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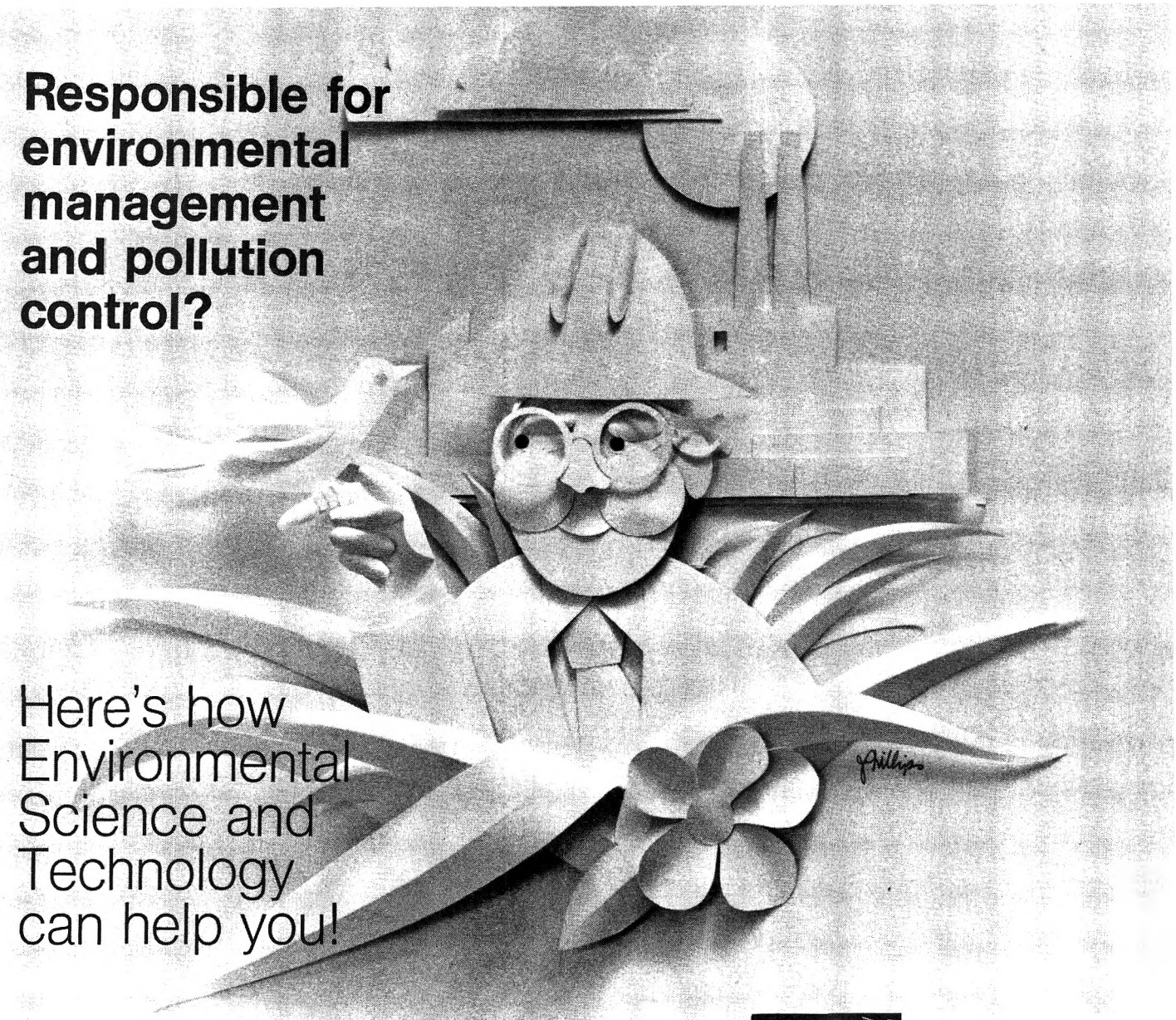

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Precursors to Apomorphine and Morphinan Analogs. Studies on Catalytic Reduction of Quinoline and Isoquinoline*

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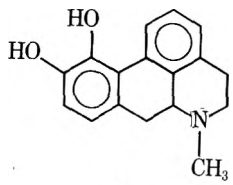
Hydrogenation of isoquinoline and quinoline over PtO_2 at atmospheric pressure in methanolic hydrochloric acid led predominantly to reduction of the benzene ring, whereas reaction of 5,6,7,8-tetrahydroisoquinoline with sodium–ethanol gave chiefly 1,2,3,4,5,6,7,8-octahydroisoquinoline. The experimental conditions established for the above reactions may be used in the synthesis of precursors of apomorphine and morphinan analogs from the readily synthesized derivatives of 1-benzylisoquinoline.

Apomorphine (**1**) has potentiated the therapeutic effects of levodopa (L-dopa, 3,4-dihydroxyphenylalanine) while diminishing some of its side effects in the treatment of Parkinsonism.[1] To separate synergistic from antagonistic effects we have been synthesizing analogs of **1**.[2] We report here findings obtained in exploring synthetic routes to new analogs.



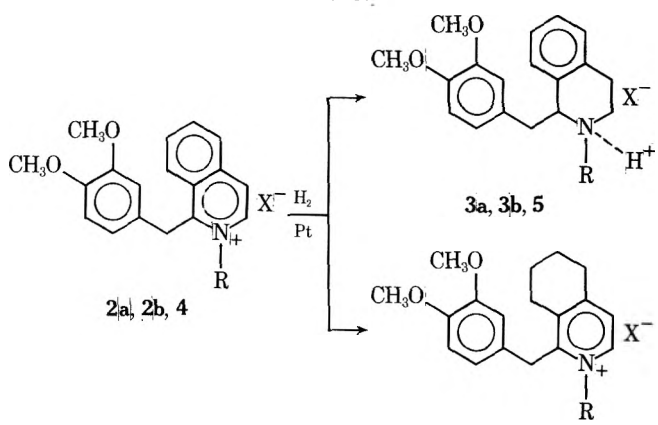
1

In the hydrogenation of 1-(3′,4′-dimethoxybenzyl)-2-methyl- (**2a**) and 1-(3′,4′-dimethoxybenzyl)-2-*n*-propylisoquinolinium iodide (**2b**) over PtO_2 at atmospheric pressure and room temperature, the pyridine ring was invariably reduced to piperidine to give **3a** and **3b** in yields of >90% (Scheme I). In contrast, under the same conditions, the hydrochloride of **4** yielded two products, 43–46% of 1-(3′,4′-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**5**) and 54–57% of 1-(3′,4′-dimethoxybenzyl)-5,6,7,8-tetrahydroisoquinoline (**6**) as the hydrochloride salts.

Until recently,[3] reports of hydrogenation of isoquinoline (**7**) and quinoline (**10**) derivatives always indicated a preferential, if not exclusive, reduction of the pyridine ring[4] depending on the experimental conditions used and the degree of ring substitution.[5] Therefore, 5,6,7,8-tetrahydroisoquinoline (**9**) and 5,6,7,8-tetrahydroquinoline (**12**) compounds have always been synthesized by multistep or indirect methods.[4a,6] It was also shown that **12** can be reduced with sodium–ethanol to the corresponding *trans*-decahydroquinoline.[3]

These observations suggested to us that the scope of synthesis of apomorphine analogs might be expanded to include derivatives of 1-benzyl-*trans*-decahydroisoquinolines obtained from their precursors, 1-benzyl-5,6,7,8-tetrahydroisoquinolines (**13**). These in turn may be reduced to 1-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinolines, potential precursors in the synthesis of morphinans[7a,b] and apomorphine analogs.[7b]

Scheme I



2a, **2b**, **4**

6

2a, R = CH_3; X = I
2b, R = $CH_2CH_2CH_3$; X = I
4, **5**, **6**, R = H; X = Cl
3a, R = CH_3; X = Cl
3b, R = $CH_2CH_2CH_3$; X = Cl

To determine optimum mild hydrogenation conditions that may lead to the synthesis of derivatives of **13** in high yields, we chose to study the reduction of **7** and **10** in methanol, an effective solvent for precursors such as **4** with varying concentrations of HCl at room temperature and atmospheric pressure.

Results and Discussion

The structure of the two compounds, **5** and **6**, proposed is consistent with the elemental analysis, ^1H NMR spectra,

* This work was supported by the National Institutes of Health (Grant NS 11131) and the U. S. Atomic Energy Commission.

Table I
Catalytic (PtO_2) Hydrogenation of Isoquinoline and Quinoline in Methanol–HCl

% products[a]	MeOH	MeOH–HCl 1.0 *N*	MeOH–HCl 4.0 *N*
Substrate: Isoquinoline·HCl			
8	87	30	13
9	13	70	87
Reaction time, min	60	140	160
Substrate: Quinoline·HCl			
11	54	43	39
12	34	37	52
Decahydro- and octahydroquinoline	7	11	Trace
Reaction time, min	345	445	450

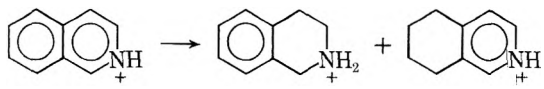
[a] Hydrogenation was carried out at room temperature and atmospheric pressure.

and TLC. In each case, TLC showed in more than one solvent system only one spot, which upon treatment with ninhydrin gave a yellow color for **5** (secondary amine)[8] and a negative reaction for **6**. The percent composition of **5** and **6** was determined in their crude yield by integration of their ^1H NMR spectra after proton bands were identified and assigned following separation and purification of **5** and **6** by successive crystallizations from absolute ethanol.

The two one-proton doublets at δ 7.60, 7.70 and 8.43, 8.53 (AB pattern, J = 5 Hz)[9a,b] were assigned respectively to H-4 and H-3 of **6**. A similar pattern was observed in the ^1H NMR spectrum of **9** (see Experimental Section). In both spectra, the doublet at the lower field was assigned to H-1.[9a] A multiplet at δ 6.90–7.25 in the spectrum of **5** represented the seven aromatic protons in this compound while the multiplet at δ 6.97–7.13 of **6** was due only to the three protons of the catechol.

To determine the percent composition of **5** and **6**, the two doublets assigned to H-3 and H-4 of **6** were integrated and the relative area for one proton was determined. From this, the relative area for three protons for **6** was derived and subtracted from the integrated area of the overlapping multiplets, δ 6.90–7.25. The difference obtained corresponded to the seven aromatic protons of **5**, from which the relative area for one proton was derived. Thus the ratio of the estimated areas associated with each proton of **5** and **6** permitted an approximate determination of the percent composition of each compound.

The two products of the hydrogenation of the hydrochloride of **7**, 1,2,3,4-tetrahydroisoquinoline (**8**) and **9** (Table I),



7 **8** **9**

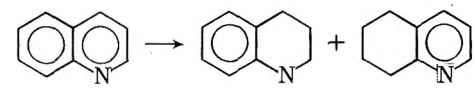
were identified by their ^1H NMR spectra, TLC, and melting points of their picrate and hydrochloride salts. The narrow band at δ 7.28 in the ^1H NMR spectrum of **8** was assigned to its aromatic protons while the AB quartet in the spectrum of **9** was assigned to H-3 and H-4. The band due to H-1 appeared coincidentally at δ 8.72. The clear separation of the aromatic band of **8** from that of **9** allowed a facile estimation of the percent composition of the two compounds by integration of their spectra.

In all the hydrogenations of the hydrochlorides of **10**, two major compounds were isolated: 1,2,3,4-tetrahydroquinoline (**11**) and **12**. Both these compounds were identified by

Table II
Reduction of Isoquinoline in Sodium–Ethanol

Compd	% composition	Retention time, min	Ninhydrin	Uv
14	22.4	14.2	Yellow	Negative
15	10.5	16.4	Purple	Negative
16	1.9	20.0	Negative	Positive
17	65.2	21.4	Yellow	Negative

the melting points of their picrate salts and their ^1H NMR spectra, and **11** also by the melting point of its hydrochloride salt. The ^1H NMR spectrum of **11** was shown to be identical with that of commercially available **11**. The two one-proton doublets of **10**, δ 8.78, 8.82 and 8.85, 8.88, were assigned to H-2[9b] and the multiplet at δ 7.14–8.01 to the remaining aromatic protons. The two two-proton multiplets, δ 6.88–7.03 and 6.28–6.57, were assigned to the aromatic protons of **11**.[10] In the spectrum of **12** the aromatic proton bands showed an ABX pattern almost identical with that of 2,3-lutidine[11] with analogous band assignments (see Experimental Section). The two doublets, δ 8.27, 8.30 and 8.35, 8.37, were assigned to H-2. Thus the nonoverlapping bands of H-2 of **10** and **12** and the multiplet at δ 6.28–6.66 of **11** were used to determine the composition of these three compounds as free bases in the hydrogenation mixtures. In addition to compounds **11** and **12**, TLC showed the presence in small amounts of two compounds which both failed to absorb in the uv but reacted positively with ninhydrin. The ^1H NMR spectra of the ether-extracted free bases from the hydrogenation mixtures showed a broad multiplet that began at δ 1.08 and overlapped with those of **11** and **12**

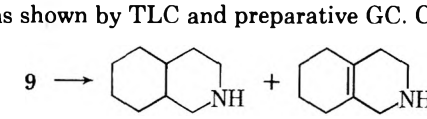


10 **11** **12**

above the aromatic region. Integration of the combined multiplets followed by subtraction of the areas ascribed to protons of **11** and **12**, derived from the integration of the bands discussed above, yielded the approximate percent composition of the two unknown compounds as decahydroquinoline.

After prolonged hydrogenation of **12** in 4 *N* HCl–methanol solution until only a trace of **12** remained, TLC revealed the same aforementioned two unknown compounds. One of the compounds was shown to be identical with a commercially available *trans*-decahydroquinoline. The ir spectrum of the above mixture showed a weak band at 1660 cm^{-1}, indicating the presence of a –C=C– stretching. Because the ^1H NMR spectrum of this mixture showed no olefinic proton band, such a double bond could exist only at the 9,10 position of the octahydroquinoline, since a positive reaction with ninhydrin ruled out the alternative 1,9 position.

Reduction of **9** with sodium–ethanol yielded four compounds as shown by TLC and preparative GC. Compounds



14 **17**

14 and **17** (Table II) were obtained in sufficient amount for extensive characterization. The spectra, physical properties, and the picrate and hydrochloride salts of **14** identified it as *trans*-decahydroisoquinoline (Table II).

The ^1H NMR spectrum of the major compound **17**, 65% of the total reaction mixture, showed no aromatic or olefinic protons and differed from that for *trans*- or *cis*-decahy-

droisoquinoline.[12] The ratio of the respective integrated areas under the broad multiplet, δ 1.33–2.00 and 2.60–3.47, was found to be 2.8. It showed a strong and sharp ir band at 1590 cm^{-1}. These findings along with the elemental analysis of its hydrochloride salt and comparison with known derivatives led us to postulate its structure as 1,2,3,4,5,6,7,8-octahydroisoquinoline. Because of inadequate amounts, **16** was characterized only by TLC. **15** was found by TLC to be unreacted **9**.

Conclusions

The results (Table I) are in general agreement with those of others[3] and show in addition that under the same experimental conditions (1) the ratios of **8** to **9** and of **11** to **12**, as well as the reaction times, increase with increasing HCl concentration; (2) satisfactory yields of **8** and **12** can be obtained at atmospheric pressure and in a relatively short time so that side reactions are minimized when sensitive functional groups are present.

Whereas others have shown that the predominant, if not exclusive, product of the sodium–ethanol reduction of **10** is *trans*-decahydroisoquinoline,[3] we have shown that under similar reaction conditions **9** yields predominantly **17** with **14** as a minor product. This is in accord with the finding that 1-(*p*-hydroxybenzyl)-5,6,7,8-tetrahydroisoquinoline and its methyl ether yield the corresponding octahydro compound when treated with sodium–isoamyl alcohol.[13] Further reduction of **17** to the *trans*-decahydroisoquinoline is possible under more strenuous hydrogenation conditions.[13]

In conclusion, the above results indicate that ring-substituted compounds of the type **16**, precursors to morphinan and apomorphine analogs,[7b,13] can be prepared directly from readily synthesized 1-benzylisoquinoline derivatives.

Experimental Section

Uncorrected melting points were determined on a capillary melting point apparatus. ^1H NMR spectra were obtained on a Varian T-60 NMR spectrometer at room temperature in $CDCl_3$ or DMSO-d_6 with Me_4Si used as an internal standard. Eastman Chromagram sheets (6060 silica gel with fluorescent indicator) were used for TLC. The following TLC solvent systems were used: 1-butanol–acetic acid–water, 4:1:1 (A), 9:1:2.5 (B); chloroform–MeOH–acetic acid, 17:2:1 (C); benzene–ethyl acetate, 4:1 (D); cyclohexane–ethyl acetate, 1:4 (E); benzene–MeOH, 4:1 (F). A preparative gas chromatograph, Perkin-Elmer F-21, with a flame ionization detector and a 15 ft × 8.0 mm column (20% Carbowax 20M + 4% KOH on Chromosorb W) was used for determining the percent composition and separating and identifying the products obtained from the sodium–EtOH reduction of **9**. Infrared spectra were obtained on a Perkin-Elmer 337 grating spectrometer. Elemental analyses were determined by Galbraith Laboratories, Inc., and Schwarzkopf Microanalytical Laboratories.

Materials. 3,4-Dimethoxybenzyl alcohol was obtained from International Chemical and Nuclear Corp.; K & K Laboratories; 3,4-dimethoxyphenylacetic acid, isoquinoline, 1,2,3,4-tetrahydroisoquinoline, and 1,2,3,4-tetrahydroquinoline were obtained from Aldrich Chemical Co.; *trans*-decahydroquinoline, 1-iodopropane, and MeI were obtained from Eastman Organic; picric acid was obtained from J. T. Baker Chemical Co.; PtO_2 (83.4%) was obtained from Engelhard Industries.

3,4-Dimethoxybenzyl Chloride (18). The method of synthesizing **18** was adapted from an early method.[14] HCl was bubbled through a solution of 3,4-dimethoxybenzyl alcohol (25.0 g, 0.149 mol) in absolute ether (80 ml) under anhydrous conditions and at ice–water temperature. After 35 min, the color of the ether solution changed to deep red. The ether solution was washed successively with water, saturated $NaHCO_3$ solution, and water to a pH of about 6.0. The ether layer was dried over anhydrous $MgSO_4$ and then filtered, and the ether was removed under reduced pressure. The residue, a colorless, viscous oil, slowly crystallized on standing, yielding 25.0 g (90%), mp 48–51° (lit. mp 50–50.5°,[15] 48°[14]).

1-Cyano-2-benzoyl-1,2-dihydroisoquinoline (Reissert's Compound). This compound was prepared as described in the literature.[16]

1-(3′,4′-Dimethoxybenzyl)isoquinoline Hydrochloride (4). The method of preparing **4** was essentially as reported elsewhere,[17] with the following modifications. After hydrolysis in CH_3OH–KOH and isolation of the crude free base, the base was extracted with ether (2 × 70 ml) and the extract was dried over anhydrous Na_2SO_4, filtered, and reduced in volume to 40 ml; then HCl-saturated ether was added. The precipitated HCl salt was filtered, triturated with ether repeatedly, and dried, 11.5 g (94%). This was recrystallized from EtOH–ethyl acetate, yielding 9.4 g (75%): mp 188–189.5°; ^1H NMR (DMSO-d_6) δ 3.63 (s, 3, $-OCH_3$), 3.73 (s, 3, $-OCH_3$), 4.92 (broad s, 2, $-CH_2-$), 6.69–8.30 [m, 3, $(MeO)_2C_6H_3-$], 7.64–8.75 (m, 6, isoquinoline H).

Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.74; N, 4.44; Cl, 11.23. Found: C, 68.52; H, 5.74; N, 4.43; Cl, 11.33.

1-(3′,4′-Dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (5). **4** (3.86 g, 12.3 mmol) was hydrogenated at atmospheric pressure in MeOH (100 ml) over PtO_2 (0.60 g, 2.2 mmol). The reaction was completed 80 min later after the theoretical amount of H_2 (2 equiv) was absorbed. TLC (A, C) revealed two spots on visualization with uv, of which one yielded a yellow color when exposed to ninhydrin and the other reacted negatively. After removal of the catalyst, the solvent was evaporated under reduced pressure, yielding 3.7 g (94%) of a white, amorphous solid. Recrystallization from boiling EtOH (22 ml) yielded 3.1 g of colorless crystals, mp 194–197°. TLC again revealed the two spots upon visualization with uv and ninhydrin. Recrystallization was repeated in EtOH (30 ml) and allowed to proceed slowly overnight after seeding with crystals of **5** obtained previously. Colorless, heavy crystals were filtered off and washed with cold EtOH followed by ether, 0.97 g, mp 227–228°. TLC showed a single spot on visualization with uv and I_2 and yielded a yellow color when exposed to ninhydrin; ^1H NMR (DMSO-d_6) δ 2.97–3.50 [broad m, 6, $(MeO)_2PhCH_2-$, H-3, H-4], 3.77 [s, 6, $(-OCH_3)_2$], 4.60 (broad t, J = 5 Hz, H-1), 6.90–7.07 [broad, overlap, 3, $(MeO)_2C_6H_3-$], 7.25 (broad s, 4, H-4, H-5, H-6, H-7).

Anal. Calcd for $C_{18}H_{22}ClNO_2$: C, 67.59; H, 6.93; N, 4.38; Cl, 11.09. Found: C, 67.60; H, 6.88; N, 4.41; Cl, 11.06.

1-(3′,4′-Dimethoxybenzyl)-5,6,7,8-tetrahydroisoquinoline Hydrochloride (6). The mother liquor obtained after filtering off **5** was concentrated under reduced pressure to 20 ml and allowed to stand at room temperature. Colorless crystals were filtered off and washed with cold EtOH followed by ether, 1.30 g, mp 209–212°. Recrystallization from EtOH yielded 0.98 g: mp 211–212°; TLC (A, C) one spot (uv, I_2), negative to ninhydrin; ^1H NMR (DMSO-d_6) δ 1.53–2.0 (broad m, 4, H-6, H-7), 2.45–3.13 (broad m, 4, H-5, H-8), 3.72, 3.75 (2 s, 6, $-OCH_3$), 4.42 [s, 2, $(MeO)_2PhCH_2-$], 6.97–7.13 [broad m, 3, $(MeO)_2C_6H_3-$], 7.60, 7.70 (d, J = 5 Hz, 1, H-4), 8.43, 8.53 (d, J = 5 Hz, 1, H-3).

Anal. Calcd for $C_{18}H_{22}NO_2Cl$: C, 67.59; H, 6.93; N, 4.38; Cl, 11.09. Found: C, 67.60; H, 6.79; N, 4.28; Cl, 11.14.

1-(3′,4′-Dimethoxybenzyl)-2-methylisoquinolinium Iodide (2a). The free base of **2a** (6.88 g, 24.2 mmol) was dissolved in $MeNO_2$ (50 ml) and MeI (3.44 g, 242 mmol) was added. After 5 hr at room temperature copious long, yellow needles appeared. After 18 hr, only a trace of the starting material was evident by TLC (F). The addition of ethyl acetate (100 ml) completed the precipitation. The product was filtered off and recrystallized from absolute EtOH: 9.9 g (97%); mp 202–203° (lit.[17] mp 139–140°); ^1H NMR (DMSO-d_6) δ 3.72, 3.78 (s, 6, $-OCH_3$), 4.50 (s, 3, NCH_3), 5.15 [s, 2, $(MeO)_2C_6H_3CH_2-$], 6.31–7.17 [m, 3, $(MeO)_2C_6H_3-$], 7.96–9.0 (m, 6, isoquinoline H's).

Anal. Calcd for $C_{19}H_{20}INO_2$: C, 54.16; H, 4.79; I, 30.12; N, 3.33. Found: C, 54.19; H, 4.81; I, 30.05; N, 3.31.

1-(3′,4′-Dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3a). **2a** (4.6 g, 98.6 mmol) was hydrogenated at atmospheric pressure in MeOH (120 ml) over PtO_2 (0.60 g, 22 mmol). After 0.5 hr, the theoretical amount of H_2 (2 equiv) was absorbed with a concomitant clumping of the catalyst signaling the end of the reaction. After removal of the catalyst by filtration and of the solvent under reduced pressure, the solid residue was dissolved in water (90 ml) and treated with excess $NaHCO_3$. The free base was extracted with ethyl acetate (2 × 50 ml), and the combined extracts were washed with water (30 ml), dried over anhydrous Na_2SO_4, and then filtered. The solvent was removed under reduced pressure, and the residue, a viscous oil, was dissolved in 40 ml of absolute ether to which another 40 ml of HCl-saturated ether was added. The HCl salt precipitate was isolated and washed with ether, 2.94 g (91%). The crude product was

recrystallized from absolute EtOH (45 ml), yielding colorless, stick-shaped crystals: 2.65 g (80%); mp 233–235° dec (lit.[17] mp 227–230°); ^{1}H NMR ($CDCl_3$) δ 2.92 (broad s, 3, NCH_3), 2.77–4.17 [broad m, H-3, H-4, and $(MeO)_2C_6H_3CH_2$–], 4.23–4.60 (m, 1, H-1), 3.77 (s, 3, $-OCH_3$), 3.87 (s, 3, $-OCH_3$), 6.4–6.8 (m, 4, H-5, H-6, H-7, H-8), 6.87–7.33 [m, 3, $(MeO)_2C_6H_3$–].

Anal. Calcd for $C_{19}H_{24}ClNO_2$: C, 68.35; H, 7.24; Cl, 10.62; N, 4.20. Found: C, 67.94; H, 7.25; Cl, 11.01; N, 4.25.

1-(3′,4′-Dimethoxybenzyl)-2-*n*-propylisoquinolinium Iodide (2b). The free base of **4** (0.93 g, 3.33 mmol) was treated at 90° with iodopropane (11.6 g, 70 mmol) in $MeNO_2$ (15 ml). Reaction was completed after 4–5 hr as shown by TLC (F). The product was precipitated by the addition of ether and allowed to stand overnight at 4°. The product was filtered and washed with ether, 1.45 g (91%), mp 205–206°. Recrystallization from absolute EtOH (35 ml) yielded 1.33 g (89%) of yellow, needle-shaped crystals: mp 211–212° dec; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3, J = 7 Hz, CCH_3), 1.92 (m, 2, J = 7 Hz, $-CH_2Me$), 3.82 (s, 3, $-OCH_3$), 3.88 (s, 3, $-OCH_3$), 4.97 (t, 2, J = 7 Hz, $-CH_2CH_2CH_3$), 5.25 [s, 2, $(MeO)_2PhCH_2$–], 6.7–7.39 [m, 3, $(MeO)_2C_6H_3$–], 7.82–8.72 (m, 4, H-5, H-6, H-7, H-8), 8.47 (d, 1, J = 7 Hz, H-4), 9.23 (d, 1, J = 7 Hz, H-3).

Anal. Calcd for $C_{21}H_{24}INO_2$: C, 56.13; H, 5.38; I, 28.25; N, 3.12. Found: C, 56.21; H, 5.31; I, 28.38; N, 3.07.

1-(3′,4′-Dimethoxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3b). **2b** (1.23 g, 2.74 mmol) was hydrogenated at atmospheric pressure in MeOH (35 ml) over PtO_2 (0.20 g, 0.73 mmol). In less than 0.5 hr, the theoretical amount of H_2 (2 equiv) was absorbed and clumping of the catalyst occurred. TLC (A) showed the presence of only one compound. The catalyst was removed by filtration and the solvent under reduced pressure. The yellow, amorphous solid residue was dissolved in MeOH (15 ml) and basified with 5% aqueous NaOH (45 ml). The free base was extracted with ether (3 × 40 ml), washed with water to a neutral pH, and then dried over anhydrous Na_2SO_4. The solution was filtered, and the light amber-colored oil remaining upon removal of the ether was converted to the HCl salt as described above, 0.77 g (77%), mp 201–203.5°. Recrystallization from a solution of MeOH (12 ml) and ether (20 ml) yielded a crystalline product: 0.60 g; mp 203–204°; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, CCH_3), 1.93–2.27 (m, J = 6 Hz, 2, $-CH_2Me$), 2.75–4.05 (m, 9), 3.75 (s, 3, $-OCH_3$), 3.87 (s, 3, $-OCH_3$), 4.30 [t, J = 7 Hz, 2, $(CH_3O)_2PhCH_2$–], 6.37–7.38 (m, 7, aromatic H's).

Anal. Calcd for $C_{21}H_{28}ClNO_2$: C, 69.69; H, 7.80; Cl, 9.80; N, 3.87. Found: C, 69.67; H, 7.78; Cl, 9.82; N, 3.89.

Hydrogenation of Isoquinoline and Quinoline Hydrochlorides. General Procedure. The hydrogenation was carried out in absolute MeOH solution or MeOH solution of gaseous HCl with 0.25 M of substrate and a 10:1 ratio of substrate to PtO_2 at atmospheric pressure and room temperature with maximum agitation (magnetic stirrer) in a baffled hydrogenation flask. Reaction was discontinued when approximately 2 equiv of H_2 was absorbed. After removal of the catalyst by filtration, the solvent was removed under reduced pressure, and the residue salt was dried under high vacuum. The approximate percent composition of the crude products (as HCl salts of reduced **7** and free bases of **10**) was determined by integration of their ^{1}H NMR spectra. Free base components of these mixtures obtained by extraction with ether from basic aqueous solutions were separated by successive fractionation under reduced pressure followed by a final purification step in which the free bases were converted to picrate salts, recrystallized from absolute EtOH, and characterized by comparing their melting points with those in the literature (Table I). The picrates were then decomposed with aqueous 4 N HCl, and, after removal of the picric acid by ether extraction, the purified free bases were obtained by ether extraction from their basic solutions and converted to their hydrochloride salts. ^{1}H NMR spectra of these and of commercially available **8**, *trans*-, and a mixture of *cis*- and *trans*-decahydroquinolines were used for the assignment of bands in the spectra of their crude mixture. TLC (A, B, C, D, E) served to identify them further and to certify their purity. Melting points of picrates, °C (lit.): **8**, 199–201 (197–198,[18a] 202[18b]); **9**, 144–145 (142–144[19]); **11**, 142–143 (143[20]); **12**, 158–160 (157,[21] 158–159[6c]). Melting points of HCl salts, °C (lit.): 8, 198–199 (195–197[18a]); **9**, 196–198 (196–197[18a]); **11**, 179–181 (179–180[20]).

^{1}H NMR Spectra (DMSO-d_6), δ: 8, 2.82–3.55 (symmetrical m, 4, H-3, H-4), 4.20 (s, 2, H-1), 7.28 (s, 4, aromatic H's); **9**, 1.66–1.90 (m, 4, H-6, H-7), 2.92–3.00 (two overlap broad s, 4, H-5, H-8), 7.84 (d, 1, J = 6 Hz, H-4), 8.68 (d, 1, J = 6 Hz, H-3), 8.72 (s, 1, H-1).

^{1}H NMR Spectra ($CDCl_3$), δ: 11, 1.89 (m, 2, H-3), 2.73 (t, 3, J = 6 Hz, H-2), 3.25 (t, 2, J = 6 Hz, H-4), 3.77 (broad s, 1, NH), 6.28–7.03 (m, **4**, H-5, H-6, H-7, H-8); **12**, 1.70–1.93 (m, 4, H-6, H-7), 2.84 (m, 4, H-5, H-8), 6.85–7.07 (m, 1, H-3), 7.23–7.38 (m, 1, H-4), 8.32 (m, 1, H-2).

5,6,7,8-Tetrahydroisoquinoline (9). **7** (9.04 g, 0.07 mol) was hydrogenated over PtO_2 (1.99 g, 8.76 mmol) in 4 N HCl–MeOH (200 ml) at atmospheric pressure and room temperature. Reaction was discontinued after 2 equiv of H_2 was absorbed; the catalyst was filtered off and the solvent was removed under reduced pressure. The solid residue was dissolved in water (70 ml), basified with $NaHCO_3$, and extracted with ether (4 × 40 ml). The combined ether extracts were washed with water, dried over anhydrous $MgSO_4$, and then filtered. The solvent was removed under reduced pressure, and the oil residue was dried under vacuum to a constant weight, 7.2 g: TLC (A), one major spot (uv positive, ninhydrin negative), one trace spot (uv negative, ninhydrin yellow); ir 1600 cm^{-1} (–C=N–); ^{1}H NMR ($CDCl_3$) δ 1.45–2.05 (m, 4, H-6, H-7), 2.31–3.05 (m, 4, H-5, H-8), 6.93 (d, 1, J = 5 Hz, H-4), 8.24 (d, 1, J = 5 Hz, H-3), 8.20 (s, 1, H-1). **9** (7.0 g) was dissolved in absolute EtOH (15 ml) and picric acid–EtOH solution (300 ml, 4.4 g/100 ml) was added. The picrate salt, small yellow crystals, was filtered off and dried, 17.5 g (92%), mp 144–145°. The picrate salt was decomposed with aqueous 6 N HCl (100 ml), and the picric acid was removed by ether extraction. The aqueous layer was basified with excess $NaHCO_3$, and the free base **9** was extracted with ether, 6.3 g. TLC (A): one spot (uv positive, ninhydrin negative).

Reduction of 9 with Na–EtOH. **9** (3.0 g, 22.5 mmol) was dissolved in absolute EtOH (40 ml) and treated under anhydrous conditions while stirring with small pieces of freshly cut Na metal introduced over a period of about 1 hr. For the last 0.5 hr the reaction solution was heated to maintain a satisfactory rate of reaction. At the end of 1 hr, more EtOH (25 ml) was added, and the solution was refluxed for 0.5 hr to effect complete reaction of the metal. The solvent was removed under reduced pressure, and the white residue was dissolved in 200 ml of water and acidified with 6 N HCl to a pH of ca. 1.0; it was then extracted with ether (2 × 50 ml), which was discarded. The aqueous solution was basified with 50% aqueous NaOH to a pH of ca. 11, and the free amine was extracted with ether (4 × 40 ml). The ether extracts were combined and washed with water, and then the solvent was removed under reduced pressure after drying over $MgSO_4$. The colorless, oily residue was dried to a constant weight, 2.91 g (93%). TLC (A, C, E, F) revealed the presence of at least four compounds, two of which, including the major product, reacted with ninhydrin to yield a yellow color (secondary amine). One spot, a trace, reacted negatively to ninhydrin and, in contrast to the other three products, could be visualized under uv. The fourth spot, more than a trace, yielded a purple color with ninhydrin (primary amine). A preparative GC separation of the crude mixture yielded four peaks, well resolved and fairly symmetrical. The relative composition was estimated by dividing the area under each peak by the sum of the areas of all peaks. The area under each peak was estimated by multiplying the maximum height of the peak by the width at half the height. Two of the compounds, **14** and **17**, were collected in sufficient amount to permit the preparation of picrate and hydrochloride salts for melting points and, in the case of **17**, for ^{1}H NMR, ir, Bayers test, and elemental analysis. All isolated compounds were subjected to TLC analysis (A, C) and exposed to ninhydrin. In each case only one spot was shown.

Compound 14: mp of picrate 176–177° (lit.[12] mp 175–176°); mp of HCl salt 224–226° (lit.[22] mp 222–223°).

Compound 17: mp of picrate 176–178° (lit.[7a] mp 172°); mp of HCl salt 152–153° (lit.[7a] mp 150°); ^{1}H NMR ($CDCl_3$) δ 1.33–2.0 (m, 11, H-2, H-4, H-5, H-6, H-7, H-8), 2.60–3.47 (m, 4, H-1, H-3); ir 1590 cm^{-1} (s).

Anal. Calcd for $C_9H_{16}ClN$: C, 62.23; H, 9.29; Cl, 20.42; N, 8.07. Found: C, 62.28; H, 9.27; Cl, 20.49; N, 8.02.

Registry No.—**2a**, 50370-93-9; **2a** free base, 21965-92-4; **2b**, 54446-54-7; **3a**, 50370-94-0; **3b**, 54384-20-2; **4**, 51866-10-5; **5**, 3972-77-8; **6**, 54384-21-3; **7** HCl, 49563-76-0; **8**, 91-21-4; **9**, 36556-06-6; **10** HCl, 530-64-3; **11**, 635-46-1; **12**, 10500-57-9; **14**, 2744-09-4; **17**, 2721-62-2; **18**, 7306-46-9; 3,4-dimethoxybenzyl alcohol, 93-03-8; iodopropane, 107-08-4.

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Cycloaddition Reactions of Some 5-Substituted Isoquinolinium Salts[1]

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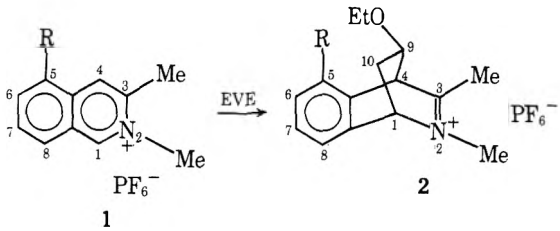
The reactivity of the 2,3-dimethylisoquinolinium nucleus (**1**) toward 1,4 cycloaddition with alkenes is greatly enhanced by the introduction of a nitro group at position 5, making possible new synthetic applications. The reactivity of the 2-methylisoquinolinium ion (**15**) is also enhanced by introduction of a nitro group into position 5, and the product (**18**) with cyclopentadiene is the first simple 1,4 adduct obtained from an isoquinolinium salt with no substituent at position 3.

The discovery that 2,3-disubstituted isoquinolinium salts (**1a**) would undergo cycloaddition reactions with alkyl vinyl ethers[2–4] and cyclopentadiene[4,5] offered the promise of easy access to a host of benzisoquinuclidine derivatives.



a, R = H
b, R = NO_2
c, R = NHCOMe

Unfortunately, the sluggishness of the cycloaddition at room temperature and the easy reversibility at higher temperatures have greatly limited the usefulness of the reaction. For example, 2,3-dimethyl-1,3-butadiene, which stands next below cyclopentadiene in reactivity toward the acridizinium ion,[6] does not react noticeably with **1a** in 3 months at room temperature.

In earlier work[7] it was shown that the introduction of the electron-withdrawing nitro group at position 9 of the acridizinium nucleus resulted in a 21-fold increase in the rate of cycloaddition toward styrene. This led us to examine the reactivity of 5-nitro-2,3-dimethylisoquinolinium ion (**1b**) toward activated alkenes. As measured by its reactivity with ethyl vinyl ether, the nitro derivative (**1b**) reacted approximately 120 times faster than the parent compound (**1a**). The magnitude of this rate enhancement raised the question whether the enhancement was entirely electronic in its origin or whether steric acceleration of cycloaddition[8] must play some part. A group at position 5 would tend to crowd the adjacent peri hydrogen, which is constrained further by the flanking methyl at position 3. Much of the resulting steric strain should be relieved during the cycloaddition, since the peri hydrogen moves out of plane. That some steric contribution is involved is suggested by the observation that the analog (**1c**) having an electron-releasing acetylamino group at position 5 is still twice as reactive as the parent compound (**1a**).

The 5-nitro-2,3-dimethylisoquinolinium ion (**1b**) reacts in good to excellent yield with a variety of the less reactive alkenes, including styrene, vinyl acetate, β-pinene, and norbornene (Table I). For none of the adducts was there any indication in the NMR spectrum of the presence of mixtures of regioisomers (always one set, rather than two, of bridgehead hydrogens). This is in conformity with all reported cycloadditions of unsymmetrical alkenes with quaternary aromatic salts.[9] Assignment of structure of the adducts has been made by analogy to the addition of unsymmetrical addends to the 2,3-dimethylisoquinolinium ion (**1a**) and to the acridizinium ion.[6] Direct assignment of the regiochemistry of the adducts on the basis of NMR evidence, following the method of Fields et al.,[6] was not possible. As usual, the quaternary nitrogen caused a characteristic deshielding of the adjacent bridgehead proton attached to C-1, but the nitro group at position 5 had a similar effect on the other bridgehead hydrogen at position 4, making the usual distinction between the bridgehead hydrogens on the basis of differences in chemical shift impossible.

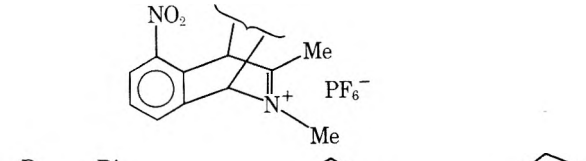
At least four of the addends appeared to afford only a single geometrical isomer. Three of these, the ethyl vinyl ether (**2b**), the cyclopentadiene (**8**), and the norbornene (**12**) adducts, can definitely be assigned as syn (with respect to the phenylene ring). The first two of these (**2b** and **8**) had NMR spectra similar to those of the unnitrated prototype (e.g., **2a**) and in both of these cases, the structure of

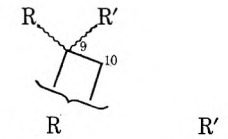
Table I
Reaction of Some Alkenes with 5-Nitro-2,3-dimethylisoquinolinium Hexafluorophosphate (1b) in Acetonitrile at Room Temperature

Addend	Adduct Compd	Adduct Formula[a]	Concn, mmol/l. 1b	Concn, mmol/l. Addend	Time, days	Yield, %	Mp, °C	^{1}H NMR chemical shifts, δ (multiplicity) Solvent	H-1	H-4	CH_3C[c]	CH_3N[c]
Styrene	3	$C_{19}H_{19}F_6N_2O_2P$	0.14	1.24	35	97	222[b]	CD_3CN	5.90 (q)	5.63 (d)	2.70	3.70
p-Methoxystyrene	4	$C_{20}H_{21}F_6N_2O_3P$	0.33	1.23	2	94	261–263.5	CF_3CO_2H	5.92 (q)	5.85 (d)	2.89	3.92
Ethyl vinyl ether	2b	$C_{15}H_{19}F_6N_2O_3P$	0.20	1.20	0.04	95	167[b]	CD_3CN	5.73 (q)	6.13 (d)	2.64	3.67
Vinyl acetate	5	$C_{15}H_{17}F_6N_2O_4P$	0.50	14.50	60	63	253[b]	CD_3CN	5.79 (q)	5.96 (d)	2.62	3.62
2,3-Dimethylbutadiene	6	$C_{17}H_{21}F_6N_2O_2P$	0.50	2.38	25	51	171[b]	CF_3CO_2H	5.81 (q)	5.97 (d)	2.91	3.92
β-Pinene	7	$C_{21}H_{27}F_6N_2O_2P$	0.25	1.23	34	74	195[b]	CF_3CO_2H	5.68 (q)	6.07 (d)	2.67	3.80
Cyclopentadiene	8	$C_{16}H_{17}F_6N_2O_2P$	0.94	4.04	2	82	200[b]	CD_3CN	5.80 (d)	5.67 (d)	2.87	3.98
1,3-Cyclohexadiene	9	$C_{17}H_{19}F_6N_2O_2P$	0.38	1.67	12	81	192[b]	CF_3CO_2H	6.02 (d)	5.63 (d)	2.82	3.88
1-Methoxycyclohexene	10	$C_{18}H_{23}F_6N_2O_3P$	0.28	26.80	24	98	191[b]	CD_3CN	5.60 (d)	6.05 (s)	2.65	3.77
Indene	11	$C_{20}H_{19}F_6N_2O_2P$	0.25	2.33	0.29[d]	56	223–224	CF_3CO_2H	6.42 (d)	5.72 (d)	2.94	3.94
Norbornene	12	$C_{18}H_{21}F_6N_2O_2P$	0.17	1.24	33	68	224–225	$(CD_3)_2CO$	6.03 (d)	5.83 (d)	2.83	3.90

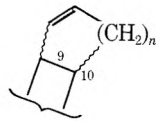
[a] Satisfactory analyses were submitted for all compounds listed in this table. Ed. [b] Decomposes. [c] All resonances in this column appeared as singlets. [d] This cycloaddition was carried out at 65°.

the prototype had been proved by single-crystal X-ray crystallography.[3,5]

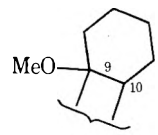




	R	R′
3	C_6H_5	H
4	*p*-$MeOC_6H_4$	H
5	MeCOO	H
6	CH_2=CMe	CH_3
7	$-CH_2CH_2CHC(Me)_2CH-$	
	CH_2	



8, $n=1$
9, $n=2$



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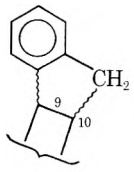

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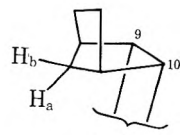
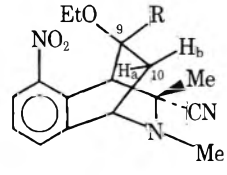


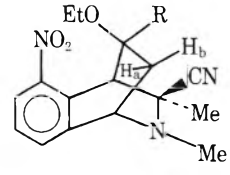
12

The structure of the norbornene adduct (12) follows from the very strong shielding of one of the methylene protons (δ −0.77) arising from its exposure to the diamagnetic ring current of the phenylene group. Despite the possibility that some of the stereoisomeric anti isomer might have been formed in the cycloaddition but lost in the recrystallization, the isolation of a 68% yield of the syn form indicates that the reaction is more stereoselective than the addition of norbornene to the acridizinium ion, which shows only a 60:40 preference for the syn configuration.[10]

The remaining case of stereoselectivity, that of the 1-methoxycyclohexene adduct (10), has been assigned the anti configuration (with the cyclohexane ring turned away from the phenylene ring on the basis of the coulombic repulsion rule).[5] Unfortunately, the NMR signal for the methine proton at C-10 is lost in the envelope arising from the methylene protons; hence there is no evidence whether it is directed toward or away from the quaternary nitrogen atom.

Earlier[4] it was shown that the initial attack of the cyanide ion on the unnitrated ethyl vinyl ether adduct (**2a**) is from the endo side, but when equilibrium is ultimately reached, the concentration of the endo and exo cyano compounds is essentially equal. Similar behavior has been observed with the nitro adduct (**2b**), affording at first mostly **13a** which isomerized to **13b**. When the cycloaddition of **1b**





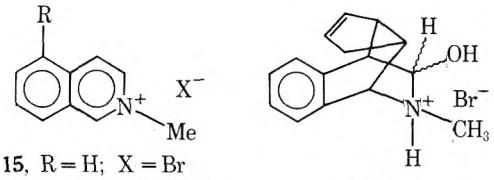
13a, R = H
14, R = Me

13b, R = H

was carried out with 2-ethoxypropene, the adduct could not be crystallized but was converted directly to the nitrile by action of cyanide. Interestingly, a single geometrical isomer was obtained, but in a yield of only 20%. On the basis of the expected polarization, the charge repulsion rule,[5] and the NMR spectrum, as well as spin-decoupling experiments, the most likely structure appears to be **14**.

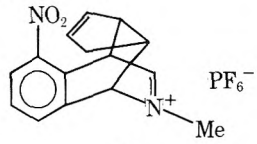
Although some of our initial experiments were directed toward the cycloaddition of alkenes with isoquinolinium salts having no substituent at position 3, these were frustrated almost certainly by the great reactivity of the cycloadduct first obtained, resulting in complicating nucleophilic attacks by the solvent or excess alkene. An illustration is the reaction of 2-methylisoquinolinium bromide with cyclopentadiene, which gave, in 80% yield, a poorly defined product, probably **17**, corresponding to the addition of 1 mol of cyclopentadiene plus 1 mol of water. When 5-nitro-2-methylisoquinolinium hexafluorophosphate (**16**)

was allowed to react with cyclopentadiene at room temperature, the simple adduct **18** was obtained in 69% yield. The



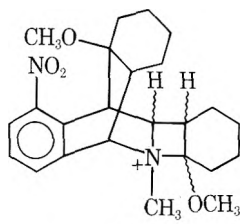
15, R = H; X = Br
16, R = NO_2; X = PF_6

17



18

iminium hydrogen of the adduct appeared as a multiplet centered at δ 8.94. This is the first example of the simple cycloaddition of an isoquinolinium salt having no substituent at position 3. Simple cycloaddition is not always characteristic of the 5-nitro-2-methylisoquinolinium salt (**16**), for addition to an excess of 1-methoxycyclohexene afforded an adduct which, from elemental analysis and NMR, clearly had 2 mol of the alkene incorporated. From mechanistic considerations and NMR evidence, it appears that the structure can best be represented as **19**.



19

Experimental Section

The elemental analyses were carried out by M-H-W Laboratories, Garden City, Mich. Melting points were determined in capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determinded on a Perkin-Elmer Model 137 or Model 237 using KBr disks. Proton magnetic resonance spectra were obtained at 60 MHz on Varian A-60 and T-60 spectrometers.

2,3-Dimethyl-5-nitroisoquinolinium Methosulfate. Refluxing 15 g of 3-methyl-5-nitroisoquinoline[11] and 10 g of dimethyl sulfate for 24 hr in 100 ml of acetonitrile followed by concentration under reduced pressure and addition of ethyl acetate afforded the salt as a yellow solid, 22.6 g (90%). It crystallized from methanol as light yellow needles, mp 178°.

Anal. Calcd for $C_{12}H_{14}N_2O_6S$: C, 45.86; H, 4.49; N, 8.91. Found: C, 45.78; H, 4.42; N, 8.83.

The hexafluorophosphate (1b) was prepared (76%) by addition of hexafluorophosphoric acid to an aqueous solution of the methosulfate salt. Recrystallization from methanol afforded colorless needles, mp 195–196°.

Anal. Calcd for $C_{11}H_{11}F_6N_2O_2P$: C, 37.94; H, 3.18; N, 8.04. Found: C, 37.72; H, 3.01; N, 7.81.

2,3-Dimethyl-5-acetylaminoisoquinoline Hexafluorophosphate (1c). 3-Methyl-5-aminoisoquinoline (10 g) was dissolved in 50 ml of acetic anhydride and the mixture was allowed to stand at room temperature for 2 hr. The semisolid mixture was poured into ice–water and made basic by addition of sodium bicarbonate. The solid (9 g) was collected and treated with 15 g of methyl iodide to afford 13.5 g of the salt. This was dissolved in hot methanol and treated with 8 g of hexafluorophosphoric acid to yield 9.2 g (40%) of crude product, mp 254–257. The analytical sample, mp 259–261°, was crystallized from methanol–acetonitrile.

Anal. Calcd for $C_{13}H_{15}N_2OPF_6$: C, 43.33; H, 4.17; N, 7.78. Found: C, 43.07; H, 4.29; N, 7.56.

General Procedure for Preparation of Cycloadducts. To a solution of the isoquinolinium salt 1 in acetonitrile, a large excess of the alkene plus a small quantity of hydroquinone were added. Except as noted, the solution was allowed to stand at room temperature until the uv or NMR spectrum showed that the isoquinolinium ring system was no longer present. The solution was then concentrated to a small residue to which ether was added. The resulting precipitate was collected and washed with ether. All adducts were crystallized from methanol containing a small quantity of acetonitrile.

5-Acetamino-2,3-dimethyl-9-ethoxy-1,4-dihydro-1,4-ethanoisoquinolinium Hexafluorophosphate (2c). This was prepared in 63% yield from 1c: mp 258–259°; NMR[12] (CD_3CN) δ 2.62 (s, C-3 CH_3), 3.58 (s, NCH_3), 5.14 (d, H-4), 5.54 ppm (q, H-1).

Anal. Calcd for $C_{17}H_{23}F_6N_2O_2P$: C, 47.22; H, 5.32; N, 6.48. Found: C, 47.37; H, 5.45; N, 6.34.

Reaction Rates for Cycloaddition of 1a–c. The comparison of reaction rates was carried out at 34.6 ± 0.5° in an acetonitrile solution that was 0.1 *M* in salt and 3.5 *M* in ethyl vinyl ether. Disappearance of the salt was measured by observing the disappearance of the long-wavelength absorption in the ultraviolet.

9-Ethoxy-1,2,3,4-tetrahydro-2,3-dimethyl-3-cyano-5-nitro-1,4-ethanoisoquinoline (13). To a solution of 1.5 g (4.6 mmol) of **2b** in a mixture containing 11 ml of acetonitrile and 4 ml of water, a solution of 0.25 g (1.5 mmol) of potassium cyanide in 1 ml of water was added dropwise. The solution was concentrated under reduced pressure and the crystalline residue was collected and washed with water. The crude product, 1.05 g (98%), mp 109–111°, was recrystallized from methanol–water as yellow microcrystals, mp 113°. The NMR suggested a mixture of geometrical isomers with the major isomer having the resonance at H-9 appearing at δ 4.12 (with methyl groups as singlets at δ 2.39 and 1.72). The H-9 resonance for the minor isomer appeared at δ 4.48 (with methyl groups as singlets at δ 2.55 and 1.28). Assignment of the major isomer as the endo cyano compound (**13a**) was based upon the long-range shielding effects[4,13] of the nitrile group on the H-9 resonance. In the endo isomer (**13a**) H-9 is approximately in the direction of the principal axis of the cyano group; hence it should be shielded. In the exo isomer (**13b**), H-9 is almost at right angles to the axis of the nitrile group; hence it should be deshielded. In a few days, the solution ($DCCl_3$) appeared to reach an equilibrium in which **13a** and **13b** were present in equal amounts: **13a** NMR ($CDCl_3$) δ 1.03 (t, 3, CH_3CH_2), 1.20 (m, 1, 10-H, syn), 1.72 (s, 3, 3-Me), 2.39 (s, 3, 2-Me), 2.62 (o, 1, 10-H, anti), 3.62 (m, 2, CH_3CH_2), 3.72 (q, 1, 1-H), 4.12 (m, 1, 9-H), 4.75 (d, 1, H-4), 7.30–8.30 (m, 3, aromatic).

Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.73; H, 6.36; N, 13.94. Found: C, 63.58,; H, 6.16; N, 13.65.

3-Cyano-9-ethoxyl-1,2,3,4-tetrahydro-2,3,9-trimethyl-5-nitroisoquinoline (14). The reaction for 1 day at room temperature of 5 g (14 mmol) of **1b** with 8 g (93 mmol) of 2-ethoxypropene[14] in 25 ml of acetonitrile, followed by removal of volatiles under reduced pressure, left a mixture of solid and oil. The solid, which was mainly starting material, was removed by dissolving the oil in cold methanol and filtering the solution. The solution was concentrated under reduced pressure and the oily residue was taken up in a mixture of 20 ml of acetonitrile and 4 ml of deionized water. To this solution, 1.2 g of potassium cyanide in 2 ml of water was added. The solvents were removed under reduced pressure, water was added to the residue, and the mixture was extracted with ether. The ether solution was dried (K_2CO_3) and concentrated and the solid product was twice recrystallized from ether, affording 1 g (20%) of colorless needles: mp 140–143°; NMR ($CDCl_3$) δ 0.98 (s, 3, 9-Me), 1.23 (t, 3, CH_3CH_2), 1.53 (d of d, 1, J_{gem} = 13, J_{vic} = 3 Hz, 10a), 1.93 (s, 3, 3-Me), 2.39 (s, 3+, MeN, 10b), 2.50 (d, J_{vic} = 3 Hz, 0.5, 10b), 3.56 (q, 2, CH_3CH_2), 3.79 (t, 1, 1 H), 4.51 (s, 1, 4 H), 7.53 (s, 1, aromatic), 7.58 (s, 1, aromatic), 8.14 (t, 1, 8 H).

Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.93; H, 6.51; N, 13.25.

2-Methyl-5-nitroisoquinolinium Hexafluorophosphate (16). A solution containing 17.8 g of 5-nitroisoquinoline,[15] 13 g of dimethyl sulfate, and 100 ml of acetonitrile was allowed to stand for 3 days at room temperature. Upon addition of ether, the methyl methosulfate salt separated as an oil. The oil was dissolved in 50 ml of methanol and added to 20 g of hexafluorophosphoric acid in a polypropylene beaker. The precipitate was collected and washed with methanol. The crude product, 21.2 g (62%), crystallized from hot methanol, afforded yellow microcrystals, mp 150°.

Anal. Calcd for $C_{10}H_9F_6N_2O_2P$: C, 35.94; H, 2.71; N, 8.38. Found: C, 35.82; H, 2.47; N, 8.18.

3-Hydroxy-2-methyl-1,4-Δ[12]-cyclopenteno)-1,2,3,4-tetrahydroisoquinolinium Bromide (17). To a solution of 2.52 g of 2-methylisoquinolinium bromide[16] in 250 ml of acetonitrile, 9 ml of

freshly cracked cyclopentadiene was added and after 3 weeks at room temperature, another 9 ml. After a total of 65 weeks, the solution was concentrated at room temperature under reduced pressure. Addition of ether precipitated a crude brown solid, mp 200–208° dec. Recrystallization from acetonitrile–ethyl acetate yielded a brown, microcrystalline solid, mp 212° dec. NMR [$(CD_3)_2SO$] was complex and poorly defined, but there was no indication of resonance in the δ 9 region (iminium hydrogen).

Anal. Calcd for $C_{15}H_{18}BrNO$: C, 58.45; H, 5.89; N, 4.54. Found: C, 58.43; H, 5.92; N, 4.59.

