another line of evidence bearing on this point is concerned with the effect of methyl substitution on the allyl side chain, which was initially examined to ascertain the magnitude of steric factors on the bimolecular kinetics. Under identical reaction circumstances the first-order rate of disappearance of 1,3-dimethylallyl phenyl sulfide[26] was compared with the rate of allyl phenyl sulfide in diethyl carbitol containing an equimolar amount of pyridine. The data listed in Table IX indicate that methyl substitution at the allylic carbon retards the rate by a factor of only about 2 for a reaction taking place at 227°. This is to be compared with a typical displacement at 25° (for example, chloride displacement on alkyl iodide),[27] where the rate ratio of ethyl to isopropyl is 32. However, since the steric rate effect is almost entirely in the entropy term, the rate ratio must be very considerably greater at 227°. It may therefore be estimated that the steric rate effect due to methyl substitution at the allylic carbon in thio-Claisen substrates is only 0.05–0.0005 as great as is observable in a reaction possessing a "full" S_N2 transition state.

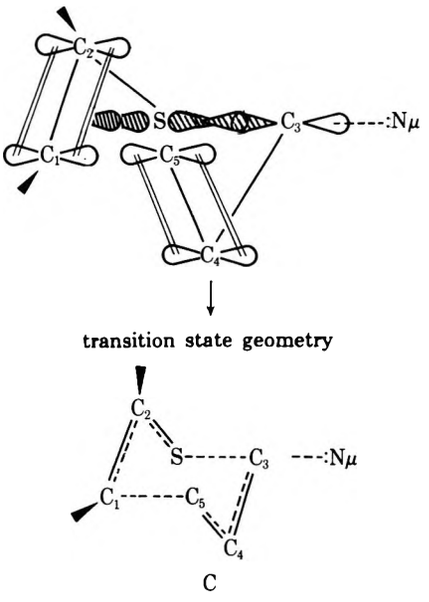
This inference is again to be correlated with the conclusion (reached in a previous section) that the nucleophilic catalyst approaches the rear of the allyl carbon in the act of displacing sulfur from its bond. However, this occurs only to a small fraction of the extent to which bond making and breaking takes place in a typical S_N2 transition state. The smaller extent of Nu–C bond formation in the thio-Claisen thus results in a much smaller steric rate effect than is experienced in the S_N2. Apparently the nucleophile causes only as much displacement of the sulfur from the allylic carbon as is necessary to trigger the concerted events of the sigmatropic rearrangement process.

IV. Proposed Reaction Mechanism. The Nucleophilic Trigger of Sigmatropic Rearrangement. The thio-Claisen is regarded as a typical hetero-Cope[28] reaction, *i.e.*, a concerted, sigmatropic rearrangement following a low-energy pathway as a consequence of orbital symmetry conservation. This thermal reaction can take place at readily accessible temperatures, but all too often it cannot be observed[1,18,29] in competition with the nonallowed[30] propenylization reaction without benefit of a *ca.* 20-fold acceleration by an exclusively nucleophilic, catalytic agent.

The (otherwise) completely analogous oxy-Claisen rearrangement is susceptible only to electrophilic catalysis, in clear distinction to the thio-Claisen, which, as demonstrated here, responds exclusively to nucleophilic agents. In both Claisen cases catalysis has altered the transition state in only a very subtle way. The evidence would seem to suggest that catalysis has not changed the concerted, sigmatropic nature of the reaction, but has merely made it easier to attain its driving force.[28b] Thus, through an understanding of the role of catalyst in a hetero-Cope[28] transition state it may be possible to define the nature of the driving force of this class of reactions.

The mechanistic picture shown appears to fulfill all the specifications and properties of the catalyzed thio-Claisen reaction which are cited above. The mechanism can be most readily considered with the aid of Scheme III, which represents the progress of reaction by a series of glimpses taken along the reaction coordinate. In a the nucleophile (Nu) approaches the rear of the allylic carbon, displacing the bonding electrons of C–S in the direction of the sulfur. This creates a 2p orbital on the allylic carbon which is still mostly coordinated with the sulfur and only slightly with the Nu. This development is diagrammed in b and is shown by Scheme IV in geometric detail as the orbital organization required to produce the arrangement of the critical bonds involved in the concerted transition state C. The transformation of the transition state C to the initial product d destroys all bonding of Nu to the substrate and frees it for further activity. Tautomerism in d produces the final product e and allows subsequent cyclization to the isolated product.

Scheme IV
Nμ: Ordering of Orbital Organization for [3,3]Sigmatropic Rearrangement



The role of the nucleophilic catalyst is, therefore, to aid in developing a 2p center on the allylic carbon which can participate in the pericyclic transition state[31] characteristic of Claisen and other hetero-Cope rearrangements. On this basis it would appear that the driving force of Claisen rearrangement derives from electron displacements in the direction of the heteroatom producing trigonal hybridization of the allylic carbon. In the case of the thio-Claisen there is almost no difference in electronegativity of sulfur and carbon which would create a heterolytic tendency in the C–S bond. Only nucleophilic assistance for this process can be utilized when the C–S bond reaches a critical level of vibrational excitement.

In the oxy-Claisen substrate, where the critical bond is comprised of two atoms (C–O) with a large electronegativity difference, the heterolytic tendency already exists to a significant extent and is enhanced by electrophilic agents which coordinate the oxygen. The rate-enhancing effect of polar solvents reported[22] for the oxy-Claisen also supports this conclusion. Failure to utilize nucleophilic catalysis can therefore be attributed to the fact that oxygen is a poorer leaving group. Thus, the activation energy for S_N2 displacement of C–O to the required degree in the transition state is higher than needed for naturally attaining the critical degree of heterolysis, *i.e.*, development of sufficient p-orbital character at the allylic carbon, in the oxy-Claisen.

In the same vein, failure of the thio-Claisen to utilize electrophilic catalysis may be an indication of unfavorable equilibria, *viz.*, in coordination of acids by sulfur, at the higher temperatures required for the thio-Claisen activated complex. On the other hand, the recently demonstrated[32] susceptibility of the amino-Claisen to electrophilic catalysis, and the increased facility when the nitrogen is in its charged (cationic) form, is to be contrasted with the ordinarily high activation energy[12] and complex character of the uncatalyzed reaction. This is yet another indication of the essentially heterolytic driving force of all Claisen rearrangements localized at the critical bond between the allylic carbon and the hetero atom.

A number of well-precedented mechanistic alternatives have been considered in the course of arriving at the proposal above. Two of the more conventional mechanisms which have been advocated for consideration by referees are treated in some detail in a footnote.[33]

Experimental Section

Analytical samples for spectrophotometric characterization were collected at the thermal conductivity detector exit port of an F and M Model 500 gas chromatograph, using a 10 ft × 0.25 in. stainless steel tube packed with 25% Silicone Oil 200 on 60–80 mesh neutral Chromosorb W or a 6 ft × 0.25 in. copper tube packed with 20% Carbowax 20M on 60–80 mesh Chromosorb W. To ensure purity, all such samples were collected from one column and recollected from the other.

Gas chromatographic quantitative analyses were conducted using an F and M Model 700 Linear-Temperature-Programmed instrument equipped with a flame ionization detector. As the case dictated, a 4 ft × 0.25 in. copper tube packed with either 25% Silicone Oil 200 or 20% Carbowax 20M, on a 60–80 mesh neutral Chromosorb W, was used to effect separation of reactants and products and monitor reaction progress. All chromatograms were obtained in the range of 150–200° using helium as a carrier gas at a flow rate of 60 ml/min (optimum for 0.25 in. column).

Infrared spectra were taken of neat liquid films between salt blocks using a Perkin-Elmer Infracord equipped with sodium chloride optics. Nuclear magnetic resonance spectra were recorded on a Varian A-60, HA-100, or HD-220 nmr spectrometer using tetramethylsilane as an internal standard and carbon tetrachloride as solvent. Mass spectral information was obtained using a C. E. C. 21-110B double focusing high resolution spectrometer. All samples whose elemental analysis is reported below to have been carried out by high-resolution mass spectroscopy (exact mass determination) were analytically pure by accepted gas chromatographic standards.

***N,N*-Diethyl *O*-*o*-Allylphenylthiocarbamate.** A solution of 134.2 g (1.00 mol) of *o*-allylphenol and 166.8 g (1.10 mol) of freshly distilled *N,N*-diethylthiocarbamyl chloride in 1 l. of dry pyridine was prepared. The solution, contained in a 3-l., three-neck, round-bottom flask equipped with a mechanical stirrer, Friedrich condenser, thermometer, and nitrogen inlet, was refluxed for 6 hr. A steady flow of nitrogen was maintained for the entire period.

The mixture was cooled to room temperature and diluted with 1 l. of cold (5°) water. A solution prepared by adding 1 l. of concentrated hydrochloric acid to 1 l. of water was slowly introduced with the aid of a dropping funnel; the flask contents were stirred and cooled during the addition and then transferred to a 5-l. flask. The acidified mixture was continuously extracted with petroleum ether (bp 40–60°) for 24 hr. This extract was washed with five 100-ml portions of water, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated.

Fractionation of the residue under reduced pressure yielded 201.5 g (80.8%) of a pale yellow liquid boiling at 130° (0.6 mm). The infrared spectrum of a sample of this product was identical with the spectrum determined by Evans[3,34] for this same material prepared by a different route. Particularly significant absorption bands were observed at λ_{max} (film) 1520 cm^{-1} (C–N bending characteristics of a monosubstituted alkene).

***N,N*-Diethyl *S*-*o*-Allylphenylthiocarbamate.** The gas-phase thermal rearrangement of the thiocarbamate was accomplished by introducing a 20% (w/v) toluene solution of the ester dropwise into the uppermost section of a 25-mm Vycor tube held vertically and heated with a temperature-regulated split furnace. The rate of addition was adjusted by a Harvard Compact Infusion Pump-Model 972 and the residence time of the volatilized material was controlled by varying the flow of a stream of dry nitrogen gas sweeping through the heated tube. A water-cooled condenser–receiver assembly attached below the tube served to trap the thermolysis product.

To determine the correct conditions for complete conversion of the carbamate, two methods proved useful. Infrared spectroscopy, the most convenient, was hampered by the presence of residual trace quantities of toluene.

After 36 hr the reaction mixture was cooled to room temperature and poured into 150 ml of water. The resulting cloudy solution was extracted with three 150-ml portions of petroleum ether to remove residual undecomposed starting material and most of the *N,N*-diethyl methyl carbamate formed during hydrolysis. The aqueous layer, which contains dissolved potassium *o*-allylthiophenolate (the desired product) and o-propenylthiophenolate, was stored as such under nitrogen.

Identification of Products. *o*-Allylphenyl methyl sulfide had bp 81.5° (2.2 mm); ir 910 (s), 990 (s), 1405 cm^{-1} (s) (monosubstituted alkene); nmr (CCl_4) τ 2.88 (m, 4, ArH), 3.76–4.40 (m, 1, β-CH=), 4.77–5.20 (m, 2, γ-CH=), 6.55 (d, 2, J = 6.5 Hz, ArCH), 7.60 (s, 3, -SCH); mass spectrum (high resolution, 10,000 at 10% valley) molecular ion 164.0671 ± 0.003 (calcd for $C_{10}H_{12}S$, 164.0660). *Anal.*[34] Calcd for $C_{10}H_{12}S$: C, 73.11; H, 7.37; S, 19.52. Found: C, 73.11; H, 7.40; S, 19.36.

***o*-Propenylphenyl methyl sulfide** had ir (film) 960 cm^{-1} (trans double bond); nmr (CCl_4) τ 2.50–3.12 (m, 4, ArH), 3.30 (m, 1, α-CH=), 3.84 (q, 1, J = 7.1 Hz, β-CH=), 7.65 (s, 3, -SCH), 8.10 (d, 3, J = 6.2 Hz, CH_3C=C); mass spectrum (high resolution, 10,000 at 10% valley) molecular ion 164.0662 ± 0.003 (calcd for $C_{10}H_{12}S$, 164.0660).

***o*-Allylthiophenol.** It was not possible to obtain pure analytical data on this substance except by conversion to the methyl sulfide derivative (above). However, by working in solution in the cold it was possible to establish the nmr spectrum, which identifies this product directly (as follows): nmr (CCl_4) τ 2.60–3.30 (m, 4, ArH), 3.80–4.44 (m, 1, β-CH=) 4.84–5.28 (m, 2, -CH_2=), 6.62 (d, 2, J = 7 Hz, ArCH_2), 6.85 (s, 1, -SH).

Allyl *o*-Allylphenyl Sulfide. This product, bp 88.5–89.5° (0.70 mm), was identified by synthesis as well as by its spectral and analytical data. It was readily prepared in 95% purity by adding allyl bromide to the aqueous basic *S*-carbamate hydrolysate containing (95% pure) potassium o-allylthiophenolate. In a manner identical with the reaction with methyl iodide described earlier, the addition of allyl bromide caused an immediate turbidity that coalesced into oily droplets of insoluble product. The allyl sulfide was extracted with petroleum ether and analytical samples were collected from the gas chromatograph: ir 6.09 (m, C=CH_2 stretch), 10.05 (s, C=CH_2 bending), 10.85 (s, C=CH_2 bending), 13.35 μ (s, aromatic); nmr (CCl_4) τ 2.50–3.02 (m, 4, ArH), 3.66–4.44 (m, 2, β-CH=), 4.71–5.20 (m, 4, γ-CH=), 6.43 (d, 2, J = 4.7 Hz, ArCH_2); mass spectrum (high resolution, 5000 at base line) molecular ion 190.0819 ± 0.003 (calcd for $C_{12}H_{14}S$, 190.0816).

7-Allyl-2-methyl-1-thiacourmaran. This component was identified, after separation from the total product by glc methods, principally by nmr and mass spectral data: nmr (CCl_4) τ 3.10 (s, 3, ArH), 3.83–4.44 (m, 1, β-CH=), 4.70–5.18 (m, 2, γ-CH=), 6.15 (q, 1, J = 7 Hz, SCH), 6.45–7.39 (m, H-3), 6.75 (d, 7-CH_2), 8.64 (d, 3, 2-CH_3); mass spectrum (high resolution, 5000 at base line) molecular ion 190.0806 ± 0.003 (calcd for $C_{12}H_{14}S$, 190.0816).

Thermolysis of *o*-Allylthiophenol in Refluxing Quinoline. A 50-ml round-bottom flask was charged with 8.5 g of purified quinoline and fitted with a 6-in. straight tube condenser. A micropipet was suspended vertically in the condenser so that its tip was just below the surface of the liquid amine. Dry, oxygen-free nitrogen was introduced through the pipet and the quinoline was heated to reflux after the system had been swept for *ca.* 5 min. *o*-Allylthiophenol (1.5 g) was drawn into a hypodermic syringe and rapidly injected into the refluxing quinoline medium. To isolate products, the cooled reaction mixture was diluted with 150 ml of ether and washed consecutively with three 25-ml portions of 3 *N* HCl, three 25-ml portions of 3 *N* KOH, and three 25-ml portions of water. The ether solution was dried with anhydrous sodium sulfate and concentrated under vacuum. The resultant liquid was analyzed by gas chromatography and its components were trapped from the glc. Product identification was accomplished by a combination of infrared and nmr spectrum matching with authentic samples of 2-methyl-1-thiacoumaran and 1-thiachroman. The presence of these materials was also verified by glc peak enhancement.

Thermolysis of Allyl Phenyl Sulfide in Refluxing Quinoline Containing Lithium Methoxide. A solution of lithium methoxide in quinoline was prepared in the following manner. High-purity lithium metal ribbon (0.09 g, 0.013 mol) was washed free of petrolatum with anhydrous ether, cut into slivers, and dropped directly into a solution of 0.32 g (0.01 mol) of anhydrous methanol in 10 ml of dry ether. A vigorous hydrogen gas evolution was noted. However, the small surface area presented by the slivers of lithium made it unnecessary to cool the reactants. When hydrogen evolution ceased, the mixture was refluxed for an additional 15 min and cooled. Residual unreacted metal particles were removed with forceps. The ether was boiled off with the aid of a nitrogen purge and 8.5 g of purified quinoline was added. Mild heating was continued until all of the ether was displaced and then stronger heating raised the quinoline solution to its boiling point (~241°). As described earlier, 1.5 g of allyl phenyl sulfide was injected into the refluxing quinoline-metholate solution; reflux was continued for 3 hr.

Two sets of products, neutral and base soluble, were isolated. The cooled reaction mixture was transferred to a small separatory funnel containing a solution of 0.6 g (0.01 mol) of KOH in 15 ml of water. The mixture was thoroughly shaken. The aqueous basic layer was separated and washed with two 25-ml portions of ether. These washings were added to the organic layer, which had been set aside. An excess of methyl iodide was added to the aqueous layer, forming a copious white dispersion of methylated thiophenolate product. These methyl sulfides were isolated in the usual manner from ether, giving 0.45 g of a colorless liquid, which was analyzed by gas chromatographic peak enhancement with previously identified samples. The base-soluble products thiophenol (23.3%), o-allylthiophenol (54.1%), and o-propenylthiophenol (21.6%) were found.

The organic layer was washed free of quinoline in the manner described in earlier experiments and 0.37 g of a pale yellow liquid was obtained as product. Glc analysis in the usual manner afforded the neutral products propenyl phenyl sulfide (27.6%), 2-methyl-1-thiacoumaran (39.9%), 1-thiachroman (2.7%), 7-allyl-2-methyl-1-thiacoumaran (22.8%), and unidentified material (7.0%).

Registry No.—**2**, 6165-54-5; **3**, 6410-53-3; **3a**, 6564-78-9; **5**, 51129-97-6; **6**, 6165-55-5; **7**, 2054-35-5; **8**, 51129-98-7; **9**, 51129-99-8; o-allylphenol, 1745-81-9; *N,N*-diethylcarbamyl chloride, 88-10-8; o-allylphenyl methyl sulfide, 51130-00-8; o-propenylphenyl methyl sulfide, 51130-01-9.

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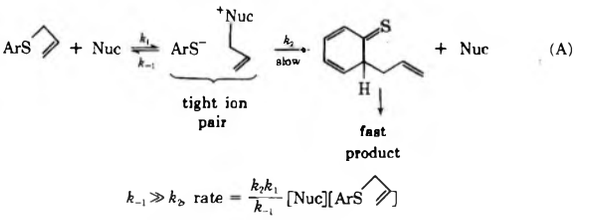
(33) Conventional mechanistic alternatives which do not appear to be in accord with the data are shown below (A and B).



$$k_{-1} \gg k_2,\ \text{rate} = \frac{k_2 k_1}{k_{-1}}[\text{Nuc}][\text{ArS}\diagup\!\!\!\!\diagup]$$

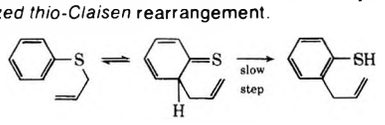
This mechanism fails because it requires a step involving the formation of a full bond between the nucleophile and carbon, which contradicts the evidence presented. The following are three of the points of evidence which exclude this pathway.

(1) If a nucleophilic bond were completed in k_1 we should see a large steric effect arising from substitution of methyls at the seat of displacement (Table IX), and from the size and steric hindrance factor in the structure of the nucleophile. No such correlations can be perceived from the data. Moreover, it would involve a very large coincidence to have k_1 and k_2 remain in essentially constant ratio in order to realize the great attentuation in the range of nucleophilicities, leaving group abilities, and steric effects encompassed by the reagents considered in Tables VII and VIII.

(2) If a bond had been formed resulting in an ion-pair intermediate the relative rates for various nucleophiles still would be enormously different depending on their charge type and leaving-group facilities. Thus, according to mechanism A, when lithium methoxide is the catalyst nucleophile the intermediate is not expected to be an ion pair since the countermolecule is the very volatile allyl methyl(oxy) ether. This bolls out of the reaction flask when one tries to heat lithium thiophenoxide with it in carbitol solution; yet when allyl phenyl sulfide is heated in the same flask with lithium methoxide in carbitol, nothing is observed to boil out and normal rearrangement occurs.

When lithium phenoxide is the catalyst, it must be expected in accordance with mechanism A that allyl phenyl ether would be formed as the reaction intermediate. Since the oxy-Claisen has a very much lower activation demand, at the same reaction temperature and medium this ether intermediate should irreversibly undergo much more rapid rearrangement than any thio-Claisen substrate tested in these studies. Since no o-allylphenol or derived coumaran is ever formed in the course of lithium phenoxide catalysis, though the yields of thio-Claisen products are upwards of 90%, it is doubtful that a bimolecular reaction between benzenethiolate anion and allyl phenyl ether, as stipulated in mechanism A, could have been the source of the thio-Claisen rearrangement products observed.

(3) An ion-pair intermediate involving a resonance-stabilized thiophenolate anion cannot account for the absence of even a trace of para thio-Claisen rearrangement product. As shown earlier,[4] when the ortho position is blocked there is no evidence for para rearrangement because the normal dienethione intermediate, which could undergo the para rearrangement, prefers to undergo an alternative sigmatropic rearrangement. This has also been used as evidence for the essentially, concerted nature of the *catalyzed thio-Claisen* rearrangement.



Here the effect of various additives in the medium reflects the rate of thienolization of the dienethione intermediate relative to its reversal to starting material; *i.e.*, thienolization is either as slow as or s ower than rearrangement. However, the most apparent weakness of this mechanism is that it cannot explain the lack of correlation with base strength of the additives. Since general acid-base catalysis cannot be identified as a factor determining the rate of thio-Claisen rearrangement, it is difficult to reconcile this reaction with a mechanism whose slow step involves proton transfer from carbon to sulfur in a triad system.

(34) o-Allylphenyl methyl sulfide has also been prepared in large quantities in analytically pure form: D. Drayer, Ph.D. Thesis, University of Delaware, June 1972.