***syn*-2-Methyl-5-nitro-1,4-(Δ^{12}-cyclopenteno)-1,4-dihydroisoquinolinium Hexafluorophosphate (18).** Freshly cracked cyclopentadiene (20 ml) was added to a solution of 5 g of 2-methyl-5-nitroisoquinolinium hexafluorophosphate (16) in 20 ml of anhydrous acetonitrile. After 17 hr was allowed for reaction at room temperature, the solution was concentrated under reduced pressure. On addition of ether to the residue, the salt precipitated as an oil which was washed with ether followed by removal under vacuum of all volatile materials. The solid residue remaining, 4.1 g (69%), was twice recrystallized from acetone–ethyl ether: mp 140° dec; NMR (CD_3CN) δ 1.47–2.87 (m, 2, C-11), 2.87–3.70 (m, 2, C-9, C-10), 3.82 (s, 3, Me), 5.33 (m, 2, C-12, C-13), 5.67 (d, 1, C-1), 5.85 (q, 1, C-4), 7.37–8.27 (m 3, aromatic), 8.94 ppm (m, 1, C-3 iminium). Spin decoupling experiments confirmed the assignment of the multiplet at δ 8.94 to the proton at position 3.

Anal. Calcd for $C_{15}H_{15}F_6N_2O_2P$: C, 45.01; H, 3.78; N, 7.00. Found: C, 45.02; H, 3.70; N, 6.90.

Addition Product (19) from Reaction of 2 Mol of 1-Methoxycyclohexene with 1 Mol of 16. To a solution of 4 g (12 mmol) of 2-methyl-5-nitroisoquinolinium hexafluorophosphate (16), 12 g (107 mmol) of 1-methoxycyclohexene was added and the mixture was allowed to stand for 30 days at room temperature. The solvents and excess methoxycyclohexene were romoved under reduced pressure. The product was precipitated by addition of ethyl ether and was collected and washed with ether, yield 5.8 g (87%). Twice recrystallized from acetonitrile–ethyl alcohol, it afforded colorless plates: mp >185° dec; NMR (CD_3CN, spectrum complex and not all resonances identified) δ 3.31 (s, 3, O-Me), 3.49 (s, 3, O-Me), 7.58–8.37 ppm (m, 3, aromatic).

Anal. Calcd for $C_{24}H_{33}F_6N_2O_4P$: C, 51.61; H, 5.96; N, 5.02. Found: C, 51.64; H, 6.07; N, 5.07.

Registry No.—**1b**, 54409-89-1; **1b** methosulfate analog, 54409-90-4; **1c**, 54409-92-6; **1c** iodide analog, 54409-93-7; **2b**, 54409-95-9; **2c**, 54446-45-6; **3**, 54409-97-1; **4**, 54409-99-3; **5**, 54410-01-4; **6**, 54410-03-6; **7**, 54446-47-8; **8**, 54446-49-0; **9**, 54410-05-8; **10**, 54410-07-0; **11**, 54410-09-2; **12**, 54446-51-4; **13a**, 54410-39-8; **13b**, 54482-30-3; **14**, 54446-53-6; **16**, 54410-10-5; **16** methosulfate analog, 54410-11-6; **17**, 54410-12-7; **18**, 54410-14-9; **19**, 54410-16-1; styrene, 100-42-5; *p*-methoxystyrene, 637-69-4; ethyl vinyl ether, 109-92-2; vinyl acetate, 108-05-4; 2,3-dimethylbutadiene, 513-81-5; β-pinene, 127-91-3; cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4; 1-methoxycyclohexene, 931-57-7; indene, 95-13-6; norbornene, 498-66-8; 3-methyl-5-nitroisoquinoline, 18222-17-8; dimethyl sulfate, 77-78-1; hexafluorophosphoric acid, 16940-81-1; 3-methyl-5-aminoisoquinoline, 54410-17-2; acetic anhydride, 108-24-7; 2-ethoxypropene, 926-66-9; 5-nitroisoquinoline, 607-32-9; 2-methylisoquinolinium bromide, 54410-18-3.

References and Notes

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Cyclization of the Quaternary Salts of Some Heterocyclic Derivatives[1]

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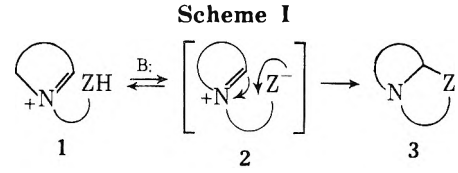
In the presence of a suitable base, certain aromatic or iminium quaternary salts having a nucleophilic group at an appropriate place of the N^+–R chain undergo nucleophilic cyclization. This cyclization has been applied to phenanthridinium, isoquinolinium, and 1,4-bridged 1,4-dihydroisoquinolinium salts using nucleophilic anions derived from the 4,4-dicarbethoxybutyl (e.g., **4** → **5**), the 2-mercaptoethyl (e.g., **10** → **12**), and 2-hydroxyethyl (**17** → **21**) groups.

In 1962, Kröhnke and Zecher[2] showed that the quaternary salt formed by the reaction of phenacyl bromide and isoquinoline would condense with hydroxylamine hydrochloride and cyclize to yield a [2,1-*a*]imidazoisoquinoline derivative.[3] Later work[4–6] showed that the use of hydrazine on quaternary salts of the same general type led to triazino derivatives.

It was suggested[5] that there must exist several types of cyclization involving a nucleophilic attack on an electron-deficient carbon atom of an aromatic quaternary salt. A more general statement of this reaction may be seen in Scheme I, in which the quaternary salt might be either an iminium or a quaternary aromatic salt. The ZH group of **1** must be sufficiently more acidic than the α methylene group of the salt to prevent nonproductive ylide formation,

Scheme I

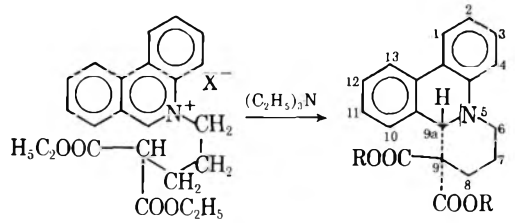


1 2 3

and the base used should be of low nucleophilicity. The tendency of the anion to undergo cyclization (**2** → **3**) is a function of the size of the ring being formed, the nucleophilicity of Z, and the proportion of the total resonance energy lost in the transformation **1** → **3**.

One possibility was the use of a carbanion as a nucleophile. The quaternary salt **4**, produced by the action of ethyl γ-bromopropyl malonate[7] on phenanthridine, was al-

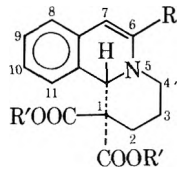
lowed to react for 2 hr at room temperature with triethylamine, affording, in 64% yield, a compound having the properties expected for the nucleophilic cyclization product (**5**). The new product (**5**) had not only a new benzylic hydrogen clearly identifiable by NMR but also *two* sets of signals corresponding to ethyl groups in different environments, a clear indication that cyclization had occurred as indicated. The cyclization product (**5**), when refluxed for 24 hr in methanol containing methoxide ion, underwent ester exchange, and the new product (**6**) clearly showed two methyl signals separated by δ 0.63. Attempts to aromatize **5** by the action of picric acid, ferric chloride, iodine, or trityl tetrafluoroborate all resulted in ring opening affording the appropriate salt of **4**. Ring opening was also effected by anhydrous or aqueous acids.



4

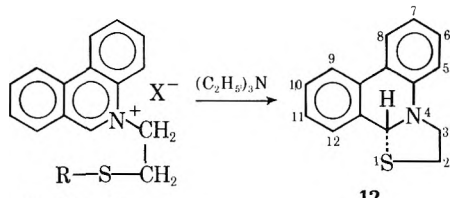
5, R = C_2H_5
6, R = CH_3

Isoquinolinium salts corresponding to **4** likewise underwent cyclization in the presence of triethylamine to yield products (**7**, **8**) which were less stable than those from phenanthridine but could be purified for analysis. The dimethyl ester (**9**) showed only a δ 0.25 difference in the position of the two OMe signals in the NMR.



7, R = H; R′ = C_2H_5
8, R = CH_3; R′ = C_2H_5
9, R = H; R′ = CH_3

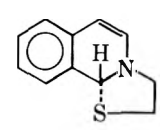
Another example of nucleophilic cyclization is afforded by the 5-(β-mercaptoethyl)phenanthridinium system (**10**). This cannot be prepared directly but is easily available through hydrolysis of the acetate ester **11**. Cyclization of the thiol **10** in the presence of triethylamine afforded 2,3-dihydro-12b*H*-thiazolo[3,2-*f*]phenanthridine (**12**) in 47% yield. The product was notable for giving NMR evidence of the lack of symmetry in the environment of the methylene protons at C-3.



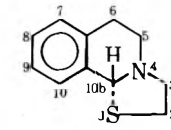
10, R = H
11, R = CH_3CO

12

The isoquinolinium analog of **10** apparently underwent a similar type of cyclization, for the crude product gave an NMR spectrum compatible with **13**, but an attempted recrystallization appeared to undergo disproportionation affording the dihydro derivative (**14**).



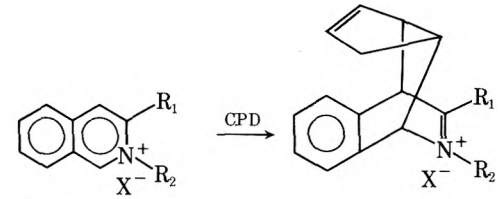
13



14

A severe limitation of the application of this general type of nucleophilic cyclization to the quaternary salts of aromatic bases is the tendency of the cyclization products to undergo ring opening with resonance energy of the restored aromatic system providing the driving force. An ideal system for the application of the nucleophilic cyclization would be a nonaromatic iminium system which would be more reactive and would lead to more stable products.

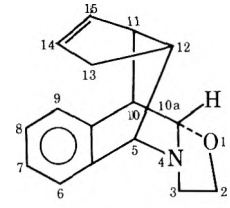
Recently it has been shown that quaternary isoquinolinium salts undergo cycloaddition (e.g., **15** → **18**) with the creation of iminium salts,[8-10] and that these can be made to undergo addition reactions[10,11] with a nucleophile. Present evidence indicates that iminium salts (e.g., **19**) derived from isoquinolinium salts (**16**) having no substituent at position 3 may be more reactive than those having such a substituent (e.g., **18**). Simple adducts of type **19** have proven elusive.[11]



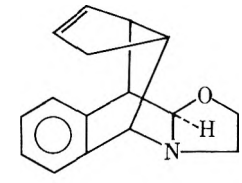
15, $R_1 = R_2 = Me$
16, $R_1 = H$; $R_2 = Me$
17, $R_1 = H$; $R_2 = CH_2CH_2OH$

18
19
20

Isoquinoline was quaternized with β-hydroxyethyl bromide, and the resulting salt (**17**, X = Br) was converted to the hexafluorophosphate (**X** = PF_6), which was allowed to react with cyclopentadiene. The adduct (presumably **20**) was allowed to react for several hours with aqueous potassium carbonate, affording a 60% yield of a base (**21**) which, on the basis of NMR evidence, is clearly a single geometrical isomer. Assuming only that the orientation of the cyclopentadiene during the cycloaddition is the same as that for the 2,3-dimethylisoquinolinium cation (**15**),[12] the product must have the endo (**21a**) or exo (**21b**) configuration. The endo configuration (**21a**) seems more attractive mechanistically, since cyclization to the exo isomer should be impeded by the cyclopenteno bridge. It is of interest that the addition of cyanide ion to an isoquinolinium adduct[10] has been found to occur most rapidly from the endo side.



21a



21b

Experimental Section

The elemental analyses were carried out by M-H-W Laboratories, Garden City, Mich. Melting points were determined in capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Except as noted, proton magnetic resonance spectra were obtained at 60 MHz on Varian A-60 and T-60 spectrometers.

5-(4,4-Dicarboxybutyl)phenanthridinium Bromide Diethyl Ester (4, X = Br). A mixture of 7.2 g (0.04 mol) of phenanthridine[13] and 14 g (0.05 mol) of ethyl 3-bromopropylmalonate[7] was heated for 24 hr at 100°. The crude product which had solidified was crystallized from ethanol–hexane, yielding 15.2 g (83%) of col-

orless crystals, mp 136–142°. The analytical sample had mp 147–148° (from hot ethanol); NMR ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz, 2 CH_3), 2.35 (br s, 4, 2 CH_2), 3.57 (br t, 1, CH), 4.15 (q, 4, J = 7 Hz, 2 CH_2O), 5.67 (br t, 2, NCH_2), 8.62 (m, 8, aromatic), 11.53 ppm (s, 1, aromatic); ir (KBr) 1690, 1670 cm^{-1} (carbonyl).

Anal. Calcd for $C_{23}H_{26}BrNO_4$: C, 60.01; H, 5.69; N, 3.04. Found: C, 59.82; H, 5.55; N, 2.96.

Diethyl 7,8-Dihydro-6*H*-pyrido[1,2-*f*]phenanthridine-9,9(9a*H*)-dicarboxylate (5). To a solution of 2.3 g (5 mmol) of 5-(4,4-dicarboxybutyl)phenanthridinium bromide diethyl ester (4) in 500 ml of chloroform, 1.01 g (10 mmol) of triethylamine was added and the mixture was allowed to remain for 2 hr at room temperature. The chloroform and excess triethylamine were removed under reduced pressure, then 50 ml of water was added and the mixture was extracted three times with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated and the residue was crystallized from hot hexane, affording 1.25 g (64%) of colorless prisms: mp 88–89°; NMR ($CDCl_3$) δ 0.66 (t, 3, J = 7 Hz, CH_3), 1.05 (t, 3, J = 7 Hz, CH_3), 2.17 (m, 3) 3.33 (m, 3), 4.12 (2 q, 4, J = 7 Hz, 2 CH_2O), 5.28 (s, 1, C-9a H), 7.22 (m, 8, aromatic).

Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 73.05; H, 6.58; N, 3.65.

The dimethyl ester (6) was obtained by suspending 1 g (2.6 mmol) of the diethyl ester 5 in 30 ml of methanol and adding a solution of sodium methoxide formed by dissolving 0.1 g (0.0043 g-atom) of sodium metal in 30 ml of methanol. The flask was protected from external moisture and refluxed for 24 hr. The methanol was evaporated and the residue was distributed between ether and water. The ethereal layer was dried (Na_2SO_4) and concentrated and the residue was crystallized from methanol: mp 64–65°; NMR ($CDCl_3$) δ 2.75 (m, 6, CH_2 at C-6, C-7, C-8), 2.88 (s, 3, CH_3), 3.52 (s, 3, CH_3), 5.22 (s, 1, C-9a H), 7.15 ppm (m, 8, aromatic).

Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.67; H, 6.16; N, 3.98. Found: C, 71.58; H, 6.10; N, 3.92.

Reactions of the Diethyl Ester (5). An attempt to dehydrogenate 5 by the action of trityl tetrafluoroborate in anhydrous acetonitrile at room temperature afforded the tetrafluoroborate of the open-chain product (4, X = BF_4), mp 170–171.5 (from ethanol).[14]

Other attempted dehydrogenations included the use of anhydrous ferric chloride for 1 hr at room temperature (in chloroform), iodine for 24 hr at room temperature (in anhydrous tetrahydrofuran), and picric acid, heating on a steam bath for 10 min (in 95% ethanol). With the exception of the last experiment, in which the product was isolated as the picrate,[14] mp 114–115°, all products were identified by conversion to the tetrafluoroborate (4, X = BF_4).

An attempt to isolate the hydrobromide of 5 by passing anhydrous hydrogen bromide into an ether solution of 5 afforded the ring-opened product (4, X = Br).

2-(4,4-Dicarboxybutyl)isoquinolinium Bromide Diethyl Ester. This was prepared by the action of ethyl 3-bromopropylmalonate on isoquinoline essentially as in the preparation of 4 (X = Br) except that the heating period was 3 days and a sample of the oily crude bromide (90% yield) was converted to the perchlorate by treating a methanol solution with a methanol–water solution of sodium perchlorate. Recrystallization from ethanol afforded colorless crystals of the perchlorate: mp 91–92°; NMR ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz, 2 CH_3), 2.13 (br s, 4, 2 CH_2), 3.50 (t, 1, J = 7 Hz, CH), 4.15 (q, 4, J = 7 Hz, 2 CH_2O), 4.88 (br t, 2, NCH_2), 8.27 (m, 6, aromatic), 9.95 ppm (s, 1, aromatic).

Anal. Calcd for $C_{19}H_{24}ClNO_8$: C, 53.09; H, 5.63; N, 3.26. Found: C, 53.21; H, 5.52; N, 3.11.

2-(4,4-Dicarboxybutyl)-3-methylisoquinolinium Bromide Diethyl Ester. This was made essentially as in the case of the lower homolog except that the bromide crystallized on addition of ether, affording 95% yield of bromide: mp 65–66°; ir (KBr pellet) 1717 cm^{-1} (carbonyl).

The perchlorate was prepared for analysis: white plates, mp 98–99.5°; uv max ($CHCl_3$) 349, 342, 279, 268, and 244 nm; NMR ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz, 2 CH_3), 2.10 (br s, 4, 2 CH_2), 2.90 (s, 3, CH_3), 3.47 (br t, 1, CH), 4.18 (q, 4, J = 7 Hz, 2 CH_2O), 4.80 (br t, 2, NCH_2), 8.15 (m, 5, aromatic), 9.83 ppm (s, 1, aromatic).

Anal. Calcd for $C_{20}H_{26}ClNO_8$: C, 54.12; H, 5.90; N, 3.15. Found: C, 54.17; H, 5.93; N, 3.16.

Diethyl 3,4-Dihydro-2*H*-benzo[*a*]quinolizine-1,1(11b*H*)-dicarboxylate (7). This was prepared essentially as was 5 except that 2-(4,4-dicarboxybutyl)isoquinolinium bromide diethyl ester was used, affording 1.19 g (36%) of yellow crystals: mp 95–96.5° (96.5–97° pure); NMR ($CDCl_3$) δ 0.82 (t, 3, J = 7 Hz, CH_3), 1.13 (t, 3, J = 7 Hz, CH_3), 1.86 (m, 4, 2 CH_2), 3.45 (m, 2, CH_2), 4.03 (2 q, 4, J = 7 Hz, 2 OCH_2), 5.03 (d, 1, J = 7 Hz, C-7 H), 5.28 (s, 1, C-11b H), 5.92 (d, 1, J = 7 Hz, C-6 H), 6.87 ppm (m, 4, aromatic).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.32; H, 7.16; N, 4.25.

Diethyl 3,4-Dihydro-6-methyl-2*H*-benzo[*a*]quinolizine-1,1(11b*H*)-dicarboxylate (8). This was prepared in 45% yield (mp 91–94°) essentially as was the lower homolog (7). The analytical sample was crystallized from hot methanol: mp 93.5–95°; NMR ($CDCl_3$) δ 0.88 (t, 3, J = 7 Hz, CH_3), 1.13 (t, 3, J = 7 Hz, CH_3), 1.90 (s, 3, CH_3), 2.58 (m, 6, CH_2, C-2, C-3, C-4), 4.13 (2 q, 4, J = 7 Hz, 2 OCH_2), 5.08 (s, 1, C-7 H), 5.37 (s, 1, C-11b H), 6.80 ppm (m, 4, aromatic); uv max ($CHCl_3$) 334, 246 nm.

Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.94; H, 7.33; N, 4.07. Found: C, 69.73; H, 7.39; N, 4.18.

Dimethyl 3,4-Dihydro-2*H*-benzo[*a*]quinolizine-1,1(11b*H*)-dicarboxylate (9). Ester interchange of the diethyl ester 7 was carried out in methanol as in the case of 5 → 6. Recrystallization from methanol afforded a 55% yield of colorless prisms: mp 89–91.5°; NMR ($CDCl_3$) δ 1.22–3.80 (m, 6, 3 CH_2), 3.40 (s, 3, CH_3), 3.67 (s, 3, CH_3), 5.27 (d, 1, J = 7 Hz, C-7 H), 5.45 (s, 1, C-11b H), 6.10 (d, 1, J = 7 Hz, C-6 H), 7.10 ppm (m, 4, aromatic).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.60; H, 6.56; N, 4.52.

5-(2-Mercaptoethyl)phenanthridinium Bromide Acetate (11, X = Br). Heating 15 g (82 mmol) of *S*-(2-bromoethyl)thiolacetate[15] at 110° for 24 hr with 14.3 g (80 mmol) of phenanthridine resulted in the solidification of the melt. The crude product was suspended in ethyl acetate and collected. Recrystallization from methanol–ethyl acetate yielded 20 g (70%) of small, yellow plates: mp 206–208° (pure 210°); NMR [$(CD_3)_2SO$–D_2O] δ 1.93 (s, 3, CH_3), 3.23 (t, 2, J = 7 Hz, SCH_2), 4.93 (t, 2, J = 7 Hz, CCH_2), 8.05 (m, 8, aromatic), 9.50 ppm (s, 1, aromatic).

Anal. Calcd for $C_{17}H_{16}BrNOS$: C, 56.36; H, 4.45; N, 3.86. Found: C, 56.26; H, 4.35; N, 3.76.

The perchlorate,[14] mp 205.5–206.5°, was crystallized from methanol.

5-(2-Mercaptoethyl)phenanthridinium Chloride (10, X = Cl). Refluxing 15 g of the bromide acetate (11, X = Br) overnight with 125 ml of 6 *N* hydrochloric acid followed by concentration of the mixture under reduced pressure afforded an oil which solidified on standing. The crude product (11.5 g, 100%, mp 98–103°) was used directly in the cyclization, but a small sample of the hexafluorophosphate (10, X = PF_6) was prepared for analysis: mp 216–217°; NMR [$(CD_3)_2SO$–D_2O] δ 3.60 (s, 2, SCH_2), 5.43 (s, 2, CH_2), 8.65 (m, 8, aromatic), 10.08 ppm (s, 1, aromatic).

Anal. Calcd for $C_{15}H_{14}F_6NPS$: C, 46.76; H, 3.66; N, 3.63. Found: C, 46.60; H, 3.39; N, 3.42.

2,3-Dihydro-12b*H*-thiazolo[3,2-*f*]phenanthridine (12). To a suspension of 11 g (40 mmol) of 5-(2-mercaptoethyl)phenanthridinium chloride (10, X = Cl) in 500 ml of reagent-grade chloroform, the minimum quantity of methanol necessary to effect complete solution was added. The solution was stirred at room temperature while 8 g (80 mmol) of triethylamine was added dropwise, after which it was allowed to stand for 12 hr. The mixture was concentrated under vacuum to a volume of about 100 ml. The solution was extracted twice with water, the chloroform layer was dried (Na_2SO_4), the chloroform and excess triethylamine were removed, and the product was further purified by chromatography on neutral alumina, using ether as a solvent, yielding 4.6 g (47.5%) of colorless crystals: mp 127–128°; NMR ($CDCl_3$) δ 2.92 (m, 3, CH_2 and C-3 H), 4.50 (m, 1, C-3 H), 6.00 (s, 1, C-12b H), 7.35 ppm (m, 8, aromatic).

Anal. Calcd for $C_{15}H_{13}NS$: C, 75.26; H, 5.49; N, 5.85. Found: C, 75.04; H, 5.48; N, 5.75.

2-(2-Mercaptoethyl)isoquinolinium Bromide Acetate. This was prepared essentially as in the case of the analog (11, X = Br), except that the quaternization of isoquinoline by *S*-(2-bromoethyl)thiolacetate was carried out for 48 hr in the dark at room temperature. Recrystallization of the crude solid from ethanol–ethyl acetate afforded a 95% yield of colorless, hygroscopic crystals: mp 133–135°; NMR ($CDCl_3$) δ 2.20 (s, 3, CH_3), 3.72 (t, 2, J = 7 Hz, SCH_2), 5.41 (t, 2, J = 7 Hz, CCH_2), 8.57 (m, 6, aromatic), 11.1 ppm (s, 1, aromatic).

The perchlorate was crystallized from methanol: mp 117–118°; uv max ($CHCl_3$) 342, 335, 330, 285, 280, 278, 252 nm.

Anal. Calcd for $C_{13}H_{14}ClNO_5S$: C, 47.06; H, 4.25; N, 4.20. Found: C, 46.86; H, 4.15; N, 4.14.

2-(2-Mercaptoethyl)isoquinolinium Bromide. Hydrolysis of 16 g (50 mmol) of 2-(2-mercaptoethyl)isoquinolinium bromide acetate was carried out by refluxing it overnight in 100 ml of 48% hy-

drobromic acid. The excess acid was removed by evaporation under reduced pressure followed by heating for 12 hr under vacuum at 100°. The product consisted of light yellow, hygroscopic crystals (13.5 g, 100%): NMR [$(CD_3)_2SO$] δ 3.37 (t, 2, J = 7 Hz, SCH_2), 3.97 (s, 1, SH), 5.01 (t, 2, J = 7 Hz, CCH_2), 8.57 (m, 6, aromatic), 10.53 ppm (s, 1, aromatic).

Anal. Calcd for $C_{11}H_{12}BrNS$: C, 48.90; H, 4.48; N, 5.18. Found: C, 48.68; H, 4.36; N, 4.99.

2,3,6,10b-Tetrahydro-5*H*-thiazolo[2,3-a]isoquinoline (14). The cyclization of 2-(2-mercaptoethyl)isoquinolinium bromide (10 g, 37 mmol) was carried out under a nitrogen atmosphere essentially as in the cyclization of **10** (X = Cl). Worked up as usual, the residue remaining after removal of the chloroform solvent and excess triethylamine consisted of oily crystals (4.9 g, 70%), which decomposed on standing at room temperature. This substance was not analyzed, but, on spectroscopic evidence, appeared to be largely **13**: uv max ($CHCl_3$) 314, 248 nm; NMR ($CDCl_3$) δ 2.66 (t, 2, J = 6 Hz, SCH_2), 3.33 (t, 2, J = 6 Hz, CH_2), 5.55 (d, 1, J = 7 Hz, C-6 H), 5.80 (d, 1, J = 7 Hz, C-5 H), 6.00 (s, 1, C-10b H), 7.20 ppm (m, 4, aromatic).

The entire crude product (4.9 g) was placed in 50 ml of absolute ethanol, in which it rapidly dissolved, but after 1 min a crystalline substance began to precipitate from solution. The flask was warmed for 10 min and cooled and the product was collected, yielding 1.91 g (27% overall from mercaptan), mp 178–179°. The analytical sample was crystallized from chloroform–hexane: mp 179–180°; NMR ($CDCl_3$) δ 2.90 (br m, 8, aliphatic), 5.07 (s, 1, C-10b H), 7.20 ppm (m, 4, aromatic).

Anal. Calcd for $C_{11}H_{13}NS$: C, 69.06; H, 6.85; N, 7.32. Found: C, 69.26; H, 6.65; N, 7.33.

2-(β-Hydroxyethyl)isoquinolinium Bromide (17, X = Br). A solution containing 20 g of isoquinoline, 20 g of 2-bromoethanol, and 200 ml of acetonitrile was refluxed for 24 hr. On cooling, 26.8 g (68%) of colorless, hygroscopic plates was collected. Recrystallization from methanol–acetonitrile yielded the analytical sample, mp 154–155.5°.

Anal. Calcd for $C_{11}H_{12}BrNO$: C, 51.99; H, 4.74; N, 5.51. Found: C, 51.82; H, 4.81; N, 5.44.

The hexafluorophosphate (17, X = PF_6), mp 154–155.5°, prepared by addition of hexafluorophosphoric acid to an aqueous solution of the bromide salt (**17**, X = Br) was crystallized from methanol–ethyl acetate.[14]

***syn*-2,3,10,10a,12,13-Hexahydro-11*H*,5,10-[1′,2′]cyclopenta-5*H*-oxazolo[3,2-*b*]isoquinoline (21a).** To a solution of 5 g of 2-(β-hydroxyethyl)isoquinolinium hexafluorophosphate (**17**, X = PF_6) in 25 ml of acetonitrile, 25 ml of freshly cracked cyclopentadiene was added and the mixture was allowed to stand for 24 days. The solution was then concentrated under reduced pressure. The addition of cyclohexane caused the precipitation of 6 g of oil. To 2 g of the oil, a solution of 6 g of potassium carbonate in 20 ml of deionized water was added, and the mixture was stirred for a few hours at room temperature. The suspension was extracted with ether and the dried (potassium carbonate) solution was concentrated. The residue (1 g) was recrystallized from ethyl ether, affording 0.75 g (60%) of light pink prisms: mp 109–110°; NMR ($CDCl_3$) δ 7.14 (m, 4, aromatic H), 5.23 (s, 2, vinyl H), 4.96 (d, 1, J = 2.5 Hz, H-10a), 3.77 (d, 1, J = 3 Hz, H-5), 3.64–1.0 ppm (overlapping m, 9, aliphatic).

Anal. Calcd for $C_{16}H_{16}NO$: C, 80.64; H, 6.77; N, 5.88. Found: C, 80.84; H, 6.95; N, 5.75.

Registry No.—**4** (X = Br), 54423-78-8; **4** (X = BF_4), 54424-04-3; **4** (X = picrate), 54423-80-2; **5**, 54423-85-7; **6**, 54423-86-8; **7**, 54423-87-9; **8**, 54423-88-0; **9**, 54423-89-1; **10** (X = Cl), 54423-81-3; **10** (X = PF_6), 54424-06-5; **11** (X = Br), 54423-82-4; **11** (X = perchlorate), 54423-84-6; **12**, 54424-03-2; **13**, 52131-57-4; **14**, 14692-38-7; **17** (X = Br), 54423-94-8; **17** (X = PF_6), 54423-96-0; **21a**, 54460-93-4; phenanthridine, 229-87-8; ethyl 3-bromopropylmalonate, 10149-21-0; 2-(4,4-dicarboxybutyl)isoquinolinium bromide diethyl ester, 54423-97-1; 2-(4,4-dicarboxybutyl)isoquinolinium perchlorate diethyl ester, 54423-99-3; 2-(4,4-dicarboxybutyl)-3-methylisoquinolinium bromide diethyl ester, 54424-00-9; 2-(4,4-dicarboxybutyl)-3-methylisoquinolinium perchlorate diethyl ester, 54424-02-1; *S*-(2-bromoethyl)thiolacetate, 927-70-8; isoquinoline, 119-65-3; 2-(2-mercaptoethyl)isoquinolinium bromide acetate, 54423-90-4; 2-(2-mercaptoethyl)isoquinolinium perchlorate acetate, 54423-92-6; 2-(2-mercaptoethyl)isoquinolinium bromide, 54423-93-7; 2-bromoethanol, 540-51-2; cyclopentadiene, 542-92-7.

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Periselectivity of Reactions of Fulvenes with Heterodienes and Heterodienophiles[1]

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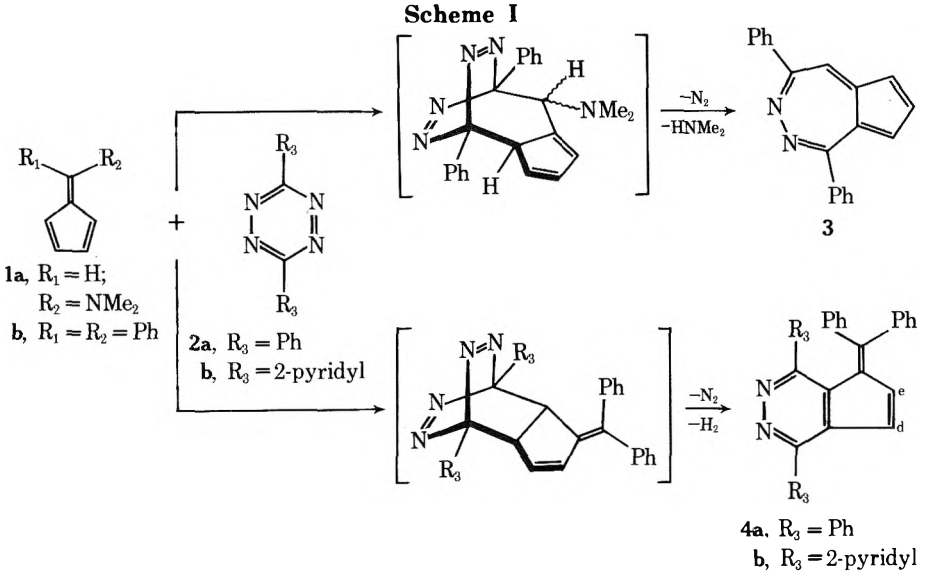
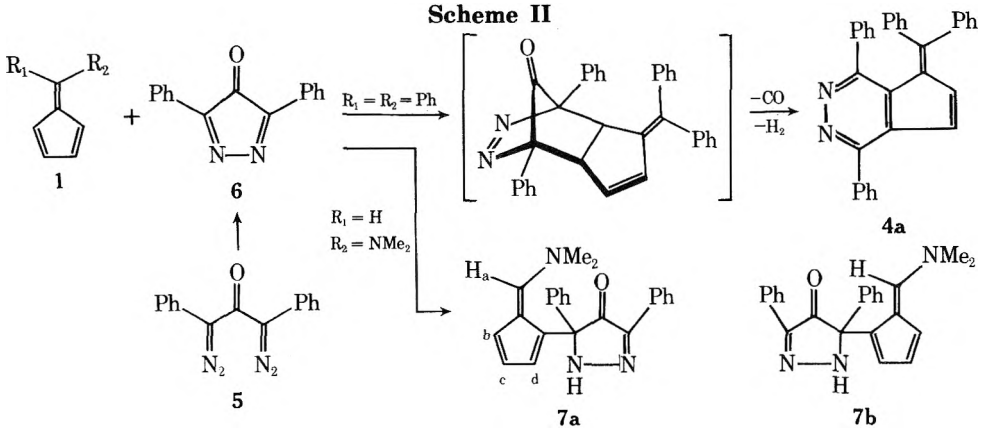
The cycloaddition reactions of 6,6-dimethylfulvene, 6,6-diphenylfulvene, and 6-dimethylaminofulvene with tetrazine, diazacyclopentadienone, and azodicarboxylate are investigated. The periselectivity observed with the tetrazine is explained using the frontier orbital model where the fulvene HOMO–olefin LUMO interaction predominates. Thus, a novel 5,6-diazaazulene was prepared by the reaction of 6-dimethylaminofulvene with the tetrazine.

Previously we reported that 6,6-diphenylfulvene reacted with tropone to afford only a [4 + 2] adduct instead of an expected [6 + 4] adduct.[2] By contrast, the reaction of 6,6-dimethylfulvene with tropone resulted in the formation of a 2:1 [6 + 4] adduct.[3] The different behavior of these fulvenes indicates sensitivity to steric and electronic requirements of substitutents at the C-6 position of the fulvene. Recently, reactivity, regioselectivity, and periselectivity in cycloaddition reactions have been explained by employing quantitative perturbation molecular orbital theory.[4] These considerations led us to further investigation of the cycloaddition reaction of substituted fulvenes.

Scheme I



Scheme II



In this paper, we report the reaction of fulvenes with electron-deficient heterodienes such as tetrazine and diazacyclopentadienone, and the heterodienophile azodicarboxylate.

Results

Reaction of 6-dimethylaminofulvene (**1a**) with 3,6-diphenyltetrazine (**2a**) in benzene at room temperature for 5 days gave a fluorescent yellow compound (**3**), $C_{20}H_{14}N_2$, in 40% yield. The uv spectrum showed a conjugated system, and resembled that of 6-dimethylamino-5,7-diazaazulene[5] as shown in Figure 1. These data indicated that the product was 4,7-diphenyl-5,6-diazaazulene, the formation of which can be rationalized via the initial [6 + 4] addition followed by loss of nitrogen and dimethylamine as shown in Scheme I.

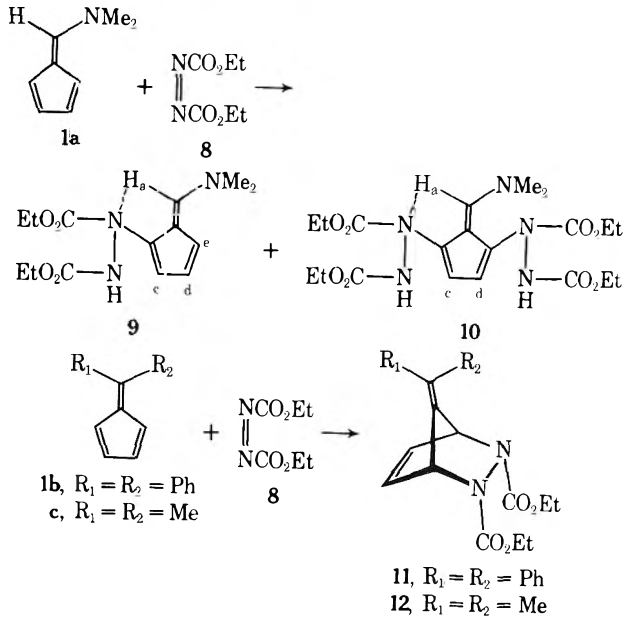
On the other hand, reaction of 6,6-diphenylfulvene (**1b**) with 3,6-diphenyltetrazine (**2a**) in benzene at 80° for 1 day gave compound **4a** in 60% yield. The NMR spectrum of **4a** showed doublets for two olefinic protons at δ 6.62 and 6.65 (J = 8.4 Hz). Presumably the formation of **4a** might proceed via the initially produced [4 + 2] adduct followed by loss of nitrogen and hydrogen as shown in Scheme I. Similar reaction of **1b** and **2b** in chloroform at room temperature for 14 hr gave **4b** in 83% yield. However, 6,6-dimethylfulvene (**1c**) reacted with **2a** or **2b** in chloroform at room temperature with evolution of nitrogen to give a mixture of several products, which decomposed during attempted separation.

Reaction of **1b** with 3,4-diaza-2,5-diphenylcyclopentadienone (**6**),[6] derived from 1,3-bisdiazo-1,3-diphenyl-2-propanone (**5**), in benzene at room temperature for 8 hr gave **4a** in 68% yield. Presumably compound **4a** was formed by initial [4 + 2] addition followed by loss of carbon monoxide and hydrogen.

Similar reaction of **1a** with **6** under the same conditions gave the 1:1 adduct (**7**) as yellow crystals in a quantitative yield. The ir spectrum of **7** showed an amino group at 3250 cm^{-1} and a ketoimino group at 1662 cm^{-1} (broad band). The NMR spectrum of **7** exhibited four olefinic protons at δ 6.85 (s, 1 H, H_a), 6.57 (dd, 1 H, H_b), 6.32 (dd, 1 H, H_c), 6.31 (t, 1 H, H_d) with coupling constants of J_{bc} = 4.4, J_{cd} = 2.5, and J_{bd} = 2.5 Hz, two N-methyl groups at δ 2.97 (s, 6 H), and aromatic and amino protons in the regions of δ 7.17–8.22 (1 H, exchangeable by D_2O). Particularly, the chemical shift of H_a (exocyclic olefin) for **7** was similar to that of **1a** (δ 6.58). These data were in accord with the proposed structure (**7a**) as depicted in Scheme II, and alternative structures such as **7b**, [4 + 2] and [6 + 4] cycloadducts could be ruled out.

Treatment of **1a** and diethyl azodicarboxylate (**8**) in benzene at room temperature for 1 day gave a mixture of **9** and **10** in 14 and 7% yields. The elemental analyses indicated that **9** and **10** consisted of 1:1 and 1:2 adducts of **1a** and **8**, respectively. The NMR spectrum of **9** showed four olefinic protons and one amino proton. Interestingly, the H_a proton suffered a downfield shift (δ 7.78) compared to those of 6-dimethylaminofulvene (δ 6.58) and compound **7** (δ 6.85). This indicated that H_a and the nitrogen of the azodicarboxylate group interacted strongly as depicted in Scheme III. The NMR spectrum of **10** showed one olefinic proton at δ 7.79 as a broad singlet, two olefinic protons at δ 6.05 as a

Scheme III



sharp singlet, and two amino protons at δ 6.80 as a singlet. These data were compatible with structures **9** and **10**, and no [4 + 2] cycloadduct was detected. By contrast, the reaction of diethyl azodicarboxylate (**8**) with 6,6-dimethylfulvene (**1c**) or 6,6-diphenylfulvene (**1b**) gave the corresponding [4 + 2] adduct **11** or **12**.[7]

Discussion

Houk et al. have recently shown that consideration of frontier orbital interactions can provide a good rationalization of reactivity, regioselectivity, and periselectivity in a variety of cycloaddition reactions,[4] and also estimated frontier orbital energies and coefficients of fulvenes[8] as shown in Figure 2.

On the other hand, it is known that ethyl azodicarboxylate (**8**), and the tetrazine **2**[9] were all electron-poor olefins. Generally, the electron-poor olefin has relatively lower LUMO (lowest unoccupied molecular orbital) and HOMO (highest occupied molecular orbital) energy levels.[4] Moreover, it is pointed out that the fulvene HOMO interaction is much more important than the fulvene LUMO interaction in the reaction of the fulvene with cyclopentadienone, cyclopentadiene, α-pyrone, and cycloheptadienone.[10] Therefore, the fulvene HOMO–heterodiene or heterodienophile LUMO interaction is expected to be more predominant than the inverse interaction of the fulvene LUMO–heterodiene or heterodienophile HOMO in the reactions of the fulvenes with the tetrazine **2**, diazacyclopentadienone (**6**), and azodicarboxylate **8**.

Since the HOMOs of 6,6-dimethylfulvene (**1c**) and 6,6-diphenylfulvene (**1b**) and the LUMO of ethyl azodicarboxylate (**8**) are also antisymmetric, the [4 + 2] cycloaddition reaction of the fulvene (4π) with ethyl azodicarboxylate (2π) is favored to give the usual Diels–Alder adduct. However, the LUMOs of the tetrazine and diazacyclopentadienone are symmetric, if considered like butadiene, and the [4 + 2] addition of the fulvene (2π) and the heterodiene (4π) should be favored.

On the other hand, the HOMO energy and coefficients of **1a** are very different from those of **1c** or **1b** (see Figure 2). Large coefficients at the C-6 position of the HOMO of 6-dimethylaminofulvene (**1a**) suggest that **1a** can act as a 6π component. Thus, the [6 + 4] cycloaddition of 1a to **2a** should be favored and resulted in the formation of the 5,6-

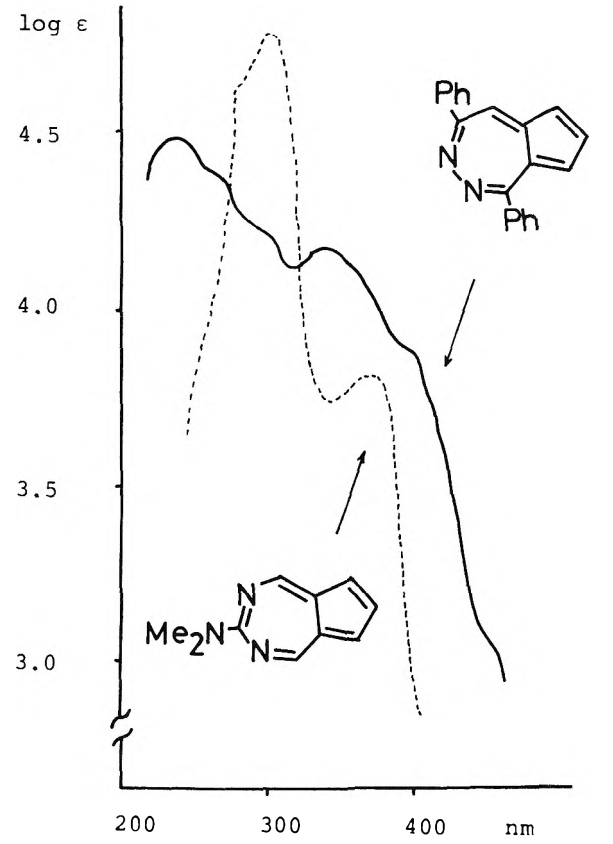


Figure 1. Uv spectra of **3** (EtOH) and 6-dimethylamino-5,7-diaza-azulene (*n*-hexane).

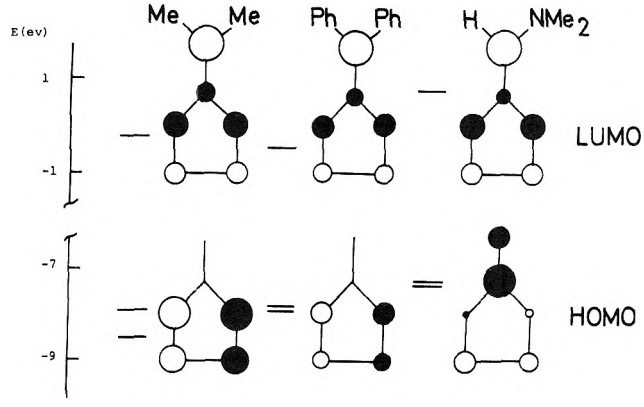
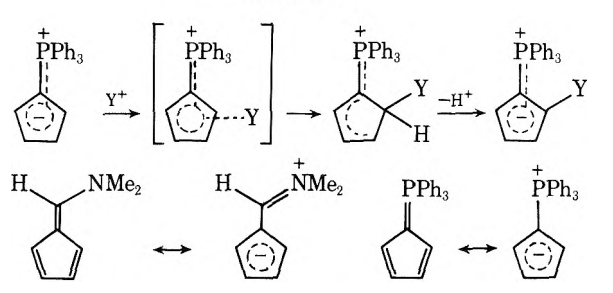


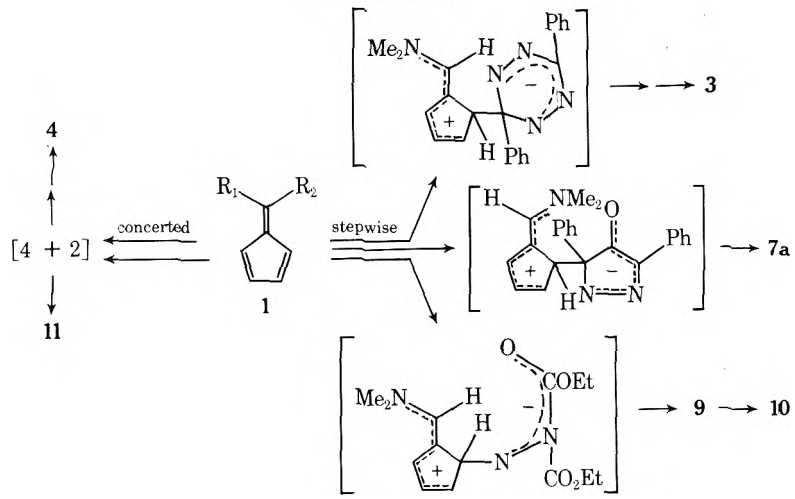
Figure 2.

diazaazulene (**3**). Furthermore, the relatively higher HOMO energy of 6-dimethylaminofulvene than that of 6,6-dimethyl- and 6,6-diphenylfulvene indicates it to be a strong electron donor, while electron-poor olefins can become a strong electron acceptor. In this connection, Yoshida et al. reported the reaction of 6-phosphafulvene with a dienophile such as tetracyanoethylene to be a Michael-type

Scheme IV



Scheme V



substitution at the C-2 position as outlined in Scheme IV.[11] Dipole moments of 6-phosphafulvene, 6-dimethylaminofulvene (**1a**), 6,6-diphenylfulvene (**1b**), and 6,6-dimethylfulvene (**1c**) are 7.0, 4.48, 1.40, and 1.44 D, respectively.[12]

From these data, 6-dimethylaminofulvene (**1a**) might be predominant in the resonance contribution (dipolar structure) at the ground state as shown in Scheme IV. Accordingly, the reactions of 6-dimethylaminofulvene (**1a**) with electron-deficient diazacyclopentadienone (**6**), tetrazine **2**, and azodicarboxylate **8** might proceed via the dipolar intermediates by either the stepwise [6 + 4] cycloaddition or the electronphilic substitution as indicated in Scheme V.

From these results, it is concluded that the interactions between the fulvene HOMO and the heterodiene or heterodienophile LUMO are stronger than the inverse interactions between the fulvene LUMO and the olefin HOMO, and the reaction of the diene or dienophile with 6,6-dimethyl- or 6,6-diphenylfulvene might proceed in a concerted fashion. By contrast, the reaction with the strongly electron-rich 6-dimethylaminofulvene gives way to a stepwise fashion involving the zwitterionic intermediates as shown in Scheme V. However, the HOMO of dimethylaminofulvene shown in Figure 2 does not rationalize the site of reaction with electrophiles. The N HOMO is also important, and the fulvenes invariably undergo attack by electrophiles *at the C-1 position. Probably charge and frontier orbital* interactions are important.[8]

Experimental Section

Melting points are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. Uv spectra were determined with a Jasco ORD/UV-5 spectrometer. NMR spectra were taken with a Jeol C-60-XL spectrometer and with a Varian A-60 recording spectrometer, with tetramethylsilane as internal standard. Ir spectra were taken with a Jasco Ir-S spectrophotometer. Mass spectra were obtained with a Hitachi RMU-D double-focusing spectrometer operating at an ionization potential of 70 eV. The solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 100–150°.

Reaction of 6-Dimethylaminofulvene (1a) with 3,6-Diphenyltetrazine (2a). A solution of **1a** (0.15 g) and **2a** (0.29 g) in benzene (20 ml) was stirred at room temperature under argon in the dark for 5 days. Then the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using chloroform to give **3** (0.14 g, 40%): mp 289–292° (from chloroform); uv (EtOH) λ_{max} 235 nm (log ϵ 4.49), 256 (4.39), 292 (4.27), 340 (4.14), 395 (3.88), and 450 (3.06); mass spectrum *m/e* 282 (M^+); *the NMR* spectrum could not be obtained because of low solubility.

Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.96; H, 5.16; N, 9.87.

Reaction of 6,6-Diphenylfulvene (1b) with 3,6-Diphenyltetrazine (2a). A solution of **1b** (0.62 g) and **2a** (0.75 g) in benzene (30 ml) was heated in a sealed tube at 80° for 1 day. Then the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel) using chloroform as an eluent to give **4a** (0.7 g, 60%): mp 174–176° (from MeOH); NMR ($CDCl_3$) δ 6.62 (d, J = 8.4 Hz, 1 H, H_d or H_e), 6.65 (d, J = 8.4 Hz, H_d or H_e), 6.38–8.10 (complex m, 20 H, aromatic H); mass spectrum *m/e* 434 (M^+).

Anal. Calcd for $C_{32}H_{22}N_2$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.23; H, 5.35; N, 6.41.

Reaction of 6,6-Diphenylfulvene (1b) with 3,6-Di(2-pyridyl)tetrazine (2b). A solution of **1b** (0.3 g) and **2b** (0.3 g) in chloroform (20 ml) was stirred at room temperature for 14 hr. Then the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using chloroform to give **4b** (0.47 g, 83%): mp 198–200° (from MeOH); NMR ($CDCl_3$) δ 6.61 (d, J = 8.0 Hz, 1 H, H_d or H_e), 6.65 (d, J = 8.0 Hz, 1 H, H_d or H_e), 6.80–8.82 (complex m, 18 H, aromatic H).

Anal. Calcd for $C_{30}H_{20}N_4$: C, 82.54; H, 4.62; N, 12.84. Found: C, 82.45; H, 4.86; N, 12.68.

Reaction of 6,6-Diphenylfulvene (1b) with 3,4-Bisdiazo-2,5-diphenylcyclopentadienone (6). To a solution of **1b** (0.2 g) in benzene (15 ml) was added powdered 1,3-bisdiazo-1,3-diphenyl-2-propanone (**5**, 0.5 g), and the mixture was stirred at room temperature for 10 hr. Then the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography using chlroform to give **4a** (0.21 g, 68%).

Reaction of 6-Dimethylaminofulvene (1a) with 3,4-Bisdiazo-2,5-diphenylcyclopentadienone (6). To a solution of **1a** (0.4 g) in benzene (30 ml) was added powdered compound **5** (0.5 g). The mixture was stirred at room temperature under argon in the dark for 8 hr. Then the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using benzene to give yellow crystals of **7** (0.58 g): mp 186–188° (from benzene); ir (KBr) 3250 (NH), 1662 cm^{-1} (N=C–C=O); NMR ($CDCl_3$) δ 2.97 (s, 6 H, NCH_3), 6.31 (t, 1 H, H_d), 6.32 (dd, 1 H, H_c), 6.57 (dd, 1 H, H_b), 6.85 (s, 1 H, H_a), 7.17–8.22 (complex m, 10 H, aromatic H); J_{bc} = 4.4, J_{cd} = 2.5, J_{bd} = 2.5 Hz.

Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.81; H, 5.85; N, 11.87.

Reaction of 6-Dimethylaminofulvene (1a) with Diethyl Azodicarboxylate (8). A solution of 6-dimethylaminofulvene (**1a**, 0.7 g) and **8** (1.0 g) in benzene (50 ml) was stirred at room temperature under argon in the dark for 1 day. Then the mixture was filtered to give **10** (0.12 g). The filtrate was evaporated under reduced pressure and the residue was purified by silica gel chromatography using benzene as an eluent to give **9** (0.24 g).

9: mp 172–173° (from EtOH); ir (KBr) 3276 (NH), 1745, 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.20 (t, J = 8.0 Hz, 3 H, CH_3), 1.23 (t, J = 8.0 Hz, 3 H, CH_3), 3.21 (s, 6 H, NCH_3), 4.13 (q, J = 8.0 Hz, 2 H, CH_2), 4.17 (q, J = 8.0 Hz, 2 H, CH_2), 6.16 (dd, 1 H, H_d), 6.36 (t, 1 H, H_c), 6.45 (dd, 1 H, H_e), 7.03 (s, 1 H, NH), 7.78 (broad s, 1 H, H_a); J_{cd} = 2.6, J_{de} = 4.5, J_{ce} = 2.6 Hz.

Anal. Calcd for $C_{14}H_{21}N_3O_4$: C, 56.93; H, 7.17; N, 14.23. Found: C, 56.91; H, 6.99; N, 14.12.

10: mp 193–195° (from MeOH); ir (KBr) 3272 (NH), 1740, 1682 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.21 (t, J = 8.0 Hz, 3 H, CH_3), 1.24

(t, J = 8.0 Hz, 3 H, CH_3), 3.15 (s, 6 H, NCH_3), 4.09 (q, J = 8.0 Hz, 2 H, CH_2), 4.13 (q, J = 8.0 Hz, 2 H, CH_2), 6.05 (s, 2 H, H_c and H_d), 6.80 (s, 2 H, NH), 7.79 (broad s, 1 H, H_a).

Anal. Calcd for $C_{20}H_{31}N_5O_8$: C, 51.16; H, 6.66; N, 14.92. Found: C, 51.30; H, 6.57; N, 14.88.

Registry No.—**1a**, 696-68-4; **1b**, 2175-90-8; **2a**, 6830-78-0; **2b**, 1671-87-0; **3**, 54384-98-4; **4a**, 54384-99-5; **4b**, 54385-00-1; **6**, 32683-51-5; **7a**, 54385-01-2; **8**, 1972-28-7; **9**, 54385-02-3; **10**, 54385-03-4.

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The Oxetane Function Spiro to Polyoxaaza Macroheterocycles

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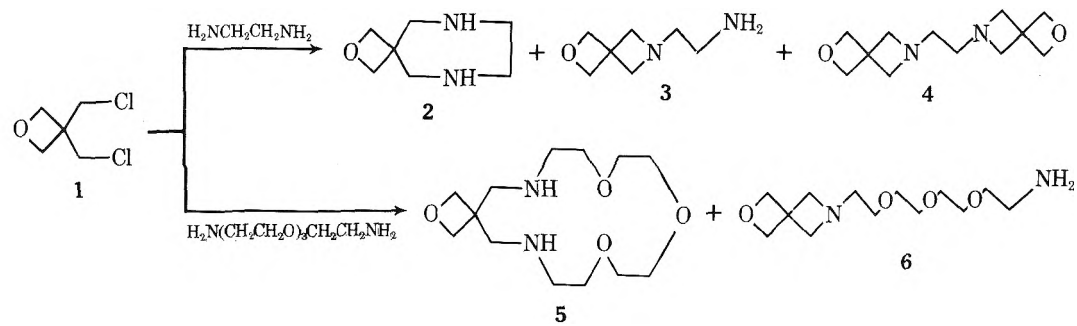
Base-induced condensation of oxaazadiols with 3,3-bis(chloromethyl)oxetane gives macrocyclic aza polyethers bearing one or two spirooxetane rings. Thermolysis of appropriately constituted oxaaza macrocycles is shown to give novel polycyclic structures, as does condensation with bis(acid chloride). Ring closure of α,ω-diamines with 3,3-bis(chloromethyl)oxetane leads to polyoxaaza macrocycles in low yield.

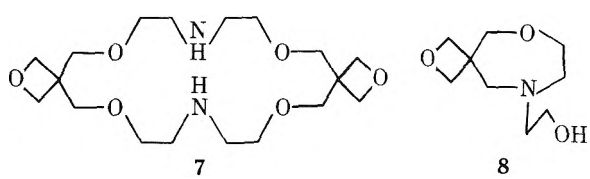
The previous paper[1] in this series described the one-step synthesis of macrocyclic polyethers and polysulfides bearing one or two spirooxetane substituents. This paper presents syntheses of a number of related polyoxaaza macrocycles and some chemistry of the imine group in such rings.

Synthesis from α,ω-Diamines. Alkylation of α,ω-diamines with dihalides does not usually lead to good yields of diaza macrocycles,[2] and reaction of 3,3-bis(chloromethyl)oxetane (1) with primary α,ω-diamines has been found to give several types of products. Ethylenediamine with 1 gave volatile products resulting from monoalkylation of both nitrogen atoms (i.e., 2) and from dialkylation (i.e., 3 and 4) along with low polymers. A similar result was observed starting from 1 and 3,6,9-trioxaundecane-1,11-diamine, since both macrocycle 5 and azetidine 6 were formed. The distillation cut which contained 5 and 6 in roughly equal amounts was separated by taking advantage of the superior ability of 5 to form complexes. The crystalline complex, 5 · NaSCN, was precipitated while 6 remained in solution.



Synthesis from α,ω-Diols. Three α,ω-diols having aza nitrogen were condensed with 1 or with 3,3-bis(bromomethyl)oxetane. Attempts to selectively benzoylate the amine function in these diols under mild conditions gave little derivatization, a result indicative of rather low nucleophilicity of the amine centers. The condensations were therefore carried out with the dipotassium salts of the diols containing unmasked imine groups. Alkylation on nitrogen appeared to be a minor side reaction, and the results are roughly comparable to those obtained with the polyethylene glycols.[1]

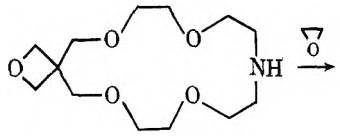
In the presence of 2 equiv of potassium *tert*-butoxide and in *tert*-butyl alcohol as solvent, diethanolamine condensed with 1 to give dispiro macrocycle 7 in 17% yield along with 1% of N-alkylated product (8). The effect of nitrogen in the macrocyclic polyether on complex formation is indicated by the fact that 7 readily displaced water from cupric acetate hydrate to form 7 · $Cu(OAc)_2$.

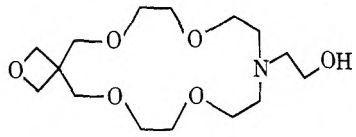


3,9-Dioxa-6-azaundecane-1,11-diol (9) was obtained by the following sequence of reactions. Interestingly, the three-stranded compound 10 was the only acyclic polyether encountered in this study which gave a crystalline complex, namely 10 · NaSCN.

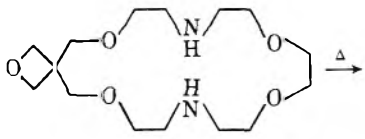
$$HO(CH_2CH_2O)_2H \xrightarrow{SOCl_2} Cl(CH_2CH_2O)_2H \xrightarrow{NH_3}$$
$$H_2N(CH_2CH_2O)_2H + HN(CH_2CH_2OCH_2CH_2OH)_2 +$$
11 9
$$N(CH_2CH_2OCH_2CH_2OH)_3$$
10

Condensation of the dipotassium salt of **9** with **1** gave macrocycle **12** in 67% yield. A 1:1 complex of **12** with NaSCN was easily prepared. The presence of a secondary amine function in **12** which can be derivatized was shown by its reaction with excess ethylene oxide to form **13.**


12


13

Finally, the dipotassium salt of 6,9-dioxa-3,12-diazatetradecane-1,14-diol[2] was condensed with **1** to form macrocycle **14** in 71% crude yield. Purification of **14** was best effected by crystallization as the 1:1 complex with sodium thiocyanate or sodium iodide. Attempted fractional distillation of crude **14** necessitated temperatures near 200°, high enough for intramolecular attack of nitrogen on the oxetane ring to occur.[3] As a result, the distillate proved to be largely the bicyclic compound **15.** This product formed a relatively insoluble 1:1 complex with sodium thiocyanate, and mixtures of **14** · NaSCN with **15** · NaSCN could be separated by fractional crystallization from acetone.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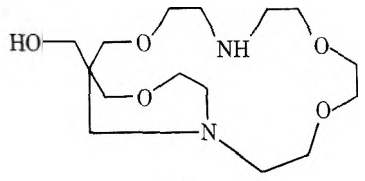
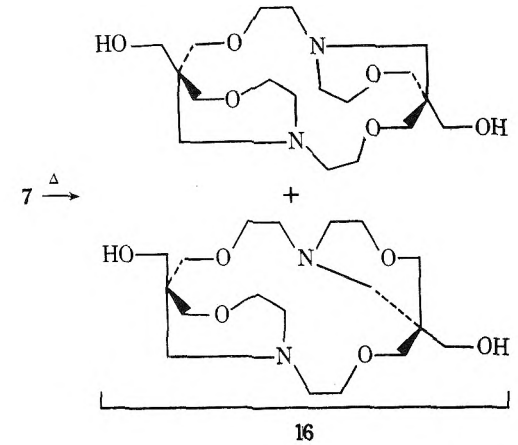

15

Further Reactions of the Oxetane and the Amine Functions. Since both amine groups in **7** are in position to close a seven-membered ring by intramolecular attack on an oxetane ring, thermolysis of neat **7** was undertaken. Little reaction occurred at 210°, but at 230° the rearrangement proceeded to give two isomers of **16,** presumably those represented below. Although no complexes of **16** have yet been prepared, the unusual cavity with both bridgehead carbon and nitrogen atoms is expected to yield interesting results.[4]

Thermolysis of **12** at 230° led mainly to recovered starting material, a result ascribable to steric crowding associated with closure of a ten-membered ring. Thus, although **7** underwent intramolecular ring closure to **16** even in the presence of a large excess of ammonia, **12** reacted with ammonia to form **17.**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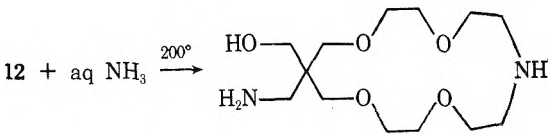
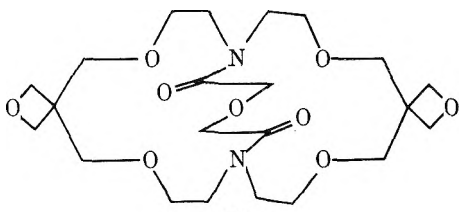

17

By means of the general technique used on related compounds by Simmons and Park[5] and Lehn and Montavan,[6] the diamines **7** and **14** were bridged with diglycolyl dichloride to give **18** and **19,** the first examples of cage polyethers bearing the oxetane function. Presumably the amide groups could be reduced to amine with diborane to provide strongly complexing ligands.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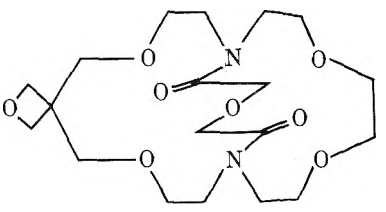
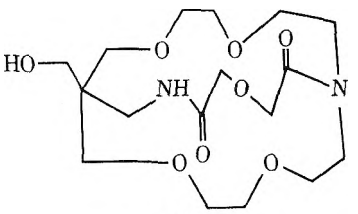

19

Diglycolyl dichloride was also treated with **17** to form the diamide **20,** in this case a cage polyether with one carbon and one nitrogen as bridgehead atoms.


20

Experimental Section[7]

2-Oxa-6,9-diazaspiro[3.6]decane (2), *N*-(2-Aminoethyl)-2-oxa-6-aza-spiro[3.3]heptane (3), and 1,2-Bis[*N*-(2-oxa-6-aza-spiro[3.3]heptyl)]ethane (4). A mixture of 15.5 g (0.10 mol) of 3,3-bis(chloromethyl)oxetane, 6.0 g (0.10 mol) of ethylenediamine, 300 ml of 1-propanol, and 31.8 g (0.30 mol) of anhydrous sodium carbonate was refluxed under nitrogen for 2 weeks. The mixture was then filtered and distilled to give 1.5 g (10%) of **3,** bp 45–47° (0.1 mm), and 0.7 g (5%) of **2,** bp 60° (0.1 mm).

For **3**: ir 2.97, 3.03, and 6.25 (NH_2), 3.40, 3.48, and 3.56 (saturated CH), 10.30, and 10.60 μ (oxetane); ^1H NMR (acetone-d_6) 4.60 (s, 2 H, oxetane), 3.30 (s, 2 H, azetidine), 1.83 ppm (broad, NH shifted by addition of D_2O), with rough triplets of AA'BB' at 197 (hidden), 190, 183, and 160, 153, 146 Hz (1 H each); mass spectrum *m/e* 142 (M^+), 112.0779 ($M^+ - CH_2NH_2$ and not $M^+ - CH_2O$), 82 ($M^+ - CH_2NH_2 - CH_2O$).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.25; H, 9.94; N, 19.82.

Compound **2** crystallized and was triturated with a small amount of ether, then ether–petroleum ether to give 0.2 g of deliquescent and somewhat impure **2**: mp 54–55°; ir (Nujol) 3.08 (NH), 10.47 μ (oxetane); ^1H NMR (acetone-d_6) δ 4.27 (s, 2 H, oxetane), 3.12 (s, 2 H, CCH_2N), 2.76 (s, 2 H, NCH_2CH_2N), 2.63 ppm (s, 1 H, NH shifted downfield with D_2O); mass spectrum *m/e* 142 (M^+), 141 ($M^+ - H$), 112.1008 ($M^+ - CH_2O$ and not $M^+ - CH_2NH_2$). Trimethylsilylation gave *m/e* 286 [M^+ for addition of two $(CH_3)_3Si$ groups], 273 ($M^+ - CH_3$), 256 ($M^+ - CH_2O$).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.76; H, 10.34; N, 18.92.

Sublimation of **4** from the distillation residue at 100° (0.3 mm) gave 0.9 g, mp 90–95°. Resublimation at 75° (0.03 mm) gave 0.64 g (6%) of **4**: mp 95–99°; ir (Nujol) 10.36 and 10.65 μ (oxetane); ^1H NMR (acetone-d_6) 4.60 (s, 2 H, oxetane), 3.25 (s, 2 H, azetidine), 2.26 ppm (s, 1 H, NCH_2CH_2N); mass spectrum *m/e* 224 (M^+), 194 ($M^+ - CH_2O$), 172, 126, 112, 82.

Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 63.83; H, 9.01; N, 12.41.

2,9,12,15-Tetraoxa-6,18-diazaspiro[3.15]nonadecane (5) and *N*-(11-Amino-3,6,9-trioxa-1-undecyl)-2-oxa-6-azaspiro[3.3]-heptane (6). A mixture of 15.5 g (0.10 mol) of 3,3-bis(chloromethyl)oxetane, 19.2 g (0.10 mol) of 3,6,9-trioxaundecane-1,11-diamine, 38.7 g (0.30 mol) of diisopropylethylamine, and 500 ml of 1-propanol was refluxed under nitrogen for 3 days. The mixture was cooled, treated with 21.2 g (0.20 mol) of anhydrous sodium carbonate, and refluxed for an additional 5 hr. The reaction mixture was then filtered and distilled in a molecular still to give 4.6 g (17%) of an approximately equimolar mixture of isomers **5** and **6**: bp 108–110° (0.1 μ); ir 2.98 (sh) and 3.02 (NH), 6.26 (NH_2, relatively weak), 8.9 (broad, COC), 10.28, and 10.61 μ (oxetane ring); NMR indicated a mixture of oxetanes for which assignments could be made as described below.

Anal. Calcd for $C_{13}H_{26}N_2O_4$: C, 56.91; H, 9.55; N, 10.21; mol wt, 274. Found: C, 56.88; H, 9.23; N, 9.93; mol wt, 274 (field ionization mass spectrum).

The mixture of **5** and **6** was separated by formation of the crystalline complex of **5** with NaSCN. A solution of 1.2 g (0.0044 mol) of the mixture and 0.32 g (0.004 mol) of NaSCN in 10 ml of acetone was evaporated to ca. 5 ml, 5 ml of ether was added, and the mixture was allowed to stand overnight. The supernatant liquid was decanted and the solid was recrystallized from acetone–ether, then from acetone to give the 1:1 complex as large, colorless cubes: mp 154.5–155.5°; ir (Nujol) 3.08 (NH), 4.85 (SCN), 8.8–9.5 (COC), 10.21, and 10.60 μ (oxetane); ^1H NMR (acetone-d_6) 4.43 (s, 2 H, oxetane CH_2), 3.67 (s, 4 H, OCH_2CH_2O), 3.12 (s, 2 H, CCH_2N), and 2.43 ppm (broad, 1 H, NH) with rough triplets of an AA'BB' pattern at 225, 220.5 (hidden), 216 (2 H, NCH_2CH_2O) and 177, 172.5, 168 Hz (2 H, NCH_2CH_2O).

Anal. Calcd for $C_{14}H_{26}N_3NaO_4S$: C, 47.31; H, 7.37; N, 11.82; Na, 6.47. Found: C, 47.49; H, 7.21; N, 11.62; Na, 7.33.

The mother liquor from complex formation was evaporated to a viscous residue and the residue was extracted with 50 ml of benzene. Evaporation of the benzene gave a residue which was extracted with 50 ml of petroleum ether. Evaporation of the petroleum ether gave an oil, nearly pure **6**: ^1H NMR (acetone-d_6) 4.60 (s, 2 H, oxetane), 3.57 and 3.54 (both s, combined area 6 H, NCH_2CH_2O-$CH_2CH_2OCH_2CH_2$), and 3.31 ppm (s, 2 H, azetidine) with rough triplets of an AA'BB' pattern hidden near 200 Hz and at 155.5, 150, and 144 Hz; NH_2 resonance uncertain owing to impurity peaks.

Subtraction of the above spectrum from that of the original mixture leaves for uncomplexed **5** ^1H NMR 4.30 (s, 2 H, oxetane), 3.55 (s, 4 H, OCH_2CH_2O), and 2.93 ppm (s, 2 H, CCH_2N) with AA'BB' triplets hidden near 210 and at 169, 164, and 159 Hz.

2,6,12,16,19,25-Hexaoxa-9,22-diazadispiro[3.9.3.9]hexacosane (7) and *N*-(2-Hydroxyethyl)-2,6-dioxa-9-azaspiro[3.6]decane (8). A solution of 105.0 g (1.0 mol) of diethanolamine, 155.0 g (1.0 mol) of 3,3-bis(chloromethyl)oxetane, and 233 g (2.08 mol) of potassium *tert*-butoxide in 2.5 l. of *tert*-butyl alcohol was refluxed and stirred under N_2 for 2 days. The addition of oxetane, glycol, and butoxide was repeated, and reaction was continued for 4 days. Filtration and evaporation of the filtrate to 60° (0.5 mm) gave a semisolid residue which was kept at 90° and extracted continuously with heptane for 3 days. Removal of heptane from the extract and recrystallization from ether gave 63.6 g (17%) of **7**, mp 118.5–119°. An analytical sample was recrystallized from tetrahydrofuran: mp 118.5–119°; ir (Nujol) 3.04 (NH), 8.6–9.5 (COC), 10.07, 10.29, 10.52, and 10.75 μ (oxetane); NMR [$(CD_3)_2CO$] 4.36 (s, 1, oxetane CH_2), 3.68 (s, 2, along with underlying OCH_2CH_2N, CCH_2O), 2.30 ppm (very broad NH) with AA'BB' branches at 221 (hidden), 216.5, and 211 (OCH_2CH_2N) and 172, 166.5, and 162 Hz (OCH_2CH_2N).

Anal. Calcd for $C_{18}H_{34}N_2O_6$: C, 57.73; H, 9.15; N, 7.48; mol wt, 374.5. Found: C, 57.62; H, 8.86; N, 7.61; mol wt, 398 (ebullioscopic, PhH).

Distillation of the ether filtrate afforded, in addition to considerable viscous residue, 4.9 g (1.3%) of **8**: bp 108–114° (0.25 mm); ir 2.92 (OH), 3.42 and 3.49 (saturate CH), 8.5–9.5 (COC, COH), and 10.4 μ (oxetane); NMR [$(CD_3)_2CO$] 4.37 (s, 4, oxetane CH_2), 3.97 (s, 2, CCH_2O), 3.07 (s, 2, CCH_2N), with multiplets at 3.7–3.4 (5, OCH_2CH_2N + OH) and 2.8–2.55 ppm (4, OCH_2CH_2N).

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.42; H, 9.27; N, 7.38.

The 1:1 complex of **7** with cupric acetate was obtained as follows. Solutions of 0.20 g (0.001 mol) of $Cu(OAc)_2 \cdot H_2O$ in 15 ml of warm absolute ethanol and 0.36 g (0.001 mol) of diamine **7** in 10 ml of ethanol were mixed to give deepening of blue color, but no precipitate. Most of the solvent was removed and 25 ml of ether was added. The precipitate was triturated thoroughly and filtered to give 0.52 g (93%) of violet 1:1 complex, mp 156–158° dec, recrystallized from tetrahydrofuran–ether for analysis: mp 159–160.5° dec; ir (Nujol) 3.08 and 3.16 (NH), 6.21 and 6.29 (CO_2^-), broad 8.6–9.5 (COC), and 10.24, 10.77 μ (oxetane); ^1H NMR signals greatly broadened by paramagnetic Cu^{2+}.

Anal. Calcd for $C_{22}H_{40}CuN_2O_{10}$: C, 47.51; H, 7.25; N, 5.04; Cu, 11.43. Found: C, 47.64; H, 7.59; N, 4.95; Cu, 11.51.

5-Chloro-3-oxapentan-1-ol and Its Reaction with Ammonia. A mixture of 1696 g (16.0 mol) of diethylene glycol and 632 g (8.0 mol) of pyridine was cooled at 0° and stirred while 952 g (8.0 mol) of thionyl chloride was added at a rate sufficient to maintain the temperature near 20°. When all the thionyl chloride had been added (3.5 hr), the temperature was raised to about 80°, at which point noticeable SO_2 evolution occurred. After 3 hr at 80°, the mixture stood over the weekend. It was then heated slowly to 125° and held at 125° until gas evolution had nearly ceased (3 hr). The mixture was distilled and the fraction of bp 60–110° (5 mm) was redistilled through a spinning band column to afford 453 g (45%) of 5-chloro-3-oxapentan-1-ol: bp 75–76° (5 mm); $n^{22}D$ 1.4519;[8] ir 2.92 (OH), 8.8–9.5 (COC), 13.4 μ (CCl).

A mixture of 110 g (0.88 mol) of the chloropentanol, 100 g of NH_3, and 500 ml of absolute alcohol was heated at 120° for 15 hr under autogenous pressure. The reaction mixture was refluxed with 150 g of anhydrous sodium carbonate for 4 hr and filtered, and the filtrate was distilled. There was thus obtained 40.6 g (44%) of **11**, bp 98–99° (5 mm), $n^{24}D$ 1.4588, and 21.6 g (25%) of **9**, bp 128° (20 μ), $n^{27}D$ 1.4717.

For **11**: ir 2.99 and 3.05 (NH_2), 3.1 (broad sh, H-bonded OH, NH_2), 6.25 (NH_2), and 8.92 and 9.33 μ (C–O); ^1H NMR 4.17 (s, partial exchange with acetone-d_6, OH), 3.56 (s atop broad multiplet, OCH_2CH_2O), 3.2–3.8 (multiplet, OCH_2CH_2N), 1.90 ppm (broad s, partial exchange with acetone-d_6, NH_2).

Anal. Calcd for $C_4H_{11}NO_2$: C, 45.69; H, 10.55; N, 13.33. Found: C, 45.75, 45.35; H, 10.05, 10.24; N, 12.41.

For **9**: ir 3.0–3.05 (broad, NH, H-bonded OH), 8.95 and 9.38 μ (C–O); ^1H NMR 3.93 (s, 3 H, OH + NH), 3.4–3.7 ppm (multiplet, 12 H, $OCH_2CH_2OCH_2$), with one branch of an AA'BB' pattern at 172, 167, and 162 Hz (4 H, CH_2N), addition of D_2O changed only the δ 3.93 peak to 4.07.

Anal. Calcd for $C_8H_{19}NO_4$: C, 49.72; H, 9.91; N, 7.25. Found: C, 49.96; H, 9.62; N, 7.60.

Scale-up of the synthesis gave an improved yield of **9**. A mixture of 450 g (3.6 mol) of 5-chloro-3-oxapentan-1-ol, 400 g of ammonia, and 2 l. of absolute ethanol was heated at 125° for 15 hr under autogenous pressure in a 3-gal autoclave. The dark reaction mixture was refluxed for 4 hr with 600 g of anhydrous Na_2CO_3, filtered, and distilled to give 164.3 g (43%) of **11**, bp 60–65° (0.2 mm), and 145.3 g (42%) of **9**, bp 140–145° (15 μ).

Diol **9** was also obtained by alkylation of by-product **11** as follows. A solution of 52.5 g (0.50 mol) of **11** and 74.7 g (0.60 mol) of 5-chloro-3-oxapentan-1-ol in 200 ml of 1-butanol was heated at

100° for 4 days. The mixture was then refluxed for 1.5 hr with 100 g of anhydrous Na_2CO_3, filtered, and distilled to give 39.3 g (41%) of **9**, $n^{22.5}D$ 1.4743, and 15.4 g (11%) of **10**, bp 174–176° (4 μ), $n^{22.5}D$ 1.4820. For **10**, ir and NMR fit the assigned structure.

Anal. Calcd for $C_{12}H_{27}NO_6$: C, 51.23; H, 9.67; N, 4.98. Found: C, 51.26; H, 9.13; N, 5.37.

A stable, crystalline complex was obtained from the acyclic compound **10** and NaSCN. Reaction of 0.50 g (0.0062 mol) of NaSCN and 1.74 g (0.0062 mol) of **10** in acetone led to 2.14 g (95%) of the 1:1 complex. Recrystallization from acetone gave an analytical sample: mp 104–105°; ir (Nujol) 2.93 (OH), 3.15 (NH), 4.79 (SCN), 8.5–9.5 μ (COC, COH). The ^1H NMR spectrum was similar to that of the uncomplexed amine.

Anal. Calcd for $C_{13}H_{27}N_2NaO_6S$: C, 43.08; H, 7.51; N, 7.73; Na, 6.34. Found: C, 43.62; H, 7.28; N, 7.74; Na, 5.7.

2,6,9,15,18-Pentaoxa-12-azaspiro[3.15]nonadecane (12). An attempt to N-benzoylate **9** with benzoic acid–dicyclohexylcarbodiimide in glyme led instead to 73% of *N*-benzoyl-*N,N'*-dicyclohexylurea. Similarly, the mixed anhydride PhCOOCOO-*i*-Bu with **9** did not give the *N*-benzoyl derivative. In view of the rather low reactivity of the N atom in **9** as a nucleophile, condensation with bis(chloromethyl)oxetane was attempted directly.

A solution of 62.0 g (0.40 mol) of bis(chloromethyl)oxetane, 94.0 g (0.84 mol) of potassium *tert*-butoxide, and 77.2 g (0.40 mol) of **9** in 1 l. of *tert*-butyl alcohol was refluxed and stirred under N_2 for 6 days. Filtration and evaporation of the reaction mixture to 50° (0.5 mm) gave a residue which crystallized on cooling. The crude **12** was kept molten at ~90° and extracted continuously with heptane for 1 day. The cooled extract was filtered, and the solid so isolated was recrystallized from ether to give 74.2 g (67%) of **12**, mp 79–81°. An analytical sample, mp 80–81°, was recrystallized from ether: ir (Nujol) 3.01 (NH), 8.6–9.1 (COC), 10.22, and 10.74 μ (oxetane); NMR [$(CD_3)_2CO$] 4.32 (s, 4, oxetane CH_2), 3.65 (s, 4, CCH_2O), 3.57 (s, 12 with underlying OCH_2CH_2N, OCH_2CH_2), and 2.32 ppm (broad s, 1, NH) with OCH_2CH_2N appearing as AA'BB' at 214 (hidden), 209, and 204 (OCH_2) and 162, 157, and 152 Hz (4, CH_2N). Addition of D_2O moved the NH resonance downfield.

Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.71; H, 9.15; N, 5.09; mol wt, 275. Found: C, 56.61; H, 8.88; N, 5.04; mol wt, 272 (cryoscopic, PhH).

A 1:1 complex of **12** with NaSCN was prepared in acetone, crystallized by concentration and addition of a small amount of ether, and isolated in 93% yield, mp 113–114°. A recrystallized sample had mp 113–114°; ir (Nujol) 3.03 (NH), 4.86 (SCN), 8.7–9.5 (COC), 10.36, 10.57, and 10.75 μ (oxetane); NMR [$(CD_3)_2CO$] 4.43 (s, 4, oxetane CH_2), 3.98 (s, 4, CCH_2O), and 3.73 ppm (s, 12 with nearby OCH_2CH_2N, OCH_2CH_2O), with OCH_2CH_2N appearing as AA'BB' at 221, 216.5, and 211.5 (OCH_2) and 174.5, 169.5, and 165 Hz (4, CH_2N).

Anal. Calcd for $C_{14}H_{25}N_2NaO_5S$: C, 47.18; H, 7.07; N, 7.86; Na, 6.45. Found: C, 47.41; H, 7.14; N, 8.16; Na, 6.06.

Reaction of 12 with Ethylene Oxide. A mixture of 27.5 g (0.10 mol) of **12**, 10 g (0.23 mol) of ethylene oxide, and 200 ml of methanol was heated in a bomb tube at 100° for 6 hr autogenous pressure. Solvent was evaporated, and the product was volatilized in a very short-path still at about 190° (~20 μ), giving 27.6 g (87%) of *N*-(2-hydroxyethyl)-2,6,9,15,18-pentaoxa-12-azaspiro[3.15]nonadecane (**13**) as a nearly colorless oil: ir (2.90 (OH), 8.7–9.5 (COC, COH), 10.23, and 10.80 μ (oxetane); NMR [$(CD_3)_2CO$] 4.29 (s, 4, oxetane CH_2), 3.74 (s, 4, CCH_2O), 3.6–3.3 (m, 15, OCH_2CH_2O + OH + OCH_2CH_2N), 2.85–2.5 ppm (m, 6, CH_2N).

Anal. Calcd for $C_{15}H_{29}NO_6$: C, 56.41; H, 9.15; N, 4.39. Found: C, 56.43; H, 8.80; N, 4.54.

The complex of **13** with NaSCN could not be induced to crystallize.

2,6,12,15,21-Pentaoxa-9,18-diazaspiro[3.18]docosane (14) and 15-Hydroxymethyl-4,7,13,17-tetraoxa-1,10-diazabicyclo[13.4.1]eicosane (15). A solution of 202 g (0.855 mol) of 6,9-dioxa-3,12-diazatetradecane-1,14-diol, 132.8 g (0.855 mol) of 3,3-bis(chloromethyl)oxetane, and 191.5 g (1.71 mol) of potassium *tert*-butoxide in 2.35 l. of *tert*-butyl alcohol was stirred and refluxed under N_2 for 5 days, cooled, and filtered. The filtrate was concentrated to 50° (0.5 mm) and the residual oil was extracted continuously with pentane for 4 days. Concentration of the extracts gave 198.4 g (71%) of crude **14** as a thick yellow oil. This product could not be purified by distillation (see below), but NMR and ir indicated it to be **14**. The structure was confirmed by isolation of the 1:1 complex of **14** with NaSCN in high yield as follows.

A solution in acetone (15 ml) of 3.18 g (0.01 mol) of crude **14** and 0.81 g (0.01 mol) of NaSCN was evaporated to a volume of 10 ml and 5 ml of ether was added. The cloudy solution was seeded with previously prepared complex and on standing gave 3.20 g (80%) of 1:1 complex, mp 147–150°. Recrystallization from a small amount of acetone gave 2.63 g of complex, mp 151–153.5°, shown by mixture melting point to be the same as authentic complex. An analytical sample of similarly prepared complex had mp 151–153°; ir (Nujol) 2.97 and 3.04 (NH), 4.82 (SCN), 8.5–9.5 (COC), 10.03, 10.48, and 10.53 μ (oxetane); NMR [$(CD_3)_2CO$] 4.36 (s, 2, oxetane CH_2), 3.90 (s, 2, CCH_2O), 3.75–3.5 with major singlet at 3.64 for OCH_2CH_2O (m, 6, OCH_2), and 2.23 ppm (broad, 1, NH), with one branch of A_2B_2 at 173.5, 168, and 164 Hz (4, NCH_2).

Anal. Calcd for $C_{16}H_{30}N_3NaO_5S$: C, 48.11; H, 7.57; N, 10.52; Na, 5.75. Found: C, 47.76; H, 7.57; N, 10.60; Na, 5.65.

A 1:1 complex of **14** with NaI was similarly obtained as hygroscopic crystals: mp 143–145°; ir (Nujol) 3.09 (NH), 8.5–9.5 (COC), 10.07, and 10.57 μ (oxetane); NMR [$(CD_3)_2CO$] 4.38 (s, 2, oxetane CH_2), 3.95 (s, 2, CCH_2O), 3.7–3.55 with major singlet at 3.67 (m, 6, OCH_2), 3.0–2.7 (m, 2, NCH_2), and 1.83 ppm (s shifted downfield by D_2O, 1, NH).

Anal. Calcd for $C_{15}H_{30}N_2NaO_5I$: C, 38.47; H, 6.46; N, 5.98; I, 27.10. Found: C, 38.36; H, 6.37; N, 5.77; I, 26.90.

Another preparation of **14** gave a similar yield of crude product, which was distilled through a Vigreux column. Fractions taken at ~160 (0.3 μ) to 180° (1.0 μ) were 65.7 g (21%) of mixtures of **14** and **15**. Product distilled at 180–185° (1.0 μ) was 85.1 g (27%) of the exceptionally viscous **15**, formed by intramolecular attack of NH on the oxetane ring: ir 2.92, 3.00, and 3.12 (OH, NH), 3.37 (sh), and 3.46 (saturate CH), 8.5–9.5 μ (COC, COH); NMR [$(CD_3)_2CO$] 3.8–3.1 (m, 2, OCH_2 + OH + NH) and 2.8–2.5 ppm (m, 1, NCH_2).

Anal. Calcd for $C_{15}H_{30}N_2O_5$: C, 56.58; H, 9.50; N, 8.80. Found: C, 56.75; H, 9.74; N, 8.57.

The 1:1 complex was prepared in acetone from 3.18 g (0.01 mol) of **15** and 0.81 g (0.01 mol) of NaSCN, 3.57 g (90%), mp 163–164°. An analytical sample was obtained from acetone–ether: mp 164–165°; ir (Nujol) 2.95 (OH), 3.02 (NH), 4.83 and 4.92 (SCN), 8.6–9.6 μ (COC, COH); NMR [$(CD_3)_2CO$] 3.7–3.15 (m, 19, OCH_2 + OH) and 2.7–2.3 ppm (m, 11, NCH_2 + NH).

Anal. Calcd for $C_{16}H_{30}N_3NaO_5S$: C, 48.11; H, 7.57; N, 10.52; Na, 5.75. Found: C, 47.84; H, 7.67; N, 10.38; Na, 5.68.

Isomers of 6,16-Bis(hydroxymethyl)-4,8,14,18-tetraoxa-1,11-diazatricyclo[14.4.1.1^{6,11}]docosane (16). Thermolysis of neat **7** at 205–210° under nitrogen for 8 hr gave recovered **7**. At 225–230° for 24 hr, 4.0 g (0.0107 mol) of **7** formed a viscous product which gave 2.7 g of isomers of **16**, mp ~155–170°, when triturated with 30 ml of benzene. Two recrystallizations from benzene gave 1.3 g of needles, isomer A, mp 177.5–177°. A second crop, 0.2 g, mp 173–176°, raised the yield to 1.5 g (38%). An analytical sample was obtained from acetone: mp 177.5–178.5°; ir (Nujol) 2.90 (OH), 8.5–9.6 μ (COC, COH); NMR [$(CD_3)_2SO$] 4.2–1.6 ppm (complex multiplet). A broad band at 4.2 ppm (OH) was shifted upfield by addition of D_2O, leaving none in the region for oxetane ring. Mass spectrum *m/e* for silylation product 518 (disilylated M^+), 503 (disilylated $M^+ - CH_3$). Mass measurement on parent gave *m/e* 518.3190 for $C_{24}H_{50}O_6N_2Si_2$ (calcd, 518.3204).

Anal. Calcd for $C_{18}H_{34}N_2O_6$: C, 57.73; H, 9.15; N, 7.48. Found: C, 58.00; H, 9.02; N, 7.44.

The filtrate from isomer A contained some lower melting isomer B, which could not be isolated by crystallization from ether or benzene.

An attempt to obtain intermolecular addition to the oxetane rings with ammonia was carried out below 210°, but in water solution. In the polar solvent, reaction proceeded at only 200° to give the two isomers of **16** rather than ammonia adducts. In this case, isomer B was isolated as follows.

A mixture of 8.2 g (0.022 mol) of **7** and 100 ml of concentrated NH_4OH was heated at 200° for 17 hr under autogenous pressure. The clear reaction mixture was evaporated to a solid residue, which was heated with 25 ml of acetone and cooled to give 2.75 g of isomer A, mp 173–177°. A second crop, 1.68 g, mp 125–135°, was mainly isomer B. A third crop, 0.34 g, mp 171–176°, raised the yield of isomer A to 3.09 g (38%). The second crop was recrystallized from methanol–acetone to give 1.21 g (15%) of isomer B, mp 126–128°. An analytical sample was obtained from acetone with a little methanol added, as large cubes: mp 127.5–129°; ir (Nujol) 2.91 (OH) and 8.5–9.5 μ (COC, COH) with no isomer A detectable; NMR [$(CD_3)_2SO$] 4.3–2.1 ppm (complex multiplet different from that for isomer A). A broad band at 4.3 ppm (OH) was shifted upfield by D_2O, leaving none in the region for oxetane ring. Mass

spectrum *m/e* for silylated derivative 518 (disilylated M^+); the spectrum is nearly identical with that of isomer A.

Anal. Calcd for $C_{18}H_{34}N_2O_6$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.50; H, 8.80; N, 7.76.

15-Aminomethyl-15-hydroxymethyl-1,4,10,13-tetraoxa-7-azacyclohexadecane (17). After neat **12** was heated under nitrogen at 220–230° for 20 hr, 81% of the starting material was recovered. Ammonia can therefore attack **12** to form an adduct.

A mixture of 27.5 g (0.01 mol) of **12** and 200 ml of concentrated NH_4OH was heated at 200° for 20 hr under autogenous pressure. Evaporation of the reaction mixture gave 28.8 g of viscous residue. Attempts to crystallize 1.4 g of the crude product failed, so the remainder was distilled in a molecular still to give 15.2 g (52%) of **17**: bp 105° (1 μ); mp 52–56°; ir (neat) 2.95 (sh), 3.03 and 3.14 (OH, NH, NH_2), 3.50 (saturated CH), 6.24 (NH_2), and broad 8.6–9.6 μ (COC, COH); NMR [$(CD_3)_2CO$] 3.7–3.5 (m, 18, OCH_2), 3.18 (broad s, 3, with partial exchange into $(CD_3)_2CO$, OH, and NH_2), 2.65–2.9 (m, 6, NCH_2), and 1.30 ppm (broad s, 1, NH). D_2O shifted the 3.18 ppm peak downfield. Mass spectrum *m/e* for silylated derivative 508 (trisilylated M^+), 493 (trisilylated $M^+ - CH_3$), 436 (disilylated M^+), and 421 (disilylated $M^+ - CH_3$). Mass measurement of trisilylated parent gave *m/e* 508.3181 (calcd for $C_{22}H_{52}O_5N_2Si_3$, 508.3181).

Anal. Calcd for $C_{13}H_{28}N_2O_5$: C, 53.40; H, 9.65; N, 9.58. Found: C, 53.73; H, 10.04; N, 9.95.

Dispiro[oxetane-3,6′-21′,25′-diketo-4′,8′,14′,18′,23′-pentaoxa-1′,11′-diazabicyclo[9.9.5]pentacosane-16′,3″-oxetane] (18). Solutions of 37.5 g (0.10 mol) of **7** in 200 ml of purified CH_2Cl_2 and 17.1 g (0.10 mol) of diglycolyl dichloride in 200 ml of dry benzene were added simultaneously and with vigorous stirring to a mixture of 50 ml of triethylamine and 1 l. of dry benzene. After the addition was completed (4 hr), the mixture was filtered and the filtrate was evaporated to give 32.3 g of solid. Extraction of the filter cake with hot benzene gave another 1 g of solid. Recrystallization of the crude product from acetone gave 20.5 g (43%) of **18**, mp 188–191°. An analytical sample, mp 190–192°, was obtained from acetone: ir (Nujol) 5.97 and 6.02 (amide CO), 8.6–9.4 (COC), 10.15, 10.33, and 10.51 μ (oxetane); ^1H NMR [$(CD_3)_2SO$] 4.5–4.0 (m, 4) and 3.8–3.2 ppm (m, 5).

Anal. Calcd for $C_{22}H_{36}N_2O_9$: C, 55.92; H, 7.68; N, 5.93; mol wt, 473. Found: C, 55.82; H, 7.74; N, 6.16; mol wt, 467 (ebullioscopic, PhH).

Spiro[20,24-diketo-4,8,14,17,22-pentaoxa-1,11-diazabicyclo-[9.8.5]tetracosane-6,3′-oxetane] (19). Solutions of 31.8 g (~0.10 mol) of crude **14** in 200 ml of dry benzene and 17.1 g (0.10 mol) of diglycolyl dichloride in 210 ml of dry benzene were added dropwise and simultaneously to a vigorously stirred mixture of 50 ml of triethylamine and 1 l. of dry benzene. After addition was completed (3.5 hr), stirring was continued for an additional 15 min, the mixture was filtered, and the filtrate was evaporated to give 26.3 g of viscous residue. Crystallization from acetone gave 12.3 g (30%) of **19**, mp 178–181°. An analytical sample was obtained from acetone: mp 180.5–182°; ir (Nujol) 6.03 (C=O), 8.6–9.6 (COC), 10.27, and 10.78 μ (oxetane); ^1H NMR [$(CD_3)_2SO$] 4.3–4.0 (m, 1) and 3.7–3.2 (m, 2).

Anal. Calcd for $C_{19}H_{32}N_2O_8$: C, 54.79; H, 7.75; N, 6.73; mol wt, 416. Found: C, 54.88; H, 7.92; N, 6.50; mol wt, 417 (ebullioscopic, PhH).

2,6-Diketo-9-hydroxymethyl-4,11,14,19,22-pentaoxa-1,7-diazabicyclo[7.7.7]tricosane (20). A solution of 12.4 g (0.0425 mol) of diamine **17** diluted to 150 ml with purified methylene chloride and a solution of 7.3 g (0.0425 mol) of diglycolyl dichloride diluted to 150 ml with dry benzene were added simultaneously to a vigorously stirred mixture of 2 l. of dry benzene and 25 ml of triethylamine. Addition required 2.75 hr. The mixture was stirred for another 0.5 hr and filtered, and the solid was rinsed with benzene. Evaporation of the filtrate and rinsings gave a solid residue which was extracted with 2 × 500 ml of hot acetone. Evaporation of acetone gave 8.7 g of crude **20**. Another 0.9 g of crude **20** was obtained by extraction of the benzene-insoluble solid with cold acetone. Recrystallization of the crude product from 1:1 methanol–acetone gave 5.8 g (35%) of **20**, mp 182–185°. An analytical sample was recrystallized from methanol, then from methanol–acetone: mp 186–187.5°; ir (Nujol) 2.94 and 3.02 (OH and NH), 5.99 and 6.07 (C=O), 6.52 (amide II), and broad 8.7–9.4 μ (COC, COH); mass spectrum *m/e* (silylated derivative) 462 (monosilylated M^+). Mass measured at *m/e* 462.2415 corresponds to $C_{20}H_{38}O_8N_2Si$ (calcd, 462.2395) with no higher mass peaks observed. A model of this compound is very compact and suggests that silylation at the amide group may be hindered.

Anal. Calcd for $C_{17}H_{30}N_2O_8$: C, 52.30; H, 7.74; N, 7.18. Found: C, 52.48; H, 7.98; N, 7.13.

Registry No.—**1**, 78-71-7; **2**, 54384-39-3; **3**, 54384-40-6; **4**, 54384-41-7; **5**, 54384-42-8; **5** NaSCN, 54384-43-9; **6**, 54384-44-0; **7**, 54384-45-1; **7** $Cu(OAc)_2$, 54484-53-6; **8**, 54384-46-2; **9**, 54384-47-3; **10**, 54384-48-4; **10** NaSCN, 54384-49-5; **11**, 929-06-6; **12**, 54384-50-8; **12** NaSCN, 54384-51-9; **13**, 54384-52-0; **14**, 54384-53-1; **14** NaSCN, 54384-54-2; **14** NaI, 54384-55-3; **15**, 54384-56-4; **15** NaSCN, 54384-57-5; **16** isomer A-B, 54384-62-2; **16** isomer B-A, 54423-05-1; **17**, 54384-58-6; **18**, 54384-59-7; **19**, 54384-60-0; **20**, 54384-61-1; ethylenediamine, 107-15-3; 3,6,9-trioxaundecane-1,11-diamine, 929-75-9; diethanolamine, 111-42-2; 5-chloro-3-oxapentan-1-ol, 628-89-7; diethylene glycol, 111-46-6; ethylene oxide, 75-21-8; 6,9-dioxa-3,12-diazatetradecane-1,14-diol, 50977-92-9; diglycolyl dichloride, 21062-20-4.

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Synthesis of 2-Azacycl[3.2.2]azine

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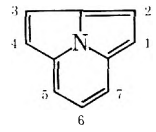
The synthesis of the aromatic 2-azacycl[3.2.2]azine is described. The results of CNDO/2 calculations point to the conclusion that the C_3–C_4 bond in this molecule seems to be only minimally involved in bond delocalizaiion with the remainder of the periphery.

Some years ago, Boekelheide and coworkers[1] prepared and studied the 10-π periphery aromatic cycl[3.2.2]azine (**1**).



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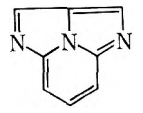
In view of the fact that resonance theory, as well as various LCAO approximations, place a substantial negative charge at positions 1 and 4 in the ground state of this molecule, we prepared the 1,4-diazacycl[3.2.2]azine (**2**) in order



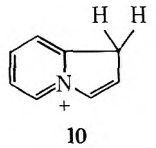
2

to examine its chemistry. To our surprise, we found this molecule to be readily hydrolyzed under rather mild acidic conditions.[2]

This result leads us to prepare 2-azacycl[3.2.2]azine (**8**) in an attempt to examine the effect that an sp^2 nitrogen has when it is in the 2 position of the cycl[3.2.2]azine (**1**) ring system rather than in the 1 position, as is the case in the 1,4-diazacycl[3.2.2]azine (**2**).

Since attempts at a cycloaddition of various dienophiles to imidazo[1,5-*a*]pyridine failed to produce the desired ring system, it was necessary to develop an alternate synthesis of 2-azacycl[3.2.2]azine (**8**). The sequence employed, and found useful, is delineated in Scheme I. The identities of the new compounds (**6, 7,** and **8**) were established by means of elemental analyses, ^{1}H NMR and ir spectral identifications, as well as mass spectroscopy.

Compound **6** could be, in principle, either the 3- or 4-substituted compound (**9** or **6**). This substance can be envisioned to be formed by cyclization of the possible intermediate **13** or by formylation of the primary product (**8**) expected from the reaction of 5-methylimidazo[1,5-*a*]pyridine (**5**) with dimethylformamide in the presence of butyllithium.



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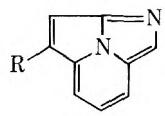
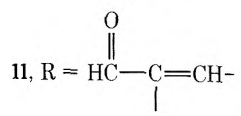
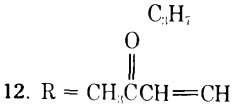
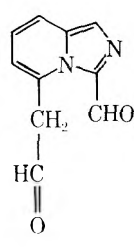




11, R = HC(=O)–C(C$_2$H$_5$)=CH–

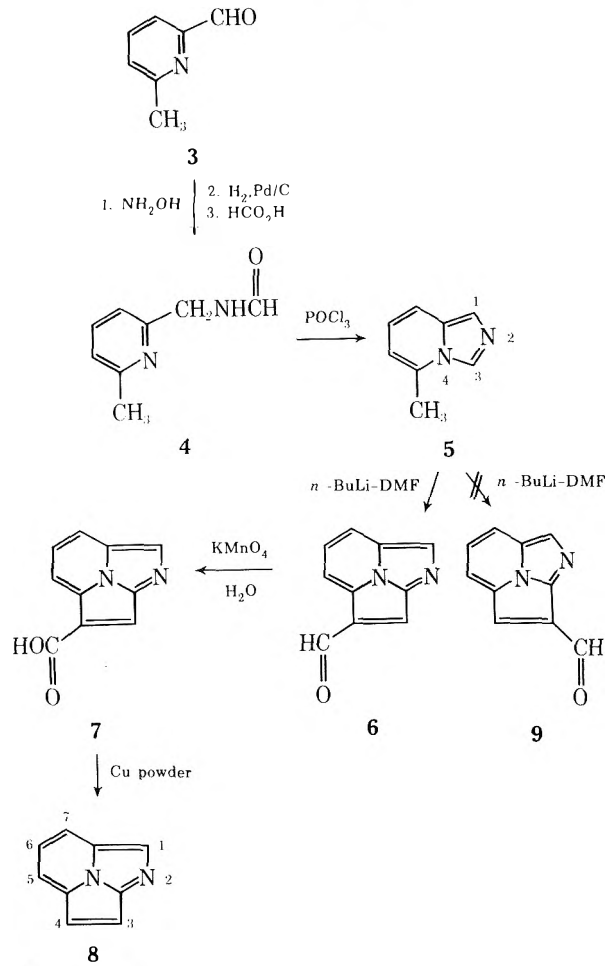


12. R = CH$_3$C(=O)CH=CH



13

Scheme I[a]



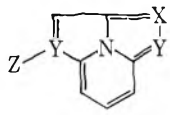
[a] DMF = dimethylformamide.

In order to establish the structure of this formyl derivative (**6** or **9**), the ^{1}H NMR spectrum of the compound was compared with those of compounds **11** and **12.**

If the substituents in these compounds were at position **3,** we would not expect any changes in the chemical shift of H-5. However, if the substituents are at C_4, the chemical shifts of H-5 in the three compounds would differ. As the tabulation of the spectral parameters (see Table I) shows, H-5 differs significantly in the formyl derivative from the chemical shifts of H-5 in the derivatives **11** and **12.** Thus, we are dealing with the 4-formyl derivative **6.**

This information is of great help in identifying the chemical shift of H-5 in the parent compound, since we can obtain $J_{5,6}$ in the formyl derivative (8.0 Hz) and thus, anticipating no change in this coupling constant in going from **6** to **8,** we can analyze the ^{1}H NMR spectrum of the parent (**8**) keeping this in mind.

Table I
^{3}H NMR PMR Spectral Parameters of Some Cycl[3.2.2]azines[a]



1, X = Y = C; Z = H
2, X = C; Y = N; Z = H
8, X = N; Y = C; Z = H
6, X = N; Y = C; Z = CHO
11, X = N; Y = C; Z = CH=C[$(CH_2)_2CH_3$](CHO)
12, X = N; Y = C; Z = HC=CH($COCH_3$)

Chemical shifts, ppm

Compd	H_1	H_2	H_3	H_4	H_5	H_6	H_7
1	2.81	2.50	2.50	2.81	2.14	2.14	2.14
2		1.30	1.30		1.88	1.88	1.88
8	1.55		2.35	2.70	2.04	2.49	2.18
6	1.28		1.86		1.45	2.02	1.74
11	1.38		2.04		1.78	2.13	1.78
12	1.40		2.11		1.72	2.13	1.76

Coupling constants, hz

1	$J_{5,6} = 8.0$,	$J_{1,2} = 4.2$		
2	$J_{5,6} = 8.0$			
8	$J_{5,6} = 7.8$,	$J_{6,7} = 7.0$,	$J_{3,4} = 4.7$,	$J_{1,4} = 1.0$
6	$J_{5,6} = 8.0$,	$J_{6,7} = 7.5$		
11	$J_{5,6} = 8.0$,	$J_{6,7} = 7.5$		
12	$J_{5,6} = 8.0$,	$J_{6,7} = 7.5$		

[a] Dilute solutions in $CDCl_3$.

Unfortunately, the ^{1}H NMR spectrum of the parent 2-azacycl[3.2.2]azine 8 cannot be analyzed by first-order principles. Consequently, it was necessary to compute a matching theoretical spectrum. The chemical shifts and coupling constants so obtained are listed in Table I, while Figure 1 shows the experimental, as well as theoretical, spectrum of the compound.

The ^{1}H NMR parameters of 2-azacycl[3.2.2]azine (8), in comparison with those of cycl[3.2.2]azine (1) and of the 1,4-diaza analog 2, allow some intriguing speculations.

If it is assumed that the ring current contribution in these three compounds is very similar, we can suggest that any differences in the chemical shifts of H_5, H_6, and H_7 between these compounds will, by and large, be a reflection of differences in the electron densities of C_5, C_6, and C_7.

A comparison of the ^{1}H NMR spectra of cycl[3.2.2]azine (1) with those of the 2-aza analog reveals their great similarity except for the expected greater deshielding of H-1 ($\Delta\delta$ 1.26) observed in the aza derivative 8, a value which is typical for the anisotropic contribution of sp^2 nitrogens to the chemical shift of protons on adjacent carbon atoms. The other difference is the chemical shift of H_3 in compound 8 as compared to H_3 (H_2) in cycl[3.2.2]azine (1). This proton is more deshielded by 0.15 ppm in the aza derivative 8. This is, of course due to the anisotropic effect of the lone pair of electrons on N_2 in compound 8 upon the peri-situated H-3. This peri effect has been previously described to be of this magnitude. It is of interest that H_5, H_6, and H_7 in 1,4-diazacycl[3.2.2]azine (2) are all more deshielded, implying a lower electron density at C_5, C_6, and C_7, than the similar protons in compounds 1 and 8. Thus, the presence of the two nitrogen atoms at positions 1 and 4 accommodate the negative charges more effectively than the corresponding carbon atoms in compounds 1 and 8.

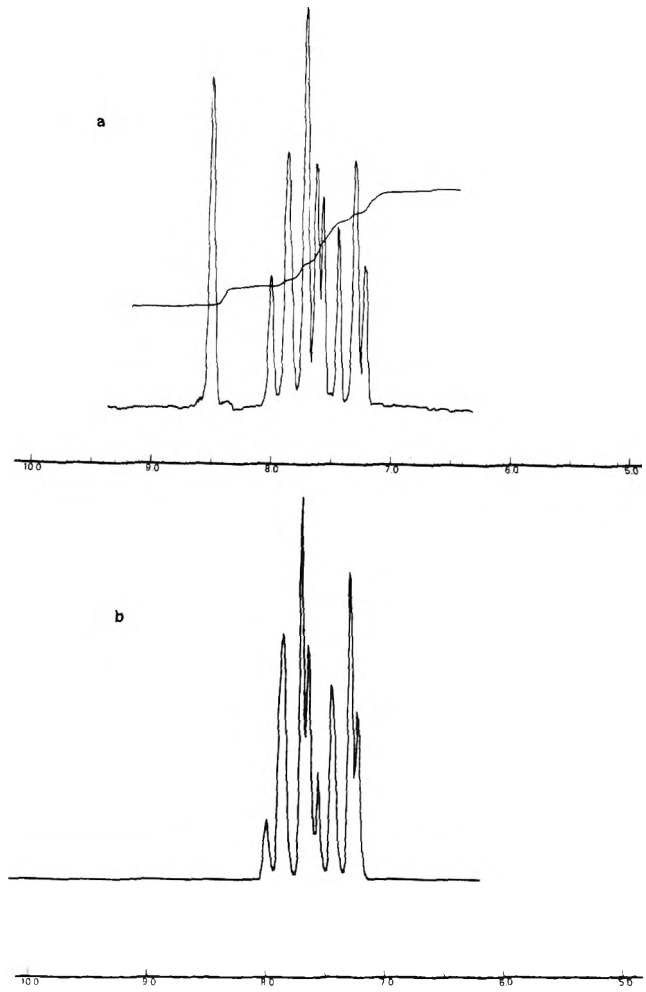
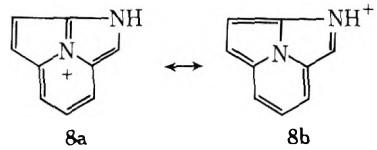


Figure 1. ^{1}H NMR spectra of 2-azacycl[3.2.2]azine: a, experimental spectrum, dilute solution in $CDCl_3$; b, computer-simulated spectrum without H-1.

The ^{1}H NMR spectrum of 2-azacycl[3.2.2]azine (8) in deuteriotrifluoroacetic acid (DTFAA) is instructive in determining the site of protonation to be N_2 rather than C_3 as is the case in the related pyrrocoline (10), since, upon basification of the DTFAA solution with sodium carbonate, the ^{1}H NMR spectrum in $CDCl_3$ of the recovered 2-azacycl[3.2.2]azine (8) is unchanged from the original spectrum.

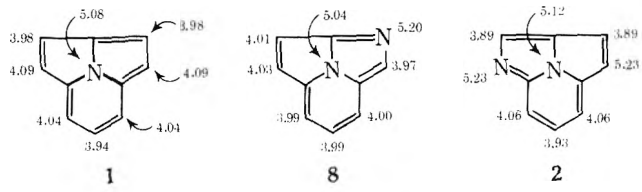
Thus, the protonated species of compound 8 is probably best represented by a resonance hybrid of **8a** and **8b**.



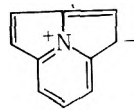
8a 8b

CNDO/2 Calculations. It is instructive to compare the results of CNDO/2 calculations on the three cyclazines, **1**, **2**, and **8**, in an attempt to examine the effects that the various nitrogen atoms in the periphery have upon the electron densities and other properties.[3]

The total electron densities at the various position for these compounds are indicated in the following structures.



In none of these compounds is there an electron withdrawal from the central nitrogen atom, thus resonance-contributing structures such as

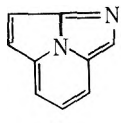


need not be considered for ground-state arguments. Quite to the contrary, there is a slight electron drift toward the central nitrogen atom, with the least pronounced one being in compound 8 and the most pronounced one in compound 2.

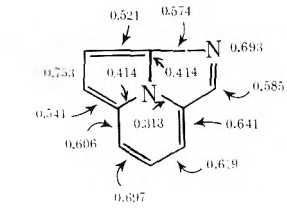
As expected, the peripheral nitrogens in compounds 2 and 8 have a substantial excess electron density. This excess density clearly derives largely from electron depletion from the carbon atoms adjacent to the periphery nitrogens.

The electron densities at the remaining carbon atoms are, not surprisingly, the same for the three cyclazines (1, 2, and 8). The great similarity of these ground-state electron densities precludes any possible predictions in terms of the expected patterns of electrophilic substitution, other than to suggest that position 1 might well be the most susceptible one toward this type of reaction.

2-Azacycl[3.2.2]azine (8), in contrast to compounds 1 and 2, has two different resonance-contributing structures, 8a and 8b.



8a

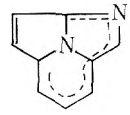


CNDO / 2 Bond orders are given

8b

An examination of the CNDO/2 bond orders given on structure 8b reveals that the size of the C_3–C_4 values is "unusually" large (indicating a "strong" double bond), and that the bond orders of the bonds emanating from the central nitrogen are rather small. This clearly displaces any thought that these bonds have any double-bond character.

Some experimental verification for the existence of a rather localized double bond is found in the size of $J_{3,4}$ (4.7 Hz), a value which suggest a π-bond order of 0.8.[5,6] Consequently, it appears that the compound should probably be written as follows (the dotted lines indicate π–π overlap of significant extent).



Thus, in terms of resonance theory, structure 8a is the more appropriate representation for this new cycl[3.2.2]azine.

Experimental Section[4]

2-Formaldoximo-6-methylpyridine. To 6-methyl-2-pyridine carboxaldehyde (6.05 g, 0.05 mol) dissolved in 10 ml of water was added a solution of hydroxylamine hydrochloride (7.0 g, 0.1 mol) in 20 ml of water. The solution was made basic with K_2CO_3 and heated gently for 3 hr. After cooling, the brown solid was separated by filtration, washed with water, and recrystallized from EtOH–H_2O to afford 6.10 g (90%) of the pure formaldoxime: mp 170–171°; NMR (DMSO) δ 8.32 (s, 1 H), 7.92–7.7 (m, 2 H), 7.40 (d, 1 H, J = 6 Hz), 2.72 (s, 3 H, CH_3); mass spectrum m/e 136 (M^+), 118 ($M^+ - 18$), 106 ($M^+ - 30$), 92 ($M^+ - 44$).

Anal. Calcd for $C_7H_8N_2O$: C, 61.76; H, 5.89; N, 20.06. Found: C, 61.37; H, 5.86; N, 20.49.

6-Methyl-2-aminomethylpyridine. 2-Formaldoximo-6-methylpridine (6.8 g, 0.05 mol) was dissolved in 200 ml of absolute methanol and 10% Pd/C (0.7 g) was added to the solution. The mixture was hydrogenated in a Parr hydrogenation apparatus at room temperature and at 40 psi for 3 hr. Most of the hydrogen was taken up after 1 hr. The mixture was filtered and the filtrate was evaporated under reduced pressure in order to remove the solvent. The remaining liquid was distilled under vacuum to afford a colorless liquid boiling at 55–57° (0.1 mm) (5.7 g, 94%) which rapidly turns yellow: NMR (D_2O) δ 7.71 (t, 1 H, J = 8 Hz), 7.26 (d, 1 H, J = 8 Hz), 7.07 (d, 1 H, J = 8 Hz), 3.91 (s, 2 H, $-CH_2-$), 2.54 (s, 3 H, CH_3), 5.13 (s, 2 H, $-NH_2$); mass spectrum (70 eV) m/e 122 (M^+), 121 ($M^+ - 1$), 107 ($M^+ - 15$), 93 ($M^+ - 29$).