Notes

A CNINDO Investigation of Diene Reactivity in the Diels–Alder Reaction between 1-(*p*-Substituted phenyl)-1,3-butadienes and Maleic Anhydride

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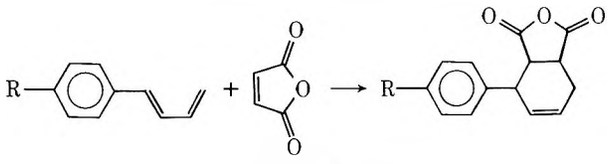
Many investigators[2-4] have indicated the importance of the energy of the highest occupied molecular orbital (HOMO) and of the lowest unoccupied molecular orbital (LUMO) in determining diene reactivity in the Diels–Alder reaction. Sustmann and Schubert[4] have recently shown a correlation of the HOMO diene–LUMO dienophile energy separation with the logarithm of the rate constant for the normal electron demand Diels–Alder reaction. However, their study used many open-chain dienes for which the relative concentrations of the cisoid conformational isomers are not known.[5] In this report we have investigated the diene reactivity of the 1-(*p*-substituted phenyl)-1,3-butadiene system in order to obtain a more precise evaluation of the effect of the energy of the HOMO and other diene molecular properties on the rate of the Diels–Alder reaction. The concentrations of the cisoid conformations of the dienes in this study should all be the same.

Earlier we had shown that the CNDO/2 and INDO methods (CNINDO)[6] can be used to predict with reasonable success the regioselectivity of the Diels–Alder reaction between unsymmetrically substituted dienes and dienophiles.[7] Therefore, in this study CNINDO calculations were utilized to investigate the diene reactivity in the Diels–Alder reaction between 1-(*p*-substituted phenyl)-1,3-butadienes and maleic anhydride. The molecular orbital calculations were performed with standard bond angles and bond lengths.[8] The conformation of the dienes used in these calculations was the cisoid planar.[7,9] We found that the interpretations from the CNINDO calculated eigenvectors and eigenvalues were independent of small changes in bond angles, bond lengths, and rotational conformations.[10]



R = H, CH_3, OCH_3, Cl, NO_2

An examination of this reaction using Sustmann's model for substituent effects[12] and HOMO and LUMO energies from the CNINDO calculations was carried out. We found that the energy difference between the HOMO of the diene and the LUMO of maleic anhydride was considerably smaller than the corresponding difference between the HOMO of maleic anhydride and the LUMO of the diene in all cases. This is the orbital arrangement[12] of a normal electron demand Diels–Alder reaction and indicates a charge donation[3a] from the diene to maleic anhydride in the transition state of this Diels–Alder reaction. The direction of this charge donation is in agreement with the observed substituent effect.[13]

A molecular property of the dienes which should be a good parameter for comparing the relative abilities of the dienes to donate electron density is the total p_z density of the butadiene moiety (Table I). We have found a linear relationship[14] between the total p_z density of the butadiene moiety and the logarithm of the relative rate[13] at 25°. A least-squares regression analysis of the relationship gave correlation coefficients of 0.899 (CNDO/2) and 0.980 (INDO). This poorer correlation of theory with experimental data for the CNDO/2 method was due to the inclusion of the data for the chlorine substituent. A possible explanation for the correlation is that the donor–acceptor interaction between the diene and the dienophile provides a mechanism through which the electron density of the diene is reduced in the transition state. Thus, when the HOMO of the diene and LUMO of the dienophile are not too different, the decrease in the electronic repulsions of the electron-rich diene through delocalization becomes an important rate-enhancing factor. By similar analysis, the delocalization of the electron density of the electron-poor diene to the dienophile becomes a rate-retarding factor.

The proposed substituent effect[12] on the energy of the HOMO of the diene is that electron-donating groups increase the energy of the HOMO and electron-withdrawing groups decrease its energy. This trend is observed in our calculations (Table I). Also, from frontier orbital theory, one would expect more stabilization of the transition state as the energy of the HOMO of the diene increases for a normal electron demand Diels–Alder reaction. This effect is observed in the linear relationship which we found between the energy of the HOMO of the diene and the logarithm of the relative rates of reaction[13] at 25°. A least-squares regression analysis of this relationship gave correlation coefficients of 0.962 (CNDO/2) and 0.989 (INDO).

Frontier electron density has been used by many inves-

Table I
Molecular Properties of 1-(*p*-Substituted phenyl)-1,3-butadienes

Registry no.	Para substituent	Log k/k_H[a]	Energy of the HOMO,[b] au		Total p_z density of butadiene moiety		Terminal FED[c]	
			INDO	CNDO/2	INDO	CNDO/2	INDO	CNDO/2
30448-78-3	OCH_3	0.4216	−0.364	−0.388	4.012	4.012	0.226	0.243
33356-85-3	CH_3	0.0453	−0.377	−0.397	4.004	4.005	0.290	0.283
1515-78-2	H	0.0	−0.387	−0.408	4.001	4.001	0.337	0.338
33356-84-2	Cl	−0.2321		−0.411		3.983		0.266
20264-89-5	NO_2	−0.5607	−0.413	−0.433	3.981	3.980	0.355	0.347

[a] Reference 12. [b] π molecular orbital. [c] The terminal frontier electron density is the sum of the squares of the p_z coefficients of the HOMO at the terminal carbon positions of the diene. The other atomic orbital coefficients are zero for HOMO.

tigators[2,3c,7,15] to predict the preferred regioisomers in the Diels–Alder reaction. A simple second-order perturbation treatment[16] predicts a decrease in the rate of reaction as the terminal frontier electron density decreases (assuming that frontier orbital energies are constant). The calculations, however, show a decrease in the terminal frontier electron density of the dienes as the logarithm of the relative rate of reaction increases (Table I).[17] This lack of correlation between the terminal frontier electron densities of the dienes and the logarithm of the relative rates is not unexpected when one considers the large change (~30 kcal) in the energy of the diene HOMO. Consequently, the terminal electron densities of the dienes are not useful in predicting diene reactivity in such cases.

In conclusion, the linear relationships between the energy of HOMO of the diene and the logarithm of the relative rates of reaction and between the total p_z density of the butadiene moiety and the logarithm of the relative rates of reaction indicate that these molecular properties do have a significant effect on the stability of the transition state of this normal electron demand Diels–Alder reaction. Subsequently, the relative reactivities of the dienes can be predicted from either the HOMO energy or the total p_z density of the butadiene moiety. Though the terminal frontier electron densities of the dienes are useful for determining regioselectivity, they were not found to be useful for predicting relative diene reactivity in cases where the energy of the diene HOMO varied significantly.

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Registry No.—Maleic anhydride, 108-31-6.

References and Notes

(1) E. I. du Pont de Nemours and Co., Analytical Research Lab, Spruance Plant, Richmond, Virginia 23261.
(2) (a) K. N. Houk, *J. Amer. Chem. Soc.*, **95**, 4092 (1973), and references cited therein; (b) K. N. Houk and R. W. Strozier, *ibid.*, **95**, 4094 (1973).
(3) (a) N. D. Epiotis, *J. Amer. Chem. Soc.*, **94**, 1924 (1972), and references cited therein; (b) *ibid.*, **95**, 1191 (1973); (c) *ibid.*, **95**, 5624 (1973), and references cited therein.
(4) R. Sustmann and R. Schubert, *Angew. Chem., Int. Ed. Engl.*, **11**, 840 (1972), and references cited therein.
(5) Only the cisoid conformational isomer of the diene can undergo a Diels-Alder addition: J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
(6) QCPE No. 141: J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970.
(7) P. V. Alston, R. M. Ottenbrite, and D. D. Shillady, *J. Org. Chem.*, **38**, 4075 (1973).
(8) J. A. Pople and M. Gordon, *J. Amer. Chem. Soc.*, **89**, 4253 (1967).
(9) The maleic anhydride molecule was assumed to be planar with a plane of symmetry bisecting the COC angle of the ring. No significant change in the energies of HOMO and LUMO was found by varying this angle between 104 and 109°.
(10) We have found that the relationship between the CNINDO energy of the highest occupied molecular orbital and the experimental ionization potential for dienes and dienophiles with electron-donating substituents (OCH_3, CH_3) and conjugating substituents (C_6H_5) is satisfactory. The general qualitative trend of the experimental ionization potential is correctly represented by the CNINDO methods in these systems. However, for electron-withdrawing substituents such as CHO and CN, the theory predicts π HOMO values which are higher than that of ethylene, while the experimental values[2a] are lower. These observations are in agreement with Bloor and Breen's CNDO study of monosubstituted benzenes.[11] Thus, we expect that the qualitative trend observed in the CNINDO HOMO energies of the 1-(*p*-substituted phenyl)-1,3-butadienes will be real. Also, the CNINDO HOMO energies of the transoid and cisoid conformations of the dienes studied varied by less than 0.1 ev. This gives some justification to the widely accepted use of experimental ionization potentials to determine the energies of the HOMO of the cisoid conformations of open-chain dienes.
(11) J. E. Bloor and D. L. Breen, *J. Phys. Chem.*, **72**, 716 (1968).
(12) R. Sustmann, *Tetrahedron Lett.*, 2721 (1972).
(13) E. J. Dewitt, C. T. Lester, and G. A. Ropp, *J. Amer. Chem. Soc.*, **78**, 2101 (1956).
(14) The Arrhenius relationship [$k = A \exp(-\Delta E^*/RT)$] leads us to expect a linear relationship between the logarithm of the relative rates of reaction and a molecular property of the dienes which affects the energy of the transition state of the reaction.
(15) O. Eisentein, J. M. Lefour, and N. T. Anh, *Chem. Commun.*, 969 (1971).
(16) R. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, **12**, 36 (1973).
(17) The same trend was found with the total frontier electron density of the HOMO for the butadiene moiety of the molecule.

Polyphenylated Cyclobuten-4-ones from Squaryl Dichloride

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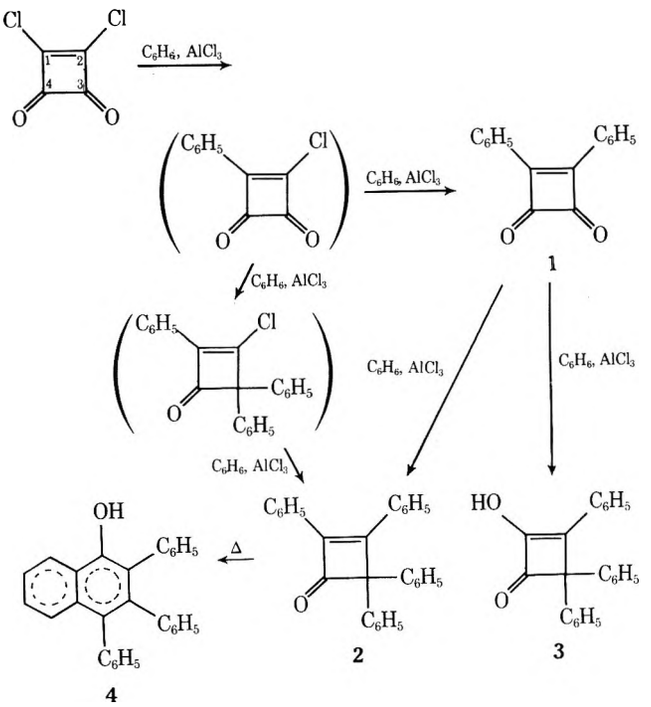
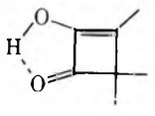
The high-yield synthesis of 1,2-diphenylcyclobutene-3,4-dione (1) from squaryl dichloride in benzene solution under Friedel–Crafts conditions was reported in a recent communication.[1] At the low temperatures (~10°) employed in that work, the reaction did not proceed substantially beyond the stage of 1 despite a benzene/squaryl dichloride molar ratio of nearly 43 and a moderate excess of Lewis acid ($AlCl_3$, freshly sublimed, 2.26 mol per mol of dichloride).

We now report that, at higher temperatures, the dichloride reacts with more than 2 mol of benzene. As a result, one observes drastically lowered yields, or even complete disappearance, of 1 in favor of the successor species 2, 1,2,3,3-tetraphenylcyclobuten-4-one, whose yield in the previous work[1] had amounted to a mere 1%. In addition, the enolone 3, 1-hydroxy-2,3,3-triphenylcyclobuten-4-one, arises in appreciable yields, and small quantities of the naphthol 4, resulting from thermal electrocyclic ring opening[2] of 2 and intramolecular cyclization of the intermediary vinyl ketene species, are also formed. For example, at the reflux temperature of the benzene medium (24 hr), with catalyst ($AlCl_3$, freshly sublimed) and reactant concentrations the same as in the preceding investigation,[1] squaryl dichloride was found to convert to 2 and 3 in 53 and 27% yields, respectively; furthermore, 4 was separated in 1.5% yield.



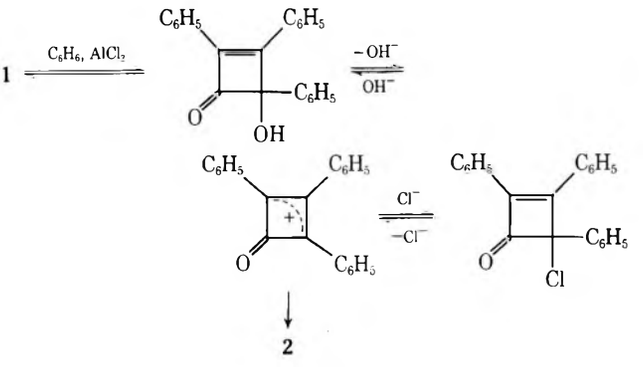
Under conditions similar to those delineated, yet with $AlCl_3$ "as received" (*i.e.*, no resublimation done prior to use), at a Lewis acid/squaryl dichloride molar ratio of 2.3, the intermediary **1** is not entirely consumed but remains in the reaction mixture in 10–20% yield. The less efficacious catalyst system in this case, moreover, produces slightly diminished yields of **3** and grossly reduced yields of **2**. Increased quantities (up to 10%) of **4** can be collected instead. For example, after a reflux period of 20 hr we obtained 10% **1**, 16% **2**, 21% **3**, and 7% **4**. The products in all reactions were separated by column chromatography. The known compounds **1**, **2**, and **4** were identified by comparison (melting point, ir) with products described in the literature. The structure of **3** derives from elemental analysis and spectral data. The parent ion peak in the mass spectrum appears at m/e 312. The ir spectrum displays the broad OH stretching absorption with maxima at 3183 and 3445 cm^{-1} characteristic of the 1-hydroxycyclobuten-4-one system capable of strong intramolecular hydrogen



bonding,[3] and $\nu_{C=O}$ is shown at the low-frequency position (1730 cm^{-1}) expected[3,4] for the hydrogen-bonded carbonyl group in this system.[5-7] The ^1H nmr spectrum reveals the anticipated low-field multiplet at δ 7.5–7.8 ppm (2 H) due to the two deshielded ortho protons of the phenyl substituent at C-2, whereas the remaining phenyl protons (13 H) resonate at 7.1–7.5 ppm.[8,9]

In order to demonstrate the anticipated intermediacy of **1** in the reaction course leading to the compounds discussed, we conducted a run in which **1** was employed in place of squaryl dichloride under conditions otherwise identical with those of the first-mentioned experiment (24 hr in refluxing benzene; freshly sublimed $AlCl_3$, 2.26 mol per mol of **1**). The same products **2**, **3**, and **4** were collected, as expected, and both the combined yield of **2** plus **3** (81%) and the yield of **4** (1.6%) were nearly identical with the corresponding yield data of the squaryl dichloride experiment. In outstanding contrast, however, the yield of **2** (40%) was found to be decreased and that of **3** (41%) increased, relative to the original experiment. This shows that the sequence **1** → **2** is not the sole path leading to the tetraphenyl ketone. A second reaction sequence involving the two monochlorides, 2-chloro-1-phenylcyclobutene-3,4-dione and 2-chloro-1,3,3-triphenylcyclobuten-4-one (not isolated here and, hence, placed in parentheses in the scheme above), is likely to contribute to the formation of **2**. As the latter sequence is not operative in the reaction starting out from **1**, **2** will arise in lower yield in that case; on the other hand, formation of **3** from **1** must be correspondingly favored because of the high initial concentration of the latter compound.

Our results, as seen against the background of the preceding work,[1] indicate that step **1** → **2** proceeds with a slightly lower activation energy than is required for path **1** → **3**. The most probable mechanism leading to **3** involves 1,3-addition of benzene across the enone system (*e.g.*, at C-1 and C-3) of **1**, a process resisted by the requirement of two rehybridization steps, to a minor extent also by the steric demand of the phenyl group at C-1.[10] At low temperatures, therefore, addition at one of the carbonyl C atoms (and further rapid reaction with benzene of the allylic-type cyclobutenyl cation[11-13] resulting from Lewis acid-induced ionization of the primary adduct carbinol) is probably the preferred path. This may account for both the formation of **2** and the absence of **3** in the low-temperature reactions of the previous study. At the boiling temperature of benzene, on the other hand, the competitiveness of the 1,3-addition becomes appreciable, as the yield data for **3** attest.



The enhanced conversion of **2** to the naphthol **4** in reactions catalyzed with low-activity Lewis acid confirms the expectation that the process of ring opening (and subsequent cycloaddition) is retarded by complexation, *i.e.*, enolate formation, of **2** with active $AlCl_3$. This question is under further investigation.

Experimental Section

Friedel–Crafts Reaction of Squaryl Dichloride with Benzene. A. With Freshly Sublimed $AlCl_3$. In oven-dried and nitrogen-purged equipment, 0.80 g (6.0 mmol) of freshly sublimed $AlCl_3$ was added to the stirred solution of 0.40 g (2.65 mmol) of resublimed squaryl dichloride[14] in 10 ml (8.79 g) of dry benzene at 18°. Under a blanket of predried nitrogen, the mixture was stirred for 1 hr at the same temperature, followed by 24 hr at reflux. After the addition of 100 ml of benzene, the reaction mixture was shaken with 100 ml of ice-cold 0.1 *M* hydrochloric acid. The benzene layer, combined with the benzene washings of the aqueous phase, was washed with water and dried over Na_2SO_4. The residue remaining after solvent removal *in vacuo* was chromatographed on silica gel, Merck 7734, with band separation monitored by tlc on silica gel. Elution with the solvents indicated (redistilled prior to use), followed by evaporation of the eluates to dryness under reduced pressure, furnished the following compounds.

Band I (40/60 benzene–hexane): 0.015 g (1.5%) of crude 2,3,4-triphenyl-1-naphthol (**4**). Repeated recrystallizations from benzene–hexane produced the compound as fine white needles: mp 163° (lit.[15] 163°); mass spectrum, m/e 372 (P^+); ir spectrum (KBr) ν_{O-H} 3535 cm^{-1} (sh 3521 cm^{-1}).

Anal. Calcd for $C_{28}H_{20}O$ (372.4): C, 90.29; H, 5.41. Found: C, 90.78, 88.99; H, 4.99, 5.40.

Band II (40/60 benzene–hexane): 0.52 g (52.7%) of crude 1,2,3,3-tetraphenylcyclobuten-4-one (**2**). Recrystallization from benzene–hexane to constant melting point gave light yellow needles, mp 129–130° (lit.[16] 139°), undepressed on admixture of authentic product prepared by Ried's procedure[16] (mp 129–130°): mass spectrum, m/e 372 (P^+).

Band III (50/50 benzene–hexane): 0.010 g of fine-crystalline, white solid decomposing over range 130–230°; not further investigated.

Band IV (50/50 benzene–acetone): 0.22 g (26.6%) of crude 1-hydroxy-2,3,3-triphenylcyclobuten-4-one (**3**). Recrystallization from benzene–hexane furnished fine, colorless needles: mp 206–208° dec; mass spectrum, m/e 312 (P^+); ir spectrum (KBr) 3445 (m–s) and 3183 (s) cm^{-1} (ν_{O-H}, H-bonded), 1730 ($\nu_{C=O}$), 1640 ($\nu_{C=C}$); ^1H nmr spectrum (60 MHz in $CDCl_3$, δ relative to TMS) 7.5–7.8 ppm (2 H), 7.1–7.5 (13 H).

Anal. Calcd for $C_{22}H_{16}O_2$ (312.4): C, 84.58; H, 5.17. Found: C, 83.81; H, 5.12.

An experiment conducted as above, yet with 2.65 mmol of **1** in place of squaryl dichloride, gave **4** (1.6%), **2** (40.2%), **1** (3.1% recovery), and **3** (40.9%), in that order, on chromatographic work-up.

B. With $AlCl_3$ "as Received." Following the addition of 1.54 g (11.5 mmol) of commercial-grade $AlCl_3$ "as received" (Merck

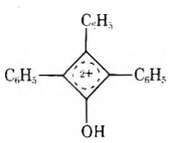
sublimed, code 1082) to the solution of 0.755 g (5.0 mmol) of squaryl dichloride, the mixture was stirred for 1 hr at 20° and another 20 hr at reflux under the conditions of the experiment described in (A). Work-up as before furnished four chromatographic bands, from which the following compounds were isolated: band I, 0.126 g (6.8%) of crude **4**, mp 163° (from benzene–hexane); band II, 0.291 g (15.6%) of crude **2**, mp 130–131° (from benzene–hexane); band III, 0.119 g (10.2%) of crude **1**, mp 95° (from benzene–chloroform) (lit. 97–97.2°,[17] 98°,[3a] 94–95°[1]), undepressed on admixture of authentic[1] compound; band IV, 0.328 g (21.0%) of crude **3**, mp 204–208° dec (from benzene–hexane).

Acknowledgment. The support given by the Council for Scientific and Industrial Research is gratefully acknowledged, as is the assistance rendered by Dr. E. Bartel, University of Stellenbosch, who kindly recorded the mass spectra of several compounds. B. R. G. thanks the National Institute for Metallurgy for a scholarship grant.

Registry No.—**2**, 28480-68-4; **3**, 51065-83-9; **4**, 2892-40-2; squaryl dichloride, 2892-63-9; benzene, 71-43-2.

References and Notes

(1) B. R. Green and E. W. Neuse, *Synthesis*, 46 (1974).
(2) Symmetry considerations predict a conrotatory mode of ring opening for this 4-π electrocyclic process, although its stereospecificity cannot be assessed in the example **2** → **4**.
(3) (a) W. Ried and D. P. Schäfer, *Chem. Ber.*, **102**, 4193 (1969); (b) W. Ried and H. Kohl, *ibid.*, **104**, 2896 (1971).
(4) W. Ried, A. H. Schmidt, and W. Kuhn, *Chem. Ber.*, **104**, 2622 (1971).
(5) Cyclobutenones lacking the capability for chelation of this type generally[4,6] show $\nu_{C=O}$ in the region of 1750–1790 cm^{-1}; in rare instances, frequencies as low as 1740 cm^{-1} have been recorded.[7]
(6) See, for example, E. J. Smutny, M. C. Caserio, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 1793 (1960); W. Ried and W. Kunstmann, *Angew. Chem.*, **80**, 121 (1968); *Chem. Ber.*, **102**, 1422 (1969).
(7) W. Ried and D. P. Schäfer, *Chem. Ber.*, **103**, 2225 (1970); W. Ried and F. Bätz, *Justus Liebigs Ann. Chem.*, **755**, 32 (1972).
(8) This nmr pattern, for which there is precedence in the spectra of 1-phenylcyclobutene-3,4-dione[9a] and some 1-chloro-2-phenylcyclobutene derivatives,[9b] rules out the alternative structure of the 3-hydroxy-1,2,3-triphenylcyclobuten-4-one isomer expected to give a 4:11 intensity ratio of the low-field to high-field phenyl proton signals.
(9) (a) W. Ried and A. H. Schmidt, *Angew. Chem.*, **84**, 1048 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 997 (1972). Much of the pioneering work done by Roberts' and Ried's schools on unsaturated four-membered ring ketones is covered in this review on phenylcyclobutenediones. (b) Y. Kitahara, M. C. Caserio, F. Scardiglia, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 3106 (1960).
(10) In the sterically more favorable case of 1-phenylcyclobutene-3,4-dione as the substrate, Ried and Schäfer[3a] observed the $AlCl_3$-catalyzed 1,3-addition of aromatics (involving positions 2 and 4 of the four-membered ring system) to proceed without restriction.
(11) The existence of suitably substituted cyclobutenyl and oxocyclobutenyl cations in acidic solution,[12a] and even in the solid state,[12b-d] has been demonstrated. On the other hand, protonation (at oxygen) of the oxocyclobutenyl cation, which would give the formally dicationic species



is most unlikely to occur in the environment of our experiments, as highly acidic conditions are required even for the generation of the tetraphenyl-substituted dication,[13] in which a higher extent of stabilization through charge delocalization is expected than in the hydroxytriphenyl species drawn above.
(12) (a) G. A. Olah, J. M. Bollinger, and A. M. White, *J. Amer. Chem. Soc.*, **91**, 3667 (1969); (b) H. H. Freedman and A. M. Frantz, *ibid.*, **84**, 4165 (1962); H. H. Freedman and A. E. Young, *ibid.*, **86**, 734 (1964); (c) G. Seitz and H. Morck, *Chimia*, **26**, 368 (1972); (d) W. Ried and R. Lantzsch, *Justus Liebigs Ann. Chem.*, **756**, 173 (1972).
(13) G. A. Olah and G. D. Mateescu, *J. Amer. Chem. Soc.*, **92**, 1430 (1970).
(14) R. C. De Selms, C. J. Fox, and R. C. Riordan, *Tetrahedron Lett.*, 781 (1970).
(15) L. I. Smith and H. H. Hoehn, *J. Amer. Chem. Soc.*, **63**, 1180 (1941).
(16) W. Ried and R. Lantzsch, *Synthesis*, 303 (1970).
(17) A. T. Blomquist and E. A. LaLancette, *J. Amer. Chem. Soc.*, **83**, 1387 (1961).

Birch Reduction of *N*-Methylindoline

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Received November 7, 1973

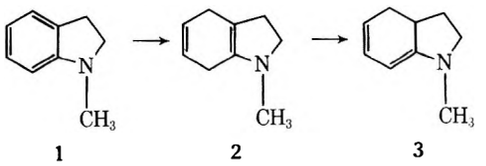
Pursuant to a need for some intermediate compounds in our development of certain synthetic routes, we investigated the Birch reduction of *N*-methylindoline[2] (**1**). It has been suggested[3] that **3** is the probable product of this reaction and that in the case of *N,N*-dimethyl-*p*-toluidine[4] a mixture of 2,3-dihydro-*N,N*-dimethyl-*p*-toluidine and 2,5-dihydro-*N,N*-dimethyl-*p*-toluidine are the products.

Our conditions for the reduction require lithium in liquid ammonia–tetrahydrofuran–isopropyl alcohol, and, upon subjection of **1** to this reaction, *N*-methyl-4,7-dihydroindoline (**2**) is the sole product. Our experience with the reduction of **1** and its product **2** indicates that no **3** is formed during the reduction. However, **2** is a very labile substance with respect to rearrangement to **3** and extreme care is required to prevent this rearrangement from occurring. As one might expect, exposure of **2** to acidic substances accelerates the conversion to **3**. For example, using commercial CCl_4 or $CDCl_3$, which may contain even trace amounts of HCl, will cause **3** to develop. We also found that the following drying agents also cause the **2** to **3** reaction: $CaCl_2$, Na_2SO_4, K_2CO_3, $MgSO_4$, and $CaSO_4$. However, **2** appears stable, neat or in ether solutions, when stored in the cold (0°) over solid KOH. Product **2** can be distilled without rearrangement but rigorous treatment of the glassware with ammonium hydroxide is necessary to prevent rearrangement from happening.

One can, of course, produce **3** directly from the reduction by purposely exposing the reduction product to acid during work-up. One such method is distillation from a small amount of acidic ion-exchange resin.

The structures for **2** and **3** follow directly from their spectral and analytical data. For **2** in its nmr spectrum the broad singlet of 2 H at τ 4.4 and the 4 H in the τ 7.2 region are fully characteristic of the 1,4-diene in a cyclohexane ring. In the case of **3**, it has three separate single proton vinyl resonances at τ 4.1, 4.9, and 5.6. The first two are multiplets and the third is a broad doublet in a chemical shift region typical of a β-vinylenamine type. In addition **3** gives a uv spectrum with λ_{max} 3306 (ϵ 5200) indicative of the conjugated enamine.

It appears from these results that **1** indeed gives the normal product (**2**) from the Birch reduction and that **2** can be used in some synthetic operations with due cau-



1 **2** **3**

tion. Also one can easily prepare **3** from **1** and it too may be of use in synthetic sequences.

It would seem to be a logical extension of our results that *N,N*-dialkyl aromatic amines will in general give the usual unconjugated diene as the sole primary product. However, due caution must be taken to see that the very facile rearrangement of the unconjugated to the conjugated diene does not take place.

Experimental Section

Preparation of 4,7-Dihydro-*N*-methylindoline (2). A 1-l. three-necked flask equipped with a mechanical stirrer, Dry Ice condenser, and gas inlet and outlet was purged with nitrogen. Ammonia was passed through a KOH gas washing tower, and about 500 ml was collected in the reaction flask. To the ammonia a solution of *N*-methylindoline (10 g, 0.075 mol) in tetrahydrofuran (100 ml) was added along with isopropyl alcohol (45 g, 0.75 mol). To this stirring mixture was added lithium ribbon (1.6 g, 0.23 g-atom) in small pieces, and the reaction was allowed to continue until the blue color had discharged, usually about 0.5 hr. At this point an aliquot of the reaction mixture was quenched in an ether–water mixture, and the ether layer was examined by nmr to determine if all aromatic protons had disappeared. Usually an additional 0.5 g of lithium was required in order to effect complete reduction and the blue color persisted for an hour or so. At this point another aliquot was checked by quenching and nmr analysis and more lithium was added if necessary. When complete reduction was indicated, the ammonia was allowed to evaporate under nitrogen flow. A mixture of water and ether (100 ml each) was added and the organic layer was washed rapidly with water and dried over solid KOH pellets. Concentration of the ether layer and rapid distillation in an apparatus carefully washed with ammonium hydroxide and dried gave 2 (8.6 g, bp 39–41° (0.07 mm)) in 86% yield; nmr (neat) τ 4.4 (s, 2 H), 6.95–7.6 (m, 8 H), 7.7 (s, 3 H).

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 6.69. Found: C, 80.08; H, 9.58.

Preparation of 4,5-Dihydro-*N*-methylindoline (3). The identical reaction as described above for the preparation of 2 was conducted again upon *N*-methylindoline (10 g). Work-up of the reaction was also identical except that *ca.* 100 mg of Dowex 50W-X2 200–400 mesh hydrogen form cation-exchange resin was added to the pot and then the product was slowly distilled to give 3 (8.1 g, bp 69–73° (3 mm)): nmr (neat τ 4.1 (m, 1 H), 4.9 (m, 1 H), 5.6 (d, 1 H), 6.8–8.7 (m, 7 H), 7.5 (s, 3 H); uv λ_{max}(*i*-PrOH) 306 (ϵ 5200).

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69. Found: C, 79.90; H, 9.62.

Acknowledgment. This investigation was supported by a Public Health Service Research Career Development Award (No. GM-70,394-01) from the Institute of General Medical Sciences.

References and Notes

(1) Fellow of the Alfred P. Sloan Foundation.
(2) This compound has been subjected to Birch conditions, but the results were incomplete and not rigorously conclusive. See footnote 3.
(3) S. O'Brien and D. C. C. Smith, *J. Chem. Soc.*, 4609 (1960).
(4) B. Millward, *J. Chem. Soc.*, 26 (1960).

Degradation of Tertiary Amines *via* Aminimines

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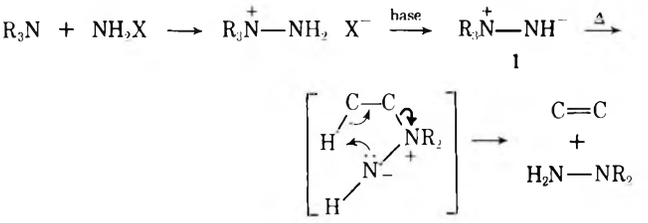
In 1879 Fischer reported[1] that, when 1,1,1-triethylhydrazinium hydroxide is refluxed in water, 1,1-diethylhydrazine is formed (eq 1). He formulated the reaction as also producing ethylene, but mentioned no experimental evidence for it; perhaps this was merely equation balancing. However, since he had previously shown[2] that some hydrazinium hydroxides give alcohols by a displacement process, he might have had unreported evidence that ethanol was not formed from the ethyl compound.

$$(CH_3CH_2)_3\overset{+}{N}-NH_2\ OH^- \xrightarrow[H_2O]{\Delta} (CH_3CH_2)NNH_2 + CH_2{=}CH_2 \quad (1)$$

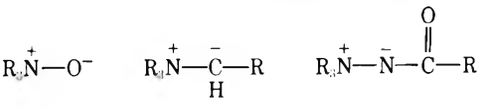
If such eliminations could be effected generally, they might furnish a useful alternative to the Hofmann and

Scheme I



Cope degradations, particularly since hydrazinium salts can be formed readily from tertiary amines.[1b,3] The overall plan for such a degradation is indicated in Scheme I.

Presumably under proper conditions, though perhaps not in water, the elimination would occur *via* an aminimine inner salt **1**,[4] and therefore would be a nitrogen analog of the Cope elimination[5] of amine oxides **2**, and the α,β' mechanism of elimination in some hindered quaternary ammonium ions *via* the ylides **3**.[6] Eliminations from the similar aminimide inner salts **4** have been reported,[7] but these occurred only at rather high temperatures.



2 **3** **4**

Accordingly, we have investigated the elimination from two hydrazinium salts in the presence of strong base (potassium *tert*-butoxide) and have obtained respectable yields of olefins. The two systems studied, *sec*-butyl and cyclohexyl, were selected as likely to reveal most quickly the characteristics and utility of the scheme. The results are what one might anticipate for a Cope-like process, a syn elimination in **1** through a cyclic transition state.

The hydrazinium chlorides were prepared from dimethyl-*sec*-butylamine and dimethylcyclohexylamine by several minor variations of Sommer's method[3a] employing hydroxylamine-*O*-sulfonic acid (the excellent method of Tamura, *et al.*,[3c] had not yet appeared when this investigation was begun). The yields were quite variable and sometimes rather low. The best yields, based on amine, were obtained in aqueous potassium carbonate to which a small amount of ethylenediaminetetraacetic acid (EDTA) was added in an effort to minimize heavy metal catalyzed side reactions. This procedure was adopted to avoid the use of excess amine as the required base.[1b,3a] It was found to be advisable to use freshly prepared hydroxylamine-*O*-sulfonic acid, since the commercial product is rather unstable and some lots gave poor results.

These hydrazinium salts displayed no detectable acidity in 0.1 *N* NaOH, and therefore their pK_a is greater than 13. When the solutions in aqueous sodium hydroxide were refluxed for 1 hr, no olefin was formed, and after acidification with hydrochloric acid the original hydrazinium salts were recovered. Since it has been reported[4] that potassium *tert*-butoxide suffices for the preparation of trimethylaminimine, this base was used in subsequent studies. The elimination from dimethyl-*sec*-butylhydrazinium chloride proceeded smoothly in refluxing *tert*-butyl alcohol containing a small excess of potassium *tert*-butoxide, giving a mixture of butene isomers in 73% isolated yield. The ratio of isomers, as determined by glc, was found to be 64.5% 1-butene, 10.5% *cis*-2-butene, and 25% *trans*-2-butene. This ratio is very nearly identical with that found for the Cope elimination of dimethyl-*sec*-butylamine oxide,[8] 67:12:21, and probably can be interpreted as implying a similar mechanism.

The elimination from dimethylcyclohexylhydrazinium

chloride in refluxing *tert*-butyl alcohol–potassium *tert*-butoxide gave only a 32% yield of cyclohexene, as determined by glc. This, however, is significantly better than the 7% yield reported for the Hofmann elimination from trimethylcyclohexylammonium chloride in the same medium.[9] When dimethyl sulfoxide was substituted for *tert*-butyl alcohol as the solvent, the yield was increased to 52%. Whether this is a solvation effect[10] or merely due to the higher boiling point of the solvent could not be ascertained, since cyclohexene cannot be distilled from the reaction mixture at 80° and direct injection into the heated port of a gas chromatograph would vitiate the attempt at temperature control.

The procedure reported here has several characteristics that may render it particularly advantageous for the degradation of amines and the synthesis of olefins: (a) the temperature required is lower than that usually employed in the Hofmann degradation and the yields were better, especially from the cyclic amine; (b) the conversion of a tertiary amine to a hydrazinium salt does not require strong oxidizing agents, as does the preparation of an amine oxide; (c) since the nitrogenous product of the elimination, a 1,1-disubstituted hydrazine, usually can be further alkylated at the 1-nitrogen atom to regenerate a hydrazinium salt,[11] sequential degradation by a repetetive methylation procedure should be possible, as in Hofmann's approach; (d) some of the side reactions encountered in the Cope reaction[12] are less likely with the aminimines. A probable disadvantage is that migrations from N-1 to N-2, especially of allylic and benzylic groups, may be expected.[13]

Experimental Section

Hydroxylamine-*O*-sulfonic acid was prepared by the method of Gösl and Meuwsen.[1b] Dimethyl-*sec*-butylamine was prepared by Eschweiler–Clarke methylation of *sec*-butylamine. The dimethylcyclohexylamine was a commercial sample.

Dimethyl-*sec*-butylhydrazinium Chloride. Dimethyl-*sec*-butylamine (5 g, 50 mmol) was suspended in a vigorously stirred cold solution of 8 g of potassium carbonate sesquihydrate (50 mmol) in 20 ml of water containing 0.1 g of EDTA. A cold solution of 5.6 g (50 mmol) of hydroxylamine-*O*-sulfonic acid in 10 ml of water was added over 40 min. Methanol (180 ml) was added and the precipitated K_2SO_4 was filtered. The filtrate was adjusted to pH 7 by addition of hydrochloric acid, and the solvent was removed in a rotary evaporator. Acetone was added to the syrupy residue to promote crystallization of the hydrazinium chloride. The salt was purified by dissolving in methanol, filtering to remove a small amount of K_2SO_4, evaporating, and reprecipitating with acetone. After drying at 100° the product weighed 5.5 g (73%), mp 170°.

Anal. Calcd for $C_6H_{17}N_2Cl$: N, 18.37. Found: N, 18.36.

Nmr ($CDCl_3$) δ 6.75 (br, 2 H, NH_2), 3.7 (br, 1 H), 3.50 [d, 6 H, $N(CH_3)_2$], 1.46 (d, 3 H + 1 H), 1.05 (t, 3 H). The C-3 methylene of the *sec*-butyl group appears to be widely split by the adjacent chiral atom into two broad regions, one centered at δ 2.35 (1 H) and the other buried under the C-1 methyl doublet at δ 1.46.

Dimethylcyclohexylhydrazinium Chloride. Following a similar procedure, 6.35 g (50 mmol) of dimethylcyclohexylamine gave 3.2 g (35%) of the hydrazinium salt: mp 225–227°; nmr ($CDCl_3$) δ 6.75 (br, 2 H, NH_2), 3.75 (br, 1 H), 3.50 [s, 6 H, $N(CH_3)_2$], 2.47 (br, 2 H, 2,6-equatorial), 1.97 (br, 2 H, 2,6-axial), 1.8–1.3 (m, br, 6 H).

Anal. Calcd for $C_8H_{19}N_2Cl$: N, 15.70. Found: N, 15.68.

When 2 equiv of either of the hydrazinium salts was added to 0.1 *N* NaOH, the pH as determined by a glass electrode remained at 13; therefore the pK_a's of these compounds must be at least that great.

Eliminations. A. To a solution of 2.25 g (20 mmol) of potassium *tert*-butoxide in 10 ml of *tert*-butyl alcohol was added 2.42 g (16 mmol) of dimethyl-*sec*-butylhydrazinium chloride. The mixture was refluxed for 90 min, using a slow stream of nitrogen to sweep the gaseous products through the condenser into a Dry Ice cooled trap. The contents of the trap were transferred to a chilled vial and weighed, yield 0.58 g (73%). The nmr spectrum indicated that the material collected consisted solely of the isomeric *n*-butenes. The ratio of isomers was determined by glc on a 6 ft × 0.125 in. column packed with saturated $AgNO_3$ in phenylacetonitrile supported on 80–100 mesh Chromosorb P, using a flame ionization detector and electronic integration.

B. Dimethylcyclohexylhydrazinium chloride, 1.6 g (9 mmol), was added to a solution of 1.2 g (10 mmol) of potassium *tert*-butoxide in 15 ml of *tert*-butyl alcohol and the mixture was refluxed for 3 hr. The presence of cyclohexene was indicated by the nmr of the reaction mixture, and the amount was determined by glc on a 6-ft silicone (SE-30) column, using toluene as an internal standard, yield 0.24 g (32%).

C. Two grams (11 mmol) of dimethylcyclohexylhydrazinium chloride was added to a solution of 1.3 g (12 mmol) of potassium *tert*-butoxide in 15 ml of dimethyl sulfoxide, and the mixture was refluxed for 90 min. After cooling, glc indicated a 52% yield of cyclohexene.

Registry No.—Dimethyl-*sec*-butylhydrazinium chloride, 51051-67-3; dimethyl-sec-butylamine, 921-04-0; hydroxylamine-*O*-sulfonic acid, 2950-43-8; dimethylcyclohexylhydrazinium chloride, 51051-68-4; dimethylcyclohexylamine, 98-94-2.

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A Convenient Synthesis of Primary Benzhydrylamines

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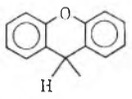
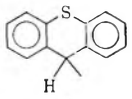
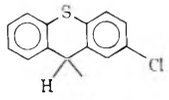
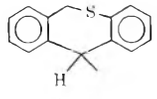
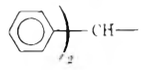
Received November 21, 1973

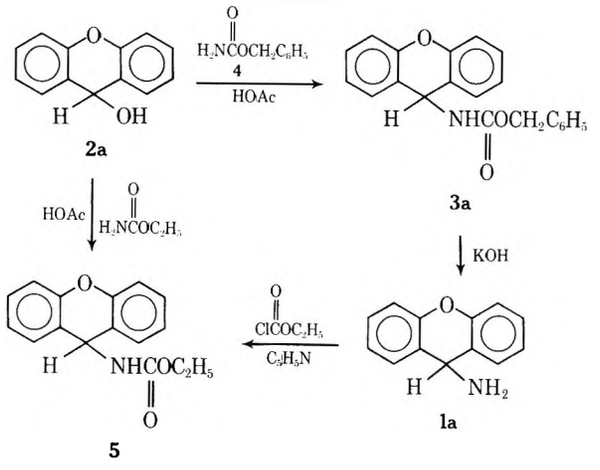
Our need for relatively large quantities of primary benzhydrylamines (1) prompted the search for a general synthetic pathway. The well-known condensation of xanthydrol (**2a**) with primary amides[1] appeared to be a good method for bonding nitrogen to the benzhydryl position. Though previous attempts to hydrolyze *N*-9-xanthylacetamide to amine **1a** failed,[2] **1a** has recently been prepared by alkaline hydrolysis of the corresponding ethyl carbamate (**5**).[3] Similarly, we have found that benzyl *N*-9-xanthylcarbamate (**3a**), prepared from **2a** and benzyl carbamate (**4**),[4] is readily hydrolyzed to 9-aminoxanthene (**1a**) by refluxing in 95% EtOH containing 15% KOH. That amine **1a** was indeed obtained was shown by its conversion to carbamate **5** (Scheme I), identical in every respect with the compound obtained by condensation of **2a** with urethane.