6-Methyl-2-formamidomethylpyridine (4). To 6-methyl-2-aminomethylpyridine (6.8 g, 0.0557 mol) was added slowly with stirring 12 ml of 88% formic acid. The mixture was refluxed for 12 hr. Removal of the excess formic acid and fractional distillation in vacuo of the remaining liquid gave a yellow oil boiling at 118° (0.1 mm), which solidifies upon standing (7.0 g, 89.6%): ^1H NMR ($CDCl_3$), δ 8.26 (s, 1 H, –CHO), 7.50 (t, 1 H, J = 8 Hz), 7.02 (d, 2 H, J = 8 Hz), 4.51 (d, 2 H, J = 5 Hz), 2.47 (s, 1 H); mass spectrum (70 eV) m/e 150 (M^+), 120 ($M^+ - 30$), 106 ($M^+ - 44$).

Anal. Calcd for $C_8H_{10}N_2O$: C, 64.00; H, 6.68; N, 18.64. Found: C, 64.12; H, 6.78; N, 18.65

5-Methylimidazo[1,5-*a*]pyridine (5). To a stirred solution of 6-methyl-2-formamidomethylpyridine (4, 35.0 g, 0.233 mol) in 200 ml of dried benzene (distilled from sodium) was added dropwise freshly distilled phosphorus oxychloride (72 ml). The mixture was refluxed for 7 hr, and the excess $POCl_3$ and solvent were removed by distillation under reduced pressure. The remaining liquid was hydrolyzed at 0° with ice–water followed by basification with concentrated ammonium hydroxide. The solid which is formed was solubilized by addition of water (25 ml). The oily layer was separated by decantation and the aqueous layer was extracted with chloroform (2 × 150 ml). The two fractions (oil and extract) were combined, dried over anhydrous sodium carbonate, and distilled in vacuo. The product (5) is thus obtained as a pale yellow liquid boiling at 95–98° (0.1 mm) (23.87 g, 78%): ^1H NMR ($CDCl_3$) δ 7.90 (s, 1 H), 7.40 (s, 1 H), 7.20 (d, 1 H, J = 9 Hz), 6.46 (dd, 1 H, J = 9, 7 Hz), 6.13 (d, 1 H, J = 7 Hz); mass spectrum (70 eV) m/e 132 (M^+), 131 ($M^+ - 1$), 104 ($M^+ - 28$), 92 ($M^+ - 40$).

Anal. Calcd for $C_8H_8N_2$: C, 72.72; H, 6.06; N, 21.21. Found: C, 72.78; H, 6.11, N, 21.07.

4-Formyl-2-azacycl[3.2.2]azine (6). To a stirred solution of 45 ml of 2 *M* BuLi (0.0908 mol) in 20 ml of sodium-dried tetrahydrofuran (THF) was added tetramethylethylenediamine (TMEDA, 10.53 g, 0.0908 mol) under a N_2 atmosphere and at −15°. Then 5-methylimidazo[1,5-*a*]pyridine (5 g, 0.0379 mol) in 20 ml of dried THF was added to the solution. After 1 min, a solution of dried dimethylformamide (DMF, 5.52 g, 0.0758 mol) in 20 ml of THF was added at once. The resulting dark blue solution was warmed to room temperature and stirred for an additional 15 min. Water (100 ml) was then added and the mixture was extracted with chloroform (3 × 150 ml). The combined extracts were dried over anhydrous Na_2CO_3 and filtered and the solvent was removed under reduced pressure. The resulting brown solid was chromatographed over Al_2O_3 (grade III) and eluted with a 25:75 mixture of *n*-hexane–benzene. The third fraction gave a yellow solid (0.950 g, 14.6%): mp 156–157°; ^1H NMR, see Table I; mass spectrum (70 eV) m/e 170 (M^+), 169 ($M^+ - 1$),141 ($M^+ - 29$), 115 ($M^+ - 55$); ir (Nujol) 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.52; N, 16.47. Found: C, 70.52; H, 3.42; N, 16.39.

2-Azacycl[3.2.2]azine-4-carboxylic Acid (7). To 4-formyl-4-azacycl[3.2.2]azine (0.1 g, 0.588 mmol) dissolved in 10 ml of pure acetone (distilled over $KMnO_4$) was added 5 ml of water. Solid $KMnO_4$ (220 mg, 1.4 mmol) was then added in five approximately equal portions with stirring until the purple color remained. The mixture was the treated with a small amount of solid sodium bisulfite to eliminate the excess $KMnO_4$. The mixture was filtered by suction through a pad of Celite and the brown cake was washed with several portions of acetone and hot water. The reddish solution was decolorized with activated charcoal and concentrated to a small volume. Aqueous HCl (5%) was then added carefully until no more yellow solid precipitated (pH ~5). The yellow solid was separated by filtration and washed with a small amount of saturated aqueous NaCl solution. Recrystallizations from DMSO–H_2O gave a yellow solid (80 mg, 73%) which decomposes at its melting point

(274–275°): mass spectrum (70 eV) *m/e* 186 (M^+), 169 ($M^+ - 17$), 141 ($M^+ - 45$), 114 ($M^+ - 72$); ir (KBr) 2530 (OH), 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_6N_2O_2$: C, 64.51; H, 3.23; N, 15.05. Found: C, 64.32; H, 3.25; N, 14.98.

2-Azacycl[3.2.2]azine (Imidazo[2,1,5-*cd*]indolizine, 8). In a 25-ml distillation flask, fitted with a short-path condenser, was placed a mixture of 2-azacycl[3.2.2]azine-4-carboxylic acid (520 mg, 2.78 mmol) and copper powder (600 mg). The flask with its content was cautiously heated with a flame; a reddish liquid was collected on the walls of the flask and the condenser. This liquid was recovered by dissolving it in anhydrous ethyl ether. The liquid was chromatographed over alumina (grade III) and eluted with petroleum ether to give a fluorescing yellow liquid (340 mg, 85.5%), bp 116–118° (0.2 Torr), which darkens eventually: ^1H NMR, see Table I; mass spectrum (70 eV) *m/e* 142 (M^+), 115 ($M^+ - 27$).

Anal. Calcd for $C_9H_6N_2$: C, 76.05; H, 4.22; N, 19.73. Found: C, 74.91; H. 4.58; N, 19.24.

Preparation of Compound 12.[8] To a stirred solution of 4-formyl-2-azacycl[3.2.2]azine (0.102 g, 0.72 mmol) in 20 ml of pure acetone was added a basic solution of Ag_2O (prepared from 270 mg of $AgNO_3$ in 4 ml of water and 127 mg of NaOH in 4 ml of water). The mixture was stirred at room temperature for 1.5 hr, and the filtrate was concentrated under reduced pressure. Acidification with 5% HCl to pH 5 and evaporation of the solution to dryness gave a dark red solid, which was further purified by sublimation to afford a fluorescing red-brick solid (110 mg, 88%): mp 159–161°; ^1H NMR, see Table I; mass spectrum (70 eV) *m/e* 210 (M^+), 195 ($M^+ - 15$), 167 ($M^+ - 43$), 140 ($M^+ - 70$); ir (Nujol) 1650 [M^{-1} (>C=O)], 1605 cm^{-1} (>C=C<), enhanced absorption.

Anal. Calcd for $C_{13}H_{10}N_2O$:C, 74.29; H, 4.76; N, 13.33. Found: C, 74.15; H, 4.80; N, 13.37.

Preparation of Compound 11.[7] To a stirred solution of 20.7 ml of 2 *M* BuLi (in hexane) and 20 ml of anhydrous ethyl ether was added imidazo[1,5-*a*]pyridine (1.085 g, 8.22 mmol) in 20 ml of THF and under a N_2 atmosphere at 0°. Then DMF (2.4 g, 32.9 mmol) in ether was added at once and the mixture was stirred for an additional 15 min. The reaction mixture was treated with 10 ml of water, acidified with 5% HCl, and washed with ethyl ether. The aqueous layer was made basic with anhydrous Na_2CO_3 and extracted with chloroform. Evaporation of the solvent under reduced pressure gave a dark solid which was chromatographed (neutral Al_2O_3 grade III) and eluted with a 27:75 mixture of hexane–benzene. The second fraction afforded a highly fluorescing reddish solid (55 mg, 3.5%): mp 162–163°; ^1H NMR, see Table I; mass spectrum (70 eV) *m/e* 238 (M^+), 239 ($M^+ - 1$), 209 ($M^+ - 29$), 181 ($M^+ - 57$), 155 ($M^+ - 83$), 142 ($M^+ - 96$); ir (Nujol) 1655 (>C=O), 1605 cm^{-1} (>C=C<).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.88; N, 11.75. Found: C, 75.56; H, 6.11; N, 11.47.

Registry No.—1, 209-81-4; 2, 10558-77-7; 3, 1122-72-1; 3 oxime, 1195-40-0; 4, 54384-88-2; 5, 6558-64-1; 6, 54446-41-2; 7, 54384-89-3; 8, 54384-90-6; 11, 54384-91-7; 12, 54384-92-8; hydroxylamine hydrochloride, 5470-11-1; 6-methyl-2-aminomethylpyridine, 6627-60-7.

References and Notes

(1) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 452 (1961), and earlier papers in this series.
(2) W. W. Paudler, R. A. VanDahm, and Y. N. Park, *J. Heterocycl. Chem.*, **9**, 81 (1972).
(3) The CNDO/2 calculations were done on the University of Alabama Univac 1110. The bond lengths used were those determined for 1,4-dibromocycl[3.2.2]azine: A. W. Hanson, *Acta Crystallogr.*, **14**, 124 (1961).
(4) The ^1H NMR spectra were obtained with a Varian HA-100 spectrometer. Elemental analyses were done by the Analytical Services Laboratory of the University of Alabama chemistry department.
(5) We wish to thank a referee for bringing this to our attention.
(6) W. B. Smith, W. H. Watson, and S. Chirangeevi, *J. Am. Chem. Soc.*, **89**, 1438 (1967).
(7) Compound **11** was obtained during the course of our investigation on the reaction of 5-methylimidazo[1,5-a]pyridine with BuLi and DMF. It was found that by using a 1:5:1 ratio of the reactants the main product was compound **11**. No attempt was made to improve the yield.
(8) Compound **12** was obtained during one attempt to oxidize the 4-formyl derivative (6) with basic silver oxide when acetone was used as solvent.

Hydrazinolysis of 1-Phenylethane Diazotate. A New Synthesis of 1-Phenylethylhydrazine (Mebanazine)[1]

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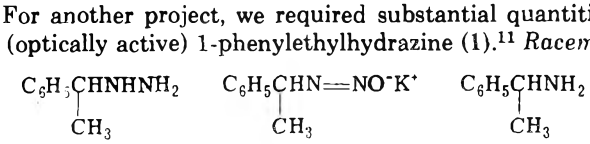
Conversion of 1-phenylethylamine to 1-phenylethane diazotate, followed by treatment of the diazotate with hydrazinium sulfate in anhydrous hydrazine, afforded 40% 1-phenylethylhydrazine (isolated as the oxalate), 35% styrene, and 15% 1-phenylethanol. Starting with optically active 1-phenylethylamine, optically active 1-phenylethylhydrazine was obtained with 54% net inversion of configuration and optically active 1-phenylethanol was obtained with 66% net retention of configuration. In peripheral experiments, optically active 1-phenylethylhydrazine and 1-phenylethylamine were catalytically reduced to optically active 1-cyclohexylethylamine.

Although the synthesis of monoalkylhydrazines is problematical,[3] a number of practical methods exist. These include the direct alkylation of hydrazine or hydrazine hydrate,[4] reaction of azines with Grignard reagents,[5] conversion of alkylamines to sydnones and thence to alkylhydrazines,[6] amination of alkylamines with chloramine[7] or hydroxylamine-*O*-sulfonic acid,[8] and syntheses of *N*-alkyldiaziridines (which may be cleaved to monoalkylhydrazines).[9,10]

For another project, we required substantial quantities of (optically active) 1-phenylethylhydrazine (1).[11] *Racemic*



1 2 3

1 has been prepared from *N*-1-phenylethyl-*N*,*N*′-dicarboethoxyhydrazine,[12] and also by the direct alkylation of hydrazine or its hydrate with 1-phenylethyl halides,[13] by the catalytic reduction of acetophenone azine,[14] and by reaction of acetaldehyde azine with phenylmagnesium bromide, followed by hydrolysis of the resulting acetaldehyde 1-phenylethylhydrazone.[5] However, the only reported preparation of optically active 1 appears to be that of Kopecky and Gillan, who prepared (*S*)-(−)-1 from (*S*)-(−)-1-phenylethylamine in 8% yield via amination with hydroxylamine-*O*-sulfonic acid.[15]

The poor yield afforded by this procedure led us to develop an alternative synthesis. Because ammonolysis of optically active 1-phenylethane diazotate (2) affords 1-phenylethylamine (3) with 46% net inversion,[16] we anticipated

that hydrazinolysis of **2**, derived[17] from optically active **3**, would afford the desired hydrazine, **1**, in reasonable yield and with substantial optical activity. We report here the successful outcome of this sequence, and comment briefly on mechanistic aspects of the results.

1-Phenylethylamine (**3**) was converted to the corresponding urethane and nitrosated with N_2O_4–ether, and the resulting *N*-nitroso-*N*-1-phenylethylurethane was cleaved[17] to diazotate **2** with KO-*t*-Bu in ether. A hydrazine solution of **2** was treated with 2 equiv of hydrazinium sulfate in hydrazine at 0–5°. The addition required 2 hr, during which 95% of the theoretical nitrogen content of **2** was evolved.

From the reaction mixture, we isolated 40% of the desired 1-phenylethylhydrazine (**1**) as its oxalate salt; 35% styrene and 15% 1-phenylethanol were also present. Product identities were established by comparison with authentic samples.

Two repetitions of this experiment with **2** derived from (*R*)-(+)-**3**, $\alpha^{22}D$ + 3.638° (neat, 0.1 dm),[18a] 95.0% optically pure,[18b] each gave optically active **1** and 1-phenylethanol. The alcohol samples, purified by GC, had $\alpha^{25}D$ + 2.743° and $\alpha^{25}D$ + 2.747°, each corresponding to an optical purity of 62.7%.[19] The stereochemical course of the (*R*)-**2** → (*R*)-(+)-1-phenylethanol conversion was therefore 66.0% *net retention*.[20]

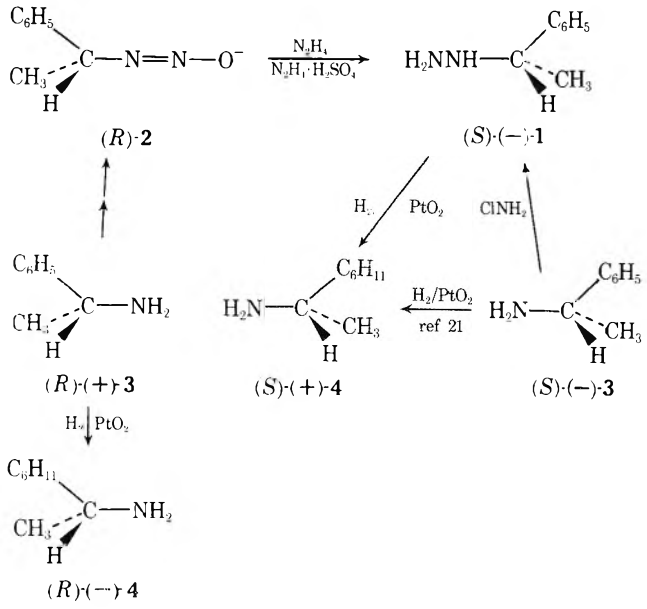
The stereochemistry of the (*R*)-**2** → **1** transformation was determined by three methods.

(1) Two hydrazinolyses of (*R*)-**2** gave samples of optically active **1** which were completely converted to the oxalate salts. Hydrogenation of the salts over PtO_2 afforded two samples of 1-cyclohexylethylamine (**4**), which, after GC purification, had $\alpha^{25}D$ +0.150° and $\alpha^{25}D$ +0.154° ($\alpha^{15}D$ +0.170°).

Leithe[21] reported $[\alpha]^{15}D$ +3.2°, $\alpha^{15}D$ +2.8° (neat, 1 dm) for optically pure (*S*)-(+)-**4** prepared by catalytic reduction of (*S*)-(−)-**3**. In our hands, reduction of 95% optically pure (*R*)-(+)-1-phenylethylamine gave (*R*)-(−)-1-cyclohexylethylamine, $\alpha^{15}D$ −0.317°. This affords an apparent value of $\alpha^{15}D$ −3.34° (neat, 1 dm) for optically pure **4**.

Using the latter value, and the observation (above) that 95% optically pure (*R*)-**2** gave, via hydrazinolysis followed by reduction, (*S*)-(+)-**4**, $\alpha^{15}D$ +1.70° (neat, 1 dm), the stereochemical course of the **2** → **1** conversion must have been 53.6% *net inversion*. The stereochemical relationships are summarized in Scheme I.

Scheme I



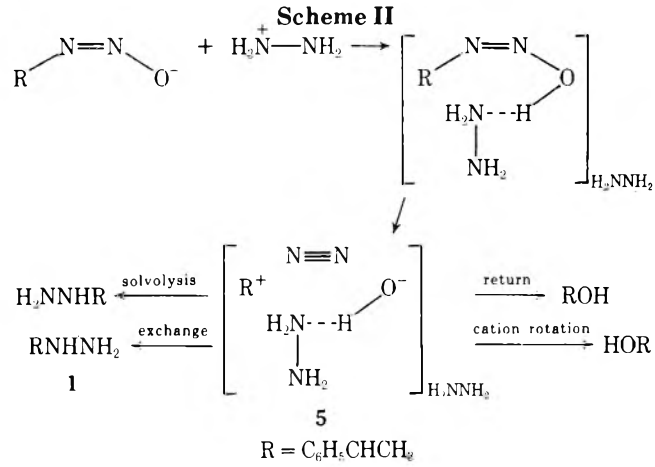
(2) Despite Leithe's report,[21] we were concerned about the possibility of racemization during the catalytic reduction of **1** or **3** to **4**.[22] Therefore, authentic (*S*)-(−)-**1** was prepared from (*S*)-(−)-**3** using the chloramine method.[7] From (*S*)-(−)-**3**, $\alpha^{22}D$ −3.636°, 95% optically pure,[18b] we obtained 10% of **1** oxalate. Without recrystallization, this material had $[\alpha]_{365}^{31.5}$ −10.5° (*c* 0.40, water).[23a] From hydrazinolysis of 95% optically pure (*R*)-**2**, we obtained a sample of **1** oxalate which had $[\alpha]_{365}^{31.5}$ −5.8° (c 0.60, water).[23b] Assuming that the former value represents optically pure **1** oxalate, comparison of the two experiments gives 5.8/10.5 = 55% *net inversion* for the **2** → **1** hydrazinolysis, which compares well with the 53.6% net inversion determined by method 1.

(3) Finally, the (*S*)-(−)-**1** formed by hydrazinolysis of 95% optically pure (*R*)-**2** was purified by GC on a Penwalt column at 160°. This sample of hydrazine **1** had $[\alpha]^{25}D$ −16.57° (*c* 2.902, benzene).[24] Comparison with $[\alpha]^{25}D$ −30.3° (*c* 0.784, benzene), which may be calculated for optically pure (*S*)-(−)-**1**,[25] determines the stereochemical course of the **2** → **1** hydrazinolysis as 54.7% *net inversion*, which agrees very well with the previous determinations.

Hydrazinolysis of optically active 1-phenylethane diazotate does indeed give 1-phenylethylhydrazine in reasonable yield and with substantial optical activity. Because the diazotate is easily obtained from 1-phenylethylamine,[17] the entire sequence constitutes a useful preparative method.

The formation of inverted **1** and retained 1-phenylethanol in the hydrazinolysis of **2** is mechanistically analyzed in Scheme II.

Scheme II



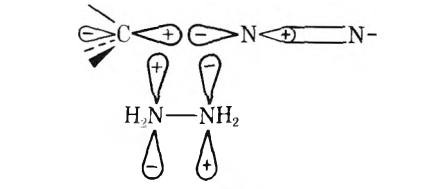
1 arises mainly by inverting hydrazinolysis of nitrogen-separated ion pair **5**, although front-side participation of hydrazine (hydrogen bonded to the hydroxide counterion) competitively affords retained **1** ("exchange" pathway), and precludes complete solvolytic inversion. The retained 1-phenylethyl alcohol forms largely by hydroxide return within **5**. Failure to obtain complete retention suggests the occurrence of cation rotation–collapse.[26]

Analogous diazotate solvolyses have been discussed in detail.[27] Here, we wish only to compare the hydrazinolysis stereochemical results with those obtained in the *ammonolysis* of **2**.[16] The *overall* stereochemistry of the return process (**2** → 1-phenylethanol) is 80% retention in ammonolysis,[16] and 83% retention in hydrazinolysis. The similar values support our conclusion that the extent of retention in deaminative return reactions depends mainly on *cation identity*, and less strongly on the nature of the solvent or the counterion.[27a]

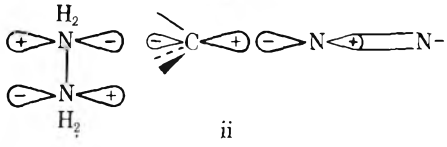
The *overall* stereochemistry of the solvolysis pathways (**2** → **3** or **2** → **1**) is 73% inversion in ammonolysis[16] and

77% inversion in hydrazinolysis. Little increase in inversion is noted when ammonia is replaced by the more nucleophilic hydrazine. Nor is there any stereochemical abnormality attributable to an "α effect" in the latter case.[28] This is perhaps not surprising, because the effect is not believed to operate at tetrahedral carbon,[29] and because hydrazine is probably present at front *and* rear sides of both 5 and its covalent precursor; see Scheme II.

However, one could have speculated a priori that an α nucleophile could preferentially react from the front side at tetrahedral carbon, i.e., with *retention*. Such an arrangement, i, might allow energetically favorable overlap of the (antisymmetric) HOMO of hydrazine and the σ^* (LUMO) of the substrate C–N bond, which could be preferable to (inverting) back-side attack, ii.[30,31] It is clear, however, that this possibility is not realized in the hydrazinolysis of 1-phenylethane diazotate, which proceeds with high inversion.[32]



i



ii

Experimental Section

1-Phenylethylurethane. 1-Phenylethylamine, distilled from Na (bp 59–60°, 6 Torr), was converted to 1-phenylethylurethane by treatment with ethyl chloroformate and K_2CO_3 in water and benzene, according to the method of Bortnick.[33] From 35 g of amine, we obtained 50 g (89%) of the urethane: bp 93–95° (0.25 Torr) [lit. bp 173° (23 Torr)];[34] infrared (film) 1715 cm^{-1} (C=O); NMR[35] (CCl_4) δ 7.20 (m, 5 H, phenyl), 5.67 (broad, 1 H, NH), 4.76 (quintet, J = 7 Hz, 1 H, benzylic), 4.00 (q, J = 7 Hz, 2 H, OCH_2), 1.38 (d, J = 7 Hz, 3 H, $CHCH_3$), and 1.12 (t, J = 7 Hz, 3 H, CH_2CH_3).

(+)-1-Phenylethylurethane ($\alpha^{24.5}D$ +8.487°)[18a] was similarly derived from Aldrich (+)-1-phenylethylamine ($\alpha^{22}D$ +3.638°, 95.0% optically pure,[18b] distilled from Na).

1-Phenylethane Diazotate (2). The 1-phenylethylurethane was nitrosated with N_2O_4 in ether, as described by Moss.[17] The NMR of the crude *N*-1-phenylethyl-*N*-nitrosourethane (CCl_4) showed, inter alia, δ 5.98 (q, J = 7 Hz, 1 H, benzylic) and 4.35 (q, J = 7 Hz, 2 H, OCH_2). The deshielding of these protons ($\Delta\delta$ = 1.22 and 0.35, respectively) is characteristic for the urethane → *N*-nitrosourethane conversion.[36]

The diazotate **2** was prepared by treating 5.0 g (22 mmol) of the nitrosourethane with 5.0 g (43 mmol) of potassium *tert*-butoxide in anhydrous ether at −30°, according to the general procedure of Moss.[17]

1-Phenylethylhydrazine (1). Ether was stripped from the solid diazotate **2**, and 25 ml of anhydrous hydrazine[37] was added. The resulting hydrazine solution of **2** was cooled to 0–5° and stirred magnetically, while a solution of 5.59 g (43 mmol) of hydrazinium sulfate in 25 ml of anhydrous hydrazine was slowly added from an addition funnel. Nitrogen evolution occurred during the addition and amounted to 468 ml (95%).

After the addition step was completed, the reaction mixture was stirred at 25° for 10 hr. Hydrazine was distilled away under reduced pressure in a nitrogen atmosphere (20 Torr). The residue was extracted with 3 × 25 ml of ether; the ether was stripped, and the residual crude **1** was distilled to afford 1.21 g (8.9 mmol, 40%) of pure 1-phenylethylhydrazine, bp 83° (1.3 Torr) [lit.[5] bp 75° (1.1 Torr)].

A solution of 1.1 g (8.8 mmol) of oxalic acid in 8 ml of absolute ethanol was added to the product **1**. The resulting white, solid **1** oxalate was filtered, washed with ether, and dried,[38] mp 169–170° (lit.[5] mp 170–171°).

The NMR spectrum of **1** (CCl_4) showed δ 7.23 ("s", 5 H, phenyl), 3.63 (q, J = 7 Hz, 1 H, benzylic), 2.97 (broad s, 3 H, NH), and 1.25 (d, J = 7 Hz, 3 H, CH_3).

Authentic **1** and **1** oxalate were prepared by "method B" of Overberger and DiGiulio;[5] the **1** oxalate had mp 169–170°. Both compounds were identical with the corresponding hydrazinolysis products (melting point or NMR).

Authentic **1** and **1** oxalate were also prepared from 1-phenylethylamine and chloramine, according to the procedure of Audrieth.[7] The **1** oxalate thus obtained had mp 169–170°. All **1** oxalate samples were dried at 78° (1 Torr) for 12 hr.

Anal. Calcd for $C_{10}H_{14}O_4N_2$ (oxalate): C, 53.09; H, 6.23; N, 12.38. Found: C, 52.83; H, 6.24; N, 12.32 (by the synthesis of ref 5); C, 52.87; H, 6.18; N, 12.34 (by the procedure of ref 7).[39]

Repetition of the hydrazinolysis experiment with 95.0% optically pure diazotate **2** afforded optically active **1** and **1** oxalate. Rotations and optical purities are discussed in the text.

Other Hydrazinolysis Products. Hydrazinolysis of **2**, as above, afforded a reaction mixture which was diluted with 50 ml of water. The mixture was extracted with 3 × 20 ml of ether. The combined ethereal extract was washed with 25 ml of 6 *N* HCl and with distilled water (3 × 50 ml). The ethereal solution was dried ($MgSO_4$) and stripped at 0° to afford a residue which contained styrene and 1-phenylethanol (GC on a 12 ft × 0.25 in., 5% Carbowax 20M on 90/100 ABS column at 160°). Absolute yields (styrene, 35%; 1-phenylethanol, 15%) were determined by GC, relative to a dodecane internal standard. 1-Phenylethanol did not dehydrate under these conditions. From 95.0% optically pure **2**, optically active 1-phenylethanol was obtained (see text).

Reduction of 1. 1-Phenylethylhydrazine oxalate (2.0 g, 6 mmol), in 50 ml of water, and 0.2 g of PtO_2 were contained in pressure vessel and attached to a Paar hydrogenation apparatus. After 48 hr, under 46 psig of hydrogen, the reaction solution was filtered, brought to pH >12 with NaOH pellets, and extracted with 4 × 25 ml of ether. The ethereal extract was dried (BaO) and stripped at 0°. Purification of the residual oil on a 10 ft × 0.25 in., 28% Penwalt 223, 4% KOH on 80/100 Gas Chrom R column at 178° gave 1-cyclohexylethylamine (**4**). The NMR spectrum (CCl_4) showed δ 2.61 (m, 1 H, H_2NCH), 1.71 and 1.06 (m, cyclohexyl and NH_2), and 1.00 (d, J = 7 Hz, CH_3). The remainder of the protons had an integral weight of 16, relative to the δ 2.61 proton.

Optically active 1-phenylethylamine (**3**) was similarly reduced to **4**, and purified on the Penwalt column. Rotational and optical purity data for this reduction and for the reduction of optically active **1** oxalate are described in the text.

Control Experiments. Styrene (5.0 g, 4.8 mmol) was stirred with 10 ml of hydrazine and 1 g of hydrazine sulfate for 14 hr at 25°. The resulting mixture was diluted with 100 ml of 10% aqueous NaOH solution and the whole was extracted with 3 × 30 ml of ether. The ethereal extract was dried (Na_2CO_3) and stripped to afford a residue which was examined by GC on the Penwalt column (see above) at 170°. No 1-phenylethylhydrazine was detected. Under comparable GC and concentration conditions, 1% of 1-phenylethylhydrazine could be detected. Hence, under our hydrazinolysis conditions, N_2H_4 does not add to product styrene to give (racemic) **1**.

(+)-1-Phenylethanol, $\alpha^{27}D$ +0.648°[18a] (1.0 g, 8.1 mmol), was stirred overnight with 10 ml of hydrazine and 1 g of hydrazine sulfate. The reaction solution was extracted with 3 × 25 ml of ether. The ether extract was washed with water and added to 3 g of oxalic acid in 15 ml of ethanol. The white precipitate was filtered and examined by NMR. It did not contain **1** oxalate. The filtrate was stripped and the residue was purified by GC on the Carbowax column to afford 1-phenylethanol of unchanged optical activity, $\alpha^{27}D$ +0.650°.

Acknowledgments. We thank the National Institutes of Health (CA 14912) and the National Science Foundation (GP 32159X) for financial support. We also thank Professor N. Epiotis for helpful discussions.

Registry No.—**1**, 54422-98-9; (*S*)-(−)-**1**, 24292-42-0; **1** oxalate, 54422-99-0; (*S*)-(−)-**1** oxalate, 54384-30-4; **2**, 54423-00-6; (*R*)-**2**, 29882-69-7; **3**, 300-62-9; (*R*)-(+)-**3**, 3886-69-9; (*S*)-(−)-**3**, 2627-86-3; **4**, 54423-01-7; (*R*)-(−)-**4**, 5913-13-3; (*S*)-(+)-**4**, 17430-98-7; 1-phenylethylurethane, 54423-02-8; ethyl chloroformate, 541-41-3; (+)-1-phenylethylurethane, 14185-43-4; *N*-1-phenylethyl-*N*-nitrosourethane, 54744-25-4; 1-phenylethanol, 13323-81-4; (*R*)-1-phenylethanol, 1517-69-7; oxalic acid, 144-62-7.

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(23) (a) $\alpha^{31.5}_{365}$ −0.040° (1 dm). The specific rotation given in the text is corrected for the optical purity of the amine precursor. (b) $\alpha^{31.5}D$ −0.033° (1 dm). The specific rotation is corrected for the optical purity of the amine.
(24) $\alpha^{25}D$ −0.457° (*c* 2.902, benzene, 1 dm). The specific rotation is corrected for the optical purity of the diazotate precursor.
(25) Reaction of 95.6% optically pure (*S*)-(−)-**3** with hydroxylamine-*O*-sulfonic acid gave 8% of pure (*S*)-**1**, $[\alpha]^{25}D$ −29.0° (c 0.784, benzene).[15]
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(39) Microanalyses were done by Micro-Tech Laboratories, Skokie, Ill.

Synthesis of Phenyl-Substituted 1-Aminotetralines

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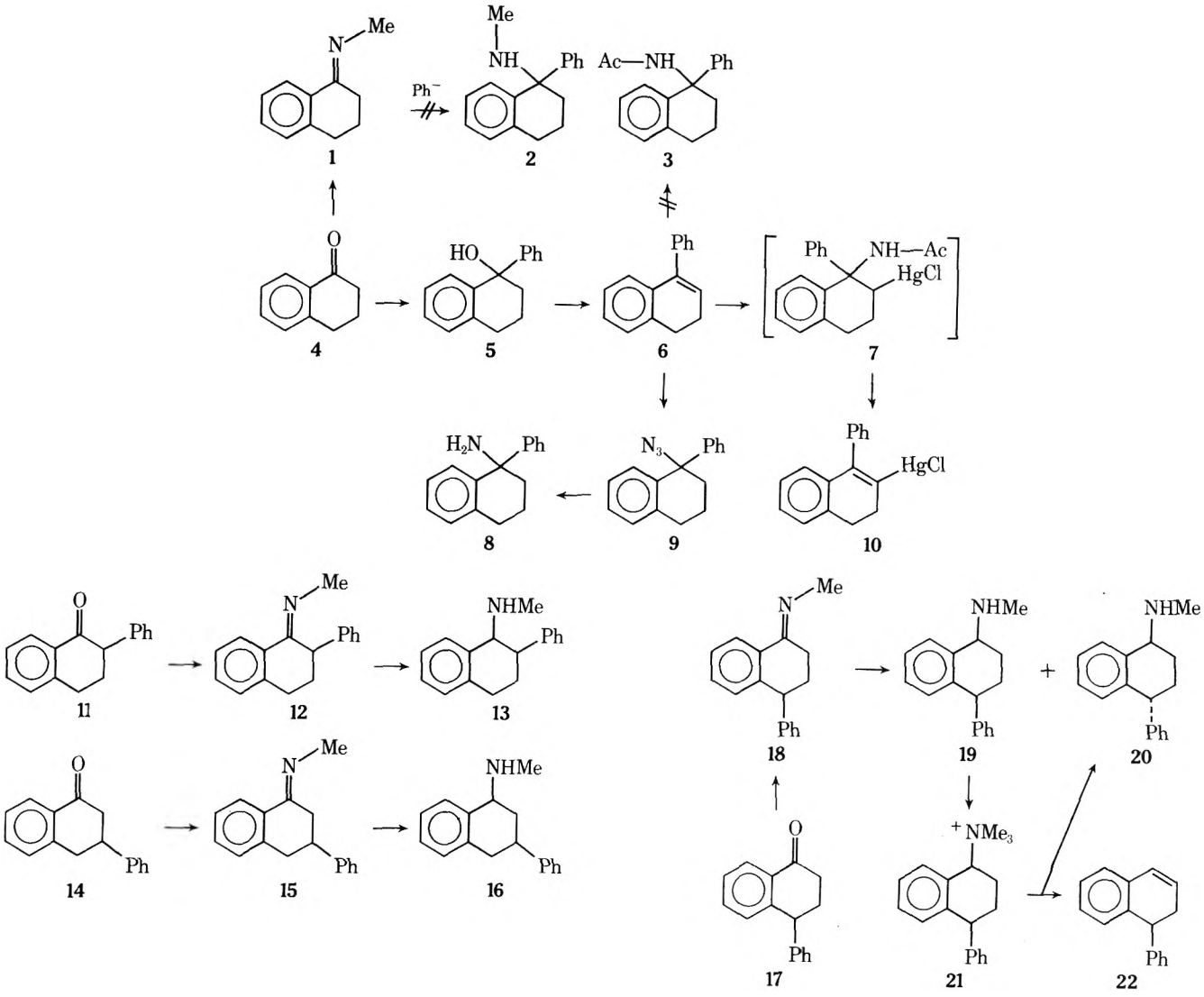
Synthetic methods were developed for 1-, 2-, 3-, or 4-phenyl-substituted 1-aminotetraline derivatives. 1-Phenyl-1-aminotetraline was obtained by hydrazoic acid addition to 1-phenyl-3,4-dihydronaphthalene, followed by lithium aluminum hydride reduction. The cis isomers of 2- or 3-phenyl-substituted *N*-methyl-1-aminotetraline resulted from sodium borohydride reduction of the methylimines derived from the corresponding ketones. Sodium borohydride treatment of the methylimine derived from 4-phenyl-1-tetralone gave a 1:1 mixture of *cis*- and *trans*-4-phenyl-1-aminotetraline, but stereoselective conversions were achieved by catalytic hydrogenation over palladium/carbon (cis isomer) and by zinc–acetic acid reduction (trans isomer). These reactions were extended to the synthesis of the corresponding 5-methoxy-8-chloro substituted analogs and to the preparation of a series of 4-phenyl-1-aminotetralines with modified nitrogen substituents. In addition, two useful reactions were discovered: the oxidation of 1-phenyltetraline to 4-phenyl-1-tetralone with potassium permanganate and the conversion of *N*-methyl-4-phenyl-1-aminotetraline to the corresponding ketone by aqueous potassium permanganate.

The interesting pharmacological activity exhibited by certain 1-aminotetralines,[1] especially the 5-methoxy-8-halogen derivatives, prompted us to investigate the synthesis of 1-aminotetralines substituted with phenyl groups in the alicyclic ring. Initially, we explored the synthesis of the simple 1-, 2-, 3-, or 4-phenyl-substituted 1-aminotetralines bearing no substituents in the aromatic ring. The synthesis of 1-phenyl-1-aminotetraline was approached in three ways. Addition of phenylmagnesium bromide or phenyllithium to the methylimine (1) derived from 1-tetralone (4) failed to give, even in the presence of polarizing agents such as BF_3, the desired 1-phenyl-1-aminotetraline derivative **2** (Scheme I), although this type of reaction had been successful in the preparation of the corresponding 1-methyl derivatives.[1] While this failure may be due to steric factors, this explanation is not entirely satisfactory, since the reaction of phenylmagnesium bromide with 1-tetralone (4) itself proceeded in good yield in accordance with published results[2,3] to the alcohol **5**. Compound **5** was dehydrated to 3,4-dihydro-1-phenyltetraline (**6**),[2] which proved to be inert in the Ritter reaction[4] (acetonitrile, sulfuric acid). The modified conditions of Chow et al.[5] (acetonitrile, mercuric nitrate) led, presumably via **7**, to the mercurated olefin **10**. The addition of hydrazoic acid to **6** in the presence

Scheme I



of trichloroacetic acid[6] gave small yields of the azide **9**, which was in turn reduced to the desired 1-phenyl-1-aminotetraline (**8**) with lithium aluminum hydride or zinc–hydrochloric acid. The yield of **9** could not be increased by using different solvents, different acid catalysts, or moderately elevated temperature, although we confirmed that this reaction sequence leads to good yields of 1,1-diphenylethylamine from the closely related "ring open" 1,1-diphenylethylene.[6]

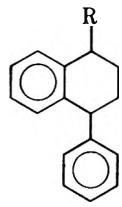
The synthesis of 2-phenyl-1-aminotetraline was straightforward. 2-Phenyl-1-tetralone (**11**)[3,7,8] was converted to the methylimine **12** with the aid of titanium tetrachloride;[1,9] reduction of **12** with sodium borohydride[1,10] yielded exclusively *cis*-*N*-methyl-2-phenyl-1-aminotetraline (**13**), presumably as a consequence of the steric influence of the phenyl group. Similarly, 3-phenyl-1-tetralone (**14**)[3,7] was converted to the methylimine derivative **15**, sodium borohydride reduction of which led to *cis*-*N*-methyl-3-phenyl-1-aminotetraline (**16**). The apparently exclusive formation of the cis isomer is somewhat surprising in this instance, since no particular steric hindrance to the approach of the reducing species from either side would be anticipated from molecular models. Sodium borohydride reduction of the methylimine (**18**) derived from 4-phenyl-1-tetralone[11] (**17**) gave the expected 1:1 mixture of *cis*- and *trans*-*N*-methyl-4-phenyl-1-aminotetraline (**19** and **20**), which were easily separated by fractional crystallization.

The intriguing "antidepressant" pharmacological activity exhibited by the trans isomer **20**[12] prompted us to investigate the stereochemical control of the reduction of **18** more thoroughly, and to develop a stereoselective synthesis of **20**. As expected, catalytic hydrogenation of **18** over palladium/carbon in ethanol gave exclusively the cis derivative **19**. Attempts to convert **19** to **20** were only partially successful: **19** proved to be stable to treatment with methylamine, and quaternization of **19** to **21**, followed by reaction with methylamine, favored elimination to **22** (70% yield) over displacement to **20** (30% yield).

All efforts to increase the trans to cis ratio by modifying the sodium borohydride reduction conditions of **18** (pH, solvent, temperature) or by using different hydrides (BH_3, $LiAlH_4$, $LiBH_4$, Redal) failed. Conceivably, the use of reducing conditions which result in the formation of radical anions, such as dissolving metal reductions, would lead to the presumably thermodynamically favored trans isomer **20**, if the reaction intermediate has an appreciable half-life. However, treatment of **18** with sodium in ethanol resulted in only a 50% yield of the trans isomer **20**. On the other hand, reduction of **18** with zinc in acetic acid produced mainly the desired trans isomer **20**. This difference between sodium and zinc may be a consequence of the size and/or the complexing properties of zinc.

Since the pharmacological profile of simple 1-aminotetralines is highly configuration specific,[1] **20** was resolved

Table I



No.	R	Configuration
23	NMe_2	Trans
24	NMe_2	Cis
25	NH_2	Trans
26	NH_2	Cis
27	NHEt	Trans
28	NHEt	Cis
29	NH-*i*-Pr	Trans
30	NH-*i*-Pr	Cis
31	NH- 	Trans
32	NH- 	Cis
33		Trans
34		Cis
35	 N-Me	Trans
36	 N-Me	Cis

into its enantiomers using D-mandelic acid and *N*-acetyl-L-tyrosine. On the basis of previous experience,[1] the isomer which precipitated with *N*-acetyl-L-tyrosine was assigned the 1*S*,4*R* configuration, and this assignment was confirmed by an X-ray analysis of its hydrobromide.[12]

The "antidepressant" activity resides exclusively in the 1*R*,4*S* isomer[12] of **20**. An economical synthesis of this isomer would require a recycling of the unwanted isomer. Consequently, we examined various conditions for the oxidation of secondary amines to the corresponding ketones, using the oxidation of **19** to **17** as a model system. Whereas literature methods[13] proved to be inadequate on a preparative scale, treatment of **19** with potassium permanganate in 50% aqueous acetone at room temperature for 1 hr gave a clean conversion to the ketone in acceptable yields.

For pharmacological comparison,[12] several analogs of **19** and **20** with modified nitrogen substituents were prepared, and these are listed in Table I. The dimethyl derivatives **23** and **24** were prepared by methylation of **20** and **19**, respectively, since treatment of the enamine obtained from dimethylamine and the tetralone **17** with formic acid resulted in hydrolysis to **17**. Conversion of **17** to the oxime, followed by catalytic hydrogenation over palladium/carbon in ethanol, gave a 1:2 mixture of the trans and cis primary amines, **25** and **26**. The trans isomer **23** was also obtained in moderate yield by zinc–acetic acid reduction[1] of the phenylhydrazone of **17**. The *N*-ethyl, *N*-isopropyl, and *N*-cyclopropyl derivatives **27–32** were obtained as mixtures of cis and trans isomers by sodium borohydride reduction of the corresponding ketimines; in all these cases catalytic hydrogenation over palladium/carbon gave predominantly the cis isomers. The pyrrolidine derivatives **33** and **34** were obtained by reaction of **25** or **26** with 1,4-dibromobutane.[1] Compounds **35** and **36** resulted from reduction of the corresponding enamine with lithium borohydride in the presence of formic acid,[1] and the cis isomer **35** was formed exclusively by catalytic hydrogenation of the enamine. Recently, compounds **19**, **20**, **23**, **24**, **25**, and **26** have been described.[30]

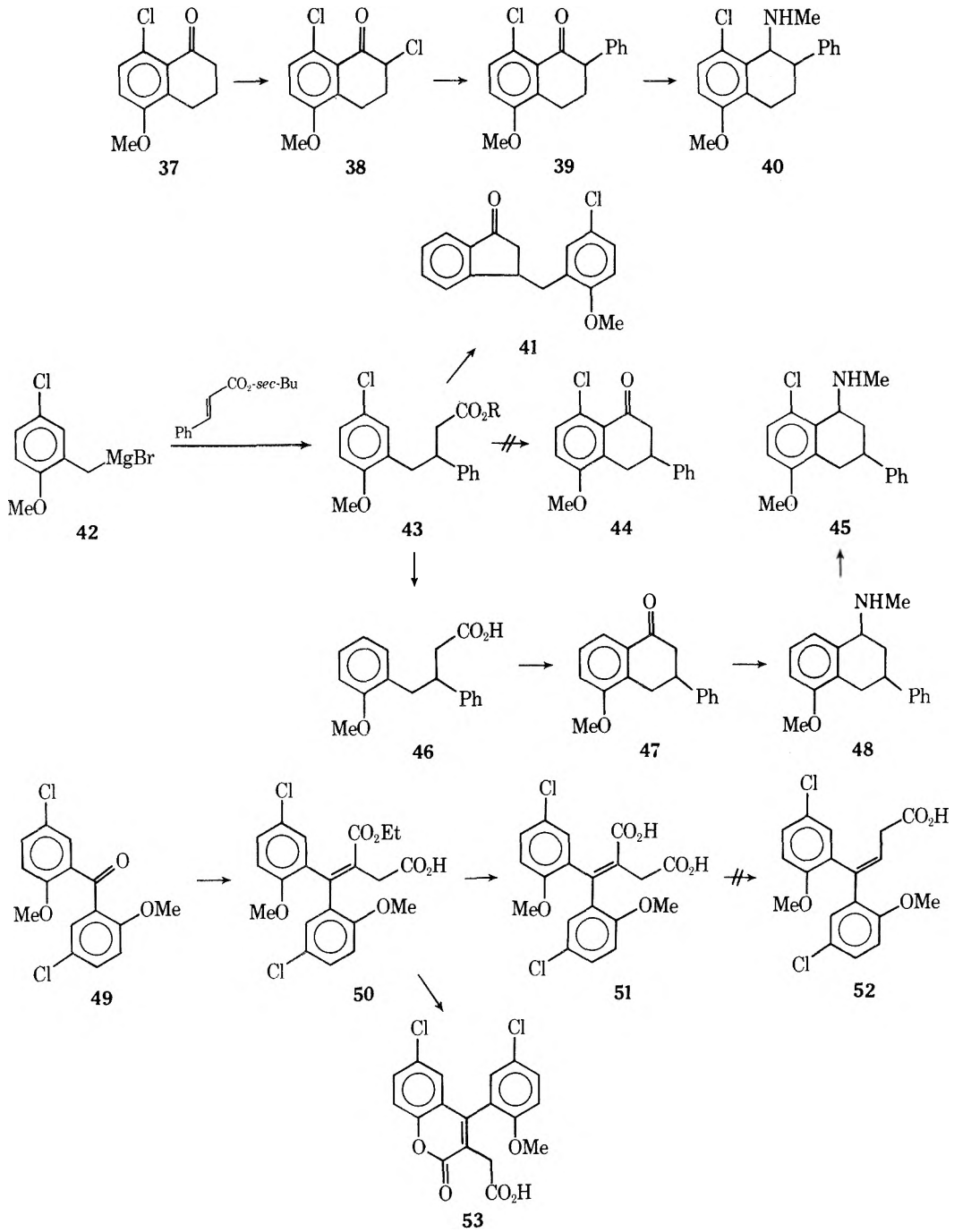
We then turned our attention to the synthesis of phenyl-substituted 5-methoxy-8-chloro-1-aminotetralines. Chlorination of 5-methoxy-8-chloro-1-tetralone[1,14] (**37**) in acetic acid,[15] followed by treatment with phenylmagnesium bromide,[15,16] gave 2-phenyl-1-tetralone (**39**) (Scheme II). This compound was converted to the methylimine and reduced with sodium borohydride to give again exclusively the cis isomer **40**. Addition of 5-chloro-2-methoxybenzylmagnesium bromide to the *sec*-butyl ester[17] of cinnamic acid in the presence of cuprous chloride, followed by saponification of the resulting ester **43** (R = *sec*-butyl) to the acid (R = H) and cyclization with polyphosphoric acid,[1] gave the 3-benzyl-substituted 1-indanone **41** instead of the desired 3-phenyl-substituted tetralone **44**. However, after removal of the deactivating chlorine function in **43** by catalytic hydrogenation, the resulting acid **46** was cyclized to give the desired tetralone **47**, indicating that formation of the six-membered ring is favored despite the presence of the deactivating *m*-methoxy group. Conversion of **47** to the methylimine, followed by reduction with sodium borohydride, resulted in mixtures of cis and trans isomers which could not be separated. Catalytic hydrogenation of the methylimine gave exclusively the cis isomer **48**, which was converted by chlorination in acetic acid[1] to the desired derivative **45**.

The synthesis of 4-phenyl-substituted chloromethoxy derivatives was initially approached from the symmetrical 5,5′-dichloro-2,2′-dimethoxybenzophenone[18] (**49**). However, both the Stobbe condensation product **50** and the diacid **51** obtained by base hydrolysis of **50** proved to be resistant to the standard hydrolysis and decarboxylation conditions (HBr–acetic acid),[19] as lactone **53** was formed instead of the expected acid **52**. Other attempts to decarboxylate **51**, such as heating either neat or in the presence of thioglycolic acid, thiophenol, copper–quinoline,[20] toluenesulfonic acid, or toluenesulfonic acid–sulfolane, led either to no reaction, partial formation of lactone **53** or an intractable mixture of products. An alternate route, reduction of the double bond of **51** followed by ring closure to the tetralone and decarboxylation under nonselective conditions, was considered. However, reduction of **50** or **51** over palladium/carbon, rhodium/carbon, or with sodium borohydride failed, presumably owing to the inaccessibility of the tetrasubstituted double bond.

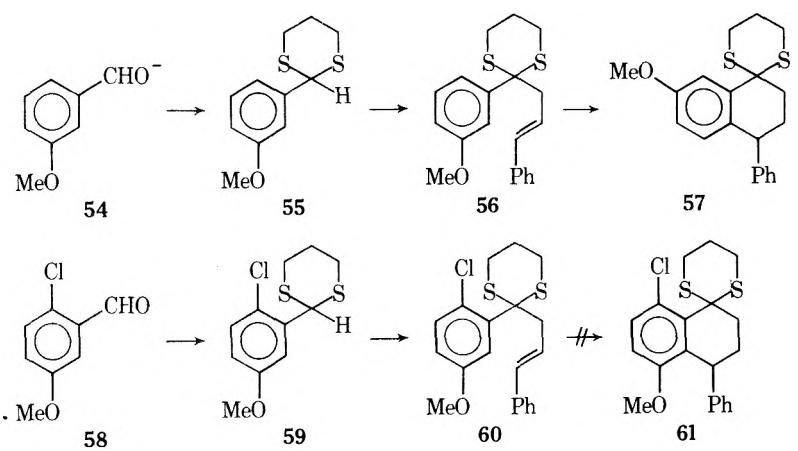
A second approach involving cyclization of an olefin containing a protected ketone group was also explored. Conversion of 3-methoxybenzaldehyde (**54**) to the 1,3-dithiane derivative **55**, followed by alkylation of the anion of **56**[21] with cinnamyl bromide, gave an excellent yield of **56** (Scheme III). Cyclization of **56** with BF_3 in methylene chloride proceeded in moderate yield, but to the undesired isomer **57**. In order to guide the cyclization into the proper direction we planned to block the position para to the methoxy group with chlorine. Conversion of 2-chloro-5-methoxybenzaldehyde[22,23] (**58**) to the dithiane derivative **59** was uneventful, but generation of the anion of **59** proved to be difficult. Even the best conditions found, methyllithium in tetrahydrofuran at 0°, resulted only in poor yields of the alkylated product **60**. The presence of the chlorine atom in **59** apparently interfered with formation of the anion and led to side reactions involving the aromatic ring, as suggested by NMR data. Furthermore, attempts to cyclize **60** were futile, presumably owing to the deactivating effects of the chlorine atom.

A successful synthesis was ultimately developed starting with 5-chloro-8-methoxy-1-tetralone (**62**).[24] Tetralone **62** was converted in three steps to the phenyltetraline derivative **65**. Although the literature[25] claims that V_2O_5–H_2O_2 gives good yields of 4-phenyl-1-tetralone from the tetraline, this oxidation procedure, as well as those employing SeO_2 or chromic acid, failed with **65**. However, treatment of **65**

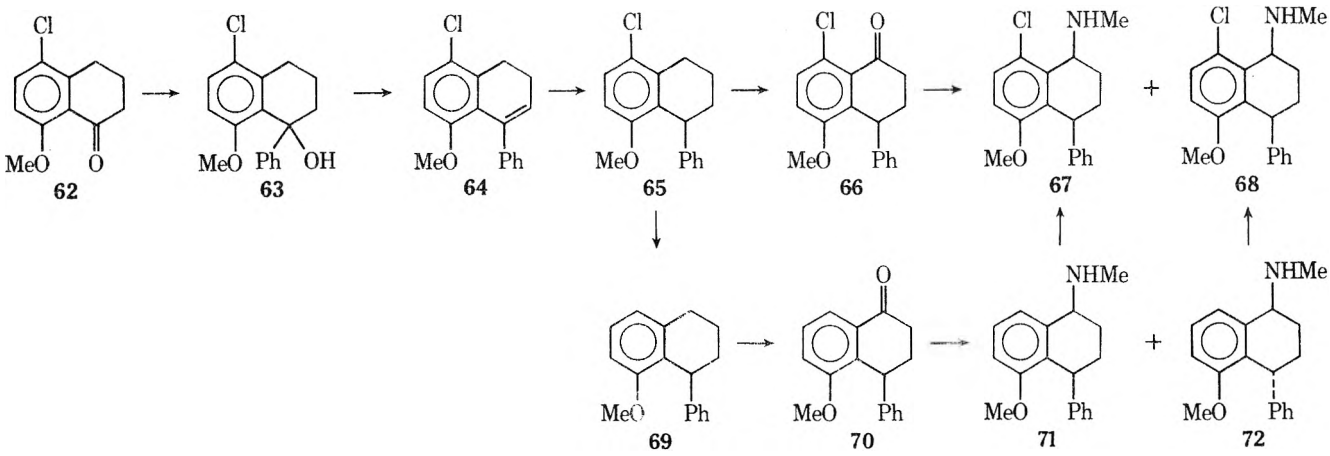
Scheme II



Scheme IIIA



Scheme IIIB



with potassium permanganate gave a clean conversion to the ketone **66**. Since this reaction proceeded rather slowly, we decided to investigate whether **69**, the dechloro analog of **65**, would react faster in the absence of the bulky chlorine atom. Indeed, **69** was oxidized more readily to give the ketone **70**. Surprisingly, conversion of either **66** or **70** to the methylimine, followed by reduction with sodium borohydride, gave predominantly the cis 1-aminotetralines, **67** and **71**, respectively. This result must be attributed to the presence of the 5-methoxy group. However, reduction of the methylimine derived from **70** with zinc–acetic acid again, as in the unsubstituted compound, gave predominantly the thermodynamically more stable trans isomer **72**. Compounds **71** and **72** were then converted by chlorination in acetic acid[1] to compounds **67** and **68**, respectively.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Pfizer Central Research. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-60 spectrometer. NMR spectra were obtained on Varian T-60 and A-60 instruments.

1-Phenyl-1,2,3,4-tetrahydro-1-naphthylamine (8). A solution of 10.4 g (0.064 mol) of trichloroacetic acid and 2.75 g (0.0134 mol) of 1-phenyl-3,4-dihydronaphthalene[2] in 100 ml of benzene containing 2.58 g (0.06 mol) of hydrazoic acid[26] was kept at room temperature for 15 hr. The mixture was washed with H_2O, dried over $MgSO_4$, and filtered, and the filtrate was evaporated. The residue was dissolved in 50 ml of Et_2O and added dropwise to a suspension of 510 mg (0.0134 mol) of lithium aluminum hydride in 150 ml of Et_2O. After refluxing overnight, the mixture was quenched with H_2O, filtered, and treated with 12 *N* HCl until a pH of 2 was reached. After three extractions with Et_2O, 2.62 g (95.5%) of starting material was recovered from the combined organic layers. Basification of the aqueous phase with 4 *N* NaOH, followed by three extractions with Et_2O and evaporation of the combined organic layers, afforded 104 mg of basic material. After treatment with HCl in Et_2O and two recrystallizations of the resulting solids from EtOH–Et_2O there was obtained 40 mg (1%) of **8** as the hydrochloride: mp 237–238°; mass spectrum *m/e* 223 (M^+), 206 (base peak), 194, 178, 146, 123.

Anal. Calcd for $C_{16}H_{17}N \cdot HCl$: C, 73.97; H, 6.99; N, 5.39. Found: C, 73.83; H, 6.81; N, 5.17.

2-Chloromercuri-1-phenyl-3,4-dihydronaphthalene (10). To a suspension of 3.24 g (0.01 mol) of mercuric nitrate in 20 ml of acetonitrile (distilled from P_2O_5) was added 0.05 ml of concentrated nitric acid and then dropwise a solution of 2.06 g (0.01 mol) of 1-phenyl-3,4-dihydronaphthalene (**6**) in 5 ml of acetonitrile; the resulting clear solution was kept at room temperature for 14 hr. The mixture was poured into 50 ml of H_2O, treated with 5 ml of 5 *N* aqueous NaCl, stirred for 5 min, and extracted three times with 50 ml of $CHCl_3$. The exracts were dried and evaporated, and the residue was crystallized from CH_2Cl_2–hexane to give 1.5 g (34%) of **10**: mp 159–160°; NMR ($CDCl_3$) δ 2.3–3.2 (m, 4 H), 6.6–7.3 (m, 4 H), 7.35 (s, 5 H).

Anal. Calcd for $C_{16}H_{13}ClHg$: C, 43.55; H, 2.98. Found: C, 43.40; H, 2.95.

***cis*-*N*-Methyl-2-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (13).** A solution of 2.22 g (0.01 mol) of 2-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (**11**) and 1.85 g (0.06 mol) of methylamine in 50 ml of benzene was cooled to 0° and treated dropwise with 0.55 ml (0.005 mol) of $TiCl_4$, keeping the temperature below 10°. The mixture was kept at room temperature overnight and then heated to reflux for 24 hr. After cooling and filtration, the filtrate was evaporated in vacuo, and the residue was dissolved in 50 ml of MeOH and treated with 0.54 g (0.02 mol) of $NaBH_4$. After stirring at room temperature for 30 min, the mixture was evaporated, and the residue was treated with 2 *N* NaOH and extracted with three 50-ml portions of CH_2Cl_2. The combined organic extracts were dried and evaporated, and the residue was dissolved in Et_2O and treated with HCl gas to give 1.7 g of crude **13** as the hydrochloride. After recrystallization from CH_2Cl_2–hexane there was obtained 1.6 g (59%): mp 257–258°; NMR (free base in $CDCl_3$) δ 1.2 (d, 2 H, J = 5 Hz), 2.15 (s, 3 H), 2.2–3.4 (m, 3 H), 3.7 (d, 1 H, J = 3.5 Hz), 7.2, 7.3 (2 s, 9 H).

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.53; H, 7.38; N, 5.00.

***cis*-*N*-Methyl-3-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (16).** 3-Phenyl-3,4-dihydro-1(2*H*)-naphthalenone (2.2 g, 0.01 mol) was treated with methylamine–$TiCl_4$ and subsequently with $NaBH_4$ as described above to give after conversion to the hydrochloride 2.0 g of crude **16**. After recrystallization from EtOH–hexane there was obtained 1.73 g (63%) of **16** as the hydrochloride: mp 177–179°; NMR (free base in $CDCl_3$) δ 1.55 (m, 2 H), 2.4 (m, 1 H), 2.45 (s, 3 H), 2.95 (m, 3 H), 4.0 (d of d, 1 H, J = 5, 10 Hz), 6.9–7.7 (m, 9 H).

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.48; H, 7.27; N, 4.92.

***cis*-*N*-Methyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (19) and Its Trans Isomer (20).** A solution of 11.2 g (0.05 mol) of 4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (**17**) in 250 ml of benzene was treated with 9.3 g of methylamine and 2.75 ml of $TiCl_4$ as described above, but the mixture was kept at room temperature overnight. After filtration and evaporation the residue was crystallized from hexane to give 11 g (93%) of the methylimine derivative **18**, mp 69–70°. A solution of 5 g (0.021 mol) of **18** in 150 ml of MeOH was treated with 2 g of $NaBH_4$ and the mixture was kept at room temperature for 30 min. After the usual work-up and conversion to the hydrochlorides, the cis isomer **19** was separated by fractional crystallization of the crude mixture from water. After two recrystallizations from MeOH–Et_2O there was obtained 2.3 g (40%) of **19** as the hydrochloride: mp 241–242°; NMR (CD_3OD) δ 1.9–2.3 (m, 4 H), 2.8 (s, 3 H), 4.1 (br t, 1 H), 4.5 (br s, 1 H), 4.9 (DOH), 6.7–7.7 (m, 9 H, sharp s at 7.23).

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.44; H, 7.46; N, 5.11.

From the aqueous mother liquor of **19** there was obtained after two recrystallizations from acetone–MeOH–Et_2O 1.9 g (33%) of the trans isomer **20** as the hydrochloride: mp 224–225°; NMR (CD_3OD) δ 1.7–2.5 (m, 4 H), 2.75 (s, 3 H), 4.25 (br t, 1 H), 4.6 (br t, 1 H), 4.9 (DOH), 6.7–7.7 (m, 9 H).

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.42; H, 7.30; N, 4.99.

Alternatively, **19** was obtained in 92% yield by hydrogenation of

18 in ethanol over 10% Pd/C at atmospheric pressure. Only trace amounts of the trans isomer **20** were found under these conditions according to VPC analysis (3% SE-30 on Varaport 30, 100/120 mesh, 3 ft × 0.125 in. column). On the other hand, treatment of 235 mg (0.001 mol) of **18** in 10 ml of glacial acetic acid with 0.5 g of activated zinc dust at 65° for 2 hr, followed by stirring at room temperature overnight, resulted after the usual work-up in the isolation of 180 mg (66%) of the trans isomer of **20** as the hydrochloride. VPC analysis of the crude reaction mixture indicated an 80:20 ratio of trans to cis isomer.

Resolution of the Trans Isomer 20. A mixture of 34 g (0.143 mol) of the cis and trans amines **19** and **20**, obtained by $NaBH_4$ reduction of **18**, and 15.9 g (0.0715 mol) of *N*-acetyl-L-tyrosine were dissolved in 300 ml of hot MeOH. After the addition of 700 ml of Et_2O, the mixture was kept at room temperature for 1 hr and at 0° for 30 min. The solids which had separated (13.6 g, mp 222–226°) were filtered and recrystallized from MeOH–Et_2O (1:2) to give 11.72 g of the *N*-acetyl-L-tyrosine salt of the 1*S*,4*R* isomer of **20**, mp 230–231°. After conversion to the hydrochloride and recrystallization from MeOH–Et_2O there was obtained 6.06 g (15%) of the hydrochloride of the 1*S*,4*R* isomer of **20**, mp 230–231°, $[\alpha]^{24}D$ −41.4° (*c* 1, MeOH). This sample was identical with a sample obtained by resolution of a specimen of pure **20**.

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.34; H, 7.31; N, 4.99.

The original mother liquor of the *N*-acetyl-L-tyrosine salt was evaporated, treated with 200 ml of 1 *N* NaOH, and extracted with three 200-ml portions of Et_2O. The combined organic extracts were dried and evaporated, and the residue (27 g) was dissolved in 300 ml of hot MeOH and treated with 8.7 g of D-(−)-mandelic acid. After cooling and the addition of 1 l. of Et_2O, the mixture was kept in the refrigerator overnight. The solids which had separated were filtered off and recrystallized twice from MeOH–Et_2O (1:2) to give 11.8 g of the D-mandelate of the 1*R*,4*S* isomer of **20**, mp 130–131°. After conversion to the hydrochloride and two recrystallizations from $CHCl_3$–Et_2O (1:3) there was obtained 6.3 g (16%) of the 1*R*,4*S* isomer of **20** as the hydrochloride, mp 230–231°, $[\alpha]^{24}D$ 41.2° (*c* 1, MeOH). Again, this compound was identical with a sample obtained previously by direct resolution of pure **20**.

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.73; H, 7.36; N, 5.09.

***cis*-4-Phenyl-*N,N,N*-trimethyl-1,2,3,4-tetrahydro-1-naphthylammonium Iodide (21).** A mixture of 165 mg (0.65 mmol) of **24** and 184 mg (1.3 mmol) of methyl iodide in 7 ml of MeOH was heated to 50° for 24 hr. After the addition of 50 ml of Et_2O, the precipitated solids were filtered and recrystallized from MeOH–Et_2O to give 155 mg (61%) of **21**, mp 174–175° dec.

Anal. Calcd for $C_{19}H_{24}IN$: C, 58.01; H, 6.16; N, 3.56. Found: C, 57.54; H, 6.12; N, 3.42.

A mixture of 10 mg of **21** and 1 ml of anhydrous methylamine in 10 ml of dimethylformamide was heated in a steel bomb to 98° for 30 min. VPC analysis of this mixture indicated the formation of ~30% trans amine **20**, in addition to 70% elimination product **22**.[27]

Oxidation of 19 with Aqueous Permanganate. To a solution of 23.7 g (0.1 mol) of **19** (free base) in 750 ml of acetone was added a solution of 23.7 g (0.15 mol) of $KMnO_4$ in 750 ml of H_2O over a period of 15 min, causing the temperature to rise to 42°. After stirring at room temperature for 1 hr, the mixture was filtered, and the filter cake was washed well with 500 ml of acetone. The combined filtrates were concentrated in vacuo to approximately 500 ml, and the mixture was extracted with CH_2Cl_2. After the usual work-up there was obtained 7.7 g (28%) of unreacted **19** as the hydrochloride, and 13.25 g (60%) of 4-phenyltetralone (**17**), mp 73–74°. In a similar run, using 0.3 mol of $KMnO_4$, the yield of **17** was 61%.

trans-*N,N*-Dimethyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (23). A mixture of 390 mg (1.64 mmol) of **20** (free base), 5 ml of 37% formaldehyde, and 5 ml of 98% formic acid was heated on a steam bath for 1 hr. After evaporation and the usual work-up there was obtained after crystallization from MeOH–Et_2O 402 mg (85%) of **23** as the hydrochloride, mp 228–230° dec. Similarly was obtained the cis isomer **24** in 85% yield, mp 192–194° after crystallization from acetone–Et_2O.

Anal. Calcd for $C_{18}H_{21}N \cdot HCl$: C, 75.12; H, 7.71; N, 4.86. Found (**23**): C, 74.87; H, 7.80; N, 4.71. Found (**24**): C, 75.18; H, 7.66; N, 4.74.

4-Phenyl-3,4-dihydro-1(2*H*)-naphthalenone Oxime. To a stirred solution of 4.9 g (0.022 mol) of **17** in 18 ml of EtOH was added 16 ml of H_2O, 1.72 g (0.025 mol) of hydroxylamine hydrochloride, and then 4.4 g of powdered NaOH. After 10 min, a clear solution had formed, which was then heated on the steam bath for 45 min. After cooling and evaporation, the residue was dissolved in $CHCl_3$ and washed with 1 *N* HCl. The organic layer was evaporated and the residue was crystallized from $CHCl_3$–hexane to give 3.58 g (69%) of the oxime, mp 114–115°.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.74; H, 6.48; N, 5.90.

4-Phenyl-3,4-dihydro-1(2*H*)-naphthalenone Phenylhydrazone. To a solution of 11.1 g (0.05 mol) of **17** in 200 ml of EtOH was added 10.8 g (0.1 mol) of phenylhydrazine and 40 ml of glacial acetic acid. The solution was heated on a steam bath for 30 min. After cooling, the crystals which had separated were collected and recrystallized from EtOH to give 13.4 g (86%) of the phenylhydrazone, mp 124–126°.

Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.26; H, 6.48; N, 8.97.

4-Phenyl-1,2,3,4-tetrahydro-1-naphthylamine (25 and 26). Hydrogenation of 2 g (8.4 mmol) of the oxime of **17** in 100 ml of EtOH over 1 g of 10% Pd/C at 50 psi for 2 hr gave after the usual work-up and fractional crystallization from MeOH–Et_2O 0.71 g (32%) of the trans isomer **25** as the hydrochloride, mp 301–302°, and 1.4 g (64%) of the cis isomer **26** as the hydrochloride, mp 279–281°. The stereochemical assignments are based on the conversion of **25** to **23** with formic acid–formaldehyde.

The trans isomer **25** was also obtained in 18% yield by suspending 10 g of the phenylhydrazone of **17** in 400 ml of acetic acid and treating the mixture with 26 g of activated zinc dust at 60° overnight, followed by the usual work-up.

Anal. Calcd for $C_{16}H_{17}N \cdot HCl$: C, 73.97; H, 6.99; N, 5.39. Found (**25**): C, 73.82; H, 6.85; N, 5.31. Found (**26**): C, 73.96; H, 7.03; N, 5.37.

***N*-Ethyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (27 and 28).** A solution of 6.66 g (0.03 mol) of **17** in 100 ml of benzene was treated with 8.1 g of ethylamine and 1.65 ml of $TiCl_4$ as described above to give, after crystallization of hexane, 5.4 g of the ethylimine derivative, mp 89–90°. Reduction of 4.9 g of this imine with 1 g of $NaBH_4$ in 75 ml of MeOH as described above gave, after fractional crystallization from MeOH–Et_2O, 490 mg (9%) of the trans isomer **27** as the hydrochloride, mp 224–225°, and 1.85 g (34%) of the cis isomer **28** as the hydrochloride, mp 261–262°. Catalytic hydrogenation of 1.5 g of the ketimine in 50 ml of EtOH over 200 mg of 10% Pd/C at 50 psi gave exclusively the cis isomer **28** according to VPC analysis.

Anal. Calcd for $C_{18}H_{21}N \cdot HCl$: C, 75.12; H, 7.71; N, 4.86. Found (**27**): C, 75.00; H, 7.78; N, 5.11. Found (**28**): C, 74.88; H, 7.63; N, 4.85.

***N*-Isopropyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (29 and 30).** When 6.66 g of **17** was treated with 10.6 g of isopropylamine as described above, there was obtained, after crystallization from hexane, 5.7 g of the ketimine, mp 74–75°. A 5.2-g sample was reduced with $NaBH_4$ to give, after multiple fractional crystallizations from MeOH–Et_2O, 2.59 g (44%) of the trans isomer **29** as the hydrochloride [mp 283–284°; NMR ($CDCl_3$ + NaOD) δ 1.1 (d, 3 H, J = 7 Hz), 1.14 (d, 3 H, J = 7 Hz), 1.3–2.4 (m, 4 H), 3.1 (m, J = 7 Hz), 3.7–4.3 (m, 2 H), 6.7–7.6 (m, 9 H)] and 0.65 g (11%) of the cis isomer **30** as the hydrochloride [mp 228–229°; NMR ($CDCl_3$ + NaOD) δ 1.25 (d, 6 H, J = 7 Hz), 1.9–2.2 (m, 4 H), 3.3 (m, J = 7 Hz), 3.8–4.6 (m, 2 H), 6.7–7.8 (m, 9 H; sharp s at 7.23)]. Catalytic hydrogenation of the ketimine gave again exclusively the cis isomer **30**.

Anal. Calcd for $C_{19}H_{23}N \cdot HCl$: C, 75.61; H, 8.01; N, 4.64. Found (**29**): C, 75.39; H, 7.96; N, 4.53. Found (**30**): C, 75.43; H, 7.97; N, 4.64.

***N*-Cyclopropyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (31 and 32).** When 6.66 g of **17** was converted to the ketimine with 10.05 g of cyclopropylamine, followed by reduction with $NaBH_4$ and multiple fractional crystallizations of the hydrochloride salts, there was ultimately obtained 1.15 g (13%) of the trans isomer **31** as the hydrochloride, mp 218–220°, and 0.4 g (4%) of the cis isomer **32** as the hydrochloride, mp 223–224°, NMR of **32** ($CDCl_3$ + NaOD) δ 0.3–0.6 (m, 4 H), 1.8–2.5 (m, 5 H), 3.8–4.2 (m, 2 H), 6.7–7.4 (m, 9 H).

Catalytic hydrogenation of the ketimine gave again predominantly the cis isomer **32**.

Anal. Calcd for $C_{19}H_{21}N \cdot HCl$: C, 76.10; H, 7.39; N, 4.67. Found (**31**): C, 75.84; H, 7.31; N, 4.67. Found (**32**): C, 75.85; H, 7.36; N, 4.68.

***N*-(4-Phenyl-1,2,3,4-tetrahydro-1-naphthyl)pyrrolidine (33 and 34).** A mixture of 380 mg (1.7 mmol) of **25** as the free base, 360 mg (1.7 mmol) of 1,4-dibromobutane, 25 ml of xylene, and 286 mg

of $NaHCO_3$ was refluxed for 62 hr. After the usual work-up there was obtained 190 mg (36%) of the trans isomer **33** as the hydrochloride, mp 258–259°. Similarly, **26** was converted to **34**, mp of the hydrochloride 256–257°.

Anal. Calcd for $C_{20}H_{23}N \cdot HCl$: C, 76.53; H, 7.70; N, 4.46. Found (**33**): C, 76.44; H, 7.70; N, 4.30. Found (**34**): C, 76.11; H, 7.89; N, 4.32.

1-(4-Phenyl-1,2,3,4-tetrahydro-1-naphthyl)-4-methylpiperazine (35 and 36). A solution of 2.2 g (0.01 mol) of **17** in 50 ml of benzene was treated with 6 g of 1-methylpiperazine and 0.55 ml of $TiCl_4$ as described above, but the mixture was kept at room temperature for 20 hr. After filtration and evaporation, the resulting enamine was dissolved in 75 ml of tetrahydrofuran and treated with 2 g of $LiBH_4$ and then dropwise with 5 ml of 98% formic acid. The mixture was refluxed for 15 min and then worked up in the usual manner to give after multiple fractional crystallizations of the hydrochlorides from MeOH–Et_2O 300 mg (9%) of **35** as the hygroscopic hydrochloride, mp 254–255°, and 560 mg (16%) of **36** as the hydrochloride, mp 249–250°. The stereochemical assignments are based on the result of a catalytic hydrogenation of a sample of the enamine which gave exclusively **36.**

Anal. Calcd for $C_{21}H_{26}N_2 \cdot HCl$: C, 73.56; H, 7.93; N, 8.17. Calcd for $C_{21}H_{26}N_2 \cdot HCl \cdot \frac{1}{4}H_2O$: C, 72.60; H, 7.94; N, 8.07. Found (**35**): C, 72.87; H, 8.07; N, 8.25. Found (**36**): C, 73.45; H, 7.92; N, 8.23.

2,8-Dichloro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (38). A solution of 21 g (0.1 mol) of 8-chloro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone[1,14] (**37**) in 500 ml of glacial acetic acid was cooled to 5° and 7.1 g of chlorine gas was introduced. After stirring for 2 hr at room temperature, the mixture was evaporated and the residue was suspended in 250 ml of 1 *N* HCl. Extraction with chloroform, evaporation of the organic solvents, and two recrystallizations of the residue from $CHCl_3$–hexane yielded 17.3 g (71%) of **38**: mp 112–113°; NMR ($CDCl_3$) δ 2.25–2.65 (m, 2 H), 2.85–3.2 (m, 2 H), 3.83 (s, 3 H), 4.55 (d of d, 1 H, *J* = 4.5, 6.5 Hz), 6.9 (d, 1 H, *J* = 9 Hz), 7.3 (d, 1 H, *J* = 9 Hz).

Anal. Calcd for $C_{11}H_{10}Cl_2O_2$: C, 53.91; H, 4.11. Found: C, 53.72; H, 4.41.

8-Chloro-5-methoxy-2-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (39). To a solution of 17 g (0.0695 mol) of **38** in 150 ml of benzene was added to a solution of phenylmagnesium bromide (obtained from 11 g of bromobenzene and 1.7 g of magnesium shavings in Et_2O) over a period of 15 min, causing a temperature rise. The mixture was kept for 2 days at room temperature and then refluxed for 1 hr. After addition of 200 ml of H_2O and 200 ml of 1 *N* HCl, the organic layer was separated and evaporated, and the residue (20 g) was crystallized from EtOAc–hexane to give 4.77 g (24%) of **39**: mp 126–128°; NMR ($CDCl_3$) δ 2.25–2.7 (m, 2 H), 2.8–4.2 (m, 3 H), 3.83 (s, 3 H), 6.85 (d, 1 H, *J* = 9 Hz), 7.0–7.8 (m, 6 H).

Anal. Calcd for $C_{17}H_{15}ClO_2$: C, 71.21; H, 5.27. Found: C, 71.50; H, 5.36.

***cis*-8-Chloro-5-methoxy-*N*-methyl-2-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (40).** A solution of 4.3 g (0.015 mol) of **39** in benzene was converted to the ketimine with methylamine and $TiCl_4$ as described above, refluxing the reaction mixture for 19 hr. After reduction with $NaBH_4$ and the usual work-up there was obtained 0.99 g (20%) of **40** as the hydrochloride, mp 238–239° (from $CHCl_3$–Et_2O), which was indistinguishable from a sample obtained by catalytic hydrogenation of the ketimine.

Anal. Calcd for $C_{18}H_{20}ClNO \cdot HCl$: C, 63.91; H, 6.26; N, 4.14. Found: C, 64.19; H, 6.40; N, 4.19.

4-(2-Methoxy-5-chlorophenyl)-3-phenylbutyric Acid (43, R = H). A solution of 20.4 g (1 mol) of the sec-butyl ester of cinnamic acid[17] in 300 ml of Et_2O was added dropwise at 0° to a solution of 5-chloro-2-methoxybenzylmagnesium chloride [prepared from 47.8 g (0.25 mol) of 5-chloro-2-methoxybenzyl chloride[28] and 36 g of magnesium shavings] and 150 mg of cuprous chloride in 300 ml of Et_2O. After standing at room temperature overnight, the mixture was poured onto ice and 100 ml of concentrated HCl. The organic layer was collected, dried, and evaporated. The residue (51 g) was distilled and the fraction (21 g, 58%) boiling at 180–182° (0.15 mm) was collected. A 15-g (0.0415 mol) portion of this fraction was saponified with 37.5 g of 87% KOH, 150 ml of EtOH, and 37.5 ml of H_2O at reflux temperature for 3 hr to give, after a crystallization of the acidic product from hexane, 8.6 g (68%) of **43** (R = H): mp 99–100°; NMR ($CDCl_3$) δ 2.5–3.0 (m, 4 H), 3.1–3.7 (m, 1 H), 3.7 (s, 3 H), 6.67 (d, 1 H, *J* = 9 Hz), 6.95 (d of d, *J* = 3, 9 Hz), 7.2 (br s, 6 H), 11.5 (br s, 1 H).

Anal. Calcd for $C_{17}H_{17}ClO_3$: C, 67.01; H, 5.62. Found: C, 67.18; H, 5.87.

3-(5-Chloro-2-methoxybenzyl)-1-indanone (41). A mixture of 7.6 g (0.025 mol) of **43** and 200 g of polyphosphoric acid was heated to 110° for 45 min and then poured onto ice. After extraction with EtOAc and washing with 10% aqueous Na_2CO_3, the organic layer was dried and evaporated and the residue was crystallized from ETOH–hexane to give 3.19 g (44%) of **41**: mp 73–74°; NMR ($CDCl_3$) δ 2.15–3.8 (m, 5 H), 3.8 (s, 3 H), 6.78 (d, 1 H, *J* = 9 Hz), 7.0–7.85 (m, 6 H).

Anal. Calcd for $C_{17}H_{15}ClO_2$: C, 71.21; H, 5.27. Found: C, 71.13; H, 5.57.

4-(2-Methoxyphenyl)-3-phenylbutyric Acid (46). A solution of 10.8 g (0.035 mol) of **43** in 400 ml of MeOH and 14.2 ml of NEt_3 was hydrogenated in the presence of 2 g of 10% Pd/C at 50 psi and ambient temperature for 40 min. After the usual work-up the acidic product was crystallized from EtOAc–hexane (1:10) to give 8.55 g (89%) of **46**: mp 98–99°; NMR ($CDCl_3$) δ 2.6 (d, 2 H, *J* = 7.5 Hz), 2.85 (d, 2 H, *J* = 7.5 Hz), 3.5 (m, 1 H), 3.7 (s, 3 H), 6.6–7.1 (m, 4 H), 7.2 (s, 5 H), 10.9 (s, 1 H).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.45; H, 6.65.

5-Methoxy-3-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (47). This compound was obtained from **46** according to the method of Johnson and Glenn[7] in 24% yield after chromatography over a SiO_2 column with benzene. After crystallization from EtOAc–hexane (1:5), **47** had mp 158–160°; NMR ($CDCl_3$) δ 2.6–3.7 (m, 5 H), 3.85 (s, 3 H), 7.05 (d of d, 1 H, *J* = 9 Hz), 7.2–7.45 (m, 1 H), 7.3 (s, 5 H), 7.7 (d of d, 1 H, *J* = 7.5, 2 Hz).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.92; H, 6.57.

***cis*-5-Methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (48).** A solution of 1 g (3.95 mmol) of **47** in 50 ml of benzene was converted with 1.0 g of methylamine and 0.25 ml $TiCl_4$ at room temperature to the ketimine. Hydrogenation of the ketimine in EtOH in the presence of 500 mg of 10% Pd/C at 50 psi gave, after conversion to the hydrochloride and recrystallization from MeOH–Et_2O (1:1), 850 mg (70%) of **48**: mp 270–271°; NMR (free base in $CDCl_3$) δ 2.5–4.1 (m, 7 H), 2.45 (s, 3 H), 3.75 (s, 3 H), 6.4–7.4 (m, 3 H), 7.3 (s, 5 H).

Anal. Calcd for $C_{18}H_{21}NO \cdot HCl$: C, 71.15; H, 7.30; N, 4.61. Found: C, 70.89; H, 7.37; N, 4.58.

***cis*-8-Chloro-5-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (45).** A solution of 304 mg (1 mmol) of **48** hydrochloride in 10 ml of AcOH was treated at room temperature with a solution of 71 mg of Cl_2 in 2 ml of AcOH[1] for 30 min to give, after evaporation and two recrystallizations of the residue from MeOH–Et_2O (1:10), 190 mg (56%) of **45** hydrochloride: mp 246–247° dec; NMR (CD_3OD) δ 2.0–3.3 (m, 5 H), 2.75 (s, 3 H), 3.85 (s, 3 H), 4.85 (s, DOH), 5.05 (t, 1 H, *J* = 9 Hz), 7.05 (d, 1 H, *J* = 9 Hz), 7.1–7.5 (m, 6 H).

Anal. Calcd for $C_{18}H_{20}ClNO \cdot HCl$: C, 63.91; H, 6.26; N, 4.14. Found: C, 63.88; H, 6.23; N, 4.02.

4,4-Di(5-chloro-2-methoxyphenyl)-3-ethoxycarbonyl-3-butenoic Acid (50). 5,5′-Dichloro-2,2′-dimethoxybenzophenone[18] was converted to the title compound in 35% yield using the conditions of Johnson et al.[19] The product melted at 98–100° after recrystallization from EtOAc–hexane: NMR ($CDCl_3$) δ 0.9 (t, 3 H, *J* = 7 Hz), 3.3 (br s, 2 H), 3.7 (s, 3 H), 3.73 (s, 3 H), 4.0 (q, 2 H, *J* = 7 Hz), 6.77 (d, 1 H, *J* = 9 Hz), 6.82 (d, 1 H, *J* = 9 Hz), 7.0–7.4 (m, 4 H), 10.3 (br s, 1 H).

Anal. Calcd for $C_{21}H_{20}Cl_2O_6$: C, 57.42; H, 4.56. Found: C, 58.01; H, 5.00.

4,4-Di(5-chloro-2-methoxyphenyl)-3-carboxy-3-butenoic Acid (51). This compound was prepared in 72% yield by treating a solution of 4 g of **50** in 30 ml of EtOH with 60 ml of 4 *N* NaOH at room temperature overnight. After a crystallization from EtOH–hexane, **51** melted at 238–239°. This compound was also obtained as a by-product in various attempts to hydrolyze and decarboxylate **50** under acidic conditions.

Anal. Calcd for $C_{19}H_{16}Cl_2O_6$: C, 55.49; H, 3.89. Found: C, 55.45; H, 4.19.

3-Carboxymethyl-6-chloro-4-(5-chloro-2-methoxyphenyl)-coumarin (53). This compound was isolated in up to 24% yield during attempts to hydrolyze and decarboxylate **50**.[19] **53** melted at 228–229° after recrystallization from EtOAc: NMR (DMSO-d_6) δ 3.2 (br s, 2 H), 3.73 (s, 3 H), 6.8–7.8 (m, 6 H).

Anal. Calcd for $C_{18}H_{12}Cl_2O_5$: C, 57.00; H, 3.17; Cl, 18.71. Found: C, 57.21; H, 3.16; Cl, 18.64.

2-(3-Methoxyphenyl)-1,3-dithiane (55). A mixture of 80.5 g (0.592 mol) of *m*-anisaldehyde and 60 ml (0.592 mol) of 1,3-propanedithiol in 450 ml of $CHCl_3$ was saturated with HCl gas,[29]

keeping the temperature at 30–40° with external cooling. The solution was stirred at room temperature for 30 min, washed with H_2O (2 × 200 ml), 1 *N* KOH (3 × 250 ml), and H_2O, dried, and evaporated. The residue was crystallized from 200 ml of MeOH to give 123 g (92%) of **55**: mp 62–63°; NMR ($CDCl_3$) δ 1.7–2.2 (m, 2 H), 2.8–3.2 (m, 4 H), 3.77 (s, 3 H), 5.13 (s, 1 H), 6.7–7.4 (m, 4 H).

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.40; H, 6.24. Found: C, 58.60; H, 6.31.

2-Cinnamyl-2-(3-methoxyphenyl)-1,3-dithiane (56). A solution of 6.8 g (0.03 mol) of **55** in 50 ml of tetrahydrofuran was cooled to −40°, and 20 ml of a 1.6 *M* solution of butyllithium (0.032 mol) was added dropwise with stirring, keeping the temperature below −30° during the addition. The mixture was then allowed to stand at room temperature for 1 hr (at that time NMR analysis of an aliquot quenched with D_2O indicated complete conversion to the lithio derivative) and cooled again to −40° while 5.8 g (0.03 mol) of cinnamyl bromide in 10 ml of tetrahydrofuran was added dropwise. After standing at room temperature overnight, the mixture was diluted with 50 ml of H_2O, concentrated in vacuo, and extracted with three 50-ml portions of $CHCl_3$. The organic layers were combined, dried, and evaporated. The residue afforded, after crystallization from MeOH, 9.5 g (93%) of **56**: mp 84–85°; NMR ($CDCl_3$) δ 1.7–2.2 (m, 2 H), 2.45–2.9 (m, 6 H), 3.8 (s, 3 H), 5.9 (d of d, 1 H, *J* = 6.5, 16 Hz), 6.35 (d, 1 H, *J* = 16 Hz), 6.6–7.7 (m, 9 H).

Anal. Calcd for $C_{20}H_{22}OS_2$: C, 70.16; H, 6.48. Found: C, 70.47; H, 6.63.

Spiro[1,3-dithiane-2,1′-(7′-methoxy-4′-phenyl-1′,2′,3′,4′-tetrahydronaphthalene)] (57). Boron trifluoride gas was introduced for 3.5 min into a solution of 680 mg (0.002 mol) of **56** in 50 ml of CH_2Cl_2. The orange mixture was kept at room temperature overnight, diluted with H_2O, and extracted twice with 50 ml of CH_2Cl_2. The organic layers afforded, after evaporation and crystallization of the residue from CH_2Cl_2–Et_2O, 310 mg (36%) of **57** as the HBF_4 adduct: mp 163–164°; NMR (DMSO-d_6) δ 1.8–4.5 (m, 10+ H), 3.83 (s, 3 H), 6.7–6.9 (m, 2 H), 7.0–7.5 (m, 7 H).

Anal. Calcd for $C_{20}H_{22}OS_2 \cdot HBF_4$: C, 55.82; H, 5.39. Found: C, 55.82; H, 5.47.

2-(2-Chloro-5-methoxyphenyl)-1,3-dithiane (59). This compound was prepared in 67% yield from 22.5 g of 2-chloro-5-methoxybenzaldehyde[23] as described above for **55**. After crystallization from MeOH, **59** melted at 66–68°; NMR ($CDCl_3$) δ 1.8–2.2 (m, 2 H), 2.8–3.2 (m, 4 H), 3.77 (s, 3 H), 5.57 (s, 1 H), 6.75 (d of d, 1 H, *J* = 3, 9 Hz), 7.20 (d, 1 H, *J* = 3 Hz), 7.23 (d, 1 H, *J* = 9 Hz).

Anal. Calcd for $C_{11}H_{13}ClOS_2$: C, 50.66; H, 5.02. Found: C, 50.70; H, 5.08.

2-(2-Chloro-5-methoxyphenyl)-2-cinnamyl-1,3-dithiane (60). A solution of 1.8 g (0.0069 mol) of **59** in 12 ml of tetrahydrofuran was cooled to 0° and treated dropwise with 3.4 ml of a 2.1 *M* solution of MeLi in Et_2O. After stirring at 0° for 1 hr, NMR analysis of an aliquot quenched with D_2O indicated only a 50% conversion. Therefore, another 3.5 ml of the MeLi solution was added and the mixture was kept for another hour at 0°. At that time, NMR analysis indicated complete conversion to the lithio derivative, and 1.3 g (0.0069 mol) of cinnamyl bromide was added and the mixture was kept at room temperature overnight. The work-up procedure was identical with that described above for **56**, and afforded 0.7 g (27%) of **60**: mp 106–108° after two crystallizations from isopropyl alcohol; NMR ($CDCl_3$) δ 1.8–2.2 (m, 2 H), 2.6–2.9 (m, 4 H), 3.38 (d, 2 H, *J* = 7 Hz), 3.86 (s, 3 H), 5.85 (d of d, 1 H, *J* = 7, 16 Hz), 6.43 (d, 2 H, *J* = 16 Hz), 6.73 (d of d, 1 H, *J* = 3, 9 Hz), 7.19 (s, 5 H), 7.32 (d, 1 H, *J* = 9 Hz), 7.73 (d, 1 H, *J* = 3 Hz).

Anal. Calcd for $C_{20}H_{21}ClOS_2$: C, 63.73; H, 5.61. Found: C, 63.57; H, 5.70.

5-Chloro-8-methoxy-1-phenyl-1,2,3,4-tetrahydro-1-naphthol (63). A solution of 2.1 g (0.01 mol) of 5-chloro-8-methoxy-3,4-dihydro-1(2*H*)naphthalenone[24] (**62**) in 20 ml of Et_2O was added dropwise to a boiling solution of phenylmagnesium bromide, prepared from 0.486 g of magnesium shavings and 3.14 g of bromobenzene in 40 ml of Et_2O. After refluxing for 2 hr, the mixture was treated with 10 ml of H_2O and washed with 100 ml of 10% aqueous NH_4Cl and 200 ml of H_2O. The organic layer afforded ultimately, after crystallization from hexane, 2.2 g (76%) of **63**, mp 91–92°.

Anal. Calcd for $C_{17}H_{17}ClO_2$: C, 70.70; H, 5.93. Found: C, 70.66; H, 6.09.

5-Chloro-8-methoxy-1-phenyl-3,4-dihydronaphthalene (64). A solution of 2.2 g of **63** in 60 ml of benzene was heated to reflux in the presence of 10 mg of *p*-toluenesulfonic acid in a Dean-Stark apparatus for 1.5 hr. After evaporation and crystallization from hexane and from EtOH, 2.02 g (98%) of **64**, mp 106–107°, was obtained.

Anal. Calcd for $C_{17}H_{15}ClO$: C, 75.43; H, 5.58. Found: C, 75.62; H, 5.28.

5-Chloro-8-methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalene (65). This compound was prepared in 84% yield by hydrogenation of 1.8 g of **64** at atmospheric pressure in 55 ml of EtOH containing a few drops of concentrated HCl in the presence of 500 mg of 10% Pd/C until the theoretical amount of hydrogen had been taken up (2 hr). After crystallization from MeOH, **65** melted at 91–92°.

Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.85; H, 6.28. Found: C, 74.66; H, 6.48.

8-Chloro-5-methoxy-4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (66). A solution of 1 g of $KMnO_4$ in 50 ml of H_2O was added to a solution of 820 mg (3 mmol) of **65** in 120 ml of acetone. After stirring at room temperature for 2 days, an analysis of an aliquot of the purple mixture indicated only partial conversion to the ketone. The reaction mixture was then heated to reflux while 3 g of $KMnO_4$ in 50 ml of H_2O was added at such a rate that the color of the mixture remained purple (45 min). After filtration, the filtrate was concentrated to 50 ml in vacuo and the mixture was extracted twice with Et_2O; the combined organic layers were washed, dried, and evaporated to an oil (756 mg) which was separated by column chromatography (25 g of silica gel, 70–325 mesh, 1.5 × 50 cm column), using benzene as the solvent. From the early fractions was recovered, after a crystallization from MeOH, 447 mg (54%) of starting material, and from the later fractions, after crystallizations from MeOH, 250 mg (29%) of **66**: mp 123–124°; NMR ($CDCl_3$) δ 2.1–2.6 (m, 4 H), 3.65 (s, 3 H), 4.7 (br s, 1 H), 6.9 (d, 1 H, *J* = 9 Hz), 6.9–7.3 (m, 5 H), 7.38 (d, 1 H, *J* = 9 Hz); mass spectrum *m/e* 286 (M^+, base peak), 271, 258, 251, 243, 199.

8-Methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalene (69). This compound was obtained in 79% yield by hydrogenation of 2.06 g of **65** over 1 g of 10% Pd/C in 50 ml of EtOH, containing 2 ml of triethylamine, at atmospheric pressure (2 hr). **69** had mp 101–103° after recrystallization from EtOH.

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.39; H, 7.76.

5-Methoxy-4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (70). A solution of 1.02 g of **60** in 100 ml of acetone was treated with 10 ml of H_2O and 10 g of $KMnO_4$. The mixture was heated on the steam bath until the purple color had disappeared (4 hr). Another 10 g of $KMnO_4$ was added and the mixture was refluxed for 3 hr. The mixture was then filtered, and the filtrate was treated with 100 ml of acetone, 10 ml of H_2O, and 10 g of $KMnO_4$ and refluxed for another 3 hr. Upon work-up (concentration in vacuo, extraction with $CHCl_3$, drying, and evaporation) there was obtained, after crystallization on $CHCl_3$–hexane, 655 mg (61%) of **70**: mp 117–118°; NMR ($CDCl_3$) δ 2.1–2.7 (m, 4 H), 3.68 (s, 3 H), 4.65 (m, 1 H), 6.9–7.85 (m, 8 H).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.90; H, 6.64.

***cis*-5-Methoxy-*N*-methyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (71) and Its Trans Isomer 72.** Reduction of the methylimine, obtained from **70** and methylamine in the usual manner, with $NaBH_4$ gave **71** in 72% yield as the hydrochloride, mp 285–286°.

Anal. Calcd for $C_{18}H_{21}NO \cdot HCl \cdot \frac{1}{4}H_2O$: C, 70.11; H, 7.35; N, 4.54. Found: C, 70.55; H, 7.26; N, 4.37.

On the other hand, reduction of the methylimine derivative with zinc–acetic acid (see above for the preparation of **20**) gave a 42% yield of the trans isomer **72**; mp of the hydrochloride 240–242°.

Anal. Calcd for $C_{18}H_{21}NO \cdot HCl \cdot \frac{1}{4}H_2O$: C, 70.11; H, 7.35; N, 4.54. Found: C, 69.38; H, 7.10; N, 4.15.

***cis*-8-Chloro-*N*-methyl-5-methoxy-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (67) and Its Trans Isomer (68).** Conversion of **66** to the methylimine in the usual manner, followed by reduction with $NaBH_4$ in MeOH, gave the cis isomer **67** in 85% yield. Only traces of the trans isomer **68** were detected by TLC analysis. This isomer was identical with the one obtained by catalytic hydrogenation of the ketimine or by chlorination of **71** in acetic acid.[1] The melting point of **67** as the hydrochloride was 255–257° (from $CHCl_3$–Et_2O); NMR (CD_3OD) δ 2.0–2.25 (m, 4 H), 2.86 (s, 3 H), 3.47 (s, 3 H), 4.3 (m, 1 H), 4.8 (m, 1 H), 4.85 (CD_3OH), 6.9–7.3 (m, 6 H), 7.5 (d, 1 H, *J* = 9 Hz).

Anal. Calcd for $C_{18}H_{20}ClNO \cdot HCl \cdot \frac{1}{2}H_2O$: C, 62.25; H, 6.39; N, 4.03. Found: C, 62.26; H, 6.17; N, 3.87.

The trans isomer **68** was obtained in 40% yield by chlorination of **72** in acetic acid;[1] the melting point of **68** as the hydrochloride was 250–252°; mass spectrum *m/e* 301 (M^+), 286, 270 (base peak), 266, 235, 193, 179.

Acknowledgments. The skillful assistance of Messrs. Edmund G. Andrews, Werner H. Kappeler, and Frank W. Rusek is greatly appreciated.

Registry No.—**6**, 7469-40-1; 8 HCl, 54308-10-0; **10**, 54308-11-1; **11**, 7498-87-5; **13** HCl, 54308-12-2; **14**, 14944-26-4; **16** HCl, 54308-13-3; **17**, 14578-68-8; **17** oxime, 50845-35-7; **17** phenylhydrazone, 54308-14-4; **18**, 52789-19-2; **19**, 54308-15-5; **19** HCl, 52371-38-7; **20**, 54308-16-6; **20** HCl, 52371-37-6; (1*S*,4*R*)-**20** *N*-acetyl-L-tyrosine salt, 52795-05-8; (1*S*,4*R*)-**20** HCl, 52760-48-2; (1*R*,4*S*)-**20** D-(−)-mandelate, 52795-03-6; (1*R*,4*S*)-**20** HCl, 52760-47-1; **21**, 54308-17-7; **23** HCl, 52371-39-8; **24**, 52371-40-1; **24** HCl, 54308-18-8; **25** HCl, 52371-31-0; **26** HCl, 52371-32-1; **27** HCl, 54308-19-9; **28** HCl, 54308-20-2; **29** HCl, 54308-21-3; **30** HCl, 54308-22-4; **31** HCl, 54308-23-5; **32** HCl, 54308-24-6; **33** HCl, 54308-25-7; **34** HCl, 54308-26-8; **35** HCl, 54308-27-9; **36** HCl, 54308-28-0; **37**, 34910-81-1; **38**, 54308-29-1; **39**, 54308-30-4; **40** HCl, 54308-31-5; **41**, 54308-32-6; **43** (R = H), 54308-33-7; **45** HCl, 54308-34-8; **46**, 54308-35-9; **47**, 54308-37-1; **48**, 54308-36-0; **48** HCl, 54308-38-2; **49**, 54308-39-3; **50**, 54308-40-6; **51**, 54308-41-7; **53**, 54308-42-8; **54**, 591-31-1; **55**, 54308-43-9; **56**, 54308-44-0; **57** HBF_4 adduct, 54308-46-2; **58**, 13719-61-4; **59**, 54308-47-3; **60**, 54308-48-4; **62**, 54308-49-5; **63**, 54308-50-8; **64**, 54308-51-9; **65**, 54308-52-0; **66**, 54308-53-1; **67** HCl, 54308-54-2; **68** HCl, 54308-55-3; **69**, 54308-56-4; **70**, 54308-57-5; **71** HCl, 54308-58-6; **72** HCl, 54308-59-7; mercuric nitrate, 10045-94-0; methyl iodide, 74-88-4; hydroxylamine hydrochloride, 5470-11-1; phenylhydrazine, 100-63-0; isopropylamine, 75-31-0; 4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone isopropyl ketimine, 54308-60-0; 1-methylpiperazine, 109-01-3; *sec*-butyl cinnamate, 7726-62-7; 5-chloro-2-methoxybenzyl chloride, 7035-11-2; 1,3-propanedithiol, 109-80-8; boron trifluoride, 7637-07-2; *N*-acetyl-L-tyrosine, 537-55-3; ethylamine, 75-04-7; cyclopropylamine, 765-30-0; 1,4-dibromobutane, 110-52-1; bromobenzene, 108-86-1; D-(−)-mandelic acid, 611-71-2.

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Novel Synthesis of Aminoethanethiols[1]

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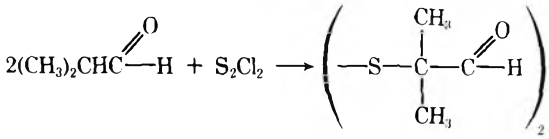
The reaction of α,α'-dithiodiisobutyraldehyde (1) with primary aromatic or aliphatic amines afforded novel Schiff bases (2–8). The reduction of these Schiff bases with sodium borohydride furnished a novel synthesis of 1,1-dimethyl 2-substituted aminoethanethiols (9–15). Two of the aminoethanethiols (13 and 14) were further characterized by the reaction with carbon disulfide to give the corresponding 3-substituted 5,5-dimethyl-2-thiazolidinethione (16 and 17).

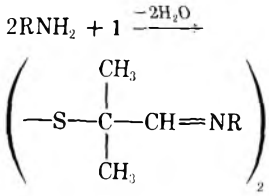
Aminoethanethiols are among the most effective radiation-protective compounds known.[2,3] 2-Aminoethanethiols have been synthesized by the addition of aromatic or aliphatic amines to episulfides or episulfide precursors.[4] However, this method requires high temperatures in sealed tubes and gives low yields because of further mercaptoethylation on sulfur or nitrogen to give bis products or polymers. The addition of excess amine has been successfully used to repress these side reactions[4,5a] but also requires separation of the excess amine from the product. Recently, Luhowy and Meneghini[6] reported that the mercaptoethylation of primary aliphatic amines can be carried out at room temperature with equimolar amounts of episulfide and amine in aqueous media containing amine–silver ion complex.

We wish to report a novel synthesis for 1,1-dimethyl 2-substituted aminoethanethiols. The key intermediate, α,α-dithiodiisobutyraldehyde[7] (1), was prepared by the reaction of isobutyraldehyde with sulfur monochloride. The reaction of 1 with primary aromatic or aliphatic amines in refluxing heptane containing a catalytic amount of *p*-toluenesulfonic acid or in methyl alcohol at 25–30° gave the Schiff bases 2–8 in yields of 82–99%. Reduction of these products with sodium borohydride in refluxing ethanol furnished the aminoethanethiols (9–15) in good yields. The structures of the Schiff bases and aminoethanethiols were

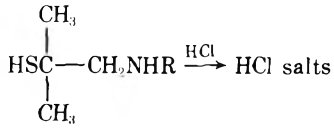
Scheme I



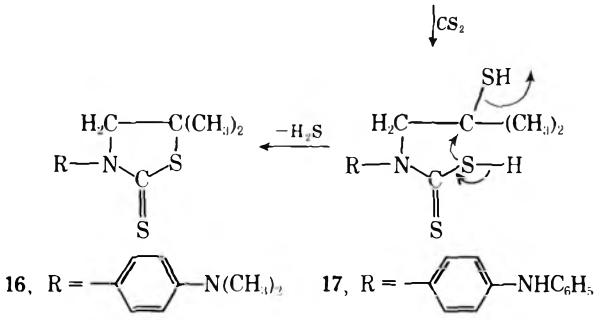
1



R = CH_3 and as shown in Table I



R = as shown in Table II



consistent with their NMR and mass spectra. Two of the aminoethanethiols, **13** and **14**, were further characterized by the reaction with carbon disulfide to give the corresponding 3-substituted 5,5-dimethyl-2-thiazolidinethione (**16** and **17**) (Scheme I).

It is worthy to note that we obtained the same product, 1,1-dimethyl-2-methylaminoethanethiol hydrochloride (**15a**), which was previously reported by Luhowy and Meneghini.[6] A mixture melting point of the two samples[8] was not depressed and the NMR spectra of the two were identical.

The advantages afforded by this novel method are (1) it eliminates the synthesis of episulfides, which are difficult to prepare and in some cases unstable when stored under ordinary conditions,[5b] and (2) a simple, efficient method is now available for the synthesis of 1,1-dimethyl- (and possibly higher 1, 1-dialkyl-) 2-aminoethanethiols.

Proposed mass spectral fragmentation routes for **2**, **9**, and **16** are depicted in Schemes II–IV, respectively.[9]

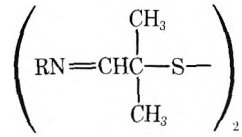
Experimental Section

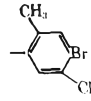
NMR spectra were obtained with a Varian A-60 NMR spectrometer. The chemical shifts are reported in δ, using tetramethylsilane as reference. All melting points were taken upon a Fisher-Johns block and are uncorrected. The mass spectra of **2**, **7**, **9**, **16**, and **17** were determined with a Varian MAT CH-7 mass spectrometer operating at an ionizing potential of 70 eV using the direct insertion probe technique with a source temperature of 250°.

α,α′-Dithiodiisobutyraldehyde (1). A modified procedure reported by Niederhauser[7] was employed. To a stirred solution containing 578 g (8.0 mol) of isobutyraldehyde in 920 g of carbon tetrachloride, 540 g (4.0 mol) of 98% sulfur monochloride was added dropwise at 40–50° in 4 hr. Hydrogen chloride was copiously liberated and occasional cooling was necessary during the addition period. The stirred solution was held at 30–40° for an additional pe-

Table I

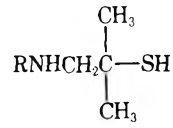
***N,N′*-[1,1′-Dithiobis(1,1-dimethyl-1-ethanyl-2-ylidene)]bis(methylamine) or (Substituted Anilines)[e]**

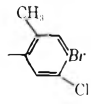
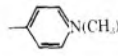
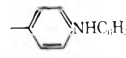


Compd	Method	R	Mp, °C	% yield (crude)	Nmr, δ, ppm, $CDCl_3$–TMS	Empirical formula
2[f]	I	$-C_6H_5$	108–109[a]	95	1.5 [s, 12, 2-C$(CH_3)_2$] 6.9–7.5 (m, 10, 2-ArH) 7.6 (s, 2, 2-CH=N)	$C_{20}H_{24}N_2S_2$
3	I		90–91[a]	99	1.4 [s, 12, 2-C$(CH_3)_2$][b] 6.8–7.5 (m, 8, 2-ArH) 7.6 (s, 2, 2-CH=N)	$C_{20}H_{22}Cl_2N_2S_2$
4	I		109–111[a]	96	1.5 [s, 12, 2-C$(CH_3)_2$] 2.2 (s, 6, 2-ArCH_3) 6.8 (s, 2, 2-CH=N) 7.5 (d, 4, 2-ArH)	$C_{22}H_{24}Br_2Cl_2N_2S_2$
5	I		*c*	95	1.5 [s, 12, 2-C$(CH_3)_2$] 6.7–7.2 (m, 8, 2-ArH) 7.6 (s, 2, 2-CH=N)	$C_{22}H_{22}F_6N_2S_2$
6	II		133–134[a]	88	1.5 [s, 12, 2-SC$(CH_3)_2$] 3.0 [s, 12, 2-N$(CH_3)_2$] 6.6–7.4 (m, 8, 2-ArH) 7.7 (s, 2, 2-CH=N)	$C_{24}H_{34}N_4S_2$
7[g]	II		97–98[d]	97	1.5 [s, 12, 2-C$(CH_3)_2$] 5.7 (br, *s*, 2, 2-NH) 6.9–7.5 (m, 18, 2-2ArH) 7.7 (s, 2, 2-CH=N)	$C_{32}H_{34}N_4S_2$

[a] Recrystallization from isopropyl alcohol. [b] Solvent DMSO-d_6. [c] Dark amber, viscous liquid, decomposes on distillation in vacuo (0.30 mm). [d] Recrystallization from ethyl alcohol. [e] Satisfactory analytical data (±0.4% for C, H, N, and S) were reported for all compounds (**2**–**7**). Ed. [f] Mass spectrum *m/e* (rel intensity) (probe temperature 60°) 147 (63.3), 146 (81.1), 145 (20.3), 144 (34.7), 132 (22.5), 131 (25.2), 130 (33.0), 104 (43.2), 77 (100), 51 (39.0). [g] Mass spectrum *m/e* (rel intensity) (probe temperature 240°) 238 (100), 237 (20.4), 236 (87.1), 235 (53.8), 221 (20.4), 195 (53.5), 168 (42.0), 167 (77.1), 144 (32.6), 77 (25.2).

Table II
1,1-Dimethyl 2-Substituted Aminoethanethiols and Hydrochloride Salts[e]



Compd	R	Mp or bp, °C	% yield (crude)	Nmr, δ, ppm ($CDCl_3$–TMS)	Empirical formula
9[f]	$-C_6H_5$	$n^{25}D$ 1.6047[a]	81	1.3 [s, 7, $C(CH_3)_2$ + SH] 3.1 (s, 2, CH_2) 3.7 (br s, 1, NH) 6.4–7.3 (m, 5, ArH)	$C_{10}H_{15}NS$
9a		153–155[b]	89		$C_{10}H_{15}NS \cdot HCl$
10		$n^{25}D$ 1.6059[a]	89	1.3 [s, 7, $C(CH_3)_2$ + SH] 3.0 (s, 2, CH_2) 3.8 (br s, 1, NH) 6.3–7.2 (m, 4, ArH)	$C_{10}H_{14}ClNS$
10a		133–135[b]	85		$C_{10}H_{14}ClNS \cdot HCl$
11		*a*	87	1.4 [s, 7, $C(CH_3)_2$ + SH] 2.1 (s, 3, $ArCH_3$) 3.1 (s, 2, CH_2) 3.9 (br s, 1, NH) 6.5–6.8 (m, 1, ArH) 7.2 (s, 1, ArH)	$C_{11}H_{15}BrClNS$
11a		168–170	50		$C_{11}H_{15}BrClNS \cdot HCl$
12		*a*	82	1.3 [s, 7, $C(CH_3)_2$ + SH] 3.1 (s, 2, CH_2) 4.1 (br s, 1, NH) 6.5–7.4 (m, 4, ArH)	$C_{11}H_{14}F_3NS$
12a		104–105[b]	81		$C_{11}H_{14}F_3NS \cdot HCl$
13		82–83[c]	98	1.4 [s, 7, $C(CH_3)_2$ + SH] 2.8 [s, 6, $N(CH_3)_2$] 3.1 (s, 2, CH_2) 3.5 (br s, 1, NH) 6.7 (s, 4, ArH)	$C_{12}H_{20}N_2S$
14		*a*	90	1.4 [s, 7, $C(CH_3)_2$ + SH] 3.1 (s, 2, CH_2) 3.8 (br s, 1, $NHCH_2$) 5.3 (br s, 1, ArNHAr) 6.4–7.4 (m, 9, 2-ArH)	$C_{16}H_{20}N_2S$
15	$-CH_3$	bp 113–114/(0.75 mm) $n^{25}D$ 1.5142	88	1.1 (br s, 1, SH) 1.3 [s, 6, $C(CH_3)_2$] 2.5 (s, 3, NCH_3) 2.6 (s, 2, CH_2)	$C_5H_{13}NS$
15a		222–224[d]	90	1.4 [s, 7, $C(CH_3)_2$ + SH] 2.7 (s, 3, NCH_3) 3.1 (s, 2, CH_2)	$C_5H_{13}NS \cdot HCl$

[a] Amber viscous liquid, decomposes on distillation in vacuo (0.25 mm). [b] Recrystallization from ethyl alcohol–diethyl ether. [c] Recrystallization from heptane. [d] Recrystallization from methyl alcohol. [e] Satisfactory analytical data (±0.4% for C, H, N, and S) were reported for all compounds except 9a and 11a (only N and S reported). [f] Mass spectrum *m/e* (rel intensity) (probe temperature 25°) 181 (6.5), 106 (100), 93 (23.4), 79 (8.6), 77 (22.3), 66 (12.7), 65 (9.3), 51 (11.4), 41 (10.6), 39 (13.5).

riod of 48 hr while a current of nitrogen was passed through it in order to remove the hydrogen chloride. The solution was distilled and an 80% yield of product, by 100–110° (1 mm), was obtained: NMR ($CDCl_3$) δ 1.40 [s, 12, 2-$C(CH_3)_2$], 9.09 (s, 2, 2-CHO).

***N,N'*-[1,1'-Dithiobis(1,1-dimethyl-1-ethanyl-2-ylidene)] Bis Substituted Anilines. Method I (2–5).** A stirred mixture containing 51.6 g (0.25 mol) of **1**, 1 g of *p*-toluenesulfonic acid, 200 ml of heptane, and 0.5 mol of the appropriate primary aromatic amine was heated at reflux (82–105°) for 1.5 hr. During this period, by means of a Dean-Stark condenser, 9 ml of water and 100 ml of heptane were removed. For **2–4**, the stirred mixture was cooled to 0° and held at 0–5° for 1 hr. The solids were collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 25–30°. For **5**, the reaction mixture was filtered to remove the catalyst and the heptane was removed in vacuo at a maximum temperature of 80–90° (1–2 mm). The data are summarized in Table I.

Method II (6 and 7). To a stirred solution containing 0.2 mol of *N,N*-dimethyl-*p*-phenylenediamine or *N*-phenyl-*p*-phenylenediamine in 75 ml of methyl alcohol, 20.6 g (0.1 mol) of **1** was added in one portion. An exothermic reaction set in, causing a temperature rise of approximately 10°. The reaction mixture was stirred at 25–30° for 24 hr. The solids were collected by filtration and air dried at 25–30°. The data are summarized in Table I.

***N,N'*-[1,1'-Dithiobis(1,1-dimethyl-1-ethanyl-2-ylidene)]-bis(methylamine) (8).** To a stirred solution containing 101 g (1.3 mol) of 40% aqueous methylamine in 200 ml of methyl alcohol, 82.4 g (0.4 mol) of **1** was added dropwise at 25–35° in 0.5 hr. The reaction mixture was stirred at 25–30° for 4 days. After the addition of 300 ml of water and 500 ml of ethyl ether, stirring was continued for 0.5 hr. The separated ether layer was washed with water until the washings were neutral to litmus and dried over sodium sulfate. The ether was removed in vacuo at a maximum temperature of 70° (1–2 mm). The crude product, $n^{25}D$ 1.5225, was obtained in 82% yield. The crude product was distilled and a 60% yield of **8**, bp 86–87° (0.15 mm), $n^{25}D$ 1.5220, was obtained: NMR

($CDCl_3$) δ 1.3 [s, 12, 2-SC(CH_3)$_2$], 3.2 (s, 6, 2-NCH_3), 7.4 (s, 2, 2-CH=N).