Table I
Synthesis and Hydrolysis of Substituted Benzyl *N*-Benzhydrylcarbamates (3a–e)

Benzhydrols ROH (2)	Product benzyl carbamates RNHCO$_2$CH$_2$C$_6$H$_5$ (3)[a] Condensation reaction time (hr)[b]	Mp, °C	Yield, %	Benzhydrylammonium acetates RNH$_3^+$ $^-$OAc (6) Hydrolysis time (hr)[c]	Mp, °C (lit. mp)	Yield, %
2a, R = 	2	165–166	87	24	153–154 dec (150–151 dec)[d]	76
2b, R = 	12	134–135	74	6	155–157 dec (152)[d]	78
2c, R = 	12[e]	132–134	71	3.5	153–155 dec[f]	55
2d, R = 	0.75[g]	179–180	82	1		None
2e, R = 	18[h]	116–118	85	4	140–141 (141)[i]	94

[a] Satisfactory analytical data were reported for all new compounds listed. [b] Reactions run at 25° in HOAc with *ca.* 20 mol % excess of benzyl carbamate (**4**). [c] In refluxing 95% EtOH containing 15% KOH. [d] Reference 2. [e] Prior to work-up the reaction mixture was heated at 90° for 30 min. [f] Free amine **1c** mp 67–69°. *Anal.* Calcd for $C_{13}H_{10}ClNS$: C, 63.03; H, 4.07; Cl, 14.31; N, 5.65; S, 12.94. Found: C, 62.69; H, 4.08; Cl, 14.21; N, 5.71; S, 13.34. [g] *p*-TsOH (50 mg) was required as catalyst. [h] Concentrated H_2SO_4 (0.2 ml) added as catalyst. [i] Reference 11.

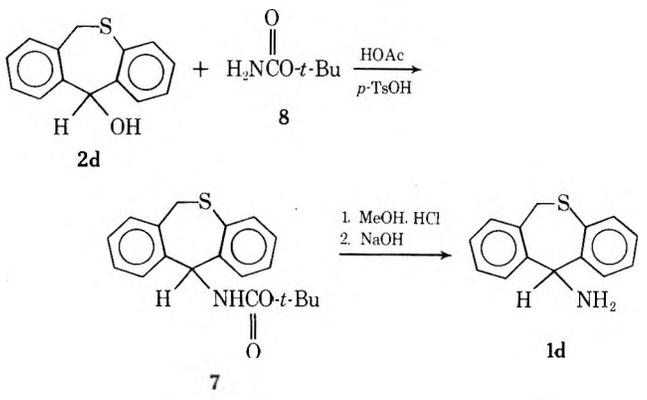
Scheme I



The condensation of various benzhydrols with benzyl carbamate (**4**) in glacial HOAc appears to be a rather general reaction. The results of several such condensations, some of which require a catalytic amount of strong acid, are summarized in Table I. The results obtained from the basic hydrolysis of the benzyl carbamates, **3**, are also shown in Table I.

Owing to the instability of several of the product amines in aqueous acid[2] and the difficulties experienced when attempting to separate the reaction products (amines plus benzyl alcohol) by conventional ether–water extraction techniques, the desired analogs **1** were generally isolated by precipitating the acetate salts (**6a–c,e**) from hexane solution. Several attempts to hydrolyze the dihydrodibenzo[*b,e*]thiepin analog **3d** in basic medium (*i.e.*, reactions were run at room temperature or at reflux with varying concentrations of KOH for periods of 1 hr to 1 week) only afforded complex mixtures apparently containing some thiepin ring-opened products. Treatment of **3d** with HBr in HOAc by the method of Ben-Ishai and Berger[5] afforded only unreacted starting material. For these reasons, carbamate **7** containing the more acid labile *tert*-butyloxy function was synthesized (Scheme II). Condensation of *tert*-butyl carbamate (**8**)[6] with alcohol **2d** afforded **7** in 52% yield. Amine **1d** was obtained in 58% yield by acid-catalyzed hydrolysis of carbamate **7**.

Scheme II



Experimental Section

Materials. Xanthydrol (**2a**),[7] 10-thioxanthydrol (**2b**),[8] 2-chloro-10-thioxanthydrol (**2c**),[9] 6,11-dihydrodibenzo[*b,e*]thiepin-11-ol (**2d**),[10] benzyl carbamate (**4**),[4] and *tert*-butyl carbamate (**8**)[6] were all prepared by methods reported in the literature.

Because of the generality of the methods for both the condensation and hydrolysis reactions, only two examples of each will be given.

Benzyl *N*-Benzhydrylcarbamate (3e). To a solution of 2.0 g (0.011 mol) of benzhydrol and 2.0 g (0.013 mol) of benzylcarbamate in 25 ml of glacial HOAc was added 0.2 ml of concentrated H_2SO_4. The mixture was stirred at room temperature for 18 hr and poured into H_2O (150 ml) and the precipitate was collected. The product was recrystallized from aqueous EtOH affording 2.94 g (85%) of the desired carbamate **3e** as white needles, mp 116–118°.

Benzhydrylammonium Acetate (6e). To a solution of KOH (5 g, 0.09 mol) in 50 ml of 95% EtOH was added 1.56 g (0.005 mol) of benzyl *N*-benzhydrylcarbamate (**3e**). The mixture was heated at reflux for 4 hr, cooled, and concentrated under reduced pressure to a volume of *ca.* 15 ml. The concentrate was shaken with 75 ml of H_2O and extracted with Et_2O. The organic layer was washed

with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The residual oil was dissolved in 200 ml of hexane. HOAc (1 ml) was added slowly with constant stirring. The white precipitate was collected, washed with hexane, and air-dried affording 1.11 g (94%) of acetate **6e**, mp 140–141° (lit.[11] mp 141°).

2-(2-Methylpropyl) *N*-[11-(6,11-Dihydrodibenzo[*b*,*e*]thiepin)]-carbamate (7). A solution of 2.28 g (0.010 mol) of freshly recrystallized 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (**2d**), 1.5 g (0.013 mol) of *tert*-butyl carbamate (8), and 50 mg of *p*-toluenesulfonic acid in 25 ml of HOAc was stirred at 25° for 1 hr. The mixture was poured into H_2O (50 ml) and allowed to stand for 30 min; the solid was collected by filtration and recrystallized from EtOH affording 1.7 g (52%) of carbamate **7** as white needles, mp 168–170°.

Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 69.48; H, 6.44; N, 4.24; S, 10.07.

11-Amino-6,11-dihydrodibenzo[*b*,*e*]thiepin (1d). To a solution of 0.65 g (0.002 mol) of carbamate **7** in 30 ml of MeOH was added 2.5 ml of 12 *N* HCl. The mixture was heated at reflux for 15 min, cooled, and concentrated under reduced pressure. The residue was partitioned between 5% NaOH and Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was recrystallized from absolute EtOH affording 0.26 g (58%) of off-white crystalline amine **1d**, mp 146–147° (lit.[10] mp 149–150°).

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Registry No.—**1c**, 51065-24-8; **1d**, 1745-53-5; **2a**, 90-46-0; **2b**, 6783-74-0; **2c**, 6470-02-6; **2d**, 1745-46-6; **2e**, 91-01-0; **3a**, 6331-77-7; **3b**, 51065-25-9; **3c**, 51065-26-0; **3d**, 51065-27-1; **3e**, 5180-34-7; **4**, 621-84-1; **6a**, 51065-28-2; **6b**, 51065-29-3; **6c**, 51065-30-6; **6e**, 51065-31-7; **7**, 51065-32-8; **8**, 4248-19-5.

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The Azido Transfer Reaction to Aliphatic Carbons

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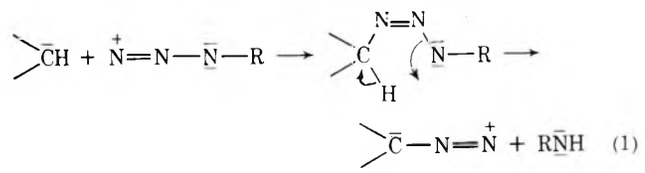
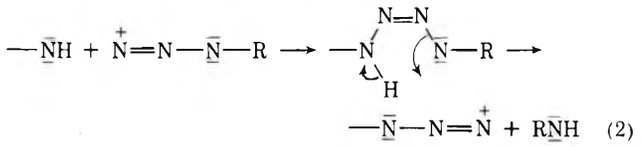
The *diazo transfer* reaction (eq 1), originally studied by Dimroth[1] and Curtius,[2] remained dormant until its epochal revival by Doering and De Puy in 1953.[3] Since that time, it has become a well-established route to α-diazocarbonyl compounds, largely through the extensive work of Regitz and his group.[4] This reaction has recently been developed into an azide synthesis[5] by the use of anions of primary amines,[6] hydrazines,[7] and hydrazones (eq 2).[8]



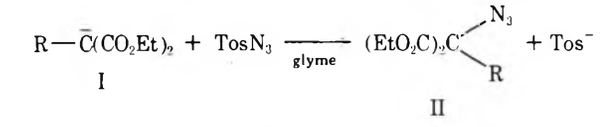
(1)



(2)

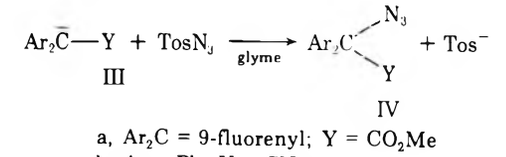
Although other diazo transfer agents such as nitrous oxide,[9] various azides,[10] azidinium salts,[11] and diazoalkanes[12] have been investigated, the most widely used reagent has been *p*-toluenesulfonyl azide (tosyl azide).[13] The availability of *three* nitrogens, coupled with the good nucleofugal property of the *p*-toluenesulfinate ion, suggests that sulfonyl azides should also be capable of acting as *azido transfer agent*. Indeed, the azido group has been transferred to anions having no α hydrogen[14a-e] or an α-carbonyl group[14f-h] to permit completion of the diazo transfer step. The recent report of Reed and Lwowski[15] of an azido transfer to an aliphatic bridgehead carbanion prompts us to report our own results to broaden the scope of this reaction.

The reaction of the sodium salts of diethyl phenyl- and 7-cycloheptatrienylmalonate (Ia and Ib) with tosyl azide gave the corresponding azidomalonates (IIa and IIb) in 77 and 65% yields, respectively. The replacement of one



a, R = Ph
b, R = 7-cycloheptatrienyl

carbethoxy group with the fluorenyl moiety did not affect the course of the reaction and 9-carbomethoxy-9-azidofluorene (IVa) was isolated in 57% yield. Similarly, α-azidodiphenylacetonitrile (IVb) was obtained from the reaction of the sodium salt of diphenylacetonitrile, albeit in only 18% yield of isolated product.[16]



a, Ar_2C = 9-fluorenyl; Y = CO_2Me
b, Ar = Ph; Y = CN

These results show the azido transfer reaction to be applicable to both aliphatic and aromatic anions, as well as secondary amine anions.[14b,c]

Experimental Section[17]

Diethyl Azidophenylmalonate (IIa). A solution of 5.0 g (0.021 mol) of diethyl phenylmalonate in 25 ml of dry glyme was dripped into a suspension of 0.82 g (0.021 mol) of sodium hydride (which was previously freed of mineral oil with ether and hexane) in 30 ml of dry glyme at room temperature. The reaction was carried out in a 150-ml three-neck flask equipped with a nitrogen inlet, a pressure-equalizing dropping funnel, a magnetic stirring bar, and a gas outlet. The apparatus was flushed with nitrogen prior to the addition of diethyl phenylmalonate. After gas evolution had stopped, a solution of 4.07 g (0.021 mol) of tosyl azide in 25 ml of dry glyme was dripped into the reaction mixture over a 30-min period. After the addition was complete, the mixture was stirred at 35–40° for 1 hr; a white solid started to precipitate at that time and stirring was continued for an additional 2 hr. The mixture was cooled and the solvent was evaporated on a rotary evaporator at 40° under reduced pressure. Ether (100 ml) and water (50 ml) were added to the pasty residue. The ethereal layer was separated, washed three times with 25-ml portions of water, and dried over sodium sulfate. A yellowish oil was obtained (4.5

g, 77%) after evaporation of the solvent, ir (CCl_4) 2120 (N_3), 1750 1770 (C=O), 690 cm^{-1}.

The infrared spectrum of the product was identical with that of diethyl azidophenylmalonate prepared from diethyl bromophenylmalonate and sodium azide according to a published procedure.[18]

Diethyl Azido(7-cycloheptatrienyl)malonate (IIb). A procedure similar to that used in the synthesis of the azidophenylmalonate was employed, starting with 5.29 g (0.021 mol) of diethyl (7-cycloheptatrienyl)malonate.[19] The usual work-up procedure yielded 3.80 g (65%) of a yellow oil, ir (CCl_4) 2120, 1750, 1740, and 700 cm^{-1}.

The crude product was purified by chromatography on activated alumina and eluted with benzene-hexane (1:3), nmr (CCl_4) δ 1.30 (t, 6 H), 2.19 (t, 1 H), 4.20 (q, 4 H), 5.20, 6.15, 6.60 (m, 6 H).

9-Carbomethoxy-9-azidofluorene (IVa). The sodium salt of 9-carbomethoxyfluorene (2.80 g, 0.0125 mol) was prepared from reaction with sodium hydride as described above. To the brown solution of the anion was added dropwise a solution of 2.46 g (0.0125 mol) of tosyl azide in glyme at room temperature, and the reaction mixture was then heated under reflux for 2 hr. After having been cooled to room temperature, it was poured into ice water and extracted with ether. The dried ethereal extract was then evaporated *in vacuo* to give a pale yellow oil which crystallized on standing. Upon filtration and washing with petroleum ether, 1.90 g (57%) of colorless crystals of essentially pure product, mp 76–78°, were isolated, ir 2100 (N_3), 1740–1710 cm^{-1} (CO_2CH_3). An analytical sample was obtained by recrystallization from petroleum ether, mp 80–81°.

Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.91; H, 4.18; N, 15.84. Found: C, 67.86; H, 4.21; N, 15.68.

α-Azidodiphenylacetonitrile (IVb). The procedure was essentially identical with that described for IVa. The dark red oil obtained was refluxed with *petroleum ether* for 1 hr and the extract was decanted from the insoluble residue. Evaporation gave a red oil which was chromatographed on Florisil, using *petroleum ether* as eluent. A second chromatography of the second fraction gave 0.92 g (18%) of pure product, mp 40–42° (lit.[20] mp 41°), ir 2170 (CN), 2170 cm^{-1} (N_3).

Acknowledgment. S. K. and S. J. W. thank the Society of the Sigma X (Worcester Polytechnic Institute Chapter) for support. S. M., G. K., and J.-P. A. hereby gratefully acknowledge the support of this work by the National Institutes of Health under Grant GM 13689.

Registry No.—Ia, 28744-77-6; Ib, 51157-37-0; IIa, 51065-36-2; IIb, 51157-38-1; IIIa, 51065-38-4; IIIb, 51065-37-3; IVa, 51065-39-5; IVb, 51065-40-8; tosyl azide, 941-55-9.

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(16) Other products were formed during this reaction. With methyllithium as the base, a compound analyzing for $C_5H_{13}N_3$ was isolated. In the case of sodium hydride, an orange compound corresponding to $C_{28}H_{21}N_3$ was isolated in good yield. The structures of these two by-products remain unclear at this time.
(17) All melting points are uncorrected. Infrared spectra were recorded in solution (CCl_4) or potassium bromide pellets; nmr spectra were recorded as solutions in deuteriochloroform, using TMS as an internal standard.
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Cleavage of δ-Keto β,γ-Unsaturated Esters by 1,4-Diazabicyclo[2.2.2]octane

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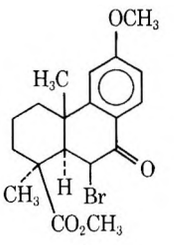
Received November 27, 1973

As a result of a continuing study into the improvement of the yield of lactone **2** from bromo ketone **1** by utilizing a variety of bases[4-6] we now wish to report that 1,4-diazabicyclo[2.2.2]octane (Dabco) is useful for the cleavage of δ-keto β,γ-unsaturated esters to their corresponding α,β-unsaturated ketones.



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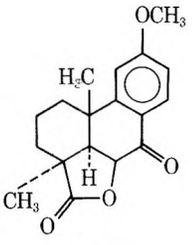

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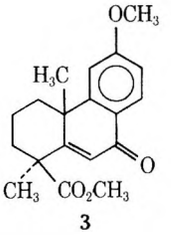

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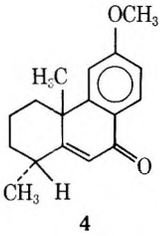

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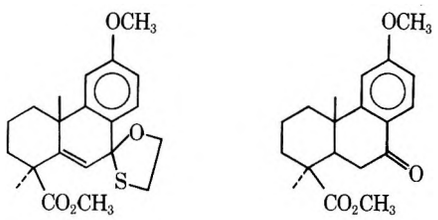
Bromo ketone **1** was reacted with 6 equiv of Dabco in 16 equiv of o-xylene at reflux (165°) for 6 hr. Fractional crystallization of the product mixture gave compound **4** in 80% yield and compound **2** in 10% yield. Compounds **2** and **4** were identical by ir, nmr, glc retention time, and mixture melting points with authentic samples.[4,5] Thus this reaction did produce some of the desired lactone **2** in contrast to the bases 1,5-diazabicyclo[4.3.0]nonene-5 (DBN)[4] and 1,5-diazabicyclo[5.4.0]undecene-5 (DBU).[5] However, the major component was the decarbmethoxylation product **4**. When the proposed intermediate **3** was treated with Dabco under the conditions previously described, a high (90%) yield of decarbmethoxylation product was obtained.

Since the bases DBN and DBU are *O*-alkyl cleavage reagents,[4,5] Dabco was allowed to react with esters **5**–**8** to determine if similar results could be obtained. The fact that no reaction occurred eliminates the possibility that Dabco is an *O*-alkyl cleavage reagent and indicates that this reagent cleaves δ-keto β,γ-unsaturated esters selectively.

The generality of Dabco as a reagent for cleaving δ-keto β,γ-unsaturated esters is demonstrated by the application



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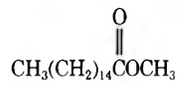
6



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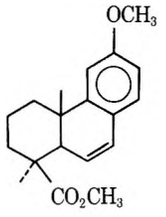
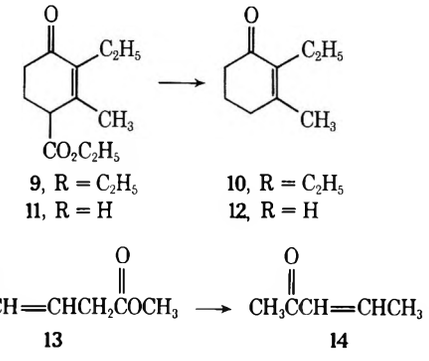


8

of this reagent to the esters shown in Scheme I. A mixture of 6 equiv of Dabco and 1 equiv of the appropriate ester was dissolved in 16 equiv of o-xylene and refluxed (165°) for 6 hr. The resulting olefins were obtained in approximately 98% yield by glc analysis and were identical by ir, nmr, and gc-mass spectral comparison with authentic samples.

Scheme I



The facile cleavage of ethyl and methyl δ-keto β,γ-unsaturated esters with a reagent (Dabco) that does not cleave saturated esters by either the *O*-alkyl cleavage or hydrolytic routes suggests that a mechanism similar to that reported by Krapcho and Lovey[7] for the cleavage of β-keto esters with sodium chloride and DMSO is probably operative.

Experimental Section

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nuclear magnetic resonance spectra were obtained using a Jeolco Minimar spectrometer. Tetramethylsilane was used as an internal standard. Infrared spectra were obtained using a Perkin-Elmer Model 137 G spectrophotometer. Gas-liquid chromatography (glc) was performed using a Hewlett-Packard Model 402 gas chromatograph with a hydrogen flame detector. A glass column (6 ft × 0.25 in. o.d.) bent in a U shape and packed with 3% SE-30 on 100/120 mesh GCQ at a column temperature of 270° with a helium flow rate of 90 ml/min was used for all glc analyses.

Dehydrobromination-Decarbmethylation of Bromo Ketone 1. Bromo ketone **1** (500 mg, 1.27 mmol) was added to a solution of 1,4-diazabicyclo[2.2.2]octane (Dabco, 856 mg, 7.62 mmol) and 2.42 ml of o-xylene. The reaction was allowed to reflux at 165° for 6 hr. The ether extract of the acidified (5% HCl) reaction mixture was washed with 5% aqueous sodium carbonate solution, dried over anhydrous sulfate, and evaporated *in vacuo*. Fractional crystallization of the residue from 20:1 methylene chloride–methanol yielded 318.5 mg (80%) of a white, crystalline compound **4** and 24.7 mg (10%) of white, crystalline compound **2**. Compounds **2** and **4** were identical by ir, nmr, glc retention time, and mixture melting points with authentic samples.

General Procedure for the Decarbalkylation of δ-Keto β,γ-Unsaturated Esters. δ-Keto β,γ-Unsaturated Keto Esters 5–9, 11, and 13. A solution of Dabco (1.712 g, 15.24 mmol) and 2.54 mmol of the appropriate ester was dissolved in 4.85 ml of *o*-xylene and the resulting mixture was allowed to reflux at 165° for 6 hr. The usual work-up of the acidified reaction mixture yielded the corresponding ketone, which was identical by ir, nmr, glc retention time, and mixture melting points with an authentic sample.

Acknowledgments. We wish to thank the graduate school and the Biological and Physical Sciences Institute for partial financial support. We express our sincere appreciation to Dr. Ian K. Walker, Department of Scientific and Industrial Research, Wellington, New Zealand, for generous supplies of podocarpic acid.