Anal. Calcd for $C_{10}H_{20}N_2S_2$: C, 51.68; H, 8.67; N, 12.05; S, 27.59; mol wt, 232.4. Found: C, 51.76; H, 8.86; N, 11.73; S, 27.69; mol wt, 232 ($CHCl_3$).

1,1-Dimethyl 2-Substituted Aminoethanethiols (9–15). To a stirred solution containing 0.2 mol of **2, 3, 4, 5, 6,** 7, or 8 in 500 ml of ethanol at 60°, a solution containing 23.4 g (0.6 mol) of sodium borohydride in 600 ml of ethanol was added slowly at 65–70° over a 1-hr period. The stirred reaction mixture was heated at reflux for 1 hr and then allowed to cool to 30°. The reaction mixture was added to 2000 g of ice water and stirred at 0–10° for 1 hr. For **13**, the precipitate was collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 25–30°. For the remainder, the viscous liquids were extracted by the addition of 1 l. of ethyl ether and filtered to remove any impurities. The separated ether layer was washed with water until the washings were neutral to litmus and dried over sodium sulfate. The ether was removed in vacuo at maximum temperature at 80–90° (1–2 mm). The data are summarized in Table II.

Hydrochloride Salts (9a–12a and 15a). To a stirred solution containing 9–12 or 15 in 300 ml of ethyl ether, hydrogen chloride gas was bubbled through the solution at 0–10° over a 0.5-hr period. The precipitate was collected by filtration, washed with 200 ml of ethyl ether, and air dried at 50°. The data are summarized in Table II.

3-[*p*-(Dimethylamino)phenyl]-5,5-dimethyl-2-thiazolidinethione (16) and 3-(*p*-Anilinophenyl)-5,5-dimethyl-2-thiazolidinethione (17). A stirred slurry containing 0.15 mol of 13 or **14**, 9.8 g (0.15 mol) of 85% potassium hydroxide, 22.8 g (0.3 mol) of carbon disulfide, and 50 ml of ethanol was heated at reflux for 24 hr. After the stirred reaction mixture was cooled to 0°, the precipitate was collected by filtration, washed successively with 25 ml of ethanol and 300 ml of water, and air dried at 25–30°. The crude **16**, mp 142–146°, and 17, mp 165–166°, were obtained in yields of 75 and 99%, respectively. After recrystallization from ethyl acetate and toluene, respectively, **16** and **17** melted at 157–158 and 166–167°, respectively: NMR ($CDCl_3$) of **16**, δ 1.60 [s, 6, -C(CH_3)$_2$], 2.92 [s, 6, -N(CH_3)$_2$], 4.08 (s, 2, NCH_2C), 6.50–7.30 (m, 4, ArH), and **17**, δ 1.60 [s, 6, -C(CH_3)$_2$], 4.10 (s, 2, NCH_2C), 5.90 (br s, 1, -NH), 6.90–7.50 (m, 9, 2 ArH); mass spectrum *m/e* (rel intensity) of **16**, probe temperature 125°, 266 (86.8), 190 (39.1), 178 (16.7), 152 (26.8), 147 (100), 145 (31.5), 135 (22.4), 120 (21.7), 77 (22.5), and 42 (32.6), and **17**, probe temperature 200°, 314 (100), 238 (32.8), 226 (17.3), 200 (14.3) 195 (52.1), 183 (12.5), 168 (26.9), 167 (44.9), 77 (17.5), and 65 (10.1).

Anal. Calcd for $C_{13}H_{18}N_2S_2$ (**16**): C, 58.61; H, 6.81; N, 10.51; S, 24.07; mol wt, 266.4. Found: C, 58.82; H, 6.79; N, 10.46; S, 24.16; mol wt, 265 ($CHCl_3$). Calcd for $C_{17}H_{18}N_2S_2$ (**17**): C, 64.93; H, 5.77; N, 8.91; S, 20.39. Found: C, 64.80; H, 5.66; N, 8.83; S, 20.60.

Registry No.—**1**, 15581-80-3; **2**, 54410-19-4; **3**, 54410-20-7; **4**, 54410-21-8; **5**, 54410-22-9; **6**, 54410-23-0; **7**, 54410-24-1; **8**, 54410-25-2; **9**, 54410-26-3; **9a**, 54410-27-4; **10**, 54410-28-5; **10a**, 54410-29-6; **11**, 54410-30-9; **11a**, 54410-31-0; **12**, 54446-52-5; **12a**, 54410-32-1; **13**, 54410-33-2; **14**, 54410-34-3; **15**, 54410-35-4; **15a**, 39981-47-0; **16**, 54410-36-5; **17**, 54410-37-6; isobutyraldehyde, 78-84-2; sulfur chloride, 10025-67-9; *N,N*-dimethyl-*p*-phenylenediamine, 99-98-9; *N*-phenyl-*p*-phenylenediamine, 101-54-2; methylamine, 74-89-5; *m*-trifluoromethylaniline, 98-16-8; aniline, 62-53-3; *p*-chloroaniline, 106-47-8; 4-bromo-5-chloro-2-methylaniline, 30273-47-3.

Supplementary Material Available. Mass spectral fragmentation routes for **2, 9,** and **16** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1224.

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(8) **15a** prepared by their method kindly furnished by F. Meneghini.
(9) See paragraph at end of paper regarding supplementary material.

Preparation of Protected Peptide Intermediates for a Synthesis of the Ovine Pituitary Growth Hormone Sequence 96–135

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The preparation of seven protected peptides (tri- to dodecapeptides) which span the sequence of the "active core" region 96–135 of ovine pituitary growth hormone is described. These peptides were synthesized through modified solid-phase techniques, i.e., use of *p*-alkoxybenzyl alcohol resin and hydroxymethyl resin or successive applications of both solid-phase and conventional procedures. The purity of all peptides was carefully ascertained.

The biochemical studies of Li and others[1-6] have led to the conclusion that an intact molecule of pituitary growth hormone is not essential for the manifestation of its biological activities. Indeed, an "active core" was isolated from tryptic digest of bovine growth hormone by Sonenberg et al.[4] and its amino acid sequence delineated.[7] The compound was reported to possess 20–30% of the activity[4,8] of the intact hormone both by the tibia test[9] and the body weight gain test.[10] Moreover, the species specificity appeared to become less stringent. The bovine core peptide exhibited activity in man whereas the intact bovine growth hormone did not. Comparison of the core fragment with the amino acid sequence of bovine growth hormone[11-13] revealed its identity with the sequence region 96–133 (Chart I). In a recent communication Li et al.[14] have described a solid-phase synthesis of the corresponding region of human growth hormone (i.e., sequence 95–136) and showed that the product stimulated the growth of rat tibia. Li and Yam-

Chart I

Amino Acid Sequence in the Region of Residues 96–135 for Ovine Growth Hormone (OGH), Bovine Growth Hormone (BGH), Human Growth Hormone (HGH), and Porcine Growth Hormone (PGH)

```
        96                  100                 105
OGH: -Val-Phe-Thr-Asp-Ser-Leu-Val-Phe-Gly-Thr-Ser-Asp-   Arg-Val-
BGH: -Val-Phe-Thr-Asn-Ser-Leu-Val-Phe-Gly-Thr-Ser-Asp-   Arg-Val-
HGH: -Val-Phe-Ala-Asn-Ser-Leu-Val-Tyr-Gly-Ala-Ser-Asn-Ser-Asp-Val-

        110                 115                 120
OGH: -Tyr-Glu-Lys-Leu-Lys-Asp-Leu-Glu-Glu-Gly-Ile-Leu-Ala-Leu-Met-
BGH: -Tyr-Glu-Lys-Leu-Lys-Asp-Leu-Glu-Glu-Gly-Ile-Leu-Ala-Leu-Met-
HGH: -Tyr-Asp-Leu-Leu-Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln-Thr-Leu-Met-
PGH:                      -Asp-Leu-Glu-Glu-Gly-Ile-Gln-Ala-Leu-Met-

        125                 130                 135
OGH: -Arg-Glu-Leu-Glu-Asp-Val-Thr-Pro-Arg-Ala-Gly-
BGH: -Arg-Glu-Leu-Glu-Asp-Gly-Thr-Pro-Arg-Ala-Gly-
HGH: -Gly-Arg-Leu-Glu-Asp-Gly-Ser-Pro-Arg-Thr-Gly-
PGH: -Arg-Glu-Leu-Glu-Asp-Gly-Ser-Pro-Arg-Ala-Gly-
```

ashiro[15] have also reported the synthesis of human growth hormone-like protein by the standard solid-phase method[16–19] based on a partly incorrect amino acid sequence.[20] Conventional synthesis of protected peptide components with sequences corresponding to residues 1–27,[21] 28–52,[22] 53–67,[23] and 166–188[22] were also communicated by Li and his coworkers. Syntheses of other partial sequences of human growth hormone in attempts to locate active sites have also been reported by several authors.[24–26]

In a previous communication[27] we have described the synthesis of the COOH-terminal nonapeptide sequence H-Arg-Glu-Leu-Glu-Asp-Gly-Thr-Pro-Arg-OH of the active core of the bovine hormone. This nonapeptide possessed significant rat tibia growth promoting activity at dose levels of 5–15 μg/rat per day. However, in the rat body weight gain test, the peptide was inactive up to the doses of 50 μg/rat per day, which might be due to metabolic instability of the compound or, alternatively, might indicate that the tibia test could give misleading results with small peptides.[28] We concluded that it was desirable to synthesize and investigate a series of increasingly longer peptides. In this report, the synthesis of protected peptides needed for a total synthesis of the core peptide 96–135 of ovine growth hormone is described. These peptides were prepared through a modified solid-phase technique[29] or a combination of solid-phase[16–29] and conventional procedures.[30,31] The protected intermediates will serve to synthesize the tetracontapeptide active core by conventional fragment condensation methods.

Results and Discussion

The protected peptides which have been prepared to date as intermediates for a total synthesis of the ovine growth hormone fragment 96–135 are listed in Table I with some of their physicochemical characteristics. A thin layer chromatogram of these peptide intermediates is shown in Figure 1. Z-Val-Phe-Thr(Bzl)-OH (I)[32] was synthesized by a modified solid-phase technique.[27,29] Bpoc-Thr(Bzl)-OH was esterified to *p*-alkoxybenzyl alcohol resin with the aid of DCC[33,34] using 4-dimethylaminopyridine[35] as catalyst.[27] The ensuing Bpoc-Thr(Bzl)-$OCH_2C_6H_4OCH_2C_6H_4$-Resin was benzoylated[29] to block unreacted hydroxymethyl groups. Following cleavage of the Bpoc group by 0.5% TFA in CH_2Cl_2 and neutralization with 10% TEA, Bpoc-Phe-OH was coupled to the aminoacyl resin using DCC as described previously, followed by another cycle in which Z-Val-OH was coupled to the peptide resin. The protected tripeptide I was cleaved from the solid support by treatment with 50% TFA in CH_2Cl_2 (25°, 30 min) and isolated as an analytically pure, crystalline solid in 75% overall yield. Similarly prepared on the *p*-alkoxybenzyl alcohol resin were the intermediates H-Ser(Bzl)-Leu-Val-Phe-Gly-OH (II), H-Lys(Z)-Asp(OBzl)-Leu-Glu(OBzl)-OH (III), H-Gly-Ile-Leu-Ala-Leu-OH (IV), H-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Val-OH (V), and H-Thr(Bzl)-Pro-Arg(Tos)-Ala-Gly-OH (VI). With the exception of compound VI, which required chromatographic purification on a Sephadex LH-20 column, all of these side chain protected peptides crystallized directly after cleavage from the resin, giving pure products with overall yields of 30–90% based on the respective amino acid contents of the starting aminoacyl resins.

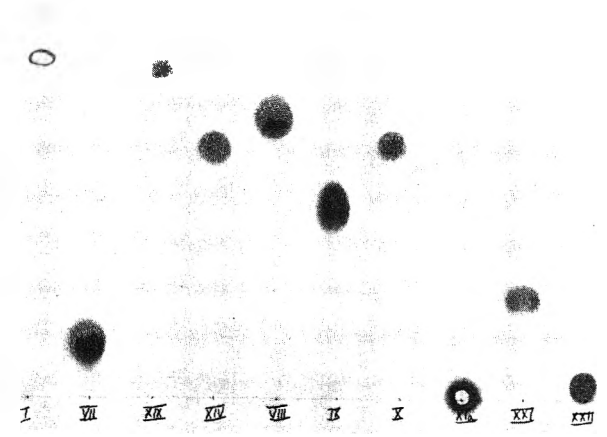


Figure 1. Thin layer chromatogram of the synthetic protected peptide intermediates. Solvent system: methanol–chloroform–acetic acid (51:6:3). Color developed by chlorine–tolidine.

Compound II, H-Ser(Bzl)-Leu-Val-Phe-Gly-OH, prepared by the solid-phase method as described above, was further treated with Boc-Asn-OSu to form the protected hexapeptide Boc-Asn-Ser(Bzl)-Leu-Val-Phe-Gly-OH (VII) as an analytically pure solid. Reactions of H-Lys(Z)-Asp(OBzl)-Leu-Glu(OBzl)-OH (III) with Boc-Leu-OSc[36] similarly gave the protected crystalline pentapeptide Boc-Leu-Lys(Z)-Asp(OBzl)-Leu-Glu(OBzl)-OH (VIII). In the same fashion the protected hexapeptide Boc-Glu(OBzl)-Gly-Ile-Leu-Ala-Leu-OH (IX) was prepared by coupling Boc-Glu(OBzl)-OSu with H-Gly-Ile-Leu-Ala-Leu-OH (IV) and the protected heptapeptide Bpoc-Met-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Val-OH (X) by cou-

Table I
Peptide Intermediates for the Synthesis of Ovine Growth Hormone Fragment 96–135

Compd[a]	Mp, °C	$[\alpha]^{25}D$, deg	Elemental analysis, %[b]		
			C	H	N
^{96}Z-Val-Phe-Thr^{98}(Bzl)-OH (I)	209–211 cryst	−3.50 (*c* 0.7, MeOH)	$C_{33}H_{39}N_3O_7$ (589.69) 67.22 66.83	6.67 6.73	7.13 7.13
Boc-Asn^{99}-Ser(Bzl)-Leu-Val-Phe-Gly^{104}-OH (VII)	Amorphous	−31.92 (*c* 1, DMF)	$C_{41}H_{59}N_7O_{11}$ (825.96) 59.62 59.32	7.20 7.28	11.87 11.78
Boc-Thr^{105}(Bzl)-Ser(Bzl)-Asp(OBzl)OH (XIX)	113–116 cryst	+6.90 (*c* 1, DMSO)	$C_{37}H_{45}N_3O_{10}$ (691.75) 64.24 64.39	6.56 6.98	6.07 6.37
Boc-Arg^{108}(Tos)-Val-Tyr(Cl$_2$Bzl)-Glu(OBzl)-Lys^{112}(Z)-OH (XIV)	138–141 cryst	−7.49 (*c* 1, DMF)	$C_{65}H_{81}N_9O_{15}Cl_2S$ (1331.35) 58.64 58.31	6.13 6.20	9.47 9.49
Boc-Leu^{113}-Lys(Z)-Asp(OBzl)-Leu-Glu(OBzl)-OH^{117} (VIII)	155–157 cryst	−25.50 (*c* 1, DMF)	$C_{54}H_{74}N_6O_{14}$ (1031.18) 62.90 62.77	7.23 7.14	8.15 8.07
Boc-Glu^{118}(OBzl)-Gly-Ile-Leu-Ala-Leu^{123}-OH (IX)	182–184 cryst	−28.59 (*c* 1, DMF)	$C_{40}H_{64}N_6O_{11}$ (804.96) 59.68 59.56	8.01 8.24	10.44 10.42
HCl·H-Met^{124}-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Val-Thr^{135}(Bzl)-Pro-Arg(Tos)-Ala-Gly-NH$_2$ (XXII)	238–241 cryst	−21.01 (*c* 1, DMF)	$C_{98}H_{133}N_{19}O_{23}S_3 \cdot HCl$ (2077.87) 56.65 56.02	6.50 6.65	12.81 12.66

[a] The numbers above the sequence refer to the position in ovine growth hormone. [b] Calculated over found. Molecular weights are given in parentheses.

pling Bpoc-Met-ONp with H-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Val-OH (V). All active ester couplings proceeded smoothly. Slight excess of the corresponding active esters were used.

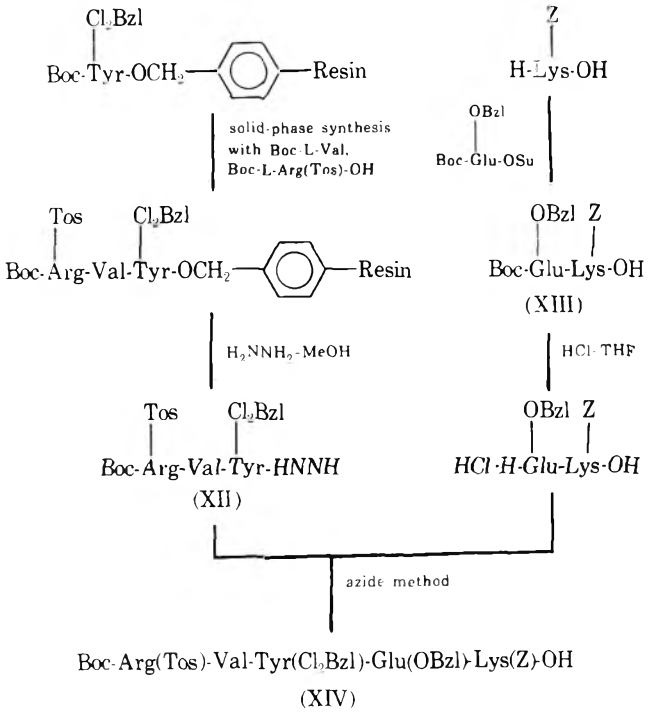
The synthesis of Boc-Thr(Bzl)-Pro-Arg(Tos)-Ala-Gly-NH$_2$ (XI) on hydroxymethyl resin[37] followed closely the original methodology of Merrifield,[16-19] i.e., Boc-amino acids were used in the repetitive synthetic cycles and the peptide chain was released from the resin by ammonolytic cleavage of the benzyl-ester-like anchoring bond. The protected peptapeptide amide was obtained as an amorphous solid in 60% overall yield. The amino protecting group was then removed by treatment with 3.4 *N* HCl in tetrahydrofuran to afford HCl·H-Thr(Bzl)-Pro-Arg(Tos)-Ala-Gly-NH$_2$ (XIa).

For the synthesis of Boc-Arg(Tos)-Val-Tyr(Cl$_2$Bzl)-Glu(OBzl)-Lys(Z)-OH (XIV), a combination of solid-phase and conventional procedures was employed (see Scheme I). Boc-Tyr(Cl$_2$Bzl)-OH[38] was esterified to the hydroxymethyl resin and the solid-phase synthesis continued by incorporation of Boc-Val-OH and Boc-Arg(Tos)-OH into the resin to form the tripeptide resin. Hydrazinolysis afforded the crystalline Boc-Arg(Tos)-Val-Tyr(Cl$_2$Bzl)-HNNH$_2$ (XII) in 63% overall yield. Coupling of this tripeptide with the dipeptide H-Glu(OBzl)-Lys(Z)-OH·HCl by the azide method[39] resulted in the formation of the crystalline pentapeptide XIV in 53% yield.

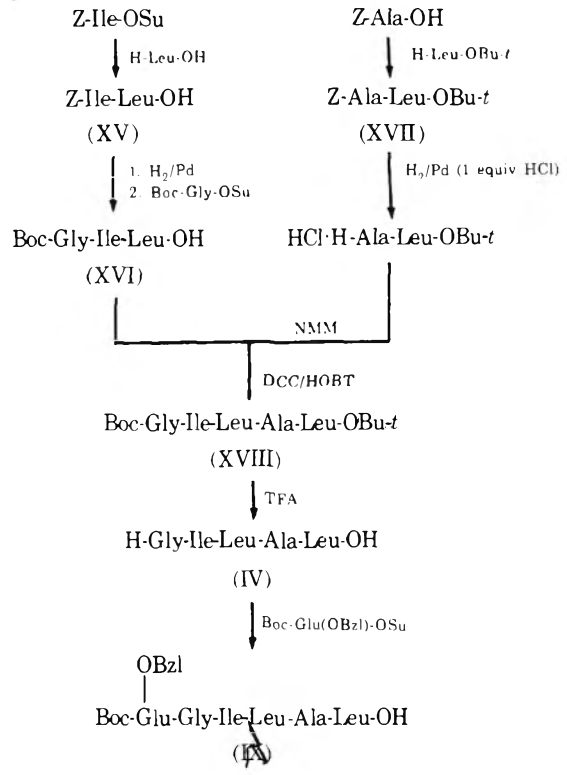
Boc-Glu(OBzl)-Gly-Ile-Leu-Ala-Leu-OH (IX) was also prepared by conventional methods as illustrated in Scheme II. Coupling of Boc-Ile-OSu with Leu gave Z-Ile-Leu-OH (XV), which on hydrogenolysis followed by coupling with Boc-Gly-OSu yielded the tripeptide Boc-Gly-Ile-Leu-OH (XVI). This tripeptide was then coupled to H-Ala-Leu-OBu-*t*·HCl derived from hydrogenolytic cleavage of the Z group from Z-Ala-Leu-OBu-*t* (XVII) using the HOBT-assisted[40] DCC reaction[41] to give the protected pentapeptide Boc-Gly-Ile-Leu-Ala-Leu-OBu-*t* (XVIII). Treatment with TFA afforded the pentapeptide H-Gly-Ile-Leu-Ala-Leu-OH (IV), which was also prepared by the above-mentioned solid-phase technique. Reaction of IV with Boc-Glu(OBzl)-OSu led smoothly to the desired product IX, a crystalline solid, in 78% yield.

Boc-Ser(Bzl)-Asp(OBzl)-OH was prepared from H-Asp(OBzl)-OH and Boc-Ser(Bzl)-OSu.[42] Deprotection of Boc group by treatment with HCl in THF gave the crystalline dipeptide salt H-Ser(Bzl)-Asp(OBzl)-OH·HCl. On reaction of this compound with Boc-Thr(Bzl)-OSu the desired protected tripeptide Boc-Thr(Bzl)-Ser(Bzl)-As-

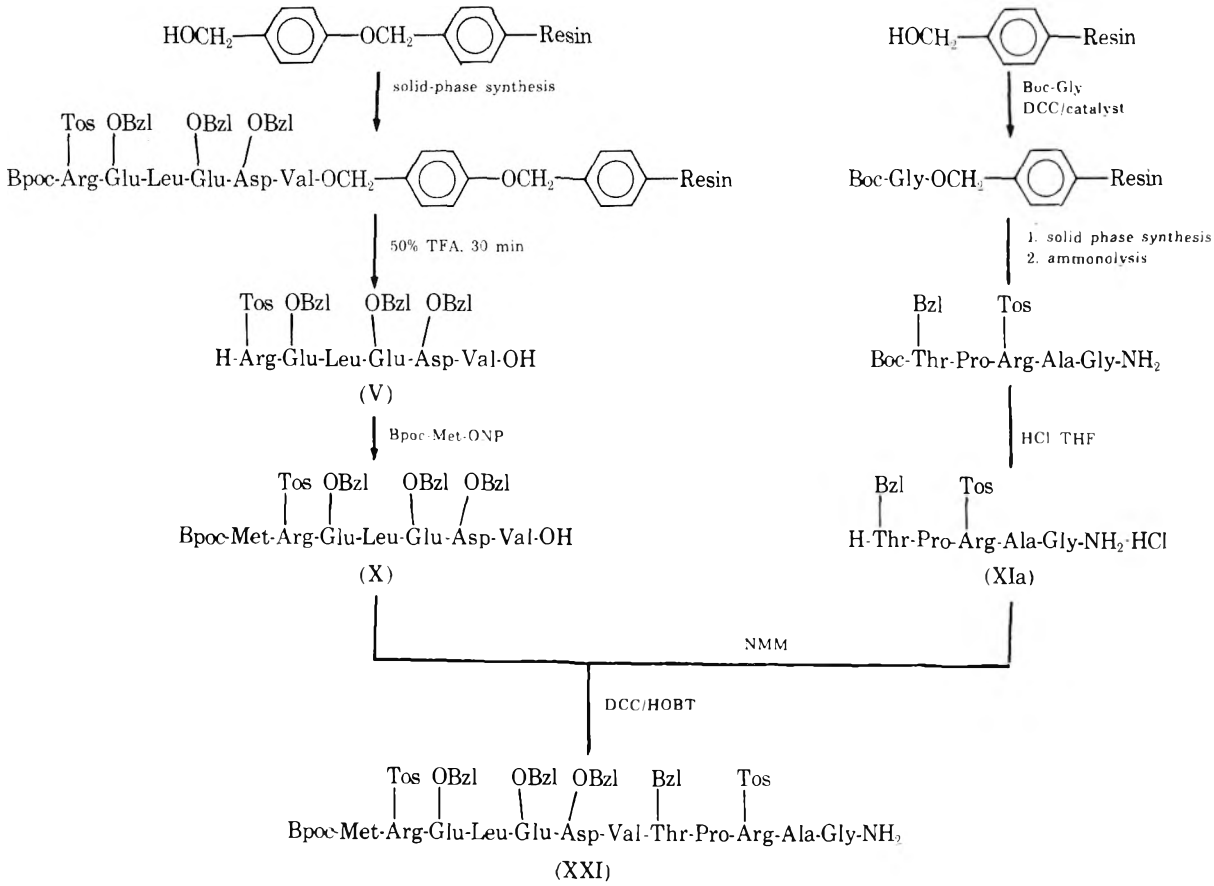
Scheme I
Synthesis of Boc-Arg(Tos)-Val-Tyr(Cl_2Bzl)-Glu(OBzl)-Lys(Z)-OH



Scheme II
Synthesis of Boc-Glu(OBzl)-Gly-Ile-Leu-Ala-Leu-OH



Scheme III
Example of Solid-Phase Fragment Approach



p(OBzl)-OH (XIX) was obtained. A similar derivative, Bpoc-Thr(Bzl)-Ser(Bzl)-Asp(OBzl)-OH, was prepared in an analogous manner from Bpoc-Thr(Bzl)-OSu and the dipeptide salt H-Ser(Bzl)-Asp(OBzl)-OH · HCl. The HCl salt of H-Thr(Bzl)-Ser(Bzl)-Asp(OBzl)-OH (XX) was obtained by treatment of either Boc-Thr(Bzl)-Ser(Bzl)-Asp(OBzl)-OH or Bpoc-Thr(Bzl)-Ser(Bzl)-Asp(OBzl)-OH with HCl in THF.

Condensation of Bpoc-Met-Arg(Tos)-Glu(OBZL(-Leu-Glu(OBzl)-Asp(OBzl)-Val-OH (X) with the HCl salt of H-Thr(Bzl)-Pro-Arg(Tos)-Ala-Gly-NH_2 (XIa) by the HOBT-assisted DCC method[40] resulted in the formation of the crystalline protected dodecapeptide Bpoc-Met-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Val-Thr(Bzl)-Pro-Arg(Tos)-Ala-Gly-NH_2 (XXI) in 59% yield. The α-amino protecting group was subsequently removed with 0.5 *N* HCl in tetrahydrofuran to give the crystalline hydrochloride salt HCl · H-Met-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Val-Thr(Bzl)-Pro-Arg(Tos)-Ala-Gly-NH_2 (XXII).

Several preparations described here represent further examples of combined use of solid phase and classical methods in peptide synthesis[29,46-49] (cf. Scheme III).

Experimental Section

Melting points are uncorrected. Amino acids analyses were performed on a Beckman Model 121 analyzer according to the procedure of Spackman et al.[43] Thin layer chromatography was carried out on precoated silica gel plates (Merck, F-254) using solvent systems described before.[27,37] Elementary analyses, optical rotation data, ir, uv, and NMR spectra were provided by the Physical Chemistry Department. Bpoc-amino acids were prepared as described in the literature[44,45] and were of L configuration. Other amino acid derivatives were purchased from Bachem Inc., Marina Del Rey, Calif., or from Chemical Dynamics Corp., South Plainfield, N.J. *p*-Alkoxybenzyl alcohol resin was prepared as reported previously.[29] Bpoc-amino acid CHA or DCHA salts were converted into free acids prior to use.[45] For hydrogenolysis, 5% Pd on $BaSO_4$ was used as catalyst.

Bpoc-Met-ONp. A suspension of Bpoc-Met-OH · DCHA (11.11 g, 19.6 mmol) in a mixture of water and ether at 0° was treated with 1 *M* citric acid until the solid dissolved. The ether layer was washed with water, dried (Na_2SO_4), and evaporated at 30° to yield Bpoc-Met-OH as an oil which was treated with 3.3 g of *p*-nitrophenol (23.5 mmol) and 4.85 g of DCC (23.5 mmol) in 200 ml of THF (0°, 2 hr; 25°, 2 hr). The insoluble by-product was filtered off and the filtrate evaporated to a syrup which was crystallized from *i*-PrOH by the addition of a small amount of petroleum ether: yield 6.8 g (68%); mp 90–92°; $[\alpha]^{25}D$ −71.1° (c 1, MeOH).

Anal. Calcd for $C_{27}H_{28}N_2O_6S$ (508.59): C, 63.76; H, 5.55; N, 5.51. Found: C, 63.60; H, 5.48; N, 5.44.

Bpoc-Thr(Bzl)-OSu. Bpoc-Thr(Bzl)-OH (1 g, 2.2 mmol) was stirred in 5 ml of THF with HOSu (0.27 g, 2.33 mmol) and DCC (0.49 g, 2.37 mmol). Work-up as above gave an oily material which was precipitated from ethyl acetate with petroleum ether: yield 1.19 g (97%); homogeneous on TLC; NMR spectral data agreed with expected values.

Anal. Calcd for $C_{31}H_{32}N_2O_7$ (544.59): C, 68.37; H, 5.92; N, 5.19. Found: C, 68.41; H, 6.01; N, 5.21.

Boc-Glu(OBzl)-OSu. Boc-Glu(OBzl)-OH (9.0 g, 26.7 mmol) in 200 ml of THF was treated with HOSu (3.25 g, 28.2 mmol) and DCC (5.95 g, 28.9 mmol) (0°, 1 hr; 25°, 3 hr). It was filtered and evaporated to a semisolid mass which was crystallized from *i*-PrOH: yield 9.5 g (81%); mp 103–104°; $[\alpha]^{25}D$ +23.67° (c 1, THF).

Anal. Calcd for $C_{21}H_{26}N_2O_8$ (434.44): C, 58.06; H, 6.03; N, 6.45. Found: C, 58.20; H, 6.15; N, 6.40.

Z-Val-Tyr(Bzl)-OCH_3. H-Tyr-OCH_3 · HCl (4.43 g, 13.8 mmol) in 100 ml of CH_2Cl_2 was treated with TEA (1.94 ml, 13.8 mmol), Z-Val-OH (3.48 g, 13.8 mmol), and DCC (3.27 g, 15.9 mmol) (0°, 1 hr; 25°, 3 hr). It was filtered and washed with water, dried (Na_2SO_4), and evaporated to a solid mass, crystallized from EtOH: yield 6.5 g (91%); mp 163–165°.

Anal. Calcd for $C_{30}H_{34}N_2O_6$ (518.58): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.48; H, 6.58; N, 5.43.

H-Val-Tyr-OCH_3 · HCl. The above compound (5.45 g, 10.6 mmol) in a mixture of THF (100 ml), MeOH (80 ml), and water (20 ml) was hydrogenated at 46 psi overnight in a Parr hydrogenator in the presence of 1.76 ml of concentrated HCl and 2.5 g of catalyst. It was filtered and evaporated at 35° to give an oil which was crystallized from methanol–ether: yield 3.1 g (81%); mp 121–124°; $[\alpha]^{25}D$ +30.53° (c 1, MeOH).

Anal. Calcd for $C_{15}H_{22}N_2O_4$ · HCl · CH_3OH (362.85): C, 52.96; H, 7.50; N, 7.72; Cl, 9.77. Found: C, 52.69; H, 7.34; N, 7.68; Cl, 9.71.

Aoc-Arg(Tos)-Val-Tyr-OCH_3. The HCl salt of H-Val-Tyr-OCH_3 (1.0 g, 2.76 mmol) in 30 ml of CH_2Cl_2 was stirred with 0.39 ml of TEA, 1.02 g of Aoc-Arg(Tos)-OH (2.76 mmol), and 0.66 g of DCC (3.2 mmol) (0°, 1 hr; 25°, 3 hr). The reaction mixture was filtered and diluted with 100 ml of ethyl acetate, washed (H_2O), dried (Na_2SO_4), and evaporated to an oil which on treatment with ether solidified immediately. It was reprecipitated from ethyl acetate with ether: yield 0.92 g (46.5%); homogeneous on tlc; NMR spectral data agreed with the structure; $[\alpha]^{25}D$ −1.66° (c 5, MeOH).

Anal. Calcd for $C_{34}H_{52}N_6O_9S$ (718.66): C, 56.81; H, 7.01; N, 11.69; S, 4.46. Found: C, 56.22; H, 6.99; N, 11.46; S, 4.51.

Z-Ile-Leu-OH (XV). Leucine (3.64 g, 27.6 mmol) was dissolved in 13 ml of Triton B (40% methanolic solution of trimethylbenzylammonium hydroxide), evaporated to dryness at 35°, twice re-evaporated each with 20-ml portions of DMF, and then treated with 10 g of Z-Leu-OSu (27.6 mmol) in 50 ml of DMF (0°, 2 hr; 25°, 24 hr). The reaction mixture was partitioned between ether and 2% citric acid (500 ml each) and the organic layer was washed several times with water, dried (Na_2SO_4), and evaporated to a solid mass. It was crystallized from ethyl acetate and petroleum ether: yield 7.86 g (75.5%); mp 139–140°; $[\alpha]^{25}D$ −28.76° (c 1, MeOH).

Anal. Calcd for $C_{20}H_{30}N_2O_5$ (378.47): C, 63.47; H, 7.99; N, 7.40. Found: C, 63.48; H, 7.90; N, 7.37.

H-Ile-Leu-OH · HCl. The above compound (5.7 g, 15.1 mmol) was hydrogenated at 50 psi in a mixture of MeOH (100 ml), H_2O (33 ml), and 1 *N* HCl (16.6 ml) overnight in the presence of 1.5 g of catalyst. It was filtered and evaporated to an oil, and crystallized from EtOH and ether: 3.79 g (89%); mp 222–224°.

Anal. Calcd for $C_{12}H_{24}N_2O_3$ · HCl (280.79): C, 51.33; H, 8.95; N, 9.99. Found: C, 51.07; H, 8.82; N, 9.89.

Boc-Gly-Ile-Leu-OH (XVI). Boc-Gly-OSu (3.6 g, 13.2 mmol)[36] in DMF (50 ml) was stirred with 3.79 g of H-Ile-Leu-OH · HCl (13.2 mmol) and 1.91 ml of TEA (0°, 2 hr; 25°, 17 hr). A few drops of TEA were added occasionally during this time in order to maintain the reaction slightly basic. The mixture was diluted with 650 ml of ethyl acetate, washed with 460 ml of 0.1 *N* HCl followed by water (three times), dried (Na_2SO_4), and evaporated to a small volume. Upon addition of petroleum ether, crystallization began. The crude product was recrystallized from ethyl acetate and petroleum ether: yield 4.82 g (91%); mp 144–146°; $[\alpha]^{25}D$ −30.92° (c 1, MeOH).

Anal. Calcd for $C_{19}H_{35}N_3O_6$ (401.49): C, 56.84; H, 8.79; N, 10.47. Found: C, 57.02; H, 9.03; N, 10.28.

Z-Ala-Leu-OBu-*t* (XVII). H-Leu-OBu-*t* · HCl (5 g, 22.4 mmol) in 100 ml of CH_2Cl_2 was stirred with 5 g of Z-Ala-OH (22.4 mmol), 3.16 ml of TEA, and 5.36 g of DCC (26 mmol) (0°, 1 hr; 25°, 2 hr). It was filtered, washed (H_2O), dried (Na_2SO_4), and evaporated to give an oil, which was crystallized from ether and petroleum ether: yield 6.9 g (78%); mp 97–98°.

Anal. Calcd for $C_{21}H_{32}N_2O_5$ (392.49): C, 64.26; H, 8.22; N, 7.14. Found: C, 64.54; H, 8.06; N, 7.17.

Boc-Gly-Ile-Leu-Ala-Leu-OBu-*t* (XVIII). Z-Ala-Leu-OBu-*t* (4.9 g, 12.5 mmol) was hydrogenated in a mixture of MeOH (75 ml), H_2O (25 ml), and 1 *N* HCl (12.5 ml) overnight at 50 psi in the presence of 2 g of catalyst and worked up as usual to give 3.53 g of amorphous H-Ala-Leu-OBu-*t* · HCl. This was treated with Boc-Gly-Ile-Leu-OH (4.82 g, 12 mmol), 1.5 ml of NMM, HOBT (3.24 g, 22 mmol), and DCC (2.9 g, 14 mmol) in 100 ml of DMF (−10°, 4 hr; 25°, 72 hr). It was filtered and evaporated to a syrup which on treatment with ethyl acetate solidified immediately. It was taken up in CH_2Cl_2, washed (H_2O), dried (Na_2SO_4), evaporated to an oil, and crystallized from ethyl acetate: yield 5.45 g (72%); mp 227–228°; $[\alpha]^{25}D$ −64.9° (c 1, MeOH).

Anal. Calcd for $C_{32}H_{59}N_5O_8$ (641.85): C, 59.88; H, 9.27; N, 10.91. Found: C, 59.75; H, 9.46; N, 11.01.

H-Ser(Bzl)-Asp(OBzl)-OH · HCl. H-Asp(OBzl)-OH (15 g, 67.2 mmol) in 500 ml of DMF was stirred with 9.45 ml of TEA (67.2 mmol) and Boc-Ser(Bzl)-OSu (26.3 g, 67.2 mmol) in an analogous manner as in the preparation of XVI and worked up as usual to give an oil which resisted attempts at crystallization. It was thus treated with 400 ml of freshly prepared 3.1 *N* HCl in THF for 30 min to remove the Boc group. Evaporation at 35° gave an oil which was crystallized from *i*-PrOH and ether: yield 19.0 g (65%); mp 160–162°; $[\alpha]^{25}D$ +12.73° (c 1, MeOH).

Anal. Calcd for $C_{21}H_{24}N_2O_6$ · HCl (436.89): C, 57.73; H, 5.77; N, 6.41; Cl, 8.11. Found: C, 57.56; H, 5.60; N, 6.38; Cl, 8.26.

Boc-Thr(Bzl)-Ser(Bzl)-Asp(OBzl)-OH (XIX). Part of the above compound (13.5 g, 30.9 mmol) was stirred in 250 ml of DMF with 8.7 ml of TEA (61.8 mmol) and Boc-Thr(Bzl)-OSu (12.6 g, 30.9 mmol) (0°, 2 hr; 25°, 24 hr) and treated in an analogous manner as in the preparation of XVI. The product started to crystallize

when the ethyl acetate solution was concentrated to a small volume. It was recrystallized from ethyl acetate: yield 11.1 g (52%); mp 113–116°; $[\alpha]^{25}D$ +6.90° (c 1, DMSO); NMR spectral data agreed with expected values.

Anal. Calcd for $C_{37}H_{45}N_3O_{10}$ (691.75): C, 64.24; H, 6.56; N, 6.07. Found: C, 64.39; H, 6.68; N, 6.37.

H-Thr(Bzl)-Ser(Bzl)-Asp(OBzl)-OH · HCl (XX). H-Ser(Bzl)-Asp(OBzl)-OH (0.1 g, 0.23 mmol) in 3 ml of DMF was treated with Bpoc-Thr(Bzl)-OSu (0.125 g, 0.23 mmol) and 65 mg of TEA (0° 90 min, 25° 24 h). The rction mixture was poured into a small volume of water and acidified to pH 3 with 1 *M* citric acid. The product was extracted into ethyl acetate and washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The oily residue was dissolved in 7 ml of freshly prepared 0.3 *N* HCl in THF and evaporated to dryness after 10 min standing. The compound was crystallized from THF and ether: yield 0.075 g (52%); mp 160–162°; $[\alpha]^{25}D$ +9.85° (c 0.5, MeOH).

Anal. Calcd for $C_{32}H_{37}N_3O_8 \cdot HCl$ (628.11): C, 61.19; H, 6.10; N, 6.69; Cl, 5.64. Found: C, 61.37; H, 6.20; N, 6.80; Cl, 5.63.

The same compound was also prepared from Boc-Thr(Bzl)-Ser(Bzl)-Asp(OBzl)-OH (XIX) by a 30-min treatment with 3 *N* HCl in THF and similar work-up: yield 71%; mp 160–162°.

Boc-Glu(OBzl)-Lys(Z)-OH (XIII). Boc-Glu(OBzl)-OSu (12.98 g, 30 mmol) and H-Lys(Z)-OH (8.42 g, 29.8 mmol) in DMF (260 ml) were allowed to react in the presence of 4.2 ml of TEA (30 mmol) in a manner similar to that for the preparation of XVI and worked up. The oily product crystallized on addition of ether. It was recrystallized from ether: yield 14.9 g (83%); mp 115–118°; $[\alpha]^{25}D$ −2.77° (c 1, MeOH).

Anal. Calcd for $C_{31}H_{41}N_3O_9$ (599.66): C, 62.09; H, 6.89; N, 7.01 Found: C, 62.06; H, 7.16; N, 7.02.

Treatment of this compound with 100 ml of 4.7 *N* HCl in THF for 60 min and work-up as usual gave an amorphous H-Glu(OBzl)-Lys(Z)-OH · HCl (13.4 g), homogeneous on TLC. Without further purification, part of the product was used as described below.

Boc-Arg(Tos)-Val-Tyr(Cl_2Bzl)-HNNH$_2$ (XII). Boc-Tyr(Cl_2Bzl)-O$CH_2C_6H_4$-Resin[37] (13.9 g, 8.64 mmol) was deprotected (50% TFA, 30 min) and neutralized (10% TEA, 10 min) and the standard solid-phase synthesis[17,18] conducted by sequential incorporation of Boc-Val-OH (4.7 g, 21.6 mmol) and Boc-Arg(Tos)-OH (7.6 g, 21.6 mmol) into the resin to give Boc-Arg(Tos)-Val-Tyr(Cl_2Bzl)-O$CH_2C_6H_4$-Resin (18.9 g). It was hyrazinolyzed in 700 ml of MeOH containing 70 ml H_2NNH_2 for 72 hr (25°) and worked up to produce an oil which was crystallized from *i*-PrOH: yield 4.66 g (62.5%); mp 189–191°; $[\alpha]^{25}D$ −6.19° (c 0.5, DMSO).

Anal. Calcd for $C_{39}H_{52}N_8O_8SCl_2$ (863.86): C, 54.23; H, 6.07; N, 12.97; S, 3.71; Cl, 8.21. Found: C, 53.87; H, 6.50; N, 12.92; S, 3.70; Cl, 8.00.

Boc-Arg(Tos)-Val-Tyr(Cl_2Bzl)-Glu(OBzl)-Lys(Z)-OH (XIV). Boc-Arg(Tos)-Val-Tyr(Cl_2Bzl)-HNNH$_2$ (5.63 g, 6.5 mmol) was dissolved in 65 ml of DMF, cooled to −20°, and treated with 10.6 ml of 3.68 *N* HCl in THF followed by 12.5 ml of 10% isoamyl nitrite in DMF. After stirring for 30 min at −20° the temperature was lowered to −30°, when 6.27 ml of TEA was added followed by 3.75 g of the HCl salt of H-Glu(OBzl)-Lys(Z)-OH (7.0 mmol). The mixture was stirred at −20° for 30 min and then at 0° for 48 hr. Small amounts of TEA were added periodically in order to maintain the reaction medium slightly basic. The insoluble by-products were filtered off and the filtrate evaporated to 40° to an oil. The material was taken up in 150 ml of ethyl acetate, washed (3% acetic acid and then water), and evaporated several times with benzene to give a solid mass, recrystallized from *i*-PrOH: yield 4.74 g (53%); mp 138–141°; $[\alpha]^{25}D$ −7.49° (c 1, DMF); NMR spectral data agreed with the expected values.

Anal. Calcd for $C_{65}H_{81}N_9O_{15}Cl_2S$ (1331.35): C, 58.64; H, 6.13; N, 9.47; Cl, 5.32. Found: C, 58.31; H, 6.20; N, 9.49; Cl, 5.42.

Amino Acid Anal. Glu, 1.00; Val, 0.95; Tyr, 0.89; Lys, 1.07; Arg, 1.10.

H-Gly-Ile-Leu-Ala-Leu-OH (IV). Boc-Gly-Ile-Leu-Ala-Leu-OBu-*t* (XVIII) (5.45 g, 8.5 mmol) was stirred in 140 ml of TFA for 150 min. The product was precipitated with ether and dried over NaOH in vacuo to give 4.24 g of white powder. The solid was triturated in hot MeOH: yield, 4.1 g (89%); mp > 300°; homogeneous on TLC; NMR spectral data agreed with expected values.

Anal. Calcd for $C_{23}H_{43}N_5O_6 \cdot \frac{1}{2}CF_3COOH$ (542.62): C, 53.29; H, 8.08; N, 12.90; F, 5.27. Found: C, 53.19; H, 8.10; N, 12.94; F, 5.12.

The same peptide was also prepared by the solid-phase method. *p*-Alkoxybenzyl alcohol resin[29] (10 g) was stirred in 100 ml of CH_2Cl_2 with pyridine (2.18 ml), Bpoc-Leu-OH (9.75 g, 26.5 mmol), and DCC (5.56 g, 26.9 mmol) for 2 hr. The protected aminoacyl resin thus obtained (10.25 g, 0.41% N, 0.29 mmol/g) was treated with benzoyl chloride,[29] giving rise to 10.3 g of Bpoc-Leu-OCH_2-$C_6H_4OCH_2C_6H_4$-Resin. Solid-phase synthesis was then conducted with Bpoc-Ala-OH (3.04 g), Bpoc-Leu-OH (3.42 g), Bpoc-Ile-OH (3.42 g), and Boc-Gly-OH (1.62 g) using DCC (2.01 g) as coupling agent in each cycle.[50,51] The protected pentapeptide resin was then stirred with 300 ml of 50% TFA in CH_2Cl_2 for 30 min. The liberated pentapeptide was separated from the resin by filtration and concentrated to a syrup, again evaporated several times with fresh CH_2Cl_2, and treated with ether. The solid obtained was washed with CH_3CN, H_2O, and DMF: yield 0.44 g (30.2%); mp > 320°; homogeneous on TLC; NMR spectrum agreed with the structure.

Anal. Calcd for $C_{23}H_{43}N_5O_6 \cdot H_2O$ (503.63): C, 54.95; H, 9.01; N, 13.98. Found: C, 54.80; H, 8.89; N, 13.75.

Amino Acid Anal. Gly, 0.95; Ala, 1.01; Ile, 0.99; Leu, 2.03.

Boc-Glu(OBzl)-Gly-Ile-Leu-Ala-Leu-OH (IX). H-Gly-Ile-Leu-Ala-Leu-OH (3.9 g, 7.18 mmol) suspended in 130 ml of DMF was allowed to react with Boc-Glu(OBzl)-OSu (4.7 g, 10.7 mmol) in the presence of 2.5 ml of TEA (17.8 mmol) for 24 hr. The reaction mixture was then diluted with 1500 ml of ethyl acetate and shaken with 1200 ml of 3% citric acid. The product in the organic layer was washed with water, during which time crystallization began. The suspension was mixed with 20 ml of DMF to dissolve the solid and evaporated to a syrup which on evaporation with fresh DMF gave a solid mass. It was crystallized from DMF (80 ml) with ether (240 ml): yield 4.55 g (78.7%); mp 182–184°; $[\alpha]^{25}D$ −28.59° (c 1, DMF); NMR spectral data agreed with the structure.

Anal. Calcd for $C_{40}H_{64}N_6O_{11}$ (804.96): C, 59.68; H, 8.01; N, 10.44. Found: C, 59.56; H, 8.24; N, 10.42.

Amino Acid Anal. Glu, 1.03; Gly, 1.00; Ala, 0.99; Ile, 0.98; Leu, 2.06.

Z-Val-Phe-Thr(Bzl)-OH (I). *p*-Alkoxybenzyl alcohol resin (10 g, 18.5 mmol) was stirred in 100 ml of CH_2Cl_2 with 3.3 g of 4-dimethylaminopyridine (26.9 mmol), Bpoc-Thr(Bzl)-OH (11.86 g, 26.5 mmol), and DCC (5.56 g, 26.9 mmol) for 2 hr. The esterified resin was treated with benzoyl chloride (3.75 ml) and pyridine (3.2 ml)[29] to give Bpoc-Thr(Bzl)-O$CH_2C_6H_4OCH_2C_6H_4$-Resin (11.35 g, 0.55% N, 0.39 mmol/g). Ten grams of this material (3.9 mmol) was used for the solid-phase synthesis with Bpoc-Phe-OH (4.24 g, 11.9 mmol) and Z-Val-OH (2.96 g, 11.9 mmol) successively coupled to the amino group on the resin under the conditions described previously.[50,51] The tripeptide resin was then stirred in 300 ml of 50% TFA in CH_2Cl_2 for 30 min and worked up as usual to give a gel which on treatment with benzene began to crystallize (1.9 g, mp 211–213°). It was recrystallized from ethyl acetate with petroleum ether: yield 1.75 g (75.6%); mp 209–211°; $[\alpha]^{25}D$ −3.50° (c 0.6, MeOH); NMR spectral data agreed with the expected values.

Anal. Calcd for $C_{33}H_{39}N_3O_7$ (589.69): C, 67.22; H, 6.67; N, 7.13. Found: C, 66.63; H, 6.73; N, 7.13.

Amino Acid Anal. Thr, 1.04; Val, 0.96; Phe, 1.00.

H-Ser(Bzl)-Leu-Val-Phe-Gly-OH (II). Bpoc-Gly-OCH_2C_6-$H_4OCH_2C_6H_4$-Resin (10 g, 4.0 mmol) was used for solid-phase synthesis in which 12 mmol each of Bpoc-Phe-OH (4.84 g), Bpoc-Val-OH (4.26 g), Bpoc-Leu-OH (4.44 g), and Bpoc-Ser(Bzl)-OH · CHA (6.4 g) were successively incorporated into the growing peptide chain on the resin[50,51] to produce the pentapeptide resin (13.8 g). Cleavage with 50% TFA in CH_2Cl_2 (30 min) was followed by the usual work-up. A white solid (1.75 g) obtained was crystallized from a small volume of MeOH: yield 0.81 g (33%); mp 247° dec; $[\alpha]^{25}D$ −29.20° (c 0.7, HOAc); NMR spectral data agreed with the structure.

Anal. Calcd for $C_{32}H_{45}N_5O_7$ (611.74): C, 62.83; H, 7.41; N, 11.45. Found: C, 62.76; H, 7.58; N, 11.34.

Amino Acid Anal. Ser, 0.99; Gly, 1.03; Leu, 1.01; Val, 0.91; Phe, 1.07.

Boc-Asn-Ser(Bzl)-Leu-Val-Phe-Gly-OH (VII). Boc-Asn-OSu (0.83 g, 2.5 mmol) was treated with H-Ser(Bzl)-Leu-Val-Phe-Gly-OH (1.02 g, 1.66 mmol) in 85 ml of DMF which contained 0.35 ml of TEA under the conditions analogous to that for preparation of XVI for 24 hr. The reaction was evaporated to about ⅓ of the volume and mixed with 100 ml of 5% citric acid and the solid formed was washed with water and ethyl acetate to give a white powder. It was dissolved in 100 ml DMF, evaporated to dryness, and precipitated from a small volume of DMF with ethyl acetate: amorphous solid; yield 1.21 g (88%); $[\alpha]^{25}D$ −31.92° (c 1, DMF); homogeneous on TLC; NMR data agreed with expected values.

Anal. Calcd for $C_{41}H_{59}N_7O_{11}$ (825.96): C, 59.62; H, 7.20; N, 11.87. Found: C, 59.32; H, 7.28; N, 11.78.

Amino Acid Anal. Asp, 1.00; Ser, 0.92; Gly, 0.93; Leu, 1.06; Val, 1.03; Phe, 1.00.

H-Lys(Z)-Asp(OBzl)-Leu-Glu(OBzl)-OH (III). Solid-phase synthesis was conducted[51] with Bpoc-Glu(OBzl)-$OCH_2C_6H_4$-$OCH_2C_6H_4$-Resin (10 g, 3.15 mmol) using 9.45 mmol each of Bpoc-Leu-OH (3.49 g), Bpoc-Asp(OBzl)-OH (4.36 g), and Bpoc-Lys(Z)-OH (4.9 g) sequentially incorporated into the growing peptide chain to give tetrapeptide resin (13.9 g). Treatment with 50% TFA in CH_2Cl_2 (300 ml) for 30 min and work-up yielded a solid mass (2.83 g, mp 183–186°) which on recrystallization from EtOH afforded soft needles: yield 1.89 g (69.3%): mp 187–188°; $[\alpha]^{25}D$ −12.20° (*c* 0.8, DMF); NMR spectrum agreed with the structure.

Anal. Calcd for $C_{43}H_{55}N_5O_{11} \cdot C_2H_5OH$ (863.98): C, 62.56; H, 7.08; N, 8.12. Found: C, 62.50; H, 6.72; N, 8.36.

Amino Acid Anal. Asp, 0.97; Glu, 1.01; Leu, 1.04; Lys, 0.96.

Boc-Leu-Lys(Z)-Asp(OBzl)-Leu-Glu(OBzl)-OH (VIII). Boc-Leu-OSu (0.99 g, 3.02 mmol) in 100 ml of DMF was stirred with H-Lys(Z)-Asp(OBzl)-Leu-Glu(OBzl)-OH (1.74 g, 2.01 mmol) and 0.5 ml of TEA for 24 hr. The solvent was evaporated off and the residue was taken up in a mixture of ethyl acetate and 5% citric acid. The organic layer was washed (H_2O), dried, and concentrated to a small volume when crystallization began (2.0 g, mp 152–155°). It was recrystallized from ethyl acetate: yield 1.69 g (82%); mp 155–157°; $[\alpha]^{25}D$ −25.50° (*c* 1, DMF); NMR spectrum agreed with the structure.

Anal. Calcd for $C_{54}H_{74}N_6O_{14}$ (1031.18): C, 62.90; H, 7.23; N, 8.15. Found: C, 62.77; H, 7.14; N, 8.07.

Amino Acid Anal. Asp, 0.97; Glu, 1.00; Leu, 1.92; Lys, 1.05.

H-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Val-OH (V). Solid-phase synthesis was carried out[51] with Bpoc-Val-$OCH_2C_6H_4OCH_2C_6H_4$-Resin (9.08 g, 3.54 mmol) by successive incorporation of 11.1 mmol each of Bpoc-Asp(OBzl)-OH (4.9 g), Bpoc-Glu(OBzl)-OH · CHA (6.1 g), Bpoc-Leu-OH (3.9 g), Bpoc-Glu(OBzl)-OH · CHA (6.1 g), and Bpoc-Arg(Tos)-OH (6.0 g) into the resin. The protected hexapeptide resin (12.7 g) was treated with 300 ml of 50% TFA in CH_2Cl_2 for 30 min. Work-up as usual produced an oil which became a white powder when treated with ethyl acetate. It was crystallized from DMF and ethyl acetate: yield 3.8 g (90.5%); mp 207–209°; $[\alpha]^{25}D$ −11.84° (*c* 0.5, HOAc); NMR spectral data agreed with the expected values.

Anal. Calcd for $C_{59}H_{77}N_9O_{15}S \cdot H_2O$ (1202.39): C, 58.89; H, 6.63; N, 10.51. Found: C, 58.59; H, 6.55; N, 10.42.

Amino Acid Anal. Asp, 0.95; Glu, 2.00; Leu, 1.08; Val, 0.91; Arg, 1.06.

Bpoc-Met-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp-(OBzl)-Val-OH (X). Bpoc-Met-ONp (0.84 g, 1.65 mmol) in DMF (80 ml) that had been deaerated by purging with argon gas for 45 min was allowed to react with H-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Val-OH (1.32 g, 1.1 mmol) and TEA (0.25 ml) (0°, 1 hr; 25°, 24 hr) under argon. A few more drops of TEA were added occasionally to maintain the reaction slightly basic. The reaction mixture was neutralized, evaporated to dryness at 35°, and triturated with ethyl acetate. The solid powder (1.3 g, mp 196–199°) was dissolved in DMF and evaporated to near dryness, when *i*-PrOH was added. A crystalline product appeared when stored in the refrigerator overnight: yield 1.05 g (62%); mp 196–199°; $[\alpha]^{25}D$ −18.85° (*c* 1, MEOH); NMR spectral data agreed with the expected values.

Anal. Calcd for $C_{80}H_{100}N_{10}O_{18}S_2$ (1553.86): C, 61.84; H, 6.49; N, 9.01. Found: C, 61.30; H, 6.51; N, 9.01.

Amino Acid Anal. Asp, 1.00; Glu, 2.06; Val, 0.92; Met, 0.89; Leu, 1.01; Arg, 0.97.