Registry No.—**1**, 37931-64-9; **9**, 51051-65-1; **11**, 487-51-4; **13**, 51051-66-2; Dabco, 280-57-9.

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Solventless Preparation of Hydroquinone Clathrates

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The hydroquinone clathrates have long been recognized for their unusual physicochemical properties.[1] Structurally, these materials consist of two interpenetrating three-dimensional hydrogen-bonded networks of hydroquinone that enclose a set of cavities capable of accommodating a variety of small molecules such as O_2, N_2, CH_4, HCl, SO_2, Ar, Kr, etc. The composition of these clathrates is generally dependent upon the pressure and temperature conditions under which the material is formed, with the upper limit being one molecule of "guest" for every three molecules of the "host," hydroquinone. However, once the clathrate is formed, the materials remain stable under conditions far removed from thermodynamic equilibrium. For example, Peyronel and Barbieri[2] report the pressure required to produce the composition $CH_4 \cdot 3C_6H_4(OH)_2$ as approximately 100 atm at 22–30°. The structure is stable, however, at ambient conditions.

Many technological applications have been suggested for these clathrates,[3,4] but realization of their potential has, in part, been hampered by the inconvenience usually associated with the methods of their preparation. Generally, the hydroquinone clathrates have been prepared by precipitation from alcohol solutions. Resistance to mass transport by the intervening liquid phase generally requires that the clathrates be precipitated slowly, with time periods of days to weeks not being uncommon.[5] Furthermore, the tendency for hydroquinone to undergo oxidation in solution presents the risk of introduction of impurities into the crystalline product when the solution growth method is used.

Past experience with crystal growth by chemical vapor deposition methods leads us to believe that the hydroquinone clathrates might be prepared by direct reaction between the guest and host materials. The advantages to such an approach are obvious; the intervening liquid phase with its attendant mass transfer resistance is removed from the system, and continuous production, as opposed to batch production, is more readily attainable.

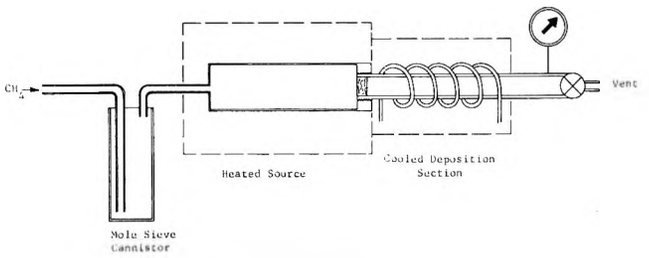

Figure 1. Schematic of clathrate formation apparatus.

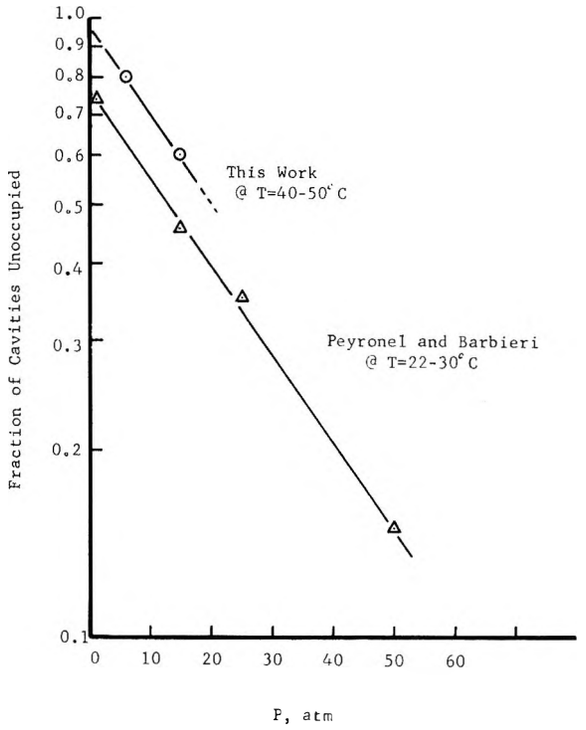

Figure 2. Pressure dependence of methane hydroquinone clathrate composition.

Hydroquinone sublimes readily at temperatures below its melting point, 170°, and the vapor pressure is adequate for transport and crystal growth at temperatures as low as 115–120°. The rate of crystal growth can be conveniently controlled by control of the sublimation or source temperature and control of the deposition temperature. We have found that, when a suitable gas such as methane is used as a carrier, enclathration of the gas tends to occur upon growth of the new hydroquinone crystals. Using this method, we have been able to produce gram quantities of the clathrate in a matter of a few hours in small-scale laboratory equipment, as opposed to the days to weeks required for the solution growth method. Inasmuch as water vapor tends to interfere with the formation of the clathrate structure, both the hydroquinone and the methane must be dried prior to use. This can be accomplished conveniently by passing both materials through a freshly outgassed mole sieve column.

A schematic of the apparatus used in this exploratory study is shown in Figure 1. Briefly, this apparatus consisted of three stainless steel chambers connected in series. The first of these was packed with mole sieve for drying the methane, and could be removed for regeneration of the sieve. The second chamber contained the source of predried hydroquinone, and was mounted in a furnace for control of the source temperature. The third chamber was water cooled for control of the deposition temperature. In operation, the system was flushed thoroughly with dry methane and then the vent valve was adjusted to discharge 10–20 cc/min at pressure. A glass wool plug between the source and deposition sections inhibited carryover of homogeneously nucleated hydroquinone crystals from the source section.

Several methane clathrate samples prepared at each of two pressures by this method were analyzed by flash injection of submilligram quantities (usually single crystals) of the clathrate into a gas chromatograph. Because of slight variations in composition, at least five analyses were made for each sample. For samples prepared at source temperatures of 120–130°, deposition temperatures of 40–50°, and a methane partial pressure of 6 atm, 20% of the cavities of the hydroquinone structure are filled with methane. At the same temperatures and a methane pressure of 15 atm, 40% cent of the cavities are occupied by methane. These data are compared with those of Peyronel and Barbieri in Figure 2. It can be seen that the pressure dependence is approximately the same as that shown by Peyronel and Barbieri, but the composition line is shifted to lower methane contents because of the higher formation temperature.

These two sets of data at different temperatures may be used to estimate the energy of formation of the methane hydroquinone clathrate as approximately 6 kcal/mol. Considering the latitude in temperature measurements of both the current work and that of Peyronel and Barbieri, agreement between this value of the energy of formation and the value of 5.9 kcal/mol calculated by Van de Waals and Platteeuw[6] seems fortuitous. However, the results suggest that the same material is produced by this solventless approach as is obtained from the conventional solution growth method.

In way of demonstration of the general applicability of the method, oxygen and nitrogen hydroquinone clathrates have also been prepared using this approach and it is believed that the method can be extended to preparation of other clathrates, such as the gas hydrates, where the host material can easily be volatilized.

Registry No.—Methane hydroquinone clathrate, 16060-36-9.

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Synthesis of 3(2*H*)-Benzofuranones and 1,2-Dihydro-3*H*-indol-3-ones by Acid-Catalyzed Cyclizations of β-Keto Sulfoxides

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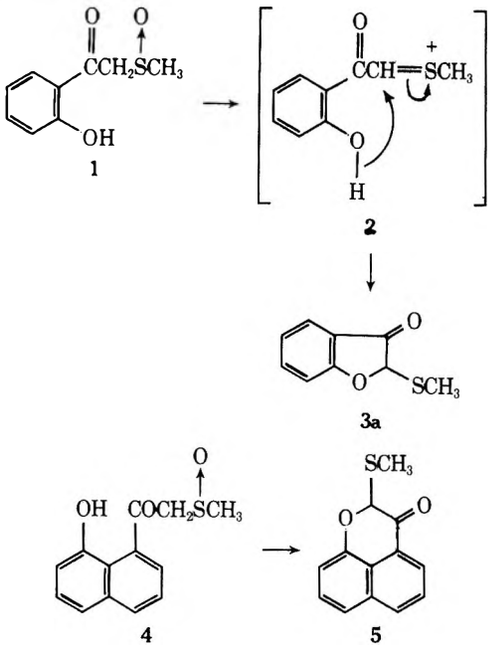
Our continuing interest in the use of β-keto sulfoxides for the synthesis of heterocyclic systems[1] led us to investigate the cyclization of 2-hydroxy-1-[(methylsulfinyl)-acetyl]benzenes, 2-amino-1-[(methylsulfinyl)acetyl]benzenes, and 2-amido-1-[(methylsulfinyl)acetyl]benzenes with trifluoroacetic acid.

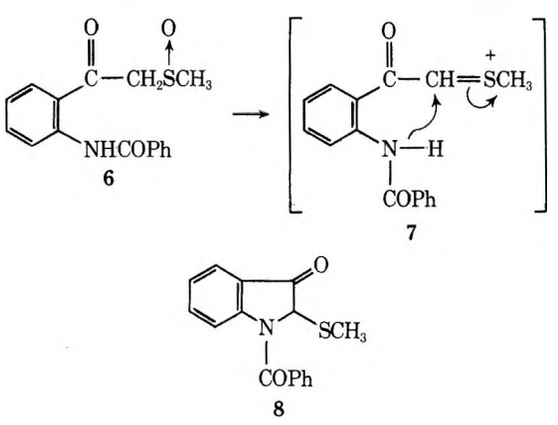
Recent publications on cyclizations involving Pummerer reaction intermediates to give carbocyclic rings,[2] 3,1-ben-

zoxathian-4-ones,[3] and pteridines[4] prompt us to report our results in this area. The Pummerer reaction[5] continues to be of great synthetic[6] and mechanistic[7] interest. We envisioned that cyclization would take place *via* intramolecular nucleophilic attack by suitably situated oxygen and nitrogen functions on the cationic Pummerer intermediates (2 and 7) to give heterocyclic systems.

When 2-hydroxy-1-[(methylsulfinyl)acetyl]benzene (1) was heated under reflux in benzene containing trifluoroacetic acid for 40 min, 2-(methylthio)-3(2*H*)-benzofuranone (**3a**) was isolated in 45% yield. The spectral and analytical data were in agreement with the assigned structure. The ir spectrum showed a carbonyl band at 1720 cm^{-1}. The nmr spectrum showed the *S*-methyl at δ 2.13 (3 H, s), the methine proton (-OCHSMe) at δ 5.65 (1 H, s), and aromatic protons at δ 7.10–8.00 (4 H, m). The compounds (**3a–d**) prepared by this method are listed in Table I. The rearrangement is readily extended to the formation of six-membered rings, as illustrated by the conversion of **4** to **5**.

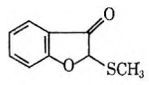
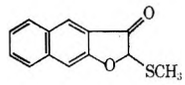
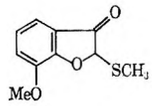
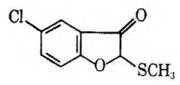
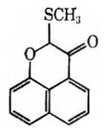
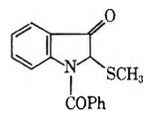


Attempts to rearrange 6-chloro-2-amino-1-[(methylsulfinyl)acetyl]benzene to the corresponding 1,2-dihydro-3*H*-indol-3-one were unsuccessful and gave a complex mixture. Protonation of the amino nitrogen, deactivating it as a nucleophile, is the probable reason for the failure of the reaction in this case. The problem was surmounted by the use of the amido function. The conversion of amide **6** to 1,2-dihydro-3*H*-indol-3-one (**8**) in 67% yield illustrates



the reaction. The analytical and spectral data for **8** are in agreement with the assigned structure. The ir spectrum showed carbonyl bands at 1730 and 1650 cm^{-1}. The nmr spectrum showed the *S*-methyl at δ 1.92 (3 H, s), the methine proton (>NCHSMe) at δ 5.25 (1 H, s), and aromatic protons at δ 7.0–8.2 (9 H, m).

Table I[a]

Compd		Mp, °C (crystn solvent)	Yield, %
3a		81–82 (EtOH)	45
3b		118–120 (EtOH)	81
3c		103–105 (EtOH)	65
3d		76–78 (EtOH)	54
5		89–91 (EtOH)	64
8		126–128 (EtAc)	67

[a] Satisfactory analytical data (±0.3% for C, H, S, and N) were reported for all compounds listed in the table.

Experimental Section

Melting points were taken in open capillary tubes and were not corrected. Nmr spectra were recorded on a Varian Model A-60 spectrometer using TMS as an internal standard ($CDCl_3$ solvent). Thin layer chromatography was performed on commercial silica gel plates containing fluorescent indicator. A solvent system of ethyl acetate–cyclohexane (4:1) was used. Visualization was with 2537-Å light and iodine vapour.

General Reaction Procedure. A solution of the β-keto sulfoxide (0.01 mol) and trifluoroacetic acid (0.01 mol) in benzene (50 ml) was refluxed until tlc indicated the absence of the β-keto sulfoxide in the reaction mixture (40–90 min). The solvent was removed under pressure to give oils which crystallized on standing. Recrystallization (Table I) gave analytically pure material.

Acknowledgments. We would like to express our gratitude to Dr. R. C. Greenough for the spectral data and Mrs. U. Zeek for the elemental analysis.

Registry No.—1, 16697-77-1; **3a**, 51175-49-6; **3b**, 51175-50-9; **3c**, 51175-51-0; **3d**, 51175-52-1; **4**, 18500-87-3; **5**, 51175-53-2; **6**, 51175-54-3; **8**, 51175-55-4; 2-hydroxy-3-[(methylsulfinyl)acetyl]naphthaline, 51175-56-5; 2-hydroxy-3-methoxy-1-[(methylsulfinyl)acetyl]-benzene, 51175-57-6; 4-chloro-1-hydroxy-2-[(methylsulfinyl)acetyl]benzene, 51175-58-7.

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An Improved Synthesis of Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane

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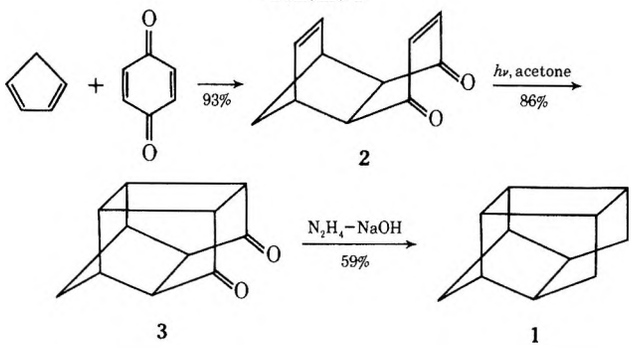
Received December 27, 1973

In connection with a study of the chemistry of strained hydrocarbons, it became necessary for us to synthesize the title compound, **1**. A six-step synthesis which affords **1** in *ca.* 14% overall yield has been reported by Stedman and coworkers.[1] In the present paper, we report an improved, three-step synthesis in which **1** is produced in 47% overall yield.

Our improved synthesis is shown in Scheme I. Diels–Alder addition of *p*-benzoquinone to cyclopentadiene has been reported[2] to afford the endo adduct **2** in high yield. Photochemical cyclization of **2** to **3** has likewise been reported to proceed smoothly.[3] We employed Wolff–Kishner reduction of diketone **3** to prepare **1**. Along with **1**, the reduction of **3** also afforded an unidentified olefin which could be readily separated from **1** by treatment of the crude reduction product with a solution of bromine in carbon tetrachloride, followed by elution chromatography.

Scheme I



The nmr and mass spectra of **1** have been discussed by Stedman.[1] Compound **1** is highly volatile, and precautions must accordingly be taken to minimize losses during its isolation.

Experimental Section

Melting points are uncorrected. Spectra were determined with the following instruments: Varian T-60 nmr spectrometer (TMS internal standard); Perkin-Elmer Model IR-8 infrared spectrophotometer; Hitachi Perkin-Elmer Model RMU-6E mass spectrometer (70 eV).

1,4,4a,8a-Tetrahydro-*endo*-1,4-methanonaphthalene-5,8-dione (2). To a solution of *p*-benzoquinone (243 g, 2.25 mol) in methanol (400 ml) at −70° was added a solution of freshly cracked cyclopentadiene (149 g, 2.27 mol) in cold methanol (100 ml). The solution was allowed to warm to room temperature, and the product was collected by suction filtration. Yellow-brown crystals (392 g, 93%) were obtained: mp 76.0–78.5° (lit. mp 75.8–76.2°,[4] 77–78°[5]); nmr ($CDCl_3$) δ 1.48 (m, 2 H, methylene bridge), 3.28 (m, 2 H, 4a, 8a protons), 3.52 (m, 2 H, bridgehead protons), 6.02 (m, 2 H, ethylene bridge protons), 6.52 (s, 2 H, enone vinyl protons); ir (KBr) 3320 (w), 1660 (vs, C=O), 1601 (s, conjugated C=C), 1295 (m), 1280 (m), 1060 (m), 875 (m), and 720 cm^{-1} (m).

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (3). A solution of **2** (40 g, 0.23 mol) in ethyl acetate (500 ml) was irradiated for 12 hr with a Hanovia medium-pressure Hg lamp (Pyrex filter). The solution was concentrated, whereupon **3** crystallized as a colorless, microcrystalline solid (34.5 g, 86%): mp 243.0–243.5° (lit.[3] mp 245°); nmr ($CDCl_3$) AB pattern, J = 12 Hz, δ_A 1.86, δ_B 2.10 (2 H, methylene bridge protons), broad envelope, δ 2.5–3.3 (8 H); ir (KBr) 2990 (s), 2930 (m), 2870 (m), 1742 (vs, C=O), 1720 (vs, C=O), 1185 (m), 1055 (s), 855 (m), and 720 cm^{-1} (m).

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (1). A solution of **3** (2.0 g, 11.5 mmol), 95% hydrazine (4 ml), and sodium hydroxide (1 g) in diethylene glycol (55 ml) was heated at 160–200° for 3 hr. The cooled reaction mixture was extracted with pentane (100 ml) and the pentane extracts were dried (Na_2SO_4). The crude product was found to contain an unidentified olefinic impurity. The filtered pentane solution was treated with excess 5% Br_2–CCl_4 solution, and the resulting product was chromatographed on neutral alumina (pentane eluent). Compound **1** was obtained as a colorless, waxy solid (990 mg, 59%): mp 204.0–204.5° (sealed tube) (lit.[1] mp 207–208°); nmr ($CDCl_3$) AB pattern, J = 12 Hz, δ_A 0.98 (br d), δ_B 1.16 (d) (4 H, 8- and 11-CH_2), AB pattern, J = 10 Hz, δ_A 1.30, δ_B 1.63 (2 H, 4-CH_2), δ 2.21 (envelope, 4 H, CH), and δ 2.55 (envelope, 4 H, CH); ir (KBr) 2950 (m), 2860 (s), 1460–1430 (w), and 1320–1270 cm^{-1} (w); mass spectrum m/e 146 (molecular ion), 131, 117, 91, and 80 (base peak).

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.66; H, 9.55.

Acknowledgments. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. Financial support of this study by the Faculty Research Committee, University of Oklahoma, is also gratefully acknowledged.

Registry No.—**1**, 4421-32-3; **2**, 51175-59-8; **3**, 2958-72-7; *p*-benzoquinone, 106-51-4; cyclopentadiene, 542-92-7.

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Reaction of 4-Nitrobenzil with Cyanide Ion in Aprotic Solvents

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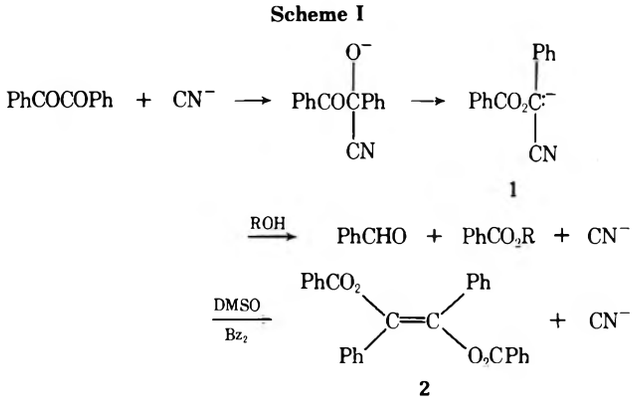
Received January 22, 1974

The reaction of benzil with cyanide ion has been shown to proceed differently in alcoholic solvents[1] than in dimethyl sulfoxide (DMSO).[2] The products in alcohol are benzaldehyde and the corresponding benzoate ester, whereas in DMSO the sole product is *trans*-α,α'-stilbenediol dibenzoate (**2**). The proposed mechanism for the reaction in both solvent systems (Scheme I) assumes cleavage of the central C–C bond in benzil by cyanide ion to form resonance-stabilized carbanion **1**. Reaction of **1** with *solvent* in the alcoholic systems leads to products, whereas in the absence of proton donor, *e.g.*, in DMSO, **1** is forced to attack a second benzil molecule with the formation of **2**.

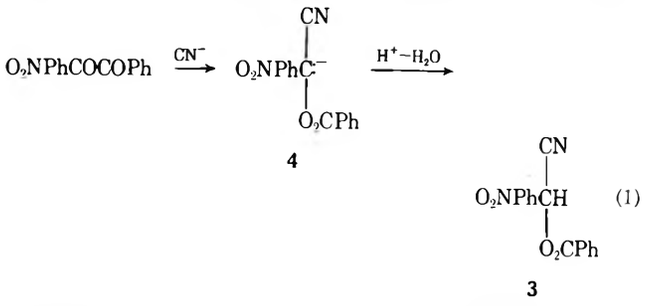
More recently, Schowen and Kuebrich[3] evaluated the usefulness of **1**, generated from benzil and cyanide ion in

Scheme I



several solvent combinations, as a model for "active aldehyde" intermediates in (a) the benzoin condensation and (b) thiamine action in biological systems. This research group[3,4] demonstrated that **1**, generated in the presence of a variety of added electrophiles, gave rise to a spectrum of products.

While in all instances[1-4] the products obtained from the benzil–cyanide reaction has been logically accounted for by invoking the intermediacy of **1**, the intermediate, *per se*, has not been isolated. In any mechanistic study, the trapping or otherwise isolation of a proposed intermediate is considered of value in the compilation of data which allows for eventual elucidation of the reaction path. As an extension of our earlier work,[2] this report notes the isolation of the nitro derivative of intermediate **1**, 4-nitromandelonitrile benzoate (**3**), in good yield from the reaction of 4-nitrobenzil with cyanide in DMSO or *N,N*-dimethylformamide (DMF). The reaction is shown in eq 1. In no experiment was the corresponding stilbenediol dibenzoate detected. Thus, the role of cyanide ion is now one of reactant in contrast to that of catalyst in the reaction with benzil.



These results are of added interest in view of the findings of Kwart and Baevsky[1] that 4-nitrobenzil and cyanide ion are unreactive in alcoholic solution. These investigators observed the formation of a stable, colored solution which readily reverted to starting material. The generation of a stable semiquinone was considered a possibility. It seems reasonable, in view of our findings, that an alternate explanation can be offered. Thus, the reaction might have failed owing to the relatively low ratio (implied, though not stated[1]) of cyanide catalyst to 4-nitrobenzil. Perhaps cyanide was simply consumed to form trace amounts of **4**.

The success of the reaction in aprotic solvents presumably results from the inertness of **4** toward another molecule of 4-nitrobenzil. The negative charge is more completely delocalized in **4** (relative to **1**) owing to the favorable location of the nitro substituent.

The obvious analogy is drawn between the benzil–cyanide reaction and the benzoin condensation where cyanide also acts both as the nucleophile and as a group which delocalizes the negative charge on the intermediate carbanion.[5] The analogy is extended in that, while 4-nitrobenzaldehyde readily undergoes cyanohydrin formation,[6] it fails in the benzoin condensation.[7] As in our reaction, the best explanation seems to be that the delocalizing influence of the nitro group renders the intermediate so inert as to react no further with starting material.

Identification of **3** was accomplished by spectral analysis and comparison with a sample of benzoylated 4-nitromandelonitrile. It is interesting that C≡N absorption, in the 2100–2400-cm^{-1} region of the ir spectrum, is absent. However, this observation is in agreement with an earlier report that the C≡N stretch in compounds where the cyano group is attached to oxygenated carbon is "quenched" to the point of being extremely weak or not observable at all.[8]

Experimental Section[9]

Starting Materials. 4-Nitrobenzil was prepared according to the method of Womack, Campbell, and Dodd.[10] The solvents, DMSO and DMF, were distilled from calcium hydride at reduced pressure. Other materials were available in reagent grade and were used without further purification.

4-Nitrobenzil and Sodium Cyanide in DMSO. Sodium cyanide (0.25 g, 5.1 mmol) was stirred into 40 ml of solvent under an atmosphere of nitrogen. 4-Nitrobenzil (1.28 g, 5.0 mmol) was added in a single portion at room temperature. The solution at once turned deep violet in color. After 1.5 min, the reaction mixture was poured into an acidified ice–water slurry. The resulting suspension was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and evaporated. The residue (red-brown oil) was triturated with ethanol to afford light yellow crystals (0.82 g, 58%) of 4-nitromandelonitrile benzoate (**3**), mp 112–114° (ethanol).

Anal. Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.54; N, 9.93. Found: C, 63.80; H, 3.69; N, 10.07.

The nmr spectrum showed a 1 H singlet (methinyl) at δ 6.9 and a 9 H multiplet at δ 7.5–8.5 (aromatic). The ir spectrum showed carbonyl absorption at 1725 cm^{-1}. No absorption for C≡N was observed.[8] The mass spectrum (30 eV) showed *m/e* (rel intensity) 282 (M^+), 255 (8), 106 (46), 77 (100), m* 230.6.

4-Nitromandelonitrile Benzoate (3). The procedure used by Cronyn[11] for the preparation of 3-nitromandelonitrile benzoate was adopted. A suspension was prepared in an ice bath from 4-nitrobenzaldehyde (3.77 g, 25 mmol) and 5 ml of water, to which was added benzoyl chloride (3.64 g, 25.8 mmol). Potassium cyanide (2.0 g, 31.5 mmol) in 3 ml of water was added in one portion with stirring. The resulting yellow crystals were filtered and triturated with ethanol to afford the crude product (5.0 g, 70.8%, mp 108–111°). Recrystallization from ethanol resulted in an almost colorless sample, mp 114–115°. The material was identical with **3** in the previous experiment as shown by mixture melting point and comparison of spectral data.

Acknowledgment. We are grateful to J. Michael Robinson, Paul Moser, and Paula Watts at Louisiana State University for assistance in obtaining some of the spectral data.

Registry No.—**3**, 51130-02-0; 4-nitrobenzil, 22711-24-6; NaCN, 143-33-9.

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Synthesis of Alkanesulfonyl Isocyanates by Thermolysis of Trimethylsilylated Sulfonyl Carbamates

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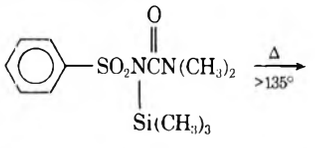
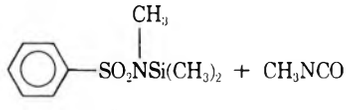
A communication by Greber and Krideldorf[1] describing the thermolysis of N-silylated carbamoyl chlorides, anhy-

drides, or urethanes to yield isocyanates stimulated our investigation of a new approach to sulfonyl isocyanate synthesis. We have found that both aryl- and alkylsulfonyl carbamates can be silylated easily and subsequent thermolysis of the trimethylsilyl intermediates produces the corresponding sulfonyl isocyanates in excellent yields. The new procedure eliminates a hazardous phosgenation step normally required in sulfonyl isocyanate synthesis[2,3] and minimizes the formation of difficultly separable by-products. The sulfonyl isocyanates are not contaminated by the sulfonyl chlorides which are normally present in isocyanates produced by a high-temperature phosgenation process. Furthermore, alkanesulfonyl isocyanates cannot be prepared by direct phosgenation and alternate procedures[4,5] are very inefficient. This paper describes a simple procedure for preparing pure aryl- or alkanesulfonyl isocyanates from readily available reagents.

Either sulfonyl carbamates or sulfonylureas can be silylated by treatment with trimethylchlorosilane in the presence of tertiary amines. Sulfonylureas are easier to synthesize but their silylated derivatives decompose to isocyanates and silylated sulfonamides rather than the desired products. In fact, Itoh, *et al.*,[6] has shown that pyrolysis of *N*-benzenesulfonyl-*N*-trimethylsilyl-*N'*,*N'*-dimethylurea (**1**) produces methyl isocyanate and *N*-trimethylsilyl-*N*-methylsulfonamide (**2**). Apparently silylated sulfonylureas do not undergo direct thermolysis; so these derivatives cannot be utilized as starting materials for a sulfonyl isocyanate synthesis.



1



2

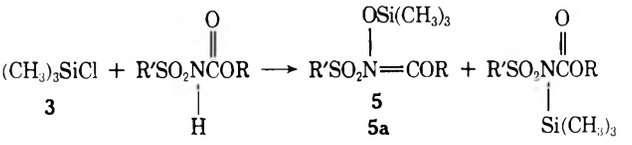
Silylated Sulfonyl Carbamates. *O*-Alkylsulfonyl carbamates can be synthesized by treatment of the appropriate sulfonamide with an alkyl chloroformate in the presence of potassium carbonate.[7] Alkyl chloroformates must be used in this step because aryl chloroformates participate in a multistep, base-catalyzed condensation to yield 1,3-bis(alkyl- or -arylsulfonyl)ureas instead of the desired *O*-aryl-*N*-alkyl- or -arylsulfonyl carbamates.[8] Silylation of *O*-alkyl-*N*-arylsulfonyl carbamates occurs readily when a hydrocarbon solution of the derivatives is treated with trimethylchlorosilane (**3**) in the presence of triethylamine. Triethylammonium hydrochloride precipitates quantitatively from the reaction medium when a solution of triethylamine is added to the reagents; subsequent isolation of the silylated intermediate simply involves removal of the amine salt by filtration followed by evaporation of the solvent under reduced pressure.

The progress of the silylation can be followed spectrophotometrically. Disappearance of the NH (3200 cm^{-1}) and a reduction in intensity of carbonyl (1760 cm^{-1}) infrared absorption bands is accompanied by the appearance of new bands at 1600 (C=N) and 1085 cm^{-1} (SiO). A linear correlation between this SiO absorption band intensity and the extent of reaction as estimated by nmr existed throughout a conversion range of 0–90%. The decrease in the carbonyl absorption intensity is indicative of extensive O-silylation; this is confirmed by the relative intensities of the silylmethyl absorptions in the nmr spectrum. The ratio of O-silylated to N-silylated derivatives is dependent upon the nature of R'. For example, *O*-neopentyl-*N*-*p*-toluenesulfonyl carbamate (**4**) yields a product mixture composed primarily of the O-silylated (**5**) derivative. In contrast, *O*-ethyl-*N*-methylsulfonyl carbamate (**4a**) exhibits a strong carbonyl absorption (1740 cm^{-1}) which is consistent with a mixture containing predominantly N-silylated product (**6a**). Both N- and O-silylated products undergo thermal decomposition to yield the corresponding sulfonyl isocyanates. This suggests that a rapid equilibration between the two isomers is occurring under the thermolysis conditions.

Table I
Thermolysis of Silylated *O*-Neopentyl-*N*-*p*-toluenesulfonyl Carbamate[a]

Run	Temp, °C	Silylated 5 concn, mol/l.	k_1, sec^{-1} [b] × 10^4	$t_{1/2}$, min
1	110	0.191	3.39	34.1
2	110	0.057	3.71	31.1
3	110	0.096	3.74	30.9
4	110	0.120	3.12	37.0
Plot of initial rates of runs 1–4			3.50	33.0
5	80	0.120	0.52	222.1
6	90	0.120	1.08	107.0
7	120	0.120	8.14	14.2

[a] Rates measured by time dependence of absorption at 2235.5 cm^{-1} (ν_{NCO}) in xylene. [b] First-order rate constants; correction coefficient >0.99.



4, R = neopentyl; R' = tolyl
4a, R = ethyl; R' = methyl

5 **5a** **6** **6a**

Thermal Dissociation. Thermolysis of trimethylsilylated carbamates can be effected by heating the derivatives in inert solvents such as xylene, chlorobenzene, or acetonitrile. The dissociation appears to be favored by polar solvents, since replacement of the hydrocarbon solvent used in the silylation procedure with acetonitrile before completing the thermolysis reduces the temperature required to liberate the sulfonyl isocyanate. Silylated *O*-phenyl-*N*-*p*-toluenesulfonyl carbamate decomposes slowly at 25°; the corresponding *O*-neopentyl derivative must be heated to 60° before a noticeable thermolysis occurs.

The thermolysis rate of a mixture of **5** and **6** was determined by observing the development of the isocyanate absorption band at 2235.5 cm^{-1}. The reaction exhibited first-order kinetics to at least 90% conversion. Furthermore, a plot of the initial rates exhibited by different concentrations of substrate was linear and yielded a rate constant comparable to those calculated for an irreversible first-order process. (Table I). An Arrhenius plot of the data is linear and indicates an activation energy of 19.4 ± 0.6 kcal/mol. The activation entropy is −24.6 ± 0.6 eu, which suggests an oriented cyclic transition state as exemplified by structures **7** or **8** in Scheme I.

We have shown that the cleavage occurs at the acyl carbon by the reaction sequence outlined in Scheme II. Optically active (*R*)-(−)-2-octanol (**9**) was allowed to react with *p*-toluenesulfonyl isocyanate to produce **10**. Silylation of **10** followed by thermolysis (path B) enabled us to isolate optically active alkoxysilane **11**, $[\alpha]^{25}D$ − 13.58°. The thermolysis proceeds with complete retention of configuration of the alkoxy substituent. The reaction sequence also suggests a new technique for resolving alcohols, since the sulfonyl carbamate intermediate would

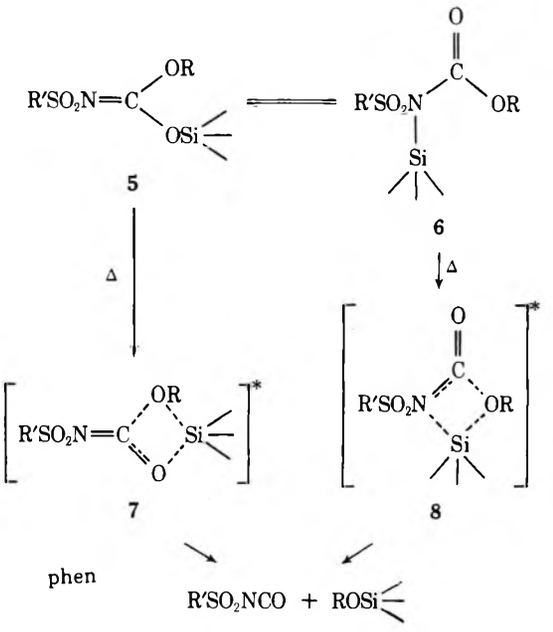
Table II
Preparation of Alkylsulfonyl Isocyanates by Thermolysis Procedure

$$RSO_2NH_2 \xrightarrow[K_2CO_3]{CH_3CH_2OCCl} RSO_2NHCOEt \xrightarrow[2.\ \Delta]{1.\ \text{silylation}} RSO_2NCO \xrightarrow{R'OH} RSO_2NHCOR'$$

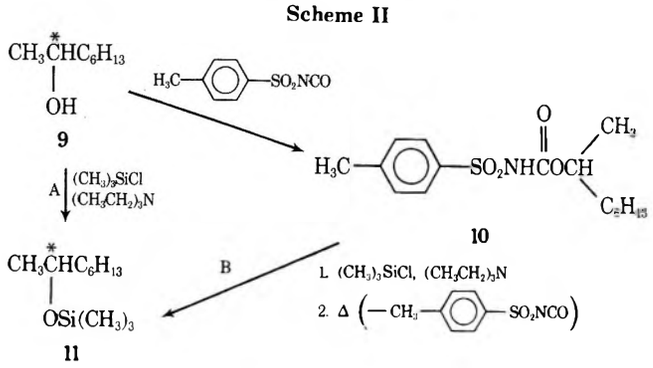
Expt	R	Sulfonyl carbamate[a] Registry no.	Yield, %	Mp, °C	Registry no.	Sulfonyl isocyanate Yield, %	Bp, °C (mm)	ν_{NCO}, cm^{-1}	Registry no.	Carbamate derivative[a] R′	Mp, °C	Registry no.
12	CH_3	3144-09-0	70.3	55–57	49671-33-2	67–79	49 (2)	2275	3611-92-5	$(CH_3)_3CCH_2$	79	51003-68-0
13	CH_3CH_2	1520-70-3	65.5	70–71	51003-65-7	45–62	76 (10)	2260	14604-85-4	Ph	125–127	51003-69-1
14	$CH_3CH_2CH_2CH_2$	3144-04-5	70	Oil	51003-66-8	72	78 (2)	2265	3670-24-4	Ph	68–69	51003-70-4
15	$PhCH_2$	4563-33-1	72	101–102	46731-59-3	62	96 (0.5)	2260	51003-67-9	$(CH_3)_3CCH_2$	109–110	51003-71-5

[a] Satisfactory analytical data were reported for all new compounds listed in the table.

Scheme I



Scheme II



probably form a diastereomeric salt mixture with an optically active amine.

Synthetic Applications. Since most arylsulfonyl isocyanates can be prepared by direct phosgenation,[3] the primary application of the thermolysis procedure is alkanesulfonyl isocyanate preparation. We have applied this procedure to the synthesis of methane- (**12**), ethane- (**13**), *n*-butane- (**14**), and α-toluenesulfonyl isocyanate (**15**) and the results are summarized in Table II. No attempt was made to isolate the silyl derivatives; the crude silylation mixture was pyrolyzed and the alkanesulfonyl isocyanate was isolated by fractional distillation. The sulfonyl isocyanates are extremely reactive liquids which are difficult to characterize; however, they react quantitatively with either neopentyl alcohol or phenol to produce stable crystalline alkanesulfonyl carbamate derivatives. The range of yields cited in Table II represents the difference between actually isolating the alkanesulfonyl isocyanate by distillation (lower values) and isolating the sulfonyl carbamate derivative which was prepared directly by adding the alcohol to the thermolysis reaction mixture.

In contrast to the reduced reactivity of alkyl isocyanates relative to aryl isocyanates, the alkanesulfonyl isocyanates appear to be comparable to benzenesulfonyl isocyanates in their reactivity toward alcohols and phenols. For example, treatment of wood cellulose with butanesulfonyl isocyanate produced an acetone-soluble alkanesulfonyl carbamylated cellulose in 30 min. Similar results were obtained using the thermolysis product mixture in place of the pure isocyanate. The properties of the cellulose derivative were analogous to those reported for *p*-toluenesulfonyl carbamylated cellulose.[9]

Experimental Section[10]

Reagents. Trimethylchlorosilane (3) was purified by distillation from 5 wt % sucrose and tri-*n*-butylamine to remove polychlorosilane derivatives.[11] The alkyl sulfonamides were prepared from the corresponding sulfonyl chlorides using a benzene solution of anhydrous ammonia.[12] Commercially available *p*-toluenesulfonyl isocyanate was used without further purification for preparative procedures. Since this material is contaminated with *p*-toluenesulfonyl chloride, which is difficult to remove, pure *p*-toluenesulfonyl isocyanate, bp 100° (0.5 mm), was prepared *via* the silylated carbamate procedure to use for infrared kinetic studies. *O*-Ethyl-*N*-alkylsulfonyl carbamates were prepared according to the general procedure of Cassady, *et al.*;[7] yields and melting points are reported in Table II. *O*-Alkyl-*p*-toluenesulfonyl carbamates were obtained by addition of the appropriate alcohol to a solution of *p*-toluenesulfonyl isocyanate in ether.

Silylation of *O*-Neopentyl-*N*-*p*-toluenesulfonyl Carbamate (4). The following general procedure was used to prepare the silylated sulfonyl carbamates. A solution of 3.84 g (13.46 mmol) of **4** in a mixture of 5 ml of acetonitrile and 30 ml of benzene was mixed with 5.85 g (54 mmol) of **3** and cooled in an ice bath. After slowly adding a solution of 1.37 g (13.5 mmol) of triethylamine in 10 ml of benzene, the reaction mixture was stirred at 20° for 1.5 hr. The excess trimethylchlorosilane was evaporated *in vacuo*, 25 ml of cyclohexane was added, and the triethylammonium salt was removed by filtration. The filtrate was concentrated *in vacuo* to yield 4.84 g of a mixture of **5** and **6**: nmr (benzene-d_6) δ 7.88 (d, 2 H), 6.87 (d, 2 H), 3.70 (s, 2 H), 2.09 (s, 3 H), 0.81 (s, 9 H), 0.23 (s, 6.8 H), 0.18 (s, 1.2 H). Although the absorptions below δ 0.5 were slightly broader than expected, it was not possible to resolve these signals and confirm the presence of an isomer mixture. The spectrum is consistent with a 90% yield of an 85:15 mixture of **5** and **6**, based upon the relative intensities of the silylmethyl proton absorption.

Silylation of *O*-ethyl-*N*-methylsulfonyl carbamate was conducted exactly as described above using 3.35 g (20 mmol) of **4a**, 8.7 g (80 mmol) of $(CH_3)_3SiCl$, and 2.02 g (20 mmol) of trimethylamine. Evaporation of the solvent mixture yielded 4.63 g of viscous oil, nmr (benzene-d_6) δ 3.99 (q, 2 H), 2.95 (s, 3 H), 1.09 (t, 3 H), 0.37 (s, 2.1 H), 0.28 (s, 4.9 H).

***O*-Ethyl-*N*-ethylsulfonyl carbamate (4b)** was silylated using 3.63 g (20 mmol) of **4b**, 8.7 g (80 mmol) of $(CH_3)_3SiCl$, and 2.02 g (20 mmol) of triethylamine; 4.71 g of oil remained, nmr (benzene-d_6) δ 3.98 (a, 2 H), 3.05 (m, 2.8 H) 1.17 (d of t, 7.7 H) 0.41, (s, 2.1 H), 0.28 (s, 4.4 H). The residual oil appears to be a mixture of **5b** and **6b**; ir (neat) 2250 (NCO), 1740 (C=O), and 1085 cm^{-1} (SiO) confirms this analysis.

Butanesulfonyl isocyanate (14) was prepared directly from *O*-ethyl-*N*-butanesulfonyl carbamate (**16**) without isolating the silylated intermediate. Addition of triethylamine (21.2 g, 0.209 mol) to a cooled solution of 43.7 g (0.209 mol) of **16** and 68.5 g (0.63 mol) of **3** in 140 ml of benzene effected the silylation. After the reaction mixture was stirred for 2 hr, the excess trimethylchlorosilane and ~25 ml of solvent were evaporated under reduced pressure. The residue was filtered under nitrogen and then the remaining solvent was evaporated. The residual oil was redissolved in 70 ml of acetonitrile and refluxed for 2 hr. Evaporation of the acetonitrile followed by vacuum distillation of the residue yielded 24.5 g (72%) of **14**: bp 78° (3 mm); ir (neat) 2240, 1350, 1150 cm^{-1}; nmr (CD_3CN) δ 3.2 (t, 2 H), 1.76–0.86 (m, 4 H), 0.67 (t, 3 H).

A similar procedure was utilized to prepare each of the sulfonyl isocyanates cited in Table II.