H-Thr(Bzl)-Pro-Arg(Tos)-Ala-Gly-OH (VI). Bpoc-Gly-$OCH_2C_6H_4OCH_2C_6H_4$-Resin (10 g, 4.0 mmol) was used for solid-phase synthesis in which 12 mmol each of Bpoc-Ala-OH (3.93 g), Bpoc-Arg(Tos)-OH (6.8 g), Bpoc-Pro-OH (4.25 g), and Bpoc-Thr(Bzl)-OH (5.37 g) were successively incorporated into the growing peptide chain on the resin under the conditions detailed before[5c,51] to produce 14.1 g of the protected pentapeptide resin. The peptide was released from the solid support by a 30-min treatment with 300 ml of 50% TFA in CH_2Cl_2. Evaporation of the solvent left a syrup which on treatment with ether solidified immediately. The product was taken up in *i*-PrOH and precipitated with ether, yielding 3.15 g of an amorphous solid. Reprecipitation from hot CH_3CN gave 1.45 g of material melting at 150–151°. TLC revealed the presence of two minor impurities. Chromatography on a Sephadex LH-20 column (2.5 × 85 cm) using *i*-PrOH–H_2O (7:3) as an eluent eliminated the contaminants: yield 0.94 g (30%); NMR spectrum agreed with the structure.

Anal. Calcd for $C_{34}H_{48}N_8O_9S \cdot 2H_2O$ (780.92): C, 52.21; H, 6.71; N, 14.33. Found: C, 51.99; H, 6.54; N, 13.95.

Amino Acid Anal. Thr, 0.93; Pro, 1.02; Gly, 0.96; Ala, 0.96; Arg, 1.11.

H-Thr(Bzl)-Pro-Arg(Tos)-Ala-Gly-NH_2 · HCl (XIa). Boc-Gly-$OCH_2C_6H_4$-Resin[37] (9.23 g, 5.55 mmol) was used in a synthesis following the standard Merrifield technique[52] with 13.8 mmol each of Boc-Ala-OH (2.61 g), Boc-Arg(Tos)-OH (4.9 g), Boc-Pro-OH (2.98 g), and Boc-Thr(Bzl)-OH (4.27 g) sequentially coupled to the resin to afford 12.3 g of pentapeptide resin. Ammonolysis in 500 ml of MeOH saturated with dry NH_3 gas for 4 days (25°) and work-up as usual[50] gave a syrup which on treatment with ether solidified immediately. The product was taken up in ethyl acetate, washed with H_2O, 5% NH_3, 5% citric acid, and H_2O, dried (Na_2SO_4), and concentrated to a clear oil. It was dissolved in *i*-PrOH and precipitated as a colorless, amorphous solid (XI) by slow addition of ether: yield 2.8 g (60.3%); $[\alpha]^{25}D$ −36.95° (*c* 1, MeOH); NMR spectrum agreed with the structure. TLC indicated that the product was contaminated with a minor fast-moving component. Without further purification at this stage, the product was converted into the HCl salt as described below.

Anal. Calcd for $C_{39}H_{59}N_9O_{10}S \cdot H_2O$ (862.00): C, 54.38; H, 6.88; N, 14.66. Found: C, 54.72; H, 6.95; N, 14.65.

The above compound (XI, 4.43 g, 5.13 mmol) was treated with 3.4 *N* HCl in THF (130 ml) for 45 min. Evaporation of the solvent gave an oil which was reevaporated three times with fresh THF, leaving a glassy solid (4.03 g). The product was dissolved in hot *i*-PrOH and an amorphous solid accumulated on standing. Reprecipitation from the same solvent gave 2.2 g (55%) of the desired material: homogeneous on TLC; NMR spectrum agreed with the structure; $[\alpha]^{25}D$ −25.57° (*c* 1, MeOH).

Anal. Calcd for $C_{34}H_{49}N_9O_8S \cdot HCl \cdot H_2O$ (798.35): C, 51.15; H, 6.67; N, 15.78. Found: C, 51.28; H, 6.68; N, 15.56.

Bpoc-Met-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp-(OBzl)-Val-Thr(Bzl)-Pro-Arg(Tos)-Ala-Gly-NH_2 (XXI). Compound XIa (0.47 g, 0.6 mmol) was dissolved in 20 ml of DMF that had been flushed with argon gas for 45 min. The solution was cooled (0°) and treated with 0.07 ml of NMM (0.6 mmol), 0.93 g of compound X (0.6 mmol), 0.161 g of HOBT (1.19 mmol), and 0.15 g of DCC (0.72 mmol). A few more drops of NMN were added to render the reaction mixture slightly basic. The reaction mixture was stirred at 0° for 1 hr and then at 25° for 42 hr. A few drops of HOAc were added to neutralize the mixture. It was filtered and evaporated (38°) to leave a yellow oil which on trituration with MeOH gave a colorless solid (1.06 g, mp 198–201°). The product was crystallized from DMF and MeOH: yield 0.80 g (58.7%); mp 195–199°; $[\alpha]^{25}D$ −23.79° (*c* 1, DMF); NMR spectrum agreed with the structure.

Anal. Calcd for $C_{114}H_{147}N_{19}O_{25}S_3$ (2279.68): C, 60.06; H, 6.56; N, 11.57. Found: C, 59.33; H, 6.61; N, 11.51.

Amino Acid Anal. Asp, 1.02; Thr, 0.89; Glu, 2.00; Pro, 1.01; Gly, 0.99; Ala, 0.95; Val, 1.03; Met, 0.92; Leu, 0.98; Arg, 2.11.

H-Met-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Val-Thr(Bzl)-Pro-Arg-(Tos)-Ala-Gly-NH_2 · HCl (XXII). Compound XXI (0.75 g, 0.33 mmol) was dissolved in 6 ml of argon-treated DMF and mixed with 100 ml of freshly prepared 0.5 *N* HCl in THF (argon treated). A white, crystalline solid started to appear immediately. After standing at 25° for 10 min, the mixture was diluted with more THF (220 ml) and left at 4° overnight. The solid was collected and recrystallized from DMF and THF: yield 0.46 g (67%); mp 238–241°; $[\alpha]^{25}D$ −21.01° (c 1, DMF); NMR spectrum agreed with the structure.

Anal. Calcd for $C_{98}H_{133}N_{19}O_{23}S_3 \cdot HCl$ (2077.87): C, 56.65; H, 6.50; N, 12.81. Found: C, 56.02; H, 6.65; N, 12.66.

Amino Acid Anal. Asp, 1.06; Thr, 1.04; Glu, 2.10; Pro, 0.98; Gly, 0.99; Ala, 0.99; Val, 1.00; Met, 0.96; Leu, 0.92; Arg, 2.00; NH_3, 1.22.

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Registry No.—I, 54244-38-1; II, 54244-39-2; III, 54244-40-5; IV, 54244-41-6; V, 54244-42-7; VI, 54244-43-8; VII, 54244-44-9; VIII,

54244-45-0; IX, 54244-46-1; X, 54244-47-2; XI, 54325-73-4; XIa, 54325-74-5; XII, 54244-48-3; XIII, 54244-49-4; XIV, 54244-50-7; XV, 38972-95-1; XVI, 54244-51-8; XVII, 27167-65-3; XVIII, 54244-52-9; XIX, 54244-53-0; XX, 54244-54-1; XXI, 54325-75-6; XXII, 54325-76-7; Bpoc-Met-OH · DCHA, 18635-05-7; *p*-nitrophenol, 100-02-7; Bpoc-Met-ONp, 54244-55-2; Bpoc-Thr(Bzl)-OSu, 54244-56-3; Bpoc-Thr(Bzl)-OH, 47733-62-0; HOSu, 6066-82-6; Boc-Glu(OBzl)-OSu, 32886-40-1; Boc-Glu(OBzl)-OH, 13574-13-5; Z-Val-Tyr(Bzl)-OCH_3, 54325-77-8; H-Tyr-OCH_3 · HCl, 3417-91-2; Z-Val-OH, 1149-26-4; H-Val-Tyr-OCH_3 · HCl, 54244-57-4; Aoc-Arg(Tos)-Val-Tyr-OCH_3, 54325-78-9; H-Val-Tyr-OCH_3, 54244-58-5; Aoc-Arg(Tos)-OH, 54244-59-6; leucine, 61-90-5; Z-Leu-OSu, 3397-35-1; H-Ile-Leu-OH · HCl, 54244-60-9; Boc-Gly-OSu, 3392-07-2; H-Leu-OBu-*t* · HCl, 2748-02-9; Z-Ala-OH, 1142-20-7; H-Ala-Leu-OBu-*t* · HCl, 54244-61-0; Boc-Gly-Ile-Leu-OH, 54244-51-8; H-Asp(OBzl)-OH, 3479-47-8; Boc-Ser(Bzl)-OSu, 13650-73-2; Boc-Thr(Bzl)-OSu, 32886-43-4; H-Ser(Bzl)-Asp(OBzl)-OH · HCl, 54244-62-1; H-Ser(Bzl)-Asp(OBzl)-OH, 54244-63-2; H-Lys(Z)-OH, 1155-64-2; Boc-Tyr(Cl_2Bzl)-OCH_2-Ph, 54244-64-3; Boc-Val-OH, 13734-41-3; Boc-Arg(Tos)-OH, 13836-37-8; H-Glu(OBzl)-Lys(Z)-OH · HCl, 54244-65-4; Bpoc-Leu-OH, 18634-99-6; Bpoc-Ala-OH, 23631-89-2; Bpoc-Ile-OH, 47553-71-9; Boc-Gly-OH, 4530-20-5; Bpoc-Phe-OH, 40099-50-1; Bpoc-Gly-OCH_2-C_6H_4-$OCH_2C_6H_5$, 54244-66-5; Bpoc-Ser(Bzl)-OH · CHA, 25692-83-5; Boc-Asn-OSu, 42002-18-6; Bpoc-Glu(OBzl)-$OCH_2C_6H_4OCH_2C_6H_5$, 54244-67-6; Bpoc-Asp(OBzl)-OH, 25692-81-3; Bpoc-Lys(Z)-OH, 25692-93-7; Bpoc-Val-$OCH_2C_6H_4OCH_2C_6H_5$, 54244-68-7; Bpoc-Glu(OBzl)-OH · CHA, 25692-85-7; Bpoc-Arg(Tos)-OH, 47820-38-2; Bpoc-Pro-OH, 25775-07-9; Boc-Gly-OCH_2-Ph, 54244-69-8; Boc-Ala-OH, 15761-38-3; Boc-Pro-OH, 2812-46-6; Boc-Leu-OSu, 3392-09-4.

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(32) Abbreviations used: Aoc, *tert*-amyloxycarbonyl; Boc, *tert*-butyloxycarbonyl; Bpoc, 2-(*p*-biphenylyl)-2-propyloxycarbonyl; Bu-*t*, *tert*-butyl; Bzl, benzyl; Tos, *p*-toluenesulfonyl; Cl_2Bzl, 2,6-dichlorobenzyl; Z, benzyloxycarbonyl; TFA, trifluoroacetic acid; TEA, triethylamine; DCC, dicyclohexylcarbodiimide; HOBT, 1-hydroxybenzotriazole; DMF, dimethylformamide; THF, tetrahydrofuran; CHA, cyclohexylamine; DCHA, dicyclohexylamine; NMM, *N*-methylmorpholine; DMSO, dimethyl sulfoxide.
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Solid-Phase Synthesis of Protected Peptide Hydrazides. Preparation and Application of Hydroxymethyl Resin and 3-(*p*-Benzyloxyphenyl)-1,1-dimethylpropyloxycarbonylhydrazide Resin

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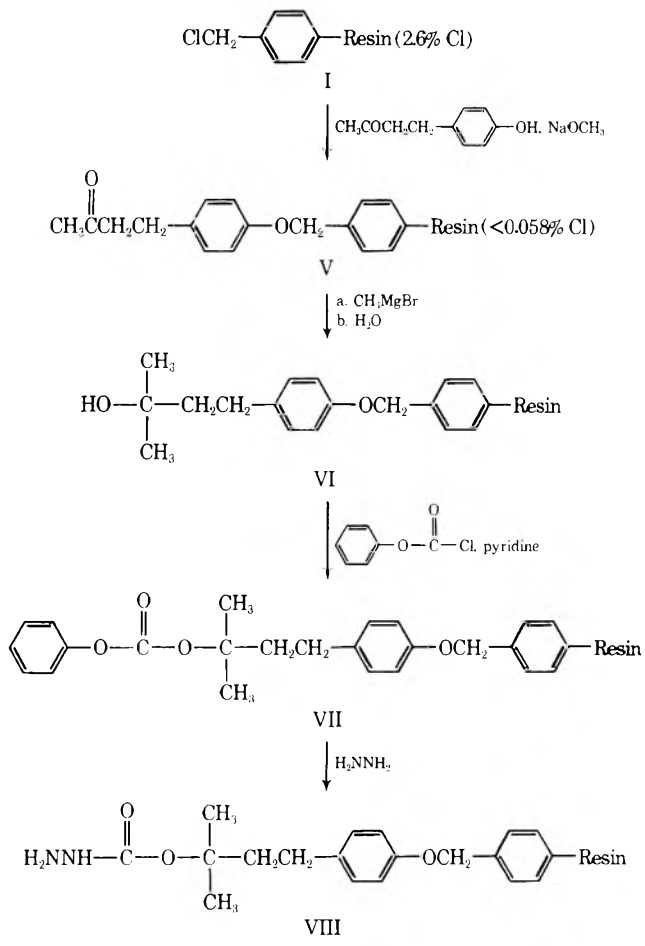
Convenient procedures for the preparation of hydroxymethyl resin (III) and 3-(*p*-benzyloxyphenyl)-1,1-dimethylpropyloxycarbonylhydrazide resin (VIII) [$H_2NNHCOOC(CH_3)_2CH_2CH_2C_6H_4OCH_2C_6H_4$ resin] were developed. Reaction of potassium acetate with Merrifield resin gave acetoxymethyl resin, which on reduction or hydrazinolysis produced III. For the preparation of VIII, Merrifield resin was treated with 4-(*p*-hydroxyphenyl)-2-butanone to give the ketone resin, which was treated with CH_3MgBr giving rise to tertiary alcohol resin. On reaction with phenyl chloroformate, followed by hydrazinolysis, VIII was obtained. Resin III was applied to the synthesis of Aoc-Arg(Tos)-Val-Tyr(Cl_2Bzl)-$HNNH_2$ and Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$ (IX) by hydrazinolysis of peptide to resin ester bond. Using the synthesis of IX as a model system, a comparative study was made of the following coupling methods: oxidation–reduction condensation, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline method; dicyclohexylcarbodiimide; dicyclohexylcarbodiimide plus *N*-hydroxybenzotriazole; and diphenylphosphoryl azide. Resin VIII was applied to the synthesis of Fmoc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$, Fmoc-Gly-Ala-Val-Leu-$HNNH_2$, and Z(2-NO_2)-Gly-Val-Ala-Leu-$HNNH_2$. These peptide hydrazides were obtained by cleavage of the anchoring bond with 50% TFA in CH_2Cl_2.

Solid-phase syntheses of protected peptide hydrazides either by hydrazinolysis of peptide chains attached to Merrifield resin[1-7] or by the application of "hydrazide resins"[8-10] has been described in the literature. These procedures can provide convenient intermediates for polypeptide synthesis via fragment condensation, allowing the combination of solid-phase techniques[11-16] and classical procedures[16-18] and retaining the best features of each method. In this report, the synthesis of protected peptide hydrazides by the use of the hydroxymethyl resin[13,19] and 3-(*p*-benzyloxyphenyl)-1,1-dimethylpropyloxycarbonylhydrazide resin is described.

The hydroxymethyl resin (III) was prepared from Merrifield resin (I) (chloromethylated copolystyrene–1% divinylbenzene, 2.6% Cl) by stirring in dimethylacetamide with slight excess of potassium acetate to form acetoxymethyl resin II, which on reduction with $LiAlH_4$ or hydrazinolysis yielded the desired hydroxymethyl resin III. These reactions were conveniently monitored either by ir spectrophotometry or microanalysis and were found to proceed smoothly. The hydroxymethyl resin (III) was then esterified with *tert*-butyloxycarbonylamino acids by the dicyclohexylcarbodiimide method[20] utilizing pyridine[10,21] or 4-dimethylaminopyridine[22,23] as catalysts. The Boc-aminoacyl resins[24] thus prepared have the degree of substitution generally in the range of 0.5–0.6 mmol/g. In order to prevent unreacted excess hydroxymethyl groups present on the resin from interfering with subsequent reactions, Boc-aminoacyl resins were benzoylated as reported previously.[10] This procedure for the preparation and use of the hydroxymethyl resin is more reproducible and adaptable to larger scale preparation than those described in the literature.[13,25,26] The advantages of using hydroxymethyl resin rather than chloromethyl resin have already been discussed.[12,25,26]

The synthesis of 3-(*p*-benzyloxyphenyl)-1,1-dimethylpropyloxycarbonylhydrazide resin (VIII) is depicted in Scheme I. The starting material I (0.73 mmol/g) was treated with 4-(*p*-hydroxyphenyl)-2-butanone in the presence of an equivalent amount of $NaOCH_3$. The resulting "ketone" resin (V) absorbed strongly at 1710 cm^{-1} and contained less than 0.058% Cl (0.016 mmol/g). Treatment of V with freshly prepared CH_3MgBr followed by hydrolysis of the ensuing product afforded the "tertiary alcohol resin"

Scheme I
Preparation of 3-(*p*-Benzyloxyphenyl)-1,1-dimethylpropyloxycarbonylhydrazide Resin



(VI). As is evident from the ir spectrum, the carbonyl function had disappeared completely while the alkyl aryl ether band at 1230 cm^{-1} remained practically unchanged. The tertiary alcohol group of VI was then converted into a mixed carbonate (VII) which on hydrazinolysis gave rise to

Table I
Synthesis of Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$ Using Different Coupling Methods

Coupling agents[a]	Mp, °C	$[\alpha]^{25}$D, deg	Yield, %	Anal., %		
				C	H	N
			Calcd	67.30	6.63	10.56
DCC[b]	227–229	−2.64	61.5	67.00	6.68	10.43
DCC + HOBT[c]	228–230	−1.18	57.5	66.72	6.65	10.54
EEDQ[c]	229–230	−1.29	55.8	66.73	6.53	10.56
TPP + DPDS[d]	229–230	−1.91	57.7	67.53	6.80	10.50

[a] DCC, dicyclohexylcarbodiimide; HOBT, *N*-hydroxybezotriazole; EEDQ, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; TPP, triphenylphosphine; DPDS, 2,2′-dipyridyl disulfide. [b] Coupling time, 2 hr (reaction progress with time not monitored). [c] Coupling time, 22 hr. [d] Coupling time, 3 hr.

the desired product VIII containing 2.0% of nitrogen (0.71 mmol/g of H_2NNH_2). The ir spectrum showed the expected changes in the wavelength of the carbonyl absorption. All reactions appeared to have proceeded completely.

The hydroxymethyl resin III was used as solid support for the synthesis of Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$ (IX). Boc-Thr(Bzl)-OCH_2-C_6H_4-Resin was deprotected (50% TFA) and neutralized (10% TEA) and the solid-phase synthesis was continued with sequential incorporation of Boc-Tyr(Bzl)-OH, Boc-Phe-OH, Boc-Phe-OH, and Boc-Gly-OH into the growing peptide chain on the resin according to the general Merrifield technique.[11-14] During the synthesis a 2.6-fold excess of both Boc-amino acid and DCC[20] was used in each of the coupling reactions. The product Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-OCH_2-C_6H_4-Resin thus obtained was treated with hydrazine in DMF to give analytically pure crystalline IX in 61.5% overall yield. The synthesis of IX was repeated under exactly the same conditions except that different coupling procedures[20,27-32] were used for evaluation in solid-phase synthesis. The results are summarized in Table I. In agreement with recent reports by Mukaiyama et al.,[29,30] it was evident that the oxidation–reduction procedure is well suited for solid-phase peptide synthesis. The method, moreover, has been claimed to be free of complications when applied to the synthesis of asparagine or glutamine containing peptides. This aspect of the oxidation–reduction procedure was further studied by the synthesis of pGlu-Gln-Ala-NH_2, and indeed the synthesis was found to proceed satisfactorily. The tripeptide amide identical with that prepared previously[33] with the *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline procedure[31] was obtained in 79% overall yield. There were no indications of nitrile formation during the synthesis as judged by ir and NMR spectrophotometry.

The hydroxymethyl resin III was also utilized for the synthesis of L-pyroglutamyl-L-serylglycinamide (X). Boc-Gly-OCH_2-C_6H_4-Resin was deprotected and neutralized as usual[11,13] and the solid-phase synthesis was carried out by coupling Boc-Ser(Bzl)-OH to the resin followed by pyroglutamic acid. The tripeptide resin thus obtained was then stirred with ammonia–saturated methanol, giving the crystalline O-protected tripeptide amide pGlu-Ser(Bzl)-Gly-NH_2 in 38% overall yield. This compound gave X upon hydrogenation. A peptide isolated from hypothalamic extracts has been reported to possess this structure and to exhibit pituitary growth hormone releasing activity.[34] However, synthetic pGlu-Ser-Gly-NH_2 (X) prepared in several laboratories, including our own,[35,36] did not elicit such activity in several systems thus far tested.

Another protected peptide hydrazide, Aoc-Arg(Tos)-Val-Tyr(Cl_2Bzl)-$HNNH_2$ (XI), was also prepared on the hydroxymethyl resin III in an analogous manner. The tripeptide resin was hydrazinolyzed in methanolic hydrazine

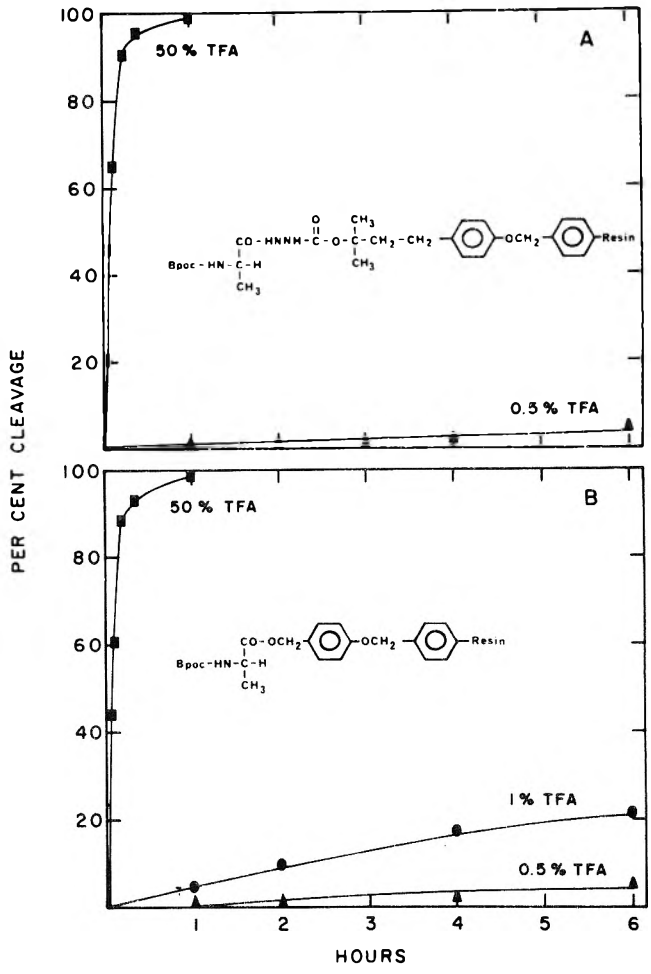


Figure 1. The rate of cleavage of the anchoring bond on Bpoc-Ala derivatives of 3-(*p*-benzyloxyphenyl)-1,1-dimethylpropyloxycarbonylhydrazide resin (A), and *p*-alkoxybenzyl alcohol resin (B) in various concentrations of trifluoroacetic acid in CH_2Cl_2. Data shown in these figures were derived from the nitrogen analyses on the corresponding aminoacyl resins.

solution and the pure crystalline product XI was obtained in 64% overall yield.

Peptide hydrazides prepared with the use of hydroxymethyl resin crystallized more readily than the products obtained by hydrazinolysis of standard chloromethyl group containing peptide resins, which are contaminated with hydrazine hydrochloride.

The 3-(*p*-benzyloxyphenyl)-1,1-dimethylpropyloxycarbonylhydrazide resin VIII was utilized to prepare Z(2-NO_2)-Gly-Val-Ala-Leu-$HNNH_2$ (XII). The photosensitive Z(2-NO_2) group[37,38] was used for amino terminal protection. The product was obtained in 44.4% overall yield as calculated from the hydrazide content of resin VIII. The solid-phase synthesis was conducted using 2.5-fold excesses

each of the respective amino acid derivatives and DCC for coupling in each cycle under previously detailed conditions.[8-10] The Bpoc-amino protecting group was removed by 10-min treatment with 0.5% TFA in CH_2Cl_2.[8] Two protected peptide hydrazides containing the base-labile Fmoc amine protecting group[39] were also prepared. Fmoc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$ (XIII) was obtained in 36% and Fmoc-Gly-Ala-Val-Leu-$HNNH_2$ (XIV) in 49% overall yield. The combined use of resin VIII with Bpoc-amino acids together with amino terminal Z(2-NO_2) or Fmoc protection provides a potential for ready preparation of a large variety of peptide intermediates which contain protecting groups suitable for polypeptide synthesis via the fragment condensation strategy. A *tert*-alkoxycarbonylhydrazide resin support[8,9] that can be used interchangeably with VIII has been described previously but its preparation required the use of the hazardous liquid HF. The procedure described in this report for the preparation of VIII appears to be simpler and more practical.

The relative stabilities of the anchoring bonds on aminoacyl resin VIII in different concentrations of TFA were studied. Bpoc-Ala-HNNH-COO-$C(CH_3)_2CH_2CH_2C_6H_6O$-$CH_2C_6H_4$-Resin was stirred with 20 volumes of 0.5 or 50% TFA in CH_2Cl_2. At various time intervals, samples were withdrawn and the resin was collected, washed, and examined by ir spectrophotometry as well as by nitrogen analysis. As the anchoring bond was cleaved, both the intense broad band at 1680–1700 cm^{-1} in the ir spectrum and the nitrogen content of the resin decreased progressively (Figure 1A). For comparison, a similar set of experiments was performed on Bpoc-Ala-$OCH_2C_6H_4OCH_2C_6H_4$-Resin[10] (Figure 1B). As expected, the anchoring bonds on both resins were stable to the conditions of Bpoc deprotection (0.5% trifluoroacetic acid, 10 min) but were rapidly cleaved by 50% trifluoroacetic acid within a few minutes.

Experimental Section

Melting points are uncorrected. The infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer using KBr pellets. Thin layer chromatography was carried out on precoated silica gel plates (Merck, F-254) with the following solvent systems: 1-butanol–acetic acid–water (4:1:1), 1-butanol–pyridine–acetic acid–water (15:10:3:12); 1-butanol–ethyl acetate–acetic acid–water (1:1:1:1); 1-propanol–water (7:3). Microanalyses and other physicochemical measurements were carried out by the Physical Chemistry Department.

Merrifield resin (chloromethylated copolystyrene–1% divinylbenzene, 200–400 mesh, 2.6% Cl) used in these experiments was purchased from Bio-Rad Laboratories. Amino acid derivatives were obtained from Bachem, Inc., Marina Del Ray, Calif., or Chemical Dynamics Corp., South Plainfield, N.J. All Bpoc-, Z(2-NO_2)-, and Fmoc-amino acid derivatives were prepared in this laboratory according to literature procedures.[38-42] All optically active amino acids used were of the L configuration.

Hydroxymethyl Polystyrene–1% Divinylbenzene Resin (III). Merrifield resin (I, 71 g, 52 mmol) was suspended in dimethylacetamide (600 ml) and stirred gently with potassium acetate (6.26 g, 64 mmol) at 85° for 24 hr. The acetoxymethyl resin (II) thus formed was washed with DMF, dioxane, and methanol to yield 77.4 g of buff-colored material: ir (KBr) 1720 cm^{-1}; Cl <0.12% (0.034 mmol/g). II was suspended in anhydrous ether (1.8 l.) and treated with $LiAlH_4$ (7.0 g) added in small portions during 20 min. After 4 hr of additional stirring, the resin was transferred to a glass filter and washed with ethyl acetate, dioxane, and methanol. The slightly grayish color was removed by stirring in a 1:2 mixture of 1 *N* H_2SO_4–dioxane (4.5 l.) for 24 hr. This operation was repeated once more and the snow-white hydroxymethyl resin thus obtained weighed 72.2 g. The carbonyl band in the ir spectrum disappeared completely.

Conversion of II (23.5 g) into III (23.0 g) was also accomplished by stirring in 250 ml of DMF containing 25 ml of anhydrous H_2NNH_2 for 76 hr. The ir spectrum of the product III was identical with that of the hydroxymethyl resin prepared by the $LiAlH_4$ procedure described above.

Esterification of Hydroxymethyl Resin III with Boc-Amino Acids. III (5 g, 3.65 mmol) was suspended in CH_2Cl_2 (50 ml) and treated with pyridine (1.5 ml), Boc-Ala-OH (3 g, 16 mmol), and DCC (3.5 g, 17 mmol) for 120 min. The product was washed with CH_2Cl_2, DMF, and methanol to yield colorless Boc-Ala-OCH_2-C_6H_4-Resin (5.33 g): ir 1720 and 1735 cm^{-1}; N, 0.88% (0.63 mmol/g); alanine, 0.62 mmol/g. The resin was further treated with pyridine (1.65 ml) and benzoyl chloride (1.95 ml) in CH_2Cl_2 (50 ml) at 0° for 15 min. The ensuing product (5.35 g) showed a slight increase in ir absorption at 1720 cm^{-1}.

For certain Boc-amino acids, esterification to III requires a more powerful catalyst. Thus, III was suspended in CH_2Cl_2–DMF mixture (20 g/200 ml) and stirred with 4-dimethylaminopyridine (3.66 g, 30 mmol), Boc-Gly-OH (5.25 g, 30 mmol), and DCC (6.6 g, 32 mmol) for 120 min. The esterified resin (20.5 g) absorbed strongly at 1720 and 1730 cm^{-1}, N, 0.90% (0.64 mmol/g). The resin was benzoylated in an analogous manner as above to give the desired Boc-Gly-OCH_2-C_6H_4-Resin (20.6 g).

Similarly prepared were resin III esters of Boc-Phe-OH, Boc-Tyr(Cl_2Bzl)-OH, Boc-Thr(Bzl)-OH, Boc-Pro-OH, Boc-β-Ala-OH, and Z-Lys(BOC)-OH.

3-(*p*-Benzyloxyphenyl)-1,1-dimethylpropyloxycarbonylhydrazide Resin (VIII). Merrifield resin (10 g, 7.3 mmol) was suspended in DMF (70 ml) and treated with 4-(*p*-hydroxyphenyl)-2-butanone (1.64 g, 10 mmol) in the presence of $NaOCH_3$ (0.54 g, 10 mmol) at 85° for 24 hr. The dark brownish reaction mixture was filtered and the resin was washed with DMF, CH_2Cl_2, and MeOH to give 10.9 g of light buff colored material: ir 1730 cm^{-1}; Cl, 0.058%. The resin was then suspended in benzene (200 ml) and treated with a Grignard reagent (CH_3MgBr) freshly prepared from 0.54 g of Mg turnings in ether (300 ml) bubbled with dry CH_3Br. After 60 min of additional stirring, the resin was washed (benzene, dioxane) and stirred in a mixture of 1 *N* H_2SO_4–dioxane (1:2) for 120 min. The tertiary alcohol resin (VI) thus formed was collected and washed with H_2O–dioxane (1:1), dioxane, DMF, and CH_2Cl_2 and then treated with pyridine (7.9 ml) and phenyl chloroformate (9.8 ml) in 120 ml of CH_2Cl_2 at 0° for 16 hr. The reaction mixture was poured into ice–water (100 ml) and filtered to collect the resin. The mixed carbonate resin (VII) thus obtained was washed with more ice–water, dioxane, and DMF. It was then stirred with 120 ml of DMF containing 10 ml of anhydrous H_2NNH_2 for 6 hr to give the desired product VIII: N, 2.00% (0.71 mmol/g).

2-Nitrobenzyl-*p*-nitrophenyl Carbonate. 2-Nitrobenzyl alcohol (25 g, 163 mmol) was dissolved in CH_2Cl_2 (300 ml) and allowed to react with pyridine (21.5 ml) and p-nitrophenyl chloroformate (34.2 g, 170 mmol) overnight at 0°. The mixture was mixed with ice–water (500 ml) and diluted with CH_2Cl_2 (300 ml) in a separatory funnel. The organic layer was then washed with 0.02 *N* HCl followed by water. After drying over Na_2SO_4, the solvent was removed by evaporation at 35° and the remaining solid was recrystallized from 200 ml ethyl acetate: yield 41.8 g (91%); mp 133–136°.

Anal. Calcd for $C_{14}H_{10}N_2O_7$ (318.24): C, 52.84; H, 3.17; N, 8.80. Found: C, 53.12; H, 3.40; H, 8.78.

2-Nitrobenzyloxycarbonylglycine. Glycine (1.5 g, 2 mmol) was mixed with 9.5 ml of Triton B (40% methanolic solution of benzyltrimethylammonium hydroxide) and evaporated to dryness at 35°. The residue was evaporated twice with 18 ml each of DMF and stirred with 7.0 g of 2-nitrobenzyl-*p*-nitrophenyl carbonate (2.2 mmol) at 40° for 120 min. The reaction mixture was partitioned between ethyl acetate and water (300 ml each) and the aqueous layer was washed twice with ethyl acetate and acidified to pH 2.5 with 1 *M* citric acid. The resulting oily product was extracted into ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated at 35°, leaving a heavy syrup. It was taken up in a small volume of ethyl acetate and treated with petroleum ether. The ensuing crystalline solid was recrystallized from the same solvents: yield 3.35 g (66%); mp 121–123°.

Anal. Calcd for $C_{10}H_{10}N_2O_6$ (254.2): C, 47.25; H, 3.97; N, 11.02. Found: C, 47.17; H, 4.18; N, 10.99.

This compound has been listed in a communication by Patchornik et al.[38] (mp 120–122°) without details of the synthesis.

Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$ (IX). Boc-Thr(Bzl)-OCH_2-C_6H_4-Resin (1.4 g, 0.77 mmol) was placed in a reaction vessel[43] on a shaker and the solid-phase peptide synthesis conducted by sequential incorporation of Boc-Tyr(Bzl)-OH (0.62 g, 2.0 mmol), Boc-Phe-OH (0.53 g, 2.0 mmol), Boc-Phe-OH (0.53 g, 2.0 mmol), and Boc-Gly-OH (0.35 g, 2.0 mmol) according to the general principles of the Merrifield technique.[11] The protected pentapeptide resin (1.8 g) thus obtained was suspended in DMF (20 ml) and stirred gently with anhydrous hydrazine (2 ml) for 66

hr. The peptide hydrazide was separated from the resin by filtration and evaporated at 35° to a syrup which upon treatment with ether solidified immediately. The solid was then triturated in hot methanol (0.54 g, mp 224–227°) and crystallized from DMF (15 ml) by slow addition of ethanol (30 ml): yield 0.44 g (61.5%); mp 227–229°; $[\alpha]^{25}D$ −2.64° (c 1, DMF); NMR spectral data agreed with the expected values.

Anal. Calcd for $C_{52}H_{61}N_7O_9$ (928.07): C, 67.30; H, 6.63; N, 10.56. Found: C, 67.00; H, 6.68; N, 10.43.

The synthesis of IX was repeated under exactly the same conditions except that different coupling methods were employed in each experiment. The results of these experiments are summarized in Table I. Thus, 1 equiv of DCC and 2 equiv of *N*-hydroxybenzotriazole relative to Boc-amino acid were employed with reaction time of 22 hr. The experiment using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline was conducted with equivalent amounts of coupling agent and Boc-amino acid with a reaction time of 22 hr. For the experiment using the oxidation–reduction method, equivalent amounts of 2,2′-dipyridyl disulfide, triphenylphosphine, and Boc-amino acid were used and the coupling time was 3 hr. As in the experiment using DCC as coupling agent, a 2.6-fold excess of Boc-amino acid derivatives relative to amino groups on the peptide resin was used throughout all of these experiments. Experiments with diphenylphosphoryl azide[32] in solid-phase synthesis (22 hr coupling time) under similar conditions were unsuccessful.

Aoc-Arg(Tos)-Val-Tyr(Cl_2Bzl)-HNNH$_2$ (XI). Hydroxymethyl resin (III, 9.4 g, 6.9 mmol) was stirred in CH_2Cl_2 (95 ml) with 4-dimethylaminopyridine (1.72 g, 14 mmol), Boc-Tyr(Cl_2Bzl)-OH (6.2 g, 14 mmol),[44] and DCC (3.3 g, 16 mmol) for 45 min and the esterified resin (11.8 g) was collected and benzoylated as described above to give 11.4 g of Boc-Tyr(Cl_2Bzl)-OCH$_2$-C_6H_4-Resin: N, 0.88% (0.63 mmol); Cl, 4.23% (0.6 mmol amino acid/g). Part of this material (6 g, 3.72 mmol) was used in the subsequent solid-phase synthesis using Boc-Val-OH (2.02 g, 9.3 mmol) and Aoc-Arg(Tos)-OH (3.41 g, 9.3 mmol) in each cycle. The tripeptide resin Aoc-Arg(Tos)-Val-Tyr(Cl_2Bzl)-OCH$_2$-C_6H_4-Resin (7.8 g) was hydrazinolyzed in 300 ml of MeOH containing 30 ml of anhydrous H_2NNH_2 for 72 hr (25°). The resin was filtered off and the filtrate was evaporated to a glassy solid (3.2 g). It was crystallized from *i*-PrOH and then recrystallized from EtOH: yield 2.1 g (64%); mp 189–191°; $[\alpha]^{25}D$ −13.66° (*c* 1, DMSO); NMR spectral data agreed with the structure.

Anal. Calcd for $C_{40}H_{54}N_8O_8SCl_2$ (877.89): C, 54.73; H, 6.20; N, 12.76; S, 3.65; Cl, 8.08. Found: C, 54.47; H, 6.39; N, 12.60; S, 3.70; Cl, 8.20.

pGlu-Ser(Bzl)-Gly-NH$_2$. Boc-Gly-OCH$_2$-C_6H_4-Resin (9.0 g, 5.76 mmol) was placed in a 200-ml peptide synthesis flask[43] and the solid-phase synthesis carried out as described above with Boc-Ser(Bzl)-OH (5.1 g, 17.3 mmol) and pyroglutamic acid (2.24 g, 17.3 mmol) sequenally incorporated into the resin using DCC (3.57 g, 17.4 mmol) as coupling agent in each cycle. The tripeptide resin (10.2 g) was suspended in dry methanol (500 ml), bubbled with dry NH_3 at 0° until nearly saturated, and stirred for 66 hr. The tripeptide amide liberated from the resin was worked up as usual, giving rise to a syrup which upon treatment with ethyl acetate solidified immediately. The crude material was dissolved in methanol (50 ml) and crystallized by slow addition of ether: yield 1.21 g (58%); mp 143–145°; $[\alpha]^{25}D$ +5.25° (*c* 0.9, MeOH); NMR spectral data agreed with the expected values.

Anal. Calcd for $C_{17}H_{22}N_4O_5$ (362.38): C, 56.35; H, 6.12; N, 15.46. Found: C, 56.26; H, 6.16; N, 15.56.

The same compound was synthesized again using the oxidation–reduction method[29,30] with a 2.0-fold excess each of amino acid derivative, 2,2′-dipyridyl disulfide, and triphenylphosphine, and a 3-hr coupling time. From 6.63 g of Boc-Gly-OCH$_2$$C_6H_4$-Resin (4.2 mmol) the desired product pGlu-Ser(Bzl)-Gly-NH$_2$ (0.85 g) was obtained in 56% overall yield: mp 143–145°; $[\alpha]^{25}D$ +6.37° (*c* 1, MeOH).

Anal. Found: C, 56.57; H, 6.10; N, 15.47.

pGlu-Ser-Gly-NH$_2$ (X). The above compound (0.5 g, 1.38 mmol) was dissolved in a solvent mixture (50 ml of methanol, 15 ml of water, 0.5 ml of acetic acid) and hydrogenated at 55 psi in a Parr hydrogenator overnight in the presence of 0.2 g of catalyst (5% Pd on $BaSO_4$). The catalyst was filtered off and the filtrate was evaporated to an oil which was taken up in 35 ml of water and lyophilized to give a hygroscopic white powder (0.53 g). It was dissolved in 15 ml of methanol, filtered to remove small insolubles, and treated with a 2:1 mixture of ether and tetrahydrofuran until turbid. The product crystallized slowly when stored in the refrigerator: yield 0.228 g (59.7%); mp 168–172°; $[\alpha]^{25}D$ −10.76° (*c* 0.7, MeOH); NMR spectral data agreed with the expected values.

Anal. Calcd for $C_{10}H_{16}N_4O_5 \cdot \frac{1}{4}H_2O$ (276.76): C, 43.33; H, 5.98; N, 20.17. Found: C, 43.36; H, 5.91; N, 20.22.

pGlu-Gln-Ala-NH$_2$. The solid-phase synthesis was carried out as usual on Boc-Ala-OCH$_2$-C_6H_4-Resin (1.42 g, 0.88 mmol) using a 2.2-fold excess each of Boc-Gln-OH (0.845 g), 2,2′-dipyridyl disulfide (0.49 g), and triphenylphosphine (0.58 g) in the first cycle and pyroglutamic acid (0.284 g) with the same amount of coupling agents in the second cycle. The reaction time was set at 3 hr. The tripeptide resin (1.6 g) obtained was ammonolyzed and worked up as usual to give 0.227 g (79%) of pGlu-Gln-Ala-NH$_2$ identical with the same compound prepared[33] by the *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline method: mp 260–262°; ir spectrum and NMR spectrum identical with the reference spectra.

Z(2-NO_2)-Gly-Val-Ala-Leu-HNNH$_2$ (XII). The hydrazide resin VIII (1.4 g, 0.98 mmol) was placed in a reaction vessel[43] and the solid-phase synthesis carried out by incorporating Bpoc-Leu-OH (0.94 g, 2.55 mmol), Bpoc-Ala-OH (0.84 g, 2.55 mmol), Bpoc-Val-OH (0.91 g, 2.55 mmol), and Z(2-NO_2)-Gly-OH (0.64 g, 2.55 mmol) successively into the resin according to the procedure described previously.[8–10] The tetrapeptide hydrazide resin thus obtained (1.86 g) was stirred in CH_2Cl_2 (18 ml) for a few minutes and an equal volume of TFA was added. After 30 min the resin was filtered off and the filtrate evaporated at 30° to a syrup. It was evaporated twice more with fresh CH_2Cl_2 and treated with ethyl acetate (100 ml). The white solid obtained was triturated in hot methanol (10 ml) and crystallized from DMF by the addition of ether: yield 0.24 g (44.4%); mp 224–228°; $[\alpha]^{25}D$ −16.20° (c 1, DMF); NMR spectral data agreed with the expected values.

Anal. Calcd for $C_{24}H_{37}N_7O_8$ (551.6): C, 52.26; H, 6.76; N, 17.78. Found: C, 52.30; H, 6.84; N, 17.63.

Fmoc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-HNNH$_2$ (XIII). The hydrazide resin VIII (1.4 g, 1.0 mmol) was placed in the peptide synthesis flask and the synthesis conducted as usual[8–10] with Bpoc-Thr(Bzl)-OH (1.12 g, 2.5 mmol), Bpoc-Tyr(Bzl)-OH (1.27 g, 2.5 mmol), Bpoc-Phe-OH (1.01 g, 2.5 mmol), Bpoc-Phe-OH (1.01 g), and Fmoc-Gly-OH (0.744 g, 2.5 mmol) sequentially incorporated into the growing peptide chain. The resultant pentapeptide hydrazide resin (2.23 g) was then stirred with 44 ml of 50% TFA in CH_2Cl_2 for 30 min and the liberated pentapeptide hydrazide was worked up in a similar manner as described above. The glassy solid obtained was crystallized from DMF by slow addition of methanol: yield 0.38 g (36%); mp 196–198°; $[\alpha]^{25}D$ −0.40° (*c* 1, DMF); NMR spectral data agreed with the expected values.

Anal. Calcd for $C_{62}H_{63}N_7O_9 \cdot H_2O$ (1068.20): C, 69.62; H, 6.13; N, 9.16. Found: C, 69.52; H, 6.00; N, 8.95.

Fmoc-Gly-Ala-Val-Leu-HNNH$_2$ (XIV). Solid-phase synthesis[8–10] with hydrazide resin VIII (1.07 g, 0.74 mmol) using a 2.5-fold excess of Bpoc-Leu-OH (0.683 g), Bpoc-Val-OH (0.657 g), Bpoc-Ala-OH (0.606 g), and Fmoc-Gly-OH (0.55 g) in each of the respective synthetic cycles gave rise to 1.45 g of tetrapeptide hydrazide resin. It was stirred in 30 ml of 50% TFA in CH_2Cl_2 for 30 min and worked up as usual. The gelatinous white solid obtained was crystallized from DMF (15 ml) by slow addition of ethanol (30 ml): yield 0.22 g (49%); mp 220–225° dec; $[\alpha]^{25}D$ −24.25° (c 1, DMF); NMR spectral data agreed with the expected value.

Anal. Calcd for $C_{31}H_{42}N_6O_6 \cdot \frac{1}{2}H_2O$ (604.7): C, 61.73; H, 7.29; N, 13.89. Found: C, 61.99; H, 7.23; N, 13.90.

Rate of Cleavage of Aminoacyl Resin Anchoring Bonds by Different Concentrations of Trifluoroacetic Acid. The hydrazide resin VIII (1.0 g, 0.71 mmol) was allowed to react with Bpoc-Ala-OH (0.66 g, 2.0 mmol) and DCC (0.412 g, 20 mmol) in CH_2Cl_2 (10 ml) for 120 min. The ensuing Bpoc-Ala-HNNH-COO-C(CH$_3$)$_2$CH$_2$CH$_2$$C_6H_4OCH_2$$C_6H_4$-Resin (1.24 g) contained 0.56 mmol/g aminoacyl hydrazide (Anal. N, 2.32). Part of the sample (0.5 g) was stirred in 5 ml of CH_2Cl_2 for a few minutes and then mixed with 5 ml of 1% trifluoroacetic acid in CH_2Cl_2 or 5 ml of trifluoroacetic acid. At various time intervals, aliquots were withdrawn and the resin in each sample washed immediately with CH_2Cl_2, DMF, and methanol. Each individual resin sample was then examined by ir spectrophotometry and also by nitrogen analysis. The rate of disappearance of the carbonyl band relative to the polystyrene band at 1600 cm^{-1} was taken as the rate of cleavage of the anchoring bond. The rate of decrease in nitrogen content of the resin was another indication for the rate of cleavage of the same anchoring bond. Both the results of ir and nitrogen analysis agreed with each other rather well. The nitrogen analysis data are plotted in Figure 1A. The anchoring bond is quite stable in 0.5% trifluoroacetic acid but rapidly cleaved by 50% trifluoroacetic acid. Similar experiments were conducted with Bpoc-Ala-OCH$_2$$C_6H_4$-

$OCH_2C_6H_4$-Resin (0.53 mmol/g)[10] with the results shown in Figure 1B. The stabilities of the anchoring bonds in these resins are similar.

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Registry No.—I, 9003-70-7; VIII, 54276-63-0; IX, 54276-64-1; X, 51095-58-0; XI, 54276-65-2; XII, 54276-66-3; XIII, 54276-67-4; XIV, 54276-68-5; potassium acetate, 127-08-2; Boc-Ala-OH, 15761-38-3; Boc-Ala-$OCH_2C_6H_5$, 51814-54-1; Boc-Gly-OH, 4530-20-5; Boc-Gly-$OCH_2C_6H_5$, 54244-69-8; 4-(*p*-hydroxyphenyl)-2-butanone, 5471-51-2; phenyl chloroformate, 1885-14-9; 2-nitrobenzyl-*p*-nitrophenyl carbonate, 54276-69-6; 2-nitrobenzyl alcohol, 612-25-9; *p*-nitrophenyl chloroformate, 7693-46-1; 2-nitrobenzyloxycarbonylglycine, 30007-79-5; glycine, 56-40-6; Boc-Thr(Bzl)-$OCH_2C_6H_5$, 54276-70-9; Boc-Tyr(Bzl)-OH, 2130-96-3; Boc-Phe-OH, 13734-34-4; Boc-Tyr(Cl_2Bzl)-OH, 40298-71-3; Boc-Tyr(Cl_2Bzl)-$OCH_2C_6H_5$, 54244-64-3; Boc-Val-OH, 13734-41-3; Aoc-Arg(Tos)-OH, 54244-59-6; pGlu-Ser(Bzl)-Gly-NH_2, 54276-71-0; pyroglutamic acid, 16891-48-8; Boc-Ser(Bzl)-OH, 23680-31-1; pGlu-Gln-Ala-NH_2, 38357-81-2; Boc-Gln-OH, 13726-85-7; Bpoc-Leu-OH, 18634-99-6; Bpoc-Ala-OH, 23631-89-2; Bpoc-Val-OH, 25692-88-0; Bpoc-Thr(Bzl)-OH, 47733-62-0; Bpoc-Tyr(Bzl)-OH, 25692-91-5; Bpoc-Phe-OH, 40099-50-1; Fmoc-Gly-OH, 29022-11-5.

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A Nuclear Magnetic Resonance Study of Structure in Some Bi- and Tricyclic *N*-Nitrosoamines[1]

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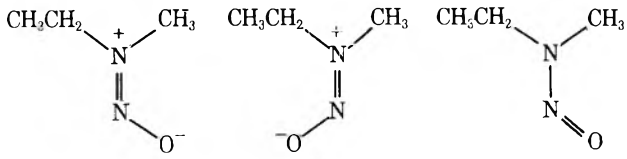
In acyclic *N*-nitrosoamines, the barrier to rotation about the N–N bond, revealed by nuclear magnetic resonance spectra, gives rise to diastereomeric structures. We have prepared a series of bi- and tricyclic *N*-nitrosoamines with a nitrogen in one of the bridges and adjacent to a bridgehead (compounds 3–7) and investigated their structures by NMR techniques, including the use of europium shift reagent. *N*-Nitrosoamines 3 and 4 were obtained as single compounds, with the nitroso oxygen anti to the vicinal bridgehead, and 5–7 were obtained as mixtures of nonequilibrating diastereomers. The size of the heterocyclic ring influences the geometry between the bridgehead hydrogen (or methyl) and the NNO group sufficiently to account for these differences.

N-Nitrosoamines are interesting as a class of compounds because they are strongly carcinogenic and because their structures are poorly represented by conventional, uncharged valence-bond formulas. This paper is concerned with a structural study of some bi- and tricyclic compounds in which the *N*-nitrosoamine (NNO) group is a member of a ring bridge and is adjacent to a bridgehead position. The geometries of these compounds are considerably more rigid than the acyclic[2] and monocyclic[3] *N*-nitrosoamines which have been studied earlier, and they illustrate substantial 1,5 nonbonded O–H interactions that strongly influence diastereomer ratios.

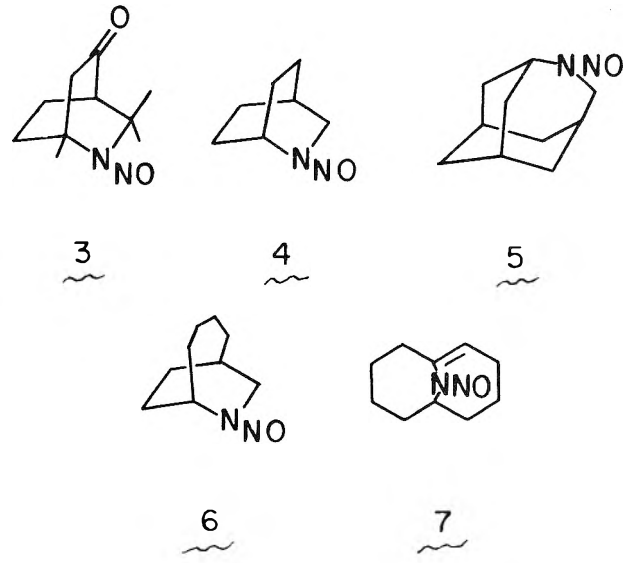
The nuclear magnetic resonance (NMR) spectrum of *N*-nitrosodimethylamine reveals that the two methyl groups are magnetically nonequivalent up to about 156°.[4] The substantial energy barrier to rotation about the N–N bond[4,5] gives rise in unsymmetrical *N*-nitrosoamines to diastereomeric structures [e.g., (*E*)-1 and (*Z*)-1] which are

formed together but give distinguishable NMR spectra.[2] The downfield chemical shifts of protons in the *N*-alkyl groups are comparable to those in structurally related carbocations.[6] These data virtually require the use of a zwitterionic formulation [(*E*)-1 and (*Z*)-1] rather than a conventional uncharged one (2).[7]



(*E*)-1 (*Z*)-1 2

We have prepared several bi- and tricyclic *N*-nitrosoamines (3–7) and investigated their structures by NMR techniques, including the use of europium shift reagent.[3,8,9] Compounds 3 and 4 each were obtained as a single configuration, but 5, 6, and 7 each was obtained as a nonequilibrating mixture of isomers. The ring size of the heterocyclic ring affects the geometrical relationship between the bridgehead hydrogen and the NNO moiety enough to account for these differences.



3 4 5 6 7

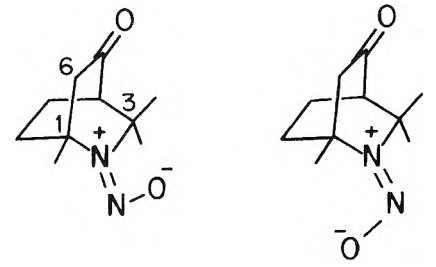
These *N*-nitrosoamines were prepared by treatment of the corresponding amines (or ammonium chlorides) with aqueous nitrous acid. The product which separated from the aqueous solution was extracted into an organic solvent or collected directly on a filter. It was used for the NMR studies without any fractionation attempts.

Compound 3. The first member of the series, *N*-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (3), contains a carbonyl group and has the positions vicinal to NNO substituted by methyl groups. It was selected because of the moderate ease with which it can be synthesized from a commercially available cyclohexenone. The most striking feature in the NMR spectrum of 3 is the presence of only three methyl singlets (δ 1.24, 1.40, and 1.61). This feature suggests that only one configurational isomer is present. If both diatereomers of the *N*-nitrosoamine were present, there should be two sets of three singlets for the methyl groups, unless rapid equilibration were occurring. The spectrum also includes a doublet of doublets (dd, δ 2.46) and a doublet (δ 2.24), which are assigned to the methylene hydrogens adjacent to the carbonyl group.

The bridgehead methyl group (Me-1) is expected to be deshielded with respect to the other methyls, because it lies in the deshielding zone of the planar NNO group.[10] The geminal methyls at position 3 (Me-3) lie above and below the plane of the C-1 (C-3) NNO group and in the shielding cone of that group.[10] The exo Me-3 lies in the shielding cone of the carbonyl group and is therefore more shielded than the endo Me-3. Therefore, the Me-1 is assigned to the absorption at δ 1.61, the endo Me-3 to the one at δ 1.40, and the exo Me-3 to the one at δ 1.24.

The two diastereotopic hydrogens at position 6 (H-6) have different splitting patterns and chemical shifts. A Dreiding molecular model shows the appropriate geometry for W coupling[11] between the H-6 syn to NNO (syn H-6) and endo H-7, but such long-range coupling seems unlikely for anti H-6. Therefore, syn H-6 is assigned to the dd (J_{gem} = 18.5, J_w = 1.8 Hz) centered at δ 2.46, whereas anti H-6 is assigned to the doublet (J_{gem} = 18.5 Hz) centered at δ 2.24.

A europium shift reagent [Eu(fod)$_3$] study[3,9] confirmed the NMR assignments above and established that a single diastereomer was present. Plots of the chemical shifts of different hydrogens vs. the shift reagent/nitrosoamine mole ratios are linear and have the following slopes:[12] exo Me-3, 5.99; endo Me-3, 5.40; Me-1, 3.20; syn H-6, 5.07; and anti H-6, 4.64. The slopes for the three methyl groups are consistent with a single configuration, illustrated by formula **3a.** Were rapid equilibration between diastereomers **3a** and **3b** occurring, we would expect the difference in slopes for the Me-1 and end Me-3 to be much smaller. The larger slopes for the two Me-3 than for the Me-1, even though they lie in the shielding cone of the NNO group, are compelling evidence for the spatial relationships between each Me and the Eu complex required by formula **3a.**

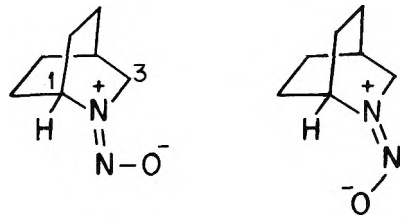


3a 3b

Configuration **3a** is in accord with previously studied examples, for which the major *N*-nitrosoamine diastereomer in a mixture was found to have the nitroso oxygen anti to the more bulky substituent on nitrogen.[2,3] It differs from them, however, in that the methyl groups in 3 are essentially locked in place with respect to the plane of the NNO group. The steric interaction between NNO and Me-1 in configuration **3b,** unrelieved by partial rotation as is possible in acyclic *N*-nitrosoamines, is apparently too large to permit NMR-detectable amounts of **3b** to exist along with **3a.** Would a hydrogen rather than a methyl at position 1 affect the diastereomer ratio similarly? To answer that question, we prepared and investigated the parent bicyclic *N*-nitrosoamine, 4.