(−)-2-Octyloxytrimethylsilane (11). Method A. A solution of 5.38 g (0.041 mol) of **9**, $[\alpha]^{25}D$ (cyclohexane) −8.57°, in 50 ml of benzene was treated with 13.3 g (0.122 mol) of **3** and cooled to 5°. Following injection of 4.12 g (0.041 mol) of triethylamine, the mixture was allowed to warm to 37° and stirred for 3 hr. The excess trimethylchlorosilane was evaporated under reduced pressure, the triethylammonium chloride was removed by filtration under nitrogen, and the filtrate was treated with 2.0 g of *p*-toluenesulfonyl isocyanate to remove unreacted alcohol. Fractional distillation of the filtrate yielded 6.12 g (74%) of **11**, bp 70° (10 mm), $[\alpha]^{25}D$ (cyclohexane) −13.58°.

Method B. A solution of 9.70 g (0.049 mol) of *p*-toluenesulfonyl isocyanate in 40 ml of ether was mixed with an ethereal solution of **9** (6.40 g in 10 ml). After 1 hr the ether was evaporated and the residual oil **10**) was used without further purification. The silylation of **10**, 14.9 g (0.045 mol), with 14.7 g (0.135 mol) of **3** was catalyzed by addition of 4.6 g of triethylamine to a benzene solution of the reagents. The silylated sulfonyl carbamate was isolated and thermolyzed in acetonitrile in the usual manner. Fractional distillation of the product mixture yielded 8.12 g (74.5%) of **11**, bp 63° (6 mm), $[\alpha]^{25}D$ (cyclohexane) −14.68°.

Anal. Calcd for $C_{11}H_{25}OSi$: C, 65.62; H, 12.41; Si, 13.92. Found: C, 65.32; H, 12.38; Si, 13.67.

Reaction of *n*-Butylsulfonyl Isocyanate with Cellulose. A stirred, nitrogen-flushed mixture of 1.00 g (0.006 molar equiv) of wood cellulose in 50 ml of anhydrous pyridine was treated with 4.00 g (0.027 mol) of *n*-butylsulfonyl isocyanate at 85° for 6 hr. A clear solution was obtained within 30 min. The product was precipitated by pouring the reaction mixture into 500 ml of cold 50% ethanol–water which had been acidified with 50 ml of concentrated HCl. The polymer was dissolved in acetone, reprecipitated with acidified ice water, washed free of excess acid, and dried *in vacuo* at 60° for 12 hr; 3.63 g (D.S. = 2.6) of white powder was obtained. The butylsulfonyl carbamylated cellulose was soluble in acetone, DMF, and 2% NaOH, and swollen by ethanol.

Registry No.—**3**, 75-77-4; **4**, 32363-28-3; **5**, 51003-72-6; **5b**, 51003-73-7; **6**, 51003-74-8; **6a**, 51003-75-9; **6b**, 51003-76-0; **9**, 51003-19-1; **11**, 51003-20-4; *p*-toluenesulfonyl isocyanate, 4083-64-1; $CH_3CH_2O_2CCl$, 541-41-3.

References and Notes

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(9) R. W. Rousseau, C. D. Callihan, and W. H. Daly, *Macromolecules*, **2**, 502 (1969).
(10) All melting points and boiling points are uncorrected. Microanalyses were performed by Mr. Ralph Seab in our Department and Galbraith Laboratories, Inc., Knoxville, Tenn.
(11) J. F. Klebe and H. L. Finkbeiner, *J. Polym. Sci., Part A-1*, **7**, 1947 (1969).
(12) L. Field and F. A. Grunwald, *J. Amer. Chem. Soc.*, **75**, 934 (1953).

Lewis Acid Catalyzed Addition of Isocyanates to Sulfonamides

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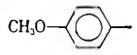
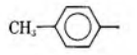
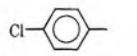
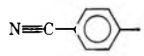
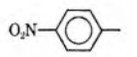
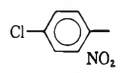
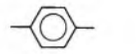
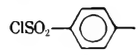
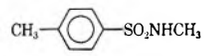
The potential chemotherapeutic value of arylsulfonylureas as oral hypoglycemic agents has promoted intensive interest in their synthesis and chemical properties. Most of the preparative procedures described in the literature utilize arylsulfonamide salts, generated by inorganic bases or tertiary amines, as nucleophiles to add to isocyanates and related derivatives,[1] or to *sym*-1,3-dialkylureas.[2] Recently, an improved method for the preparation of arylsulfonyl isocyanates has increased the applicability of these highly reactive intermediates in arylsulfonylurea preparations.[3] We wish to describe a new approach to arylsulfonylurea synthesis which involves the direct condensation of arylsulfonamides with alkyl or aryl isocyanates in the presence of Lewis acid catalysts.

The Friedel–Crafts condensation of isocyanates with aromatic compounds in the presence of aluminum chloride was first reported by Leuckart in 1885.[4] This reaction has been evaluated more recently by Effenberger and Gleiter and the electrophilic character of the condensation was established.[5] The Friedel–Crafts reactivity of an isocyanate–Lewis acid complex toward the aromatic nucleus is

Table I
Electrophilic Condensation of *n*-Butyl Isocyanate with Sulfonamides,[a] RSO_2NH_2

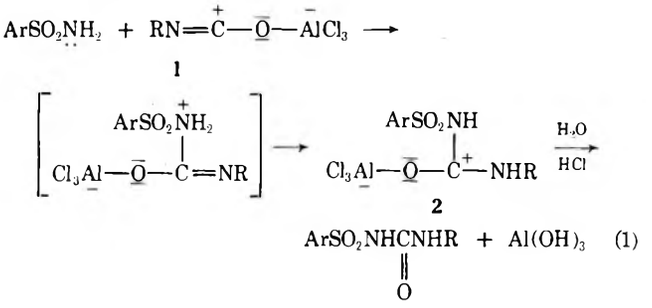
Expt	Registry no.	R	Yield, %[b]	Mp, °C[c]
1	1129-26-6		80	128 (lit.[e] 128–129)
2	70-55-3		76[j]	129 (lit.[d] 127–128)
3	98-64-6		64	119–120 (lit.[d] 118.5–120)
4	3119-02-6		78	185 (lit.[f] 181)
5	6325-93-5		84	165–166 (lit.[e] 165–168)
6	13852-81-8		85	169.5[g]
7	16993-45-6		91	220–222 dec (lit.[i] 218–220 dec)
8	46249-41-6		80.5	143–144[g]
9	640-61-9		100	46[g]
10	3144-09-0		100	172–174 (lit.[h] 168)

[a] Prepared in nitrobenzene using $AlCl_3$ as the catalyst. [b] Yield of recrystallized product. [c] Measured with a Du Pont 900 Differential Thermal Analyzer. [d] F. J. Marshall and M. V. Segal, *J. Org. Chem.*, **23**, 927 (1958). [e] R. Tull, *et al.*, *J. Chem. Soc. C*, 701 (1967). [f] J. Lederer, *J. Med. Chem.*, **7**, 370 (1964). [g] Satisfactory elemental and spectral analyses were obtained for all new compounds. [h] O. Bayer and E. Cauer, French Patent 993,465 (Oct 31, 1961); *Chem. Abstr.*, **51**, 11380*f* (1961). [i] D. F. Hayman, *et al.*, *J. Pharm. Pharmacol.*, **14**, 451 (1962). [j] *n*-Propyl isocyanate was used in place of *n*-butyl isocyanate.

similar to that of acyl halide–aluminum chloride complexes, *i.e.*, anisole ~ mesitylene > toluene > benzene > chlorobenzene. Aromatic rings deactivated by nitro or sulfonyl substituents do not react with these complexes.

Discussion

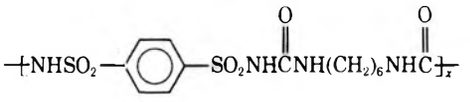
Our survey of the literature did not reveal any evaluation of the reactivity of sulfonamides with electrophilic reagents. However, the unpaired electrons on the sulfonamide linkage can attack an electrophile as illustrated in eq 1. We have ohserved that addition of an isocyanate–Lewis acid complex, such as **1**, to a sulfonamide produces an arylsulfonylurea–aluminum chloride complex (**2**), which can be hydrolyzed with dilute hydrochloric acid to liberate the desired product.



$$ArSO_2NHCNHR + Al(OH)_3 \quad (1)$$
$$\|$$
$$O$$

The scope of the reaction is illustrated in Table I. Note that two of the common hypoglycemic agents, tolbutamide (expt 2) and chlorpropamide (expt 3), can be prepared in 80 and 76% yield, respectively. The sulfonyl group effectively deactivates the aromatic nucleus; no evidence for arylcarboxamide derivatives was observed even in the presence of a strong electron-donating substituent (expt 1). Aromatic functional groups with high π-electron densities such as cyano or nitro moieties do not interfere with the condensation (expt 5–7). The procedure is ideal for preparing bis(*N'*-alkyl-*N*-aryl)sulfonyl ureas. We are able to prepare polyfunctional arylsulfonylureas with base-sensitive substituents (expt 8). This is a unique feature of our procedure and arylsulfonylureas with sulfonyl chloride substituents provide further possibilities for elaboration of sulfa drugs. N-Alkylated sulfonamides, which do not react with isocyanates under basic conditions,[6] can be converted to the corresponding sulfonylureas by our method. Alkylsulfonamides can also be utilized as substrates (expt 10).

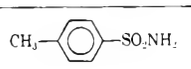
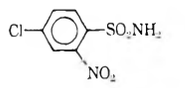
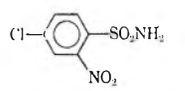
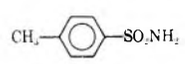
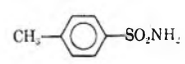
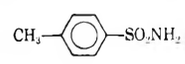
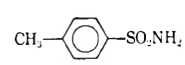
The yields cited in Table I refer to pure recrystallized product; the raw yield is essentially quantitative in most cases. The reaction can be employed to prepare poly(arylsulfonylureas) by the adding of diisocyanates to disulfonamides. For example, treatment of benzene-1,4-disulfonamide with hexamethylene diisocyanate yields a polymer of the following structure.



Polymers of this type are potentially useful as ion-exchange resins because the arylsulfonylurea linkage is a relatively strong acid.

The nature of the reagents which add electrophilically to arylsulfonamides was evaluated and the results are summarized in Table II. Aryl and alkyl isocyanates react equally well. The more sterically hindered cyclohexyl isocyanates condensed easily with ortho-substituted arylsulfonamides. Although aryl isocyanates are known to dimer-

Table II
Electrophilic Addends to Arylsulfonamides[a]

Arylsulfonamide	Addend	Registry no.	Yield,[b] %	Mp, °C[c]
	Cyclohexyl isocyanate	3173-53-3	95	178 (lit. 171–173)[d]
	Cyclohexyl isocyanate		70	210 dec[e]
	Phenyl isocyanate	103-71-9	75	163 dec[e]
	PhCCl ‖ O	98-88-4	89	148 (lit. 145–148)[f]
	CH_3CCl ‖ O	75-36-5	88	138 (lit. 136–138)[g]
	$(CH_3)_2NCCl$ ‖ X X = O, S		No reaction	
	ROCCl ‖ O R = Ph, Et		No reaction	

[a] Reaction conditions: arylsulfonamide:addend:$AlCl_3$, 0.01:0.01:0.012 *M* in 50 ml of nitrobenzene at 80° for 4 hr. [b] Yield of recrystallized product. [c] Determined by DTA. [d] G. Brzozowaki and R. Zdzislaw, *Rocz. Chem.*, **43,** 1761 (1969). [e] Satisfactory elemental and spectral analyses were obtained for all new compounds. [f] H. Bock, E. Baltin, and J. Kroner, *Chem. Ber.*, **99,** 3337 (1966). [g] A. Novacek, *Collect. Czech. Chem. Commun.*, **32,** 1712 (1967).

ize and trimerize in the presence of Lewis acid catalysts,[7] no evidence for side reactions of this type was observed. Phenyl isothiocyanate and *p*-toluenesulfonyl isocyanate failed to react with *p*-toluenesulfonamide in nitrobenzene at 80°. A potential intermediate in the condensation of isocyanates in the presence of aluminum chloride is the corresponding carbamoyl chloride. Although this possibility is unlikely because the condensation is conducted at temperatures at which carbamoyl chlorides dissociate to isocyanates and HCl,[8] a carbamoyl intermediate can be eliminated since dimethyl carbamoyl chloride failed to react with *p*-toluenesulfonamide. Benzyl chloride, phenyl chloroformate, and ethyl chloroformate failed to react with sulfonamides in the presence of aluminum chloride. On the other hand, benzoyl chloride and acetyl chloride react readily under these reaction conditions to yield *N*-(*p*-toluenesulfonyl)benzamide and *N*-(*p*-toluenesulfonyl)acetamide, respectively. These reactions demonstrate the acylation potential of aryl sulfonamides with acid chlorides.

We have attempted to elucidate the structure of the isocyanate–aluminum chloride complex by infrared analysis of nitrobenzene solutions with different aluminum chloride:butyl isocyanate ratios. The free isocyanate band at 2280 cm^{-1} is reduced to a constant minimum value when the $AlCl_3$:BuNCO ratio is 0.8:1. This disappearance is accompanied by the formation of four new bands in the spectra at 3385, 2340, 1770, and 1670 cm^{-1}. Since each of the bands develops at a different rate, it is likely that four different complexes are involved. Apparently, the aluminum chloride–isocyanate system ranges from a complex of two isocyanate moieties per $AlCl_3$ molecule to a polymeric complex capable of accepting up to 10 mol of $AlCl_3$/mol of isocyanate and elucidation of the structure of the active complex will require further experiments.

Variation of the reaction conditions also revealed some interesting phenomena. No reaction occurred in dioxane, acetonitrile, or nitromethane, but the addition proceeded normally in chloroform and carbon disulfide–benzene mixtures. The latter solvent system was less satisfactory than nitrobenzene because the isocyanate complex reacted with the benzene to produce by-products. The best procedure for synthesis of the arylsulfonylureas is to heat a slurry of the arylsulfonamide, isocyanate, and Lewis acid to 80° for 2 hr. Subsequent treatment of the solid sulfonylurea complex with cold dilute hydrochloric acid liberates pure arylsulfonylurea. Although aluminum chloride was used as a catalyst for most of this work, less reactive Lewis acids such as anhydrous ferric chloride and stannic chloride were equally effective.

Experimental Section

Reagents. Commercially available arylsulfonamides and isocyanates were used without further purification.

***N*-Arylsulfonyl-*N'*-butylureas. A. Solution Method.** A solution of *n*-butyl isocyanate (1.0 g, 0.01 mol) in 50 ml of nitrobenzene was added to 1.5 g (0.0113 mol) of anhydrous aluminum chloride, stirring was initiated, and, when a clear solution of the isocyanate–$AlCl_3$ complex formed, the arylsulfonamide (0.01 mol) was added. The solution was heated to 80° for 4 hr, and then 15–20 ml of nitrobenzene was distilled from the reaction mixture under reduced pressure. The residue was poured into 300 ml of ice water containing 10 ml of hydrochloric acid. The product was precipitated from the nitrobenzene phase by addition of petroleum ether.

B. Slurry Method. A mixture of 1.5 g (0.0113 mol) of anhydrous aluminum chloride, 0.01 mol of arylsulfonamide, and 0.01 mol of isocyanate was heated at 80° for 0.5 hr. The reaction mixture was cooled and triturated with 30 ml of cold, 10% HCl to break up the product complex, and the arylsulfonylurea was isolated by extracting the aqueous slurry with two 30-ml aliquots of ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to yield the desired product.

Poly(benzene-1,4-disulfonylhexamethyleneurea). A solution of 2.577 g (0.01 mol) of benzene-1,4-disulfonamide in 50 ml of nitrobenzene was allowed to react with 1.682 g (0.01 mol) of hexamethylene diisocyanate in the presence of 2.7 g (0.02 mol) of aluminum chloride at 80° for 15 hr. The homogeneous reaction mixture was cooled to 25° and poured into 100 ml of 5% HCl to precipitate the polyurea. The polymer was soluble in DMF, DMSO,

and 5% KOH, and could be purified by reprecipitating from a DMF solution into acetone followed by a second reprecipitation from DMF into water. The purified polymer exhibited η_{inh} = 0.132 in DMF and decomposed upon heating to 220°. *Anal.* Calcd for $C_{14}H_{20}N_4O_6S$: C, 39.5; H, 4.70; N, 13.14. Found: C, 40.63; H, 5.01; N, 13.58.

Investigation of the $AlCl_3$–*n*-Butyl Isocyanate Complex. A 0.1 *M* stock solution of *n*-butyl isocyanate in nitrobenzene was used for all of the measurements. A 1.0 *M* solution of $AlCl_3$ in nitrobenzene was used to prepare a second 0.1 *M* stock solution and these two solutions were used to prepare complex solutions where the concentration of $AlCl_3$ ranged from 0.005 to 0.5 *M* and the concentration of *n*-butyl isocyanate was held constant at 0.05 *M*. The complex solutions were allowed to stand at 25° for at least 30 min before the infrared spectra were recorded with a Perkin-Elmer Model 621 spectrometer. The spectra of the solutions were measured at ambient temperature in matched 0.4-mm sodium chloride cells using nitrobenzene as a reference.

Registry No.—*n*-Butyl isocyanate, 111-36-4; hexamethylene diisocyanate, 822-06-0; poly(benzene-1,4-disulfonylhexamethyleneurea), 51002-85-8; benzene-1,4-disulfonamide polymer with hexamethylene diisocyanate, 51002-86-9.

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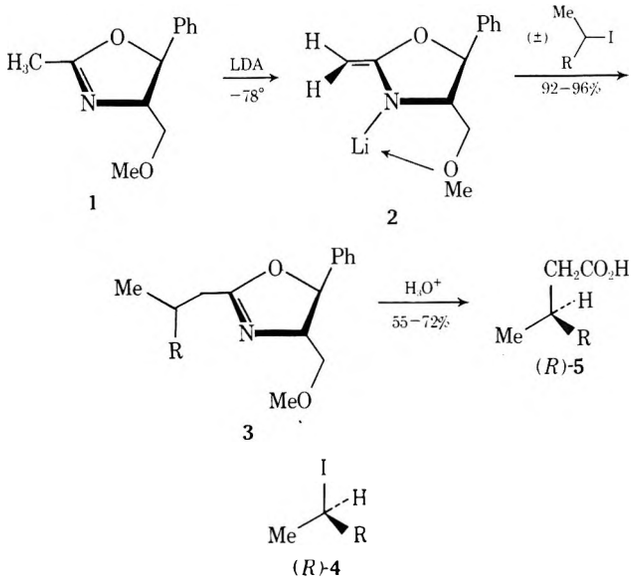
Communications

Synthesis *via* Oxazolines. V. A Simultaneous Kinetic Resolution of *sec*-Alkyl Iodides and Synthesis of Optically Active 3-Alkylalkanoic Acids. A Method for Determination of Absolute Configuration and Maximum Optical Rotations

Summary: Reaction of racemic *sec*-alkyl iodides with a chiral oxazoline carbanion results in 30–40% stereoselective alkylation of the S enantiomer of the halide and allows recovery of *R*-enriched halide.

Sir: We recently reported the use of chiral nonracemic oxazolines in the asymmetric synthesis of α-methylalkanoic acids.[1] Further studies on the 2-methyl derivative **1** of this heterocyclic system have now revealed that it is capable of chiral recognition in nucleophilic substitution of *sec*-alkyl halides resulting in simultaneous formation of optically active halides and 3-methylalkanoic acids *via* kinetic resolutions.[2]

Treatment of **1**[3] with 1.0 equiv of lithium diisopropylamide (LDA) gave the lithio salt **2** (THF, −78°). Addition of 2.0 equiv of racemic 2-iodoalkanes (−40 to −60°, 6–8 hr) produced, after quenching, the alkylated oxazoline **3** in 92–96% yield along with recovered iodoalkane **4** which



was 25–30% optically pure and possessed the *R* configuration (Table I). Hydrolysis (3 *N* HCl, 2 hr) of the alkylated oxazoline **3** afforded the 3-methylalkanoic acids **5** in comparable (±3%) optical purity and also possessing the *R* configuration (Table I). Aside from the asymmetric synthesis of the carboxylic acids and the kinetic resolution of the halides in moderate optical yields, this technique offers a rather significant dividend. *It should be feasible to predict, within a few per cent, the maximum rotation of one of the reaction products (halide or acid) provided that the other is known.* This prediction is substantiated by the following events. Reaction of **1** with 2.0 equiv of racemic 2-iodooctane gave recovered halide (*R*)-**4** (R = hexyl) in 85% yield with an optical purity of 24–30% (Table I). However, the carboxylic acid (*R*)-**5** was formed in 53% optical purity based upon a reported value of −4.7°

Table I
Optically Active *sec*-Alkyl Iodides, (*R*)-4, and 3-Methylalkanoic Acids, (*R*)-5

Iodide 4,[a,b] R	$[\alpha]_D^{25}$ (neat), degree	Optical purity,[c] %	Acid 5,[a] R	$[\alpha]_D^{25}$ (neat), degree	Optical purity, %
Et	−9.4	27–29[d]	Et	−2.6	31[e]
n-Propyl	−10.6	24–29	*n*-Propyl	+0.7	26–28[e]
n-Hexyl	−15.0	25–30[f]	*n*-Hexyl	+2.4	34[g]

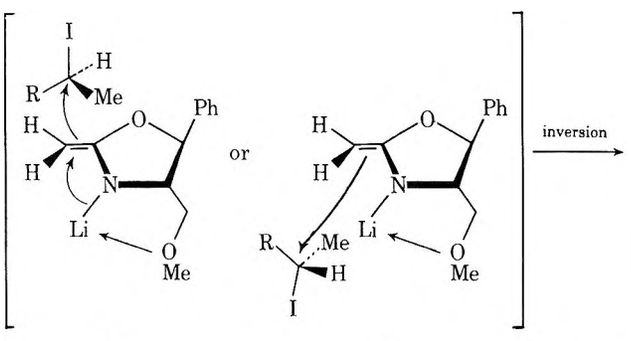
[a] Recovered in 81–96% yield. [b] To avoid enrichment by fractionating, all materials were distilled to <10% of residue. [c] Based upon highest values reported: **2-iodobutane,** $[\alpha]_D$ −31.98° (neat), and **2-iodopentane** $[\alpha]_D$ −37.15° (neat), R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911); $[\alpha]_D$ 46.7° (neat), D. H. Brauns, *Recl. Trav. Chim. Pays-Bas*, **65**, 799 (1946); **2-iodooctane,** $[\alpha]_D$ −59.5° and +62.6° (neat), M. C. Berlak and W. Gerrard, *J. Chem. Soc.*, 2309 (1949). [d] Contained 15–20% of THF formed as an azeotropic mixture. [e] Based on highest values reported: **3-methylpentanoic acid,** $[\alpha]_D$ −8.92° (neat), P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **92,** 456 (1931); **3-methylhexanoic acid,** $[\alpha]_D$ +2.50° (neat), I. A. Holiday and N. Polgar, *J. Chem. Soc.*, 2934 (1957), and $[\alpha]_D$ +2.77° (neat), P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **92,** 456 (1931). [f] Contained 6–8% octenes which accounted for the lower value as compared to the corresponding acid. [g] **3-Methylnonanoic acid** is reported to have $[\alpha]_D$ −4.71° (neat), A. Rothen and P. A. Levene, *J. Chem. Phys.*, **7,** 975 (1939). Optical purity is based on +7.1° obtained in this work.

(Table I, ref g). To preclude any error in the reported maximum rotation of either the iodide **4** or the acid **5**, the alkylation of **1** was repeated using (+)-2-iodooctane[4] (70% optical purity, 1.8 equiv). The recovered iodide had $[\alpha]_D$ +41° while the 3-methylnonanoic acid had $[\alpha]_D$ +5.25°. Assuming 74% optical purity of the acid, this is corrected to be +7.1° for a maximum rotation. Thus, the acid derived from racemic 2-iodooctane and **1** had an optical purity of only 34% and suggested to us that the reported value was too low. This experiment tends to validate the technique reported here and should allow prediction of maximum rotation in these classes of compounds.

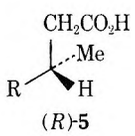
Reaction of **1** with a larger excess of racemic halide (6–8 equiv) gave recovered iodides (iodobutane and iodooctane in 6 and 9% optical purity, respectively) and increased optical purity of the corresponding acids (39–40%). Thus, the asymmetric yields of 3-methylalkanoic acids can be increased to even higher levels by employing these conditions.

Since the iodides **4** are recovered with the *R* enantiomer in excess, the transition state during alkylation must assume the orientation depicted in **6a** or **6b** which preferentially consumes the *S* enantiomer. This approach to the

via S enantiomer

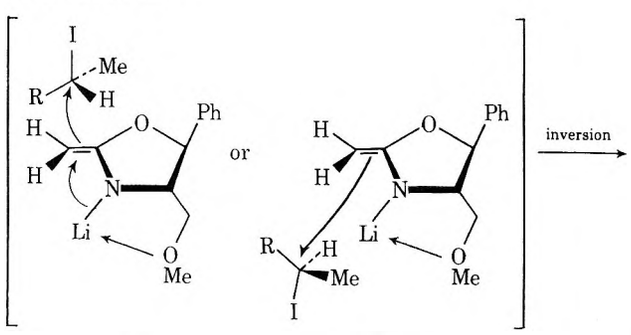


6a **6b**

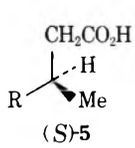


(*R*)-**5**

via R enantiomer



7a **7b**



(*S*)-**5**

transition state appears to involve a minimum of nonbonded interactions. In contrast, the *R* enantiomer of the iodide generates considerably more interactions as the transition state is approached (**7a** or **7b**). The results of the alkylations are consistent with this view since iodide displacement on the more favorably disposed *S* enantiomer (whose Cahn–Ingold–Prelog sequencing is the same in both the halide and the acid) should proceed with inversion leading to the (*R*)-acids, **5**. The absolute configurations of the acids[5] **5** and the halides[5] **4** are known to be *R*.

Although only three examples involving kinetic resolution of *sec*-alkyl iodides are reported here, this method indicates that it may now be possible, in addition to predicting maximum rotations, to correlate absolute configurations of halides (or their alcohol precursors) and 3-alkylalkanoic acids (or their derivatives, *e.g.*, alcohols, halides, ketones, etc.) by employing racemic starting materials, provided of course, that the absolute configuration of either the acid or halide is known. We continue to evaluate this useful new tool.

Acknowledgment. Financial support from the National Institutes of Health, the National Science Foundation, and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

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(3) Prepared using acetonitrile imidate ether as described in ref 1, $[\alpha]^{25}_D$ −113.8° (c 10.5, $CHCl_3$). The chiral methoxyamino alcohol was recovered after hydrolysis of **3** and recycled to the starting oxazoline **1**.
(4) Prepared according to Berlak (Table I, ref c) from commercial 2-octanol {$[\alpha]_D$ −8.97° (neat)}. The (+)-iodooctane thus obtained had $[\alpha]_D$ +44.07° (neat) which represents 70.4% optical purity (based on $[\alpha]_D$ 62.6°).
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The Degenerate Rearrangement of the Benzo-6,7-bicyclo[3.2.2]nonatrienyl Anion. The Relative Stability of a Benzylic and an Allylic Anion[1]

Summary: The benzo-6,7-bicyclo[3.2.2]nonatrienyl anion undergoes a facile degenerate 7-carbon scrambling detected using ^{13}C nmr techniques; the rearrangement has been used to probe relative anion stabilities.

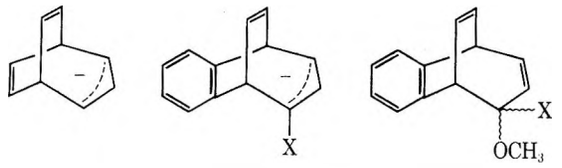
Sir: It was recently shown that the bicyclo[3.2.2]nonatrienyl anion I undergoes a degenerate rearrangement.[2] We now report that this facile rearrangement provides a convenient method for the determination of relative carbanion stabilities. When a substituent is introduced onto the bicyclo[3.2.2]nonatrienyl anion framework, a new equilibrium is established which reflects the substituent influence on carbanion stability. The benzo group is used here as a substituent to test the relative stabilities of a benzylic and an allylic anion. The literature data on this question are ambiguous.[3,4] The advantages of Stothers' method[5] for determining deuterium location by carbon-13 nmr spectroscopy are also illustrated.

Table I
Analysis of Deuterium Content of Benzo-6,7-bicyclo[3.2.2]nonatriene Derived from II-D

Position	Proton nmr integration[a] Observed	Calcd for 5 C	Calcd for 7 C	Carbon nmr, intensity ratios[b] Observed	Calcd for 5 C	Calcd for 7 C
1	0.91[c] ± 0.05	1.00	0.86	2.0 ± 1	1.5	2.0
2	0.87	0.80	0.86	2.8	3.0	2.0
3	0.79	0.80	0.86	*d*	1.0	2.0
4	1.60	1.80	1.86	1.6	3.0	2.0
5	0.91[c]	1.00	0.86	1.2	1.5	2.0
6				4.8 ± 3	∞	6.0
7				4.7 ± 3	∞	6.0
8	0.87	0.80	0.86	2.3	3.0	2.0
9	0.89	0.80	0.86	3.3	3.0	2.0

[a] Average of at least three quenches assuming that the benzo protons have intensity 4.00. [b] Ratio of "normal" peak to isotope shifted peak. [c] H-1 and H-5 overlap in the proton spectrum and these numbers are each half the observed sum. [d] Not determined owing to peak overlap.

The benzo-6,7-bicyclo[3.2.2]nonatrienyl anion II and its monodeuterated derivative II-D were prepared from the methyl ethers III by sodium–potassium alloy cleavage using previously reported methods.[2b,6] The nmr spectrum



I II, X = H; II-D, X = D III, X = H; III-D, X = D

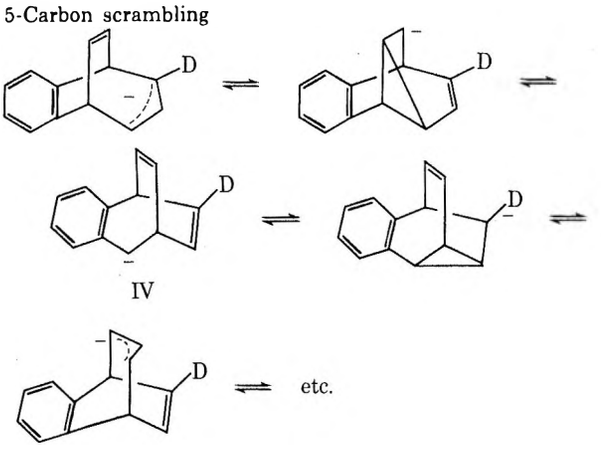
of the anion defines the symmetrical allyl structure expected for II. It shows a narrow multiplet for the benzo protons (δ 7.01, width 4 Hz), a broad triplet (δ 5.42, 7 Hz, H-3) overlapping a complex symmetrical multiplet (δ 5.33, width 8 Hz, H-8, -9) and another complex pattern (δ 3.11, 7.5 Hz, H-1, -5, and δ 3.18, 7.5 Hz, H-2, -4) which simplified to an AB pattern on irradiation in the δ 5.4 region. No other anions were detected in the spectrum (<5%) which remained unchanged after 1 year at 25° in perdeuteriotetrahydrofuran. The chemical shift of the benzo protons show limited charge delocalization into the benzene ring. The remaining shifts agree closely with those of the bicyclo[3.2.2]nona-2,6-dienyl anion.[7]

The 2-deuterio anion II-D was prepared in 30 min at 0°. The deuterium was still present at C-2 because H-3 appeared as a clean doublet. With a half-life of 1 hr at 32°, the spectrum changed. In particular, the H-3 doublet changed to an overlapping doublet and triplet. Thus the benzo anion II is rearranging in similar fashion and rate to the parent anion I. It is important to recognize that this scrambling proceeds *via* the benzylic ion IV as an intermediate. There is no evidence for IV in the anion nmr and a methanol quench of the anion gave an 85% isolated yield of benzo-6,7-bicyclonona[3.2.2]-2,6,8-triene (see also ref 6) with <1% of other volatile products detectable by gc.[8] We conclude that the benzylic anion IV is at least 2 kcal/mol less stable than its isomeric allylic ion II.

Experimental support for the rearrangement mechanism is extensive: Maercker's detailed work on the cyclopropylcarbinyl–homoallyl anion interconversion,[9] Staley's observation[10] of a barbaralane derivative from base exchange of a bicyclo[3.2.2]nonatrienyl system, and our observation that deuterium scrambling does not occur in the bicyclo[3.2.2]nona-2,6-dienyl anion.[7,11] For rearrangement to occur in the dienyl anion, ring opening to a bare secondary carbanion must compete with opening to an allylic ion.

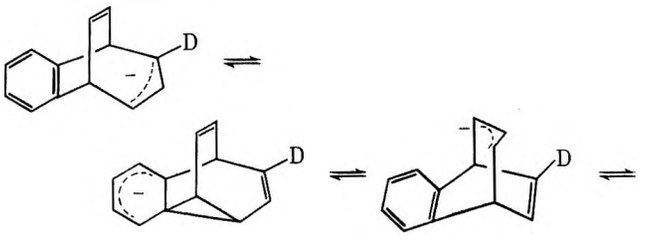
A 5-carbon scrambling (see below) results from the application of the rearrangement to II. Deuterium cannot be

5-Carbon scrambling



IV

7-Carbon scrambling



incorporated into the benzylic positions, 1 and 5, because this would require breakage of the bonds to the benzene ring. For 7-carbon scrambling to occur (see below), a phenyl migration is required and such migrations are well established.[12]

Differentiation between a 5-carbon and 7-carbon scrambling required carbon-13 nmr analysis[5,13] of the benzobicyclo[3.2.2]nonatriene derived from quenching. Neither integration nor decoupling and multiplet analysis of the proton spectrum provided definitive data. Sensitivity limitations prevented an unambiguous conclusion from deuterium spectra. However, in the carbon spectrum, the use of the isotope shift induced at the adjacent carbons was straight-forward. The aliphatic carbons, C-1, C-4, and C-5, each appeared as two peaks in the deuterated hydrocarbon with an intensity ratio of ~2:1. Also, C-6 and C-7 showed an isotope peak (approximate intensity ratio 5:1) but this observation was limited by the low sensitivity of these quaternary carbons. Thus, deuterium must be incorporated at C-1 and C-5 in accord with the 7-carbon scrambling process. Combined analysis of the carbon and proton results (Table I) shows essentially statistical scrambling of deuterium into all nonbenzo positions with a possible isotope effect slightly favoring deuterium at po-

sitions 3 and 4 at the expense of 1 and 5. These results clearly demonstrate the utility of carbon-13 nmr for the analysis of a deuterium label in highly scrambled systems.

While the experimental result that II is more stable than IV is clear-cut, its interpretation remains open to question. Do the relative stabilities of these homoaromatic[14] (if not bicycloaromatic[2,15]) ions reflect the stabilities of simple benzylic and allylic ions? In a zero-order approximation, the homoaromatic stabilization of an allylic or benzylic ion to generate a bishomocyclopentadienide or bishomoindenide ion, respectively, should be the same. In each case, the major homoaromatic stabilization arises from the antibonding MO of ethylene and the nonbonding MO of the ion. Equivalent stabilization is expected, because the nonbonding MO energies are equal. The third π bridge should have little effect on these conclusions because bicycloaromatic stabilization has little to add to homoaromatic stabilization.[7] Also, Brown[16] has shown that an ethylene bridge and a benzo bridge have similar stabilizing influence in homoaromatic interaction of anions. Thus, the stability difference between II and IV is best attributed to the difference between a benzylic and an allylic ion. However, throughout these orbital manipulations, one should not lose sight of the classical alternative that a bishomocyclopentadienide is more stable than a bishomoindenide ion as an attenuation of the known stabilities of the cyclopentadienide and indenide ions.[4]

We are continuing our investigation of substituent effects using the degenerate anion rearrangement.

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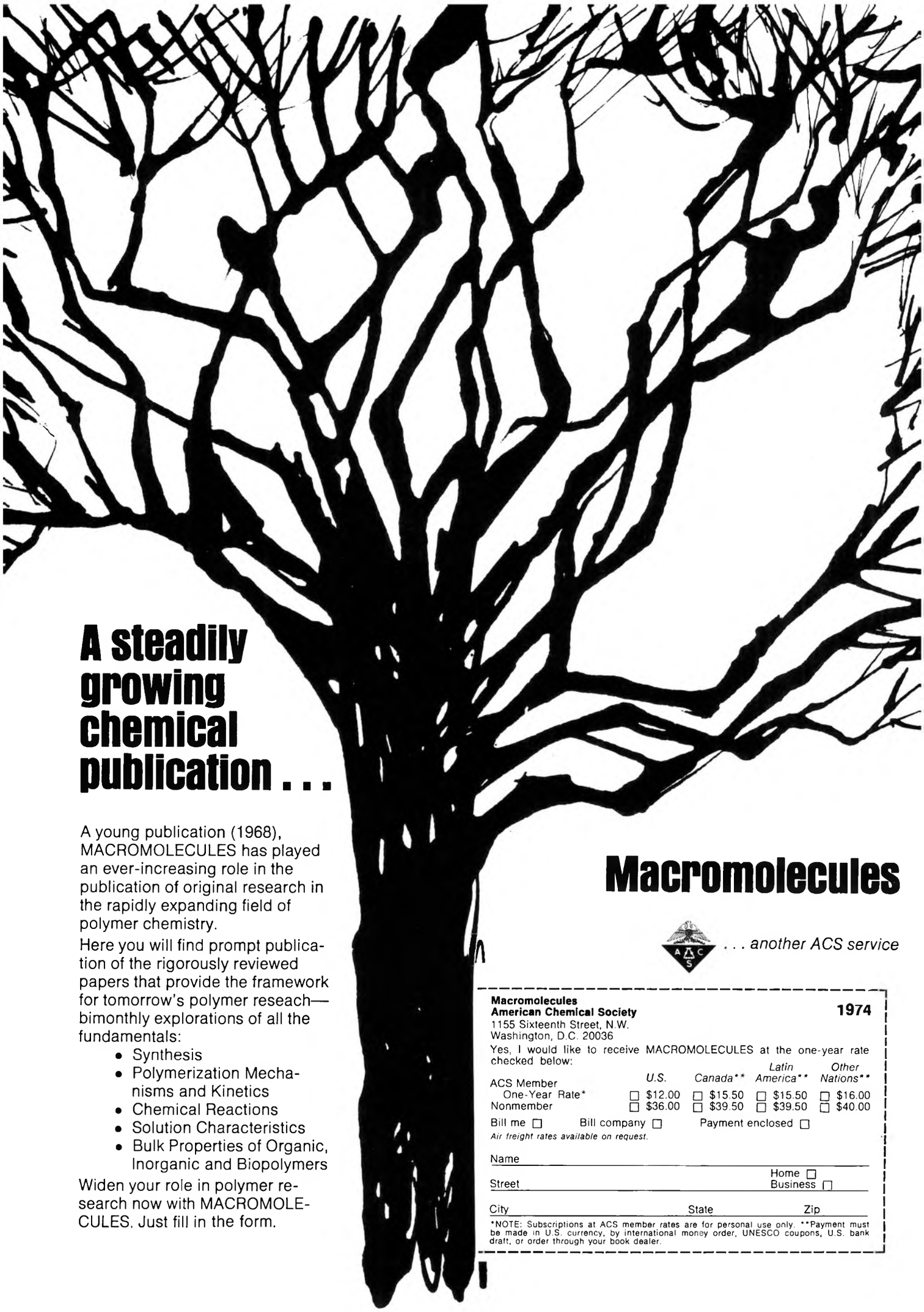

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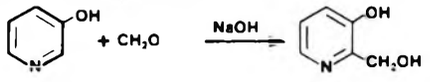
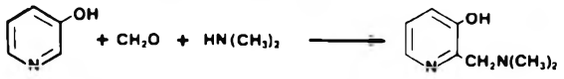
While resembling phenols chemically, 3-hydroxypyridine is a base which ranks among other 3-substituted pyridines as follows:[1] NO_2 > Cl > Br > CO_2Et > OAc > CHO > C≡CH > Ph > OCH_3 > H > **OH** > CH_3. 3-Hydroxypyridine undergoes the reactions of a phenol, *e.g.*

1) alkylation to 3-alkoxypyridines
2) acylation to 3-acyloxypyridines
3) condensation with formaldehyde[2]

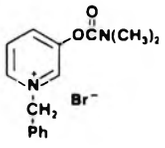


4) aminomethylation (Mannich reaction)[3,4]

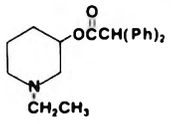


With two equivalents of formaldehyde and alkylamine, the 2,6-bis-derivative is formed.

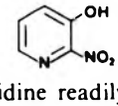
In the pharmaceutical field, 3-hydroxypyridine has yielded many useful drugs.[5] These compounds are formed either from 3-hydroxypyridine itself, as in the case of Stigmonene® Bromide,[6]



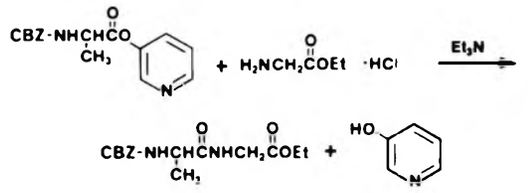
a potent anti-cholinesterase, or from reduction products of 3-hydroxypyridine, *e.g.*, Dactil,® an anti-spasmodic.[7]



Many derivatives of 3-hydroxypyridine have also been reported to be active herbicides, *e.g.*, 2-nitro-3-hydroxypyridine and its acetate.[8] In fact, one of our chemists was recently told by a researcher in the field, that just about every derivative of 3-hydroxypyridine appears to have some herbicidal activity.



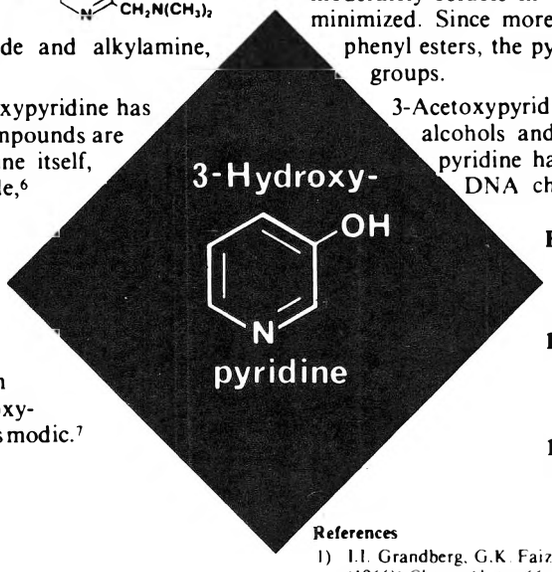
3-Hydroxypyridine readily condenses with CBZ-amino acids using DCC to give pyridyl esters which can be aminolyzed with amino acid esters to form peptides:[9]



The use of 3-hydroxypyridyl esters rather than *p*-nitrophenyl esters allows for easy product purification since the excess pyridyl ester as well as the resulting 3-hydroxypyridine can be removed with dilute acid.

Esters of 3-hydroxypyridine have been used in the study of esterases.[10] Unlike phenyl esters, the pyridyl esters are moderately soluble in water and the need for a cosolvent is minimized. Since more isomers are possible in pyridyl than phenyl esters, the pyridyl esters are more sensitive reporter groups.

3-Acetoxypyridine has been used to acylate phenols, alcohols and amines.[11] Derivatives of 3-hydroxypyridine have conferred some protection against DNA changes caused by irradiation.[12]



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