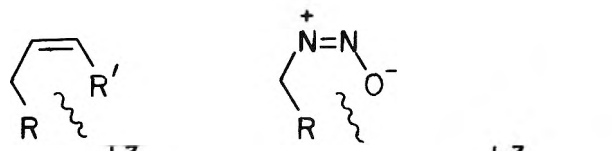
Compound 4. The NMR spectrum of *N*-nitroso-2-azabicyclo[2.2.2]octane (4) includes only one set of signals for the hydrogens at position 1 (H-1) and at position 3 (H-3), and it does not undergo change when the solution is cooled to −40°. These data indicate that, as with **3,** only one configuration was present. The effect of Eu shift reagent on the chemical shift of H-1 is substantially less than the effect for H-3. Linear plots of chemical shifts vs. the Eu: NNO mole ratios have slopes[12] of 4.33 for H-1 and 9.39 for H-3. Therefore H-1 must be anti to the Eu complexing site, and the configuration is represented by formula **4a.** Even a bridgehead hydrogen is sufficient to preclude the appear-

ance of NMR-detectable amounts of the diastereomer of **4a** (**4b**).



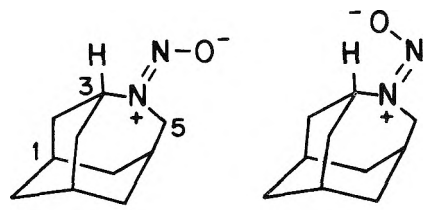
4a **4b**

The nonbonded O–H interaction which so effectively disfavors the isomers of **3** and **4** with the nitroso oxygen syn to the bridgehead is quite similar to that which has been named pseudoallylic $A^{1,3}$ strain in other systems[13] (R = H in our system).



allylic $A^{1,3}$ strain pseudo-allylic $A^{1,3}$ strain

Compound 5. The substitution pattern in the vicinity of the NNO group in **5** (*N*-nitroso-4-azahomoadamantane, *N*-nitroso-4-azatricyclo[4.3.1.$1^{3,8}$]undecane) is the same as in **4**, but the NNO group is now in a more flexible seven-membered ring. The NMR spectrum of **5** includes two doublets (^3J = 3.9 Hz), one at δ 3.65 and one at δ 4.43, with relative intensities of 87:13 and combined relative intensity equivalent to two hydrogens. These signals must be assigned to the NCH_2 (position 5, H-5) in two configurations (relative abundance 87:13) of **5** (**5a** and **5b**).[14] In accord

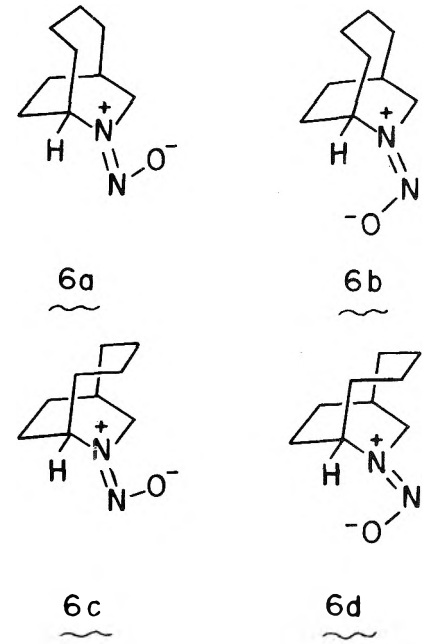


5a **5b**

with the relative chemical shifts demonstrated for other *N*-nitrosoamines,[2] we would assign the syn H-5 (**5a**) to the δ 3.65 signal, and the anti H-5 (**5b**) to the δ 4.43 one. This assignment is confirmed by the Eu shift reagent data. The effect of the Eu reagent on the δ 3.65 signal is much larger (slope[12] = 8.02) than on the δ 4.43 signal (slope[12] = 3.85). Corresponding slopes[12] are obtained for the bridgehead hydrogen vicinal to NO (H-3): 10.1 for syn H-3, 3.85 for anti H-3.[15]

Why do we find both diastereomers of **5** but only one of **3** and **4**? The close approach of O and H-3 in a symmetrical Dreiding model of **5b** is substantially relieved by twisting along the two-atom bridge. Permitted twisting in the model of **5b** is more extensive (35–40° for the dihedral angle between the bridgehead hydrogen and the plane of the NNO group) than in the model for **4b** (dihedral angle of 10–15°). Twisting in the actual compounds is probably less than these angles, because it introduces other strains, but it is probably enough to account for the appearance of the minor diastereomer, **5b**, along with the major one, **5a**.

Compound 6. While maintaining a bridgehead and a methylene position bound to nitrogen as in **4** and **5**, *N*-nitroso-7-azabicyclo[4.2.2]decane (**6**) incorporates the NNO group into an eight-membered ring. The NMR spectrum of **6** is complex, but we have been able to make peak assignments by use of Eu shift reagent and decoupling experiments. The deciphered spectrum reveals the coexistence of four diastereomers: two configurations of the NNO group and two conformations of the eight-membered ring. Formulas **6a–d** represent these four diastereomers.



6a **6b**

6c **6d**

The NMR absorptions are described in succession from those most downfield to those most upfield. Two broad multiplets appear at δ 5.04 and 4.56. The slopes[12] for the Eu shift reagent study are 8.5 and 10.2, respectively. Therefore the δ 5.04 multiplet is assigned to the anti H-6 of **6a** and **6c**, and the δ 4.56 one to the syn H-6 of **6b** and **6d**.[16] A dd pattern is partly obscured by the δ 4.56 multiplet, but it clearly emerges when Eu shift reagent is added to the solution. It (δ 4.46) and a second dd (δ 4.09) with identical coupling constants (J_{gem} = 13.8, J_{vic} = 4.0 Hz) are affected moderately and equally by the addition of Eu shift reagent (slopes[12] of 6.3). One of these absorptions is assigned to the diastereotopic anti H-8 of **6b** or **6d**, and the other absorption to the anti H-8 of **6d** or **6b**.

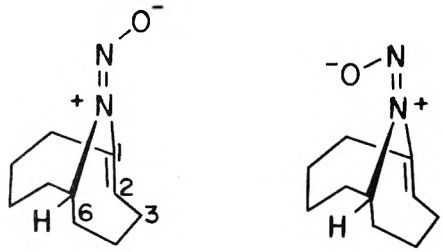
A multiplet centered at δ 3.86 and a dd centered at δ 3.18 show the same J_{gem} = 16.0 Hz and are both shifted strongly by Eu shift reagent (slopes[12] 11.9 and 10.1, respectively). These two absorptions are assigned to the diastereotopic syn H-8 of **6b** and **6d**, one to the one and one to the other. A decoupling experiment showed that all of the H-8 assigned above are coupled to the same hydrogen, presumably the bridgehead H-1, whose absorption is included in the broad envelope at δ 2.70–1.00.

We have estimated the isomer ratios by use of the ratios of integrated intensities of some absorptions in the NMR spectrum. The intensity ratio for the syn H-8 signals (δ 3.86 and 3.18) is 1:1 and that for the δ 3.18:δ 4.09 (syn H-8:anti H-8) absorptions is 58:42 (1.38:1). The ratio of the anti H-6:syn H-6 absorptions in the Eu-shifted spectra (to resolve the syn H-6 and an anti H-8 absorption) is also about 58:42. Therefore it appears that the two different ring conformers are about equally abundant in the mixture (but not rapidly equilibrating), and the two configurations of the NNO group are present in a ratio of about 58:42. The syn H-6 configuration is the less abundant one, but the geometry[14] which forces H-6 well below the plane of the NNO

group also substantially relieves the nonbonded O–H interaction, which was much more effective in compounds **3–5.**

Compound 7. *N*-Nitroso-11-azabicyclo[4.4.1]undec-1-ene (**7**) was prepared from the parent amine, which was available in our laboratory from an earlier, unrelated study.[17] Two features distinguish it from the other *N*-nitrosoamines in this series: the ring nitrogen is attached to two bridgehead carbons, and one of them is unsaturated. The NMR spectrum of **7** consists of two broadened triplets, δ 5.88 and 5.73, both with ^3J = 6.0 Hz; a broad multiplet centered near δ 5.05; and a large, broad absorption at δ 2.90–1.00. The combined area of the two triplets is equivalent to the area of the middle multiplet, and each area is equivalent to one hydrogen. The triplet absorptions are assigned to C=CH (H-2) in two configurations. The addition of Eu shift reagent resolved the middle broad multiplet into two absorptions, which appeared in a 40:60 ratio. The downfield portion, which was the lesser portion and which appeared to be centered originally at about δ 5.15, was shifted more extensively than the upfield portion, centered originally at about δ 5.02 (slopes[12] 14.4 and 5.5, respectively). The more extensively shifted absorption is assigned to syn H-6, and the other to anti H-6.[18] The major isomer again has the bridgehead H anti to the nitroso O. Even though H-6 lies essentially in the plane of the NNO group (a Dreiding model makes substantial twisting appear improbable), it is not so close to the syn-O as is the vicinal bridgehead H in **3–5.**

The spectrum for **7** does not suggest that nonequilibrating ring conformations coexist, as does the spectrum for **6.**



7a 7b

Experimental Section

Boiling and melting points are uncorrected; melting points were obtained with a Thomas-Hoover capillary melting point apparatus. Nuclear magnetic resonance (NMR) spectra were obtained on Varian Model A-60A and HA-100 spectrometers; tetramethylsilane was used as internal standard; Mr. David LaTour of these laboratories assisted with the 100-MHz spectra. Element microanalyses were obtained by Mr. Ralph Seab of these laboratories and by Galbraith Laboratories, Inc.

***N*-Nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (3).** A mixture prepared by adding piperitenone[19] (1.40 g, 9.1 mmol) to chilled aqueous ammonia (27 ml of 28.7% solution) was stirred at 2–4° for 120 hr,[20] saturated with sodium chloride, and extracted with ethyl ether. The ether solution was extracted with 15 ml of 6 *M* hydrochloric acid. The aqueous solution was made basic (pH 11–12) and extracted with two 20-ml portions of ethyl ether. This ether extract was dried and distilled. 1,3,3-Trimethyl-2-azabicycl[2.2.2]octan-5-one,[20] bp 80–83° (0.3 mm), was obtained in 26% yield (394 mg). A portion (258 mg, 1.55 mmol) of the amine was dissolved in 12 *M* hydrochloric acid (0.17 ml). This solution was added by drops from a syringe to a stirred, ice-cold solution of sodium nitrite (140 mg, 2.0 mmol) in water (2 ml). The mixture was stirred for 0.5 hr at 0°, allowed to warm to room temperature, heated at 45–50° for 2 hr, allowed to cool, and extracted with two 3-ml portions of carbon tetrachloride. When the carbon tetrachloride was removed in vacuo, the *N*-nitrosoamine (**3**) was obtained in 38% yield (114 mg): mp 125.5–126.5°; NMR (CCl_4) δ 2.46 (dd, 1, J_{gem} = 18.5, J_w = 1.8 Hz, syn H-6), 2.24 (d, 1, J_{gem} = 18.5 Hz, anti H-6), 2.13–1.65 (m, 4, H-7 + H-8), 1.61 (s, 3, CH_3-1), 1.40 (s, 3, endo CH_3-3), and 1.24 (s, 3, exo CH_3-3).

Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.2; H, 8.2; N, 14.3. Found: C, 60.9; H, 8.3; N, 14.5.

***N*-Nitroso-2-azabicyclo[2.2.2]octane (4).** A mixture prepared by adding by drops a solution of sodium nitrite (1.79 g, 2.6 mmol) in water (3 ml) to a solution of 2-azabicyclo[2.2.2]octane[21] (2.42 g, 2.2 mmol) in 8 *M* hydrochloric acid (2.7 ml) was stirred at 75–80° for 3 hr, allowed to cool to room temperature, and filtered. The collected solid (**4**) was air dried; the yield was 62% (1.78 g); mp 138.5–141.5° (lit.[22] mp 140–142°); NMR (CCl_4) δ 4.82 (br m, 1, H-1), 3.45 (d, 2, ^3J = 3.0 Hz, H-3), 2.34–1.50 (br m, 9).

***N*-Nitroso-4-azatricyclo[4.3.1.1^{3,8}]undecane (5).** 4-Azatricyclo[4.3.1.1^{3,8}]undecane[23] was synthesized by rearrangement of 2-adamantanone oxime (mp 164.5–165.5°) in polyphosphate ester[24] and reduction of the lactam with lithium aluminum hydride.[23] The ammonium chloride (mp >300°) was isolated in 34% overall yield from oxime. Nitrosation was accomplished by adding a solution of the ammonium chloride (400 mg, 2.14 mmol) in water (2 ml, containing 5 drops of 6 *M* hydrochloric acid) to a stirred solution of sodium nitrite (167 mg, 2.41 mmol) in water (1 ml) and heating the mixture at 50–60° for 1 hr. The fluffy white solid which separated was collected by filtration and dried over phosphoric anhydride in vacuo. The nitrosoamine (**5**) was obtained in 65% yield (250 mg): mp 214–214.5°; NMR ($CDCl_3$) δ 5.32 (m, H-3), 4.43 (d, ^3J = 3.8 Hz, anti H-5), 3.65 (d, ^3J = 3.5 Hz, syn H-5), 2.60–1.35 (br m, remainder of H).[25]

***N*-Nitroso-7-azabicyclo[4.2.2]decane (6).** Chlorosulfonyl isocyanate (5.7 g, 4.0 mmol) was added in 45 min to stirred cyclooctatetraene (5.2 g, 5.0 mmol) heated at 50° in a 100-ml, three-neck flask. The mixture was stirred at 50° for 7 hr. Upon cooling to room temperature, the dark mixture solidified and was dissolved in acetone (20 ml). That solution and a 4 *M* sodium hydroxide solution were added dropwise concurrently to aqueous (20 ml) acetone (10 ml). The pH was maintained at 7 and was monitored closely with a pH meter. From the resulting solution, by extraction with dichloromethane, 8-azabicyclo[4.2.2]deca-2,4,9-trien-7-one, mp 137–138° (lit.[26] mp 139–140°), was isolated in 49% yield (3.61 g).

The unsaturated lactam in methanol solution was reduced in a Paar apparatus with hydrogen and palladium on charcoal catalyst to the saturated lactam (8-azabicyclo[4.2.2]decan-7-one), mp 70–71° (lit.[27] mp 73°). The lactam (1.02 g, 6.79 mmol) was converted to the amine by reduction with lithium aluminum hydride in tetrahydrofuran solution. An ether solution of the amine was treated with hydrogen chloride; the hygroscopic ammonium chloride (444 mg, 38%) which precipitated was dried in vacuo over phosphoric anhydride.

Anal. Calcd for $C_9H_{18}ClN$: C, 61.5; H, 10.4. Found: C, 61.5; H, 10.3.

A mixture of the 7-azabicyclo[4.2.2]decane hydrochloride (100 mg), water (1.0 ml), and sodium nitrite (82.0 mg, 1.19 mmol) was heated at 50–60° for 1 hr, stirred overnight at room temperature, and filtered. The white solid *N*-nitrosoamine, **6**, was dried in vacuo over phosphoric anhydride: yield 68% (74.5 mg); mp 168–170°; NMR (CCl_4) δ 5.40 (m, anti H-6), 4.56 (m, syn H-6), 4.46 (dd, J_{gem} = 13.8, ^3J = 4.0 Hz, anti H-8), 4.09 (dd, J_{gem} = 13.8, ^3J = 4.0 Hz, anti H-8), 3.86 (br d, J_{gem} = 16.0 Hz, syn H-8), 3.18 (dd, J_{gem} = 16.0, ^3J = 6.0 Hz, syn H-8), 2.70–1.00 (br m, remainder of H).[25]

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.2; H, 9.6; N, 16.7. Found: C, 64.5; H, 9.6; N, 16.5.

***N*-Nitroso-11-azabicyclo[4.4.1]undec-1-ene (7).** To a stirred, ice-chilled sample of freshly distilled 11-azabicyclo[4.4.1]undec-1-ene[17] [bp 79–80° (3 mm), 421 mg (2.13 mmol)] was added 12 *M* hydrochloric acid (0.2 ml). After 5 min, a solution of sodium nitrite (167 mg, 242 mmol) in water (2 ml) was added to the ice-chilled, stirred ammonium chloride solution by drops. A brown solid immediately precipitated from the solution and, after the mixture had warmed to room temperature, was collected by filtration (233 mg, 61%). The crude nitrosoamine (**7**) was purified by preparative layer chromatography on silica gel with 2:1 cyclohexane–ethyl acetate: mp 65–67°; NMR (CCl_4) δ 5.88 (t, ^3J = 6.0 Hz, anti C=CH), 5.73 (t, ^3J = 6.0 Hz, syn C=CH), 5.14 (shoulder, syn H-6), 5.02 (br m anti H-6), and 2.90–1.00 (br m, remaining H).[25]

Eu Shift Reagent Studies. Europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) [Eu(fod)$_3$] was dried for at least 24 hr in vacuo over phosphoric anhydride before use. In a typical study, separate solutions of accurately weighed amounts of *N*-nitrosoamine and Eu(fod)$_3$ in the same solvent (CCl_4 or

$DCCl_3$) were prepared. The *N*-nitrosoamine solution (0.2–1 *M*) was transferred to a clean, dry NMR tube, and the spectrum was recorded. A measured amount of the $Eu(fod)_3$ solution (approximately 0.6 *M*) was added to the NMR tube from a microliter syringe, the mixture was thoroughly mixed by shaking, and the spectrum was again recorded. Further additions (6–15) and recordings were made in like manner. The ranges of Eu:NNO mole ratios for the different *N*-nitrosoamines follow ($\times 10^{-2}$): **3**, 1.68–42.1; **4**, 2.41–20.8; **5**, 2.1–23.5; **6**, 0.76–91.3; and **7**, 0.74–11.7. All of the plots of change in chemical shift vs. Eu:NNO mole ratio are linear. The data were treated by a least-squares computer program by Mr. J. H. Streiffer of these laboratories, and the calculated lines have an average correlation coefficient of 0.995 (range 0.983–0.9998). The calculated slopes[12] are reported in the discussion section.

Acknowledgment. D.R.B. acknowledges with appreciation helpful discussions about this research with Professors R. V. Nauman and N. H. Fischer, Louisiana State University, and with Professor M. A. Battiste, University of Florida.

Registry No.—**3a**, 54410-47-8; **4a**, 54410-48-9; **5a**, 54410-49-0; **5b**, 54410-50-3; **6a,c**, 54410-51-4; **6b,d**, 54410-52-5; **7a**, 54410-53-6; **7b**, 54410-54-7; piperitenone, 491-09-8; 1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one, 33069-72-6; sodium nitrite, 7632-00-0; 2-azabicyclo[2.2.2]octane, 280-38-6; 4-azabicyclo[4.3.1.$1^{3,8}$]undecane, 22776-74-5; 2-adamantanone oxime, 4500-12-3; cyclooctatetraene, 629-20-9; 8-azabicyclo[4.2.2]deca-2,4,9-trien-7-one, 17198-06-0; 8-azabicyclo[4.2.2]decan-7-one, 17198-07-1; 7-azabicyclo[4.2.2]decane hydrochloride, 54410-44-5; 11-azabicyclo[4.4.1]undec-1-ene, 7183-74-6.

References and Notes

(1) (a) Based on the Ph.D. Dissertation of D.R.B., Louisiana State University, Baton Rouge, La., May 1974. Grateful acknowledgment is made to the Dr. Charles E. Coates Memorial Fund of the LSU Foundation donated by George H. Coates for financial aid toward the preparation of that dissertation. (b) Presented in part at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1, 1974, No. ORGN 21.

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(9) (a) C. C. Hinkley, *J. Am. Chem. Soc.*, **91**, 5160 (1969); (b) C. C. Hinkley, *J. Org. Chem.*, **35**, 2834 (1970); (c) J. R. Campbell, *Aldrichimica Acta*, **4**, 55 (1971).

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(12) Slopes for the Eu shift reagent plots are given in units of ppm/Eu reagent:*N*-nitrosoamine mole ratio; they were calculated by use of a least-squares computer program.

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(14) A referee cited a related example reported by J. L. M. A. Schlatmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, **26**, 949 (1970). Homoadamantan-4-one oxime was obtained as a single isomer (OH syn to position 5) from weakly acidic solution but as a mixture of isomers, syn:anti ~ 2:3, from strongly basic solution. This mixture ratio indicates that, for oxime formation in strongly basic solutions, stereochemical influences on or in intermediates determine isomer distribution more than do the relative energies in the oxime isomers themselves.

(15) Without Eu present the absorptions for the syn and anti H-3 are not resolved but appear as a nearly symmetrical multiplet centered near δ 5.22. Eu complexing separates the signals, and the more extensively shifted one is assigned to syn H-3.

(16) This syn–anti assignment is clearly required by the shift reagent data but contrasts with the relative chemical shifts for syn and anti methine H in acyclic *N*-nitrosoamines.[2] Dreiding models of **6a–d** show that H-6 is forced to lie about 20° below the C-6 (C-8) NNO plane, i.e., in the shielding cone of the NNO group.[10] Shielding is more extensive on the syn side of the NNO than on the anti side.[10]

(17) R. R. Lilienthal, Ph.D. Dissertation, Louisiana State University, Baton Rouge, La., Dec 1971.

(18) Here the syn–anti assignments and relative chemical shifts agree with those for methine H in acyclic systems.[2,14] H-6 is essentially in the (deshielding) plane of the NNO group.

(19) Dr. J. J. Beereboom, Pfizer Central Research, sent us a generous gift of piperitenone (3-methyl-6-isopropylidene-2-cyclohexen-1-one), which was purified according to the procedure recommended by J. J. Beereboom, *J. Org. Chem.*, **31**, 2026 (1966): bp 90–95° (10 mm); NMR (CCl_4) δ 5.85 (m, 1, C=CH), 2.83–1.65 (m, 4, CH_2CH_2), 2.08 (s, 3, CH_3), 1.92 (s, 3, CH_3), 1.85 (s, 3, CH_3).

(20) A. Rassat and P. Rey, British Patent 1,231,380 (1971); *Chem. Abstr.*, **75**, 63640c (1971).

(21) We acknowledge with gratitude gifts of a small sample of 2-azabicyclo[2.2.2]octane from Professor Paul Gassman, The Ohio State University, which permitted us to begin our study, and a generous one from Dr. F. J. Villani, Schering Corp., which permitted us to complete it.

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A Direct, Low-Temperature ^{1}H, ^{13}C, and ^{19}F Nuclear Magnetic Resonance Study of Boron Trifluoride Complexes with Stigmasterol, Androstanolone, Androsterone, Testosterone, Nortestosterone, Androstenedione, and Progesterone[1,2]

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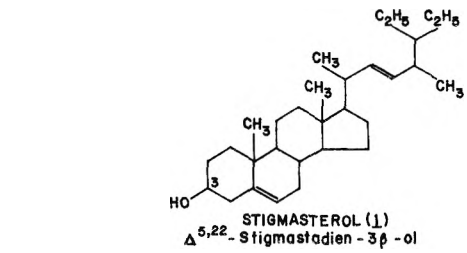
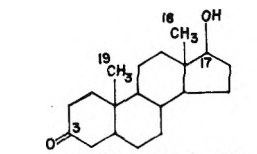
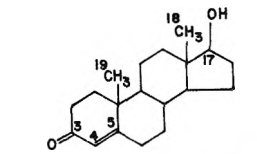
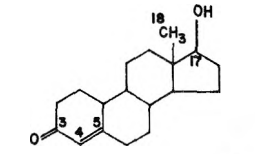
A study of boron trifluoride complexes with stigmasterol (1), androstanolone (2), androsterone (3), testosterone (4), nortestosterone (5), androstenedione (6), and progesterone (7) has been carried out by direct, low-temperature ^{1}H, ^{13}C, and ^{19}F nuclear magnetic resonance methods. A consideration of the ^{1}H and ^{19}F NMR spectra of the complexes led to an identification of the primary interaction site in each steroid. The steroid functional group basicities decrease in the order OH > C=O (α,β unsaturated) > C=O (saturated). In five of the systems, complex formation occurs at one site in the ligand, whereas competitive complexation was evident in solutions of 4 and 5. The ^{13}C NMR spectrum of BF_3-6 was interpreted in terms of possible electron density changes occurring in the molecule.

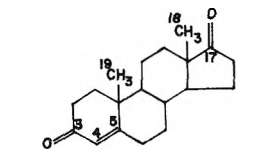
Solutions of a variety of organic bases with boron trihalides have been investigated by calorimetric[3-7] and spectroscopic[8-18] techniques to evaluate the heats of formation of the complexes and their structural features. The more recent measurements of these acid–base systems have utilized direct, low-temperature nuclear magnetic resonance (NMR) methods.[19-27] In the presence of excess base and at temperatures low enough to reduce the rate of exchange, it is possible to observe separate resonance signals for bulk and coordinated ligand. This observation leads to an accurate measure of the ^{1}H, ^{11}B, ^{13}C, and ^{19}F NMR chemical shift changes produced by complex formation and the stoichiometry of the complex, a qualitative estimate of steric factors, an evaluation of the ligand preference of a boron trihalide in a mixture of bases, and a determination of the most active site in complicated molecules. These features have been evaluated for amines and phosphines,[19] oxygen-containing bases,[20,21] pyridines[22,23] and other nitrogen heterocycles,[24] esters,[25] cyclic ketones,[26,28,29] several ethers,[27] and three steroids.[30] Steroids are of interest from the viewpoints of their physiological importance, and their structural features, particularly, the multiple potential sites for interaction with Lewis acids. Since it has been demonstrated that this low-temperature NMR technique is particularly well suited for identifying principal interaction sites in molecules,[25,30] this approach was used here. The steroids chosen were stigmasterol and several androgens, namely, androstanolone, androstenedione, androsterone, 19-nortestosterone, progesterone, and testosterone (see structures).

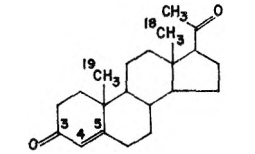












Experimental Section

Methods. The boron trifluoride was CP grade (J. T. Baker) and 99.5% pure. The dichloromethane solvent and 2-cyclohexeu-1-one were reagent grade and they were dried over $CaSO_4$ before use. The steroids were purchased from Steraloids, Inc., and they were used as received. The purity of the steroids was verified by the absence of extraneous carbon-13 (^{13}C NMR) signals and the dryness of each sample was checked by the absence of a ^{19}F NMR signal for the BF_3–H_2O adduct. The BF_3 was fractionated twice at −100° and condensed in vacuo in the NMR sample tube (Wilmad Glass Co., 504PP). The tube was sealed, warmed in an acetone–Dry Ice mixture to dissolve the components, and stored in liquid nitrogen until the spectrum could be recorded. With these precautions, sample decomposition was negligible as determined by ^{1}H, ^{13}C, and ^{19}F NMR spectra.

The ^{1}H and ^{19}F NMR chemical shift and area measurements were made on a Varian A-60 and a Varian HA-100 spectrometer, the latter operating at 94.1 MHz for the study of ^{19}F nuclei. The ^{13}C NMR spectra were recorded at 22.6 MHz with a Bruker HX-90-E instrument equipped with a Bruker-Nicolet Data System, Model B-NC-12. Pulse widths of about 3 μsec (7 μsec produces a 90° tip angle) were applied at 1-sec intervals. Hydrogen nuclei were noise decoupled at 90 MHz and 2000 Hz bandwidth. At the steroid concentration used, 5000 pulses were sufficient for a reasonable signal to noise ratio. Measurements over the temperature range of −150 to 200° are possible with the three instruments.

The procedure for carrying out the NMR measurement is described in more detail elsewhere[20-25] and it involves cooling the sample in the spectrometer probe to reduce the rate of ligand exchange. When separate ^{1}H or ^{13}C NMR signals are observed for bulk and coordinated ligand molecules, or multiple ^{19}F NMR signals for BF_3 when this molecule is bound at more than one site, the temperature is adjusted to maximize spectral resolution. The complete spectrum is recorded at this point for chemical shift data, and area integrations are measured electronically. Area data were obtained only from the ^{19}F NMR spectra, since spectral complexi-

Table I
^1H and ^{19}F Chemical Shift Data for BF_3–Steroid Complexes

Base	Mole ratios[a] BF_3:base:CH_2Cl_2	Temp, °C	δ, ppm[b,c] ^1H B[d,e]	^1H C	^{19}F
1	1.00:2.90:850	0			10.2
2	1.00:2.30:275	5	18 0.75	0.83	10.0
			19 1.25		
3	1.00:3.10:325	−5	18 0.88		10.8
			19 0.88		
4	1.00:2.70:250	5	18 0.80	0.88	10.1 (0.59)[f]
			19 1.22		13.4 (0.28)
					11.0 (0.13)
5	1.00:2.60:270	5	18 0.79	0.86	10.1 (0.59)[f]
					13.4 (0.31)
					10.9 (0.10)
6	1.00:3.10:325	−15	18 0.92		13.3
			19 1.20	1.36	
7	1.00:3.50:340	−5	18 0.66		13.3
			19 1.20	1.26	

[a] The accuracy of the mole ratios is 1–2%. [b] The ^1H chemical shifts (parts per million) are relative to internal tetramethylsilane (Me_4Si). [c] The ^{19}F chemical shifts are relative to internal hexafluorobenzene, which appeared at higher field in all cases. [d] The numbers 18 and 19 refer to the steroid methyl group carbon atoms. [e] The letters B and C refer to the signals of bulk and coordinated steroid molecules, respectively. [f] The relative signal areas are given in parentheses.

Table II
Fluorine-19 Chemical Shift and Area Data for BF_3–Steroid Mixtures

Base mixture (A:B)	Mole ratios[a] (BF_3:A:B:CH_2Cl_2)	Temp, °C	δ, ppm[b]	Assignment[c]
2:6	1.00:0.90:0.80:55	−10	13.4 (0.11)[d]	6
			11.0 (0.07)	2 or 6
			10.0 (0.82)	2
2:7	1.00:0.70:0.90:75	−10	10.0	2
3:6	1.00:0.60:0.60:120	−15	13.3 (0.32)	6
			10.7 (0.68)	3
3:7	1.00:1.90:2.00:130	0	10.9	3
4:6	1.00:1.30:1.30:85	−10	13.4 (0.19)	4 or 6
			10.6 (0.16)	4
			9.2 (0.65)	4
4:7	1.00:0.70:0.70:85	0	10.0	4
5:6	1.00:0.90:0.90:170	−10	13.4 (0.16)	5 or 6
			10.5 (0.09)	5
			10.0 (0.75)	5
5:7	1.00:0.80:0.80:50	0	13.4 (0.36)	5 or 7
			10.0 (0.64)	5

[a] The mole ratios are accurate to 1–2%. [b] The chemical shifts were measured with respect to internal C_6F_6, which appeared at higher field in all cases. [c] The steroid molecules giving rise to the signals in the preceding column are listed. [d] The relative signal areas are given in parentheses.

ty (^1H) and the nature of the Fourier transform pulse experiments prevented reliable intensity measurements with the other nuclei.

Results

The ^1H and ^{19}F NMR chemical shift and area results for the BF_3 complexes are given in Table I, and representative spectra for these nuclei are shown in Figures 1 and 2, respectively. The NMR data for each steroid were obtained

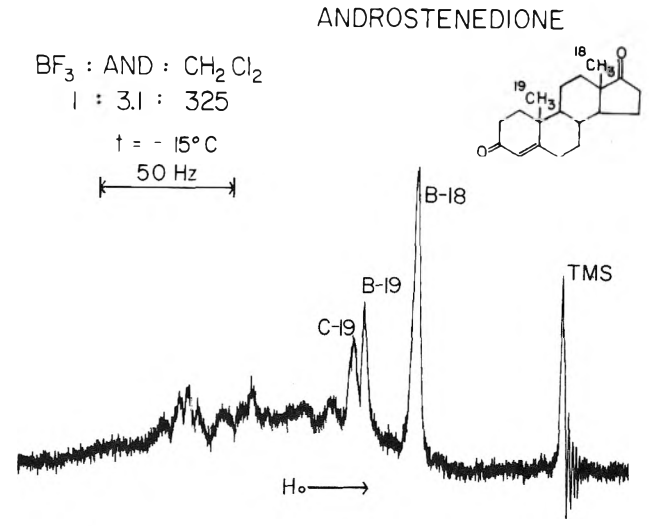


Figure 1. A portion of the ^1H NMR spectrum of a solution of BF_3 and androstenedione in methylene chloride, recorded on a Varian A-60 spectrometer, is shown. The signals arising from the 18- and 19-CH_3 groups of bulk (B) and coordinated (C) steroid are shown. Concentrations are in mole ratios.

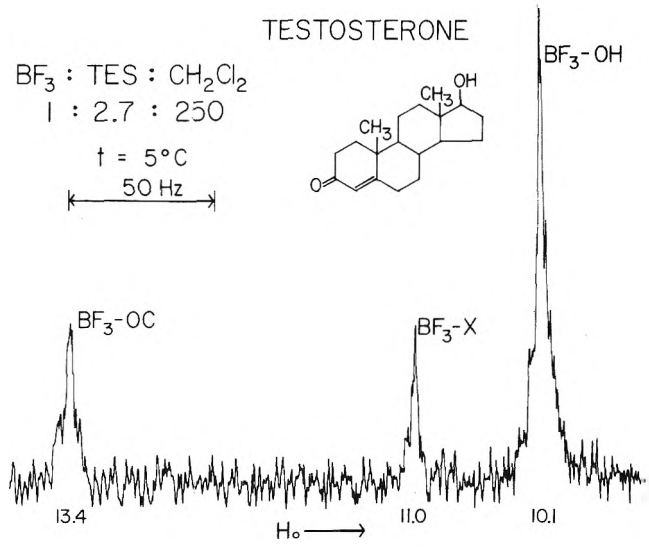


Figure 2. The ^{19}F NMR spectrum of a solution of BF_3 and testosterone in methylene chloride, recorded on a Varian HA-100 at 94.1 MHz, is shown. The linkage giving rise to each signal is identified (carbonyl and hydroxyl), although the origin of one peak (BF_3–X) is not clear (see text). Concentrations are in mole ratios.

with at least two samples, and each spectrum was recorded in triplicate. Although the composition of the BF_3–steroid complexes was not determined from the ^1H NMR signal areas, a 1:1 mole ratio was assumed for the adducts. This assumption is reasonable in view of the numerous studies of BF_3 complexes,[20–26] including those with steroids,[30] which have invariably indicated 1:1 complex formation. Since the 18-C and 19-C methyl group ^1H NMR signals were readily observed and assigned by a comparison to published spectra,[31] they were used to identify the steroid interaction site. An assignment was precluded by signal overlap only in solutions of **3**. In all cases the formation of BF_3 complexes produced low-field displacements of the methyl group ^1H NMR signals. The ^{19}F NMR chemical shift data also were used to identify the steroid interaction sites, and in solutions of **4** and **5**, in which BF_3 was bound at more than one functional group, signal areas provided a quantitative measure of this competition.

In Table II, ^{19}F NMR chemical shift and area data for

solutions of BF_3 and pairs of steroids are listed. The only mixtures given are those in which at least one ^{19}F NMR signal could be identified unambiguously. By reference to the chemical shift data of Table I, ^{19}F NMR signal assignments were made readily in the first four base mixtures listed. Signal overlap prevented a completely quantitative consideration of the remaining four mixtures.

Discussion

The condition of slow intermolecular exchange on the NMR time scale, sufficient to produce sets of resonance signals for bulk and coordinated ligand molecules, generally requires lifetimes of the order of approximately 0.1 sec. With the bases previously studied, exchange rates were inversely proportional to the ligand basicity and, consequently, the strength of the complex.[20-27] Since these experiments with alcohols and ketones require temperatures in the range of −100°, it is somewhat surprising that the slow exchange condition can be achieved here in the 0° range. The slower exchange in these solutions can be attributed to the larger size of the steroid molecules.

The identification of the principal interaction site in steroids 2–7 was accomplished primarily by a correlation of the proton and ^{19}F NMR chemical shift data, and in one case the results were supplemented by ^{13}C NMR measurements. With the exception of the complex of **3**, the observation of a separate ^1H NMR signal for the 18- or 19-CH_3 group of the coordinated steroid was possible. Since a change in diamagnetic shielding is the most significant factor causing ^1H NMR signal displacements in these complexes, it is safe to assume that the effect would be attenuated with distance from the interaction site. Thus, the signal of the methyl group closer to the site of BF_3 complexation would undergo the greater shift change. For example, in base **2**, the A-ring carbonyl and the D-ring hydroxyl are the two possible sites for complex formation with BF_3. The observation of a separate resonance signal for only the 18-CH_3 group, displaced approximately 0.1 ppm downfield from the signal of unbound steroid, indicates that binding is occurring primarily at the hydroxyl group oxygen atom. The structures of **4** and **5** differ by only one methyl group, and they are similar in that each contains an α,β-unsaturated keto group in the A ring and a D-ring hydroxyl. Again, a separate ^1H NMR signal was observed for the 18-CH_3 group of complexed steroid in both cases, implying a dominant interaction at the D-ring hydroxyl. In bases **6** and **7**, which contain two carbonyl groups as possible interaction sites, the principal interaction site is the A-ring carbonyl, as reflected by the appearance of a signal for the 19-CH_3 of coordinated steroid.

The strong dependence of the ^{19}F NMR signal position of the BF_3 complex on the nature of the ligand functional group[24-26] was used to interpret the spectral data for this nucleus in Table I. Base **1** was chosen to provide a reference ^{19}F NMR signal, in this case +10.2 ppm from C_6F_6, for the BF_3–OH linkage. Since **6** and **7** have only carbonyl groups as potential interaction sites, the ^{19}F NMR signal at +13.3 ppm is indicative of complexation at this functional group. Moreover, the similarity of the ^{19}F NMR chemical shifts for the solutions of **6** and **7** identifies the A-ring carbonyl as the principal site. This conclusion also is consistent with the ^1H NMR data of Table I for these molecules. From these reference ^{19}F NMR data, and again, taking into account the ^1H NMR results previously discussed, interaction at the D-ring hydroxyl group of **2** and the A-ring hydroxyl of **3** can be inferred from the ^{19}F NMR spectra of these complexes. Competitive complexing at more than one steroid site is indicated by the three ^{19}F NMR signals produced by complexes of **4** and **5**. The signals at +10.1 and +13.4 ppm, respectively, can be assigned to the D-ring hydroxyl group and A-ring carbonyl of these molecules. The signal at about +11 ppm in both cases may correspond to the BF_3 complex of the enol form (HO–C_3=C_4–C_5=C) of these bases, or perhaps the complex which remains after proton dissociation of the D-ring hydroxyl group (BF_3^-–OC). This latter process may account for the somewhat higher resonance observed for the BF_3–**3** complex, but, if so, it is not clear why it does not occur with the complexes of **1** and **2**. The relative areas of the ^{19}F NMR signals for the BF_3 complexes of **4** and **5** show that the D-ring hydroxyl group is the primary interaction site, with significant competition from the α,β-unsaturated keto group of the A ring. Low signal intensity is probably responsible for the lack of an observable 19-CH_3 ^1H peak for the BF_3–**4** adduct. In those cases where competitive complex formation occurs, it was not possible to determine whether sites in the same or different molecules were utilized.

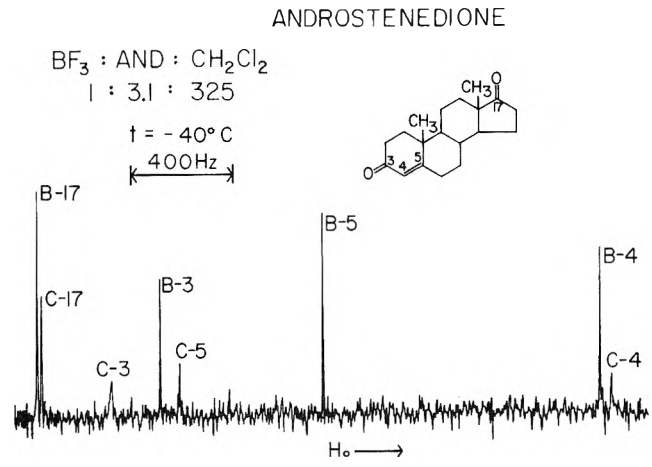


Figure 3. The low-field portion of the ^{13}C NMR spectrum of a solution of BF_3 and androstenedione in methylene chloride is shown. The spectrum is the accumulation of 5000 pulses, and it was recorded at 22.6 MHz on a Bruker HX-90-E Fourier transform spectrometer. The signals arising from carbon atoms of bulk (B) and coordinated (C) steroid are identified.

These results show that an unambiguous assignment of the principal steroid sites for interaction with Lewis acids can be deduced by a consideration of the ^1H and ^{19}F NMR spectra of their BF_3 complexes. In some cases, the availability of ^{13}C data can be a valuable supplement. For example, although the choice of the A-ring carbonyl as the interaction site in base **6** is reasonable based on the ^1H and ^{19}F NMR results, this was verified conclusively by the ^{13}C NMR spectrum of its BF_3 complex, the pertinent portion of which is shown in Figure 3. The steroid ^{13}C chemical shift assignments were made by a comparison to published spectra.[32] This spectrum clearly demonstrates a distinct advantage of ^{13}C NMR spectroscopy; that is, even nonprotonated functional groups, in this case the two carbonyl groups, can be studied. As seen in Figure 3, two sets of steroid ^{13}C NMR signals, arising from bulk and coordinated molecules, are evident. Two sets of high-field signals also were observed, but the complexity of the spectrum prevented an unambiguous assignment. From spectra such as that in Figure 3, chemical shift differences, $\delta_{complex} - \delta_{bulk}$, of +8.4, −2.2, +24.9, and −0.6 ppm were measured for the 3-, 4-, 5-, and 17-C signals, respectively, of the coordinated and bulk steroid molecules. The larger chemical shift displacement of the 3-C signal (+8.4 ppm), and the deshielding which the positive sign represents, confirm the A-ring carbonyl as the interaction site. It is surprising that com-

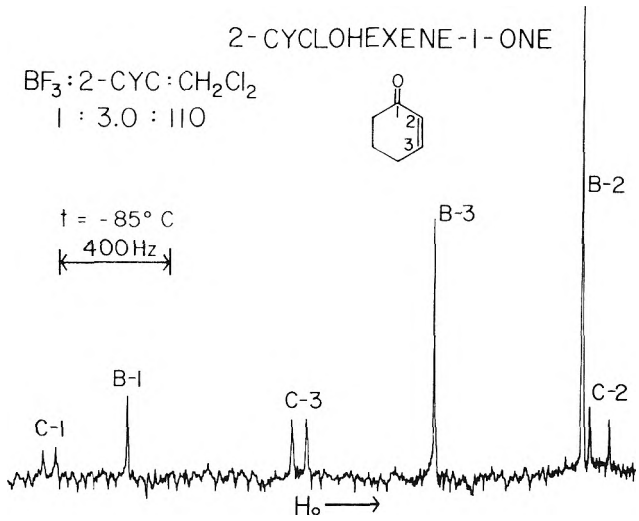


Figure 4. The low-field portion of the ^{13}C NMR spectrum of a solution of BF_3 and 2-cyclohexen-1-one in methylene chloride is shown. The spectrum is the accumulation of 5000 pulses, and it was recorded at 22.6 MHz on a Bruker HX-90-E Fourier transform spectrometer. The signals arising from carbon atoms of bulk (B) and coordinated (C) ligand are identified.

plexation at this site causes an observable shift at the 17-C position, ten bonds removed. A through-space interaction mechanism can be ruled out by the inflexibility of this steroid structure, leaving the transmission of the electronic changes through the molecular framework as the likely cause of this small shift. Also, the extremely large chemical shift displacement, +24.9 ppm, of the 5-C signal upon complex formation must reflect extensive charge withdrawal at this site. Interaction of the carbonyl oxygen and BF_3 would increase the contribution of the resonance form, $^-O-C_3{=}C_4-C_5{}^+$, and thus deshield the 5-C atom. This could account for the low-field shift. These features also were evident in the ^{13}C NMR spectrum of a mixture of BF_3 and 2-cyclohexene-1-one, which comprises the A ring of **6.** Only the low-field portion of the spectrum is shown in Figure 4, although bulk and complexed base signals were also evident in the high-field region. From such spectra, chemical shift differences of +12.5, −2.7, and +21.2 ppm were measured for the 1-, 2-, and 3-C signals, respectively, between the BF_3 complex and the free base. The magnitudes and signs of these shift differences compare well with those of Figure 3, and they again confirm complex formation at the A ring of steroid **6.** The appearance of doublets for all the ^{13}C NMR signals of complexed base is probably the result of slow cis–trans isomerization of BF_3 at the oxygen atom. This feature will be discussed in more detail in a subsequent paper dealing with a series of cyclic ketones.[33]

Although a good estimate of the relative base strengths of the steroids toward BF_3 can be made from the single base data for Table I, direct competition of ^{19}F NMR experiments with pairs of bases was carried out to establish this trend conclusively. Only those combinations for which at least one unambiguous signal assignment could be made are included in Table II. As mentioned previously, the signals at +10 and +13 ppm are attributed to the hydroxyl and carbonyl group adducts, respectively, and, with the possible exception of the entries for **3,** the peaks at +10.5 to +11 ppm in Table II are assigned to an enol or CO^- linkage with BF_3. The spectra for the first four combinations of Table II were interpreted readily. For example, **2** and **3** clearly dominate the BF_3 interactions in mixtures with **7,** since the one peak observed in both cases corresponds closely to that listed in Table I for these ligands. In the **2–6** and **3–6** mixtures, some competition is noted but **2** and **3** complex the much larger fraction of BF_3. Thus, from the first four entries, the steroid complexing abilities decrease in the order **2, 3 > 6 > 7.** In the spectra of the remaining mixtures, because of some ambiguity in signal assignment, one can only state that the binding abilities of **4** and **5** with BF_3 also are greater than those of **6** and **7.** Although no explanation can be offered, it should be noted that in the **4–7** combination, BF_3 binding occurs exclusively at the D-ring hydroxyl of **4,** in contrast to the single base study of this molecule, wherein a competition from the A-ring carbonyl was observed.

The assignment of binding abilities to the specific steroid functional groups can proceed directly from a consideration of the data of Tables I and II. The functional group basicities toward BF_3 decrease in the order OH (six-membered ring), OH (five-membered ring) > C=O (α,β-unsaturated keto) > C=O (saturated keto). Where a comparison can be made, this trend agrees with the order of proton basicities for the steroid components containing these functional groups.[34] For example, cyclohexanol is more basic than 2-cyclohexen-1-one, which in turn is more basic than cyclopentanone and cyclohexanone. These results also show that the steric hindrance introduced by the proximity of a methyl group (18-CH_3) is not sufficient to overcome the intrinsic basic strength of a nearby hydroxyl group. These results also may have some bearing on the physiological behavior of the steroids. For example, the requirement of a 17-β hydroxyl group for binding to human serum globulins has been demonstrated for several steroids, including **2, 4,** and **5,** and the biological activity of **7** is attributed to the presence of the A-ring carbonyl of this base.[35] The results presented here also show the strong binding abilities of these functional groups.

This study has demonstrated the utility of the direct, low-temperature NMR method for identifying the primary interaction sites in complicated ligands such as steroids. The availability of ^{13}C spectral data for acid–base complexes provides an insight into the electron density changes which occur upon complexation. Although solubility problems restricted the experiments to the steroids described here, the use of ^{19}F Fourier transform NMR techniques in future work should expand the scope of this area of study.

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Registry No.—**1**–BF_3, 54293-13-9; **2**–BF_3, 54293-14-0; **3**–BF_3, 54293-15-1; **4**–BF_3, 54293-16-2; **5**–BF_3, 54293-17-3; **6**–BF_3, 54293-18-4; **7**–BF_3, 54293-19-5; 2-cyclohexen-1-one–BF_3, 50781-10-7.

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Kinetics of Oxidation of Aldo Sugars by Quinquevalent Vanadium Ion in Acid Medium

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The oxidation kinetics of glucose, considered as a model compound for reducing sugars, with vanadium(V) in sulfuric and perchloric acid solutions has indicated a rate-limiting bimolecular reaction between vanadium(V) and the reducing sugars leading to the formation of a free radical. There is a linear correlation between the observed rate constant k_1 and [sugar], $[H^+]^2$, and $[HSO_4^-]$. The oxidation is faster in sulfuric acid, and various correlations between the rate and acidity have been tested. The mutarotation equilibrium is immediately attained and therefore the rate of oxidation is independent of the rate of mutarotation. The linear correlation between the rates of oxidation of sugars and their concentrations present in the solution as free aldehyde helps to explain the observed reactivity of different sugars, which is in the order xylose > arabinose > galactose > mannose > glucose.

The oxidation kinetics of reducing sugars with quadrivalent cerium in the presence of 0.5 *M* sulfuric acid has been discussed in a previous communication.[1] It is, therefore, of interest to us to investigate how the oxidation mechanism of reducing sugars is affected by a change in the one equivalent oxidant. The choice of quinquevalent vanadium ion is motivated by our additional interest in studying the correlation between the acid-catalyzed oxidation rate and various acidity scales.

The mechanism of the oxidation of various organic compounds by quinquevalent vanadium has been reviewed.[2] The kinetics of vanadium(V) oxidation of glucose and xylose in sulfuric, perchloric, and hydrochloric acid solutions was reported[3] after the review[2] was published. However, this study is not conclusive and needs a reinvestigation, as no attempt was made by the authors[3] to measure the rates of oxidation of other hexoses as well as to consider the effect of mutarotation equilibrium on the rate of oxidation of reducing sugars.

Experimental Section

Ammonium metavanadate was dissolved in sulfuric or perchloric acid solutions as required. The acid concentration of the stock vanadium(V) solution was taken as the difference between the amount initially added and the amount consumed by reaction 1.

$$NH_4VO_3 + 2H^+ \longrightarrow NH_4^+ + VO_2^+ + H_2O \quad (1)$$

The vanadium(V) solutions are quite stable. The sugar solutions were freshly prepared by direct weighing of the samples. The vanadium(V) solution was standardized against a freshly prepared standard solution of ferrous ammonium sulfate to a barium diphenylamine sulfonate end point in the presence of phosphoric acid.

The reaction has been studied in the presence of an excess of sugars and at 50° unless stated otherwise. The other experimental details for following the progress of the reaction from time to time and calculation of the observed rate constant k_1 with respect to vanadium(V) are similar to one described elsewhere.[4]

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Stoichiometry and Product Analysis. The reaction mixtures had an excess of glucose or mannose to ensure that there was no appreciable reduction of vanadium(V) by the more reactive oxidation products. Arabinose and formic acid were confirmed as the oxidation products in the glucose oxidation by paper chromatography using pure samples as reference.

In another set of experiments, the completely oxidized reaction mixtures were treated with barium carbonate to remove most of the sulfuric acid. The absence of formaldehyde, gluconic acid, and glucuronic acid in the reaction mixtures was established with color reactions of chromotropic acid[5a] and β,β'-dinaphthol,[5b] respectively. The filtrate and washings were subjected to fractional distillation in an all-glass apparatus fitted with standard joints. The distillate collected at 101–102° was made to a known volume and titrated against a standard alkali to a phenolphthalein end point. The distillate was confirmed to be formic acid by using chromotropic acid[5c] and paper chromatography.

The results of few quantitative estimations for the formic acid indicated that 2 equiv of vanadium(V) are used per mole of formic acid produced. The reaction is therefore expressed as in eq 2.

$$C_6H_{12}O_6 + 2V(V) + H_2O \longrightarrow C_5H_{10}O_5 + HCOOH + 2V(IV) + 2H^+ \quad (2)$$

Results and Discussion

The first-order dependence both in vanadium(V) and reducing sugars at any given acid concentration was established by effecting a tenfold variation in the respective concentrations at the constant concentration of the other. The rate increased with the increase in the ionic strength; lithium perchlorate was used for the purpose. (These data are available as supplementary material; see paragraph at end of paper.) There is no deviation from the first-order dependence in glucose even at 4 *M* sulfuric or perchloric acid as had been noted in the oxidation of butane-1,3-diol,[6] quinol,[7] and glycerol.[8] The linear plot (Figure 1) between the observed rate constant k_1 and [sugar] passes through the origin, thus confirming a first-order dependence in the reducing sugars.

The values of the second-order rate constant k_2 (Table I)

Table I
The Second-Order Rate Constant k_2 for Various Sugars in Sulfuric And Perchloric Acid[a]

Registry no.	Sugar	$10^4 k_2 \pm 0.1$ Sulfuric acid (40°)	Sulfuric acid (50°)	Perchloric acid (50°)
50-99-7	D(+)-Glucose	1.3	3.7	3.3
3458-28-4	D(+)-Mannose		5.0	5.8
59-23-4	D(+)-Galactose	3.6	8.4	6.5
58-86-6	D(+)-Xylose	7.2	17.4	22.7
5328-37-0	L(+)-Arabinose		16.8	18.4
3615-41-6	L(+)-Rhamnose		4.8	
154-17-6	2-Deoxy-D(+)-glucose		8.5	

[a] $k_2 = (-d[V(V)]/dt)/[V(V)][sugar]$; [vanadium(V)] = 0.02 *M*; [acid] ≈ 2 *M*.

Table II
The Observed First-Order Rate Constant k_1 at Different Concentrations of Sulfuric and Perchloric Acid When the Ionic Strength Is Not Kept Constant at 50°[a]

A. [Sulfuric acid], *M*	2.0	3.0	4.0	5.0	6.0
$10^4 k_1$, sec^{-1} (glucose)	1.1	2.6	5.4	13.2	33.6
$10^4 k_1$, sec^{-1} (mannose)	1.3	3.2	7.6	16.3	36.3
$10^4 k_1$, sec^{-1} (galactose)	3.1	7.3	14.9	32.8	
B. [Perchloric acid], *M*	2.0	3.0	4.0	5.0	6.0
$10^4 k_1$, sec^{-1} (glucose)	1.0	1.8	3.8	8.3	21.4
$10^4 k_1$, sec^{-1} (mannose)	0.7	1.5	3.0	8.7	28.3
$10^4 k_1$, sec^{-1} (galactose)	2.4	4.1	8.1	16.8	39.8

[a] [Vanadium(V)] = 0.02 *M*; [glucose] = 0.3 *M*; [mannose] = 0.25 *M*; [galactose] = 0.375 *M*.

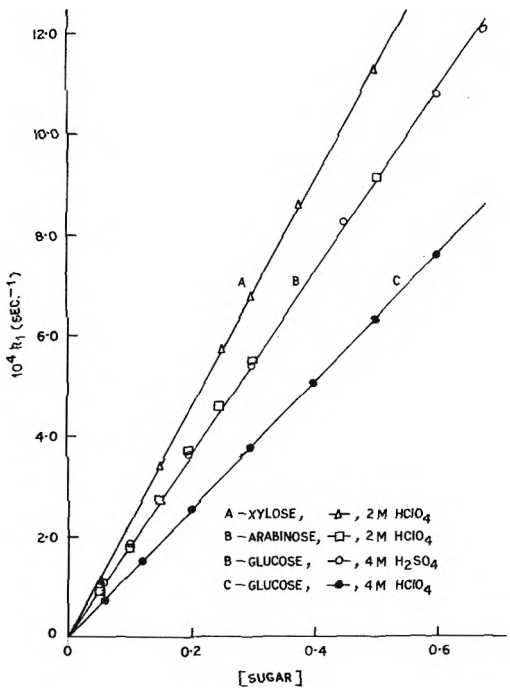

Figure 1. The linear dependence between the observed rate constant k_1 and [sugar]: [vanadium(V)] = 0.02 *M*; [sulfuric acid] = 2 *M*; *T* = 50°.

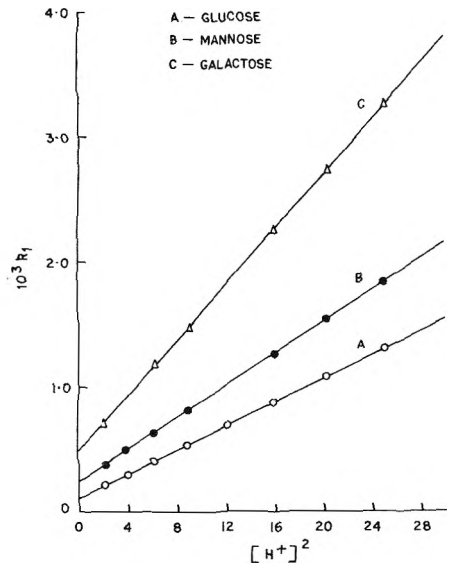

Figure 2. The linear plot between observed rate constant k_1 and $[H^+]^2$ at constant ionic strength at 50°: ($[H_2SO_4]$ + $[NaHSO_4]$) = 5 *M*; [vanadium(V)] = 0.02 *M*; [glucose] = 0.3 *M*; [mannose] = 0.3 *M*; [galactose] = 0.375 *M*; *T* = 50°.

are the average values from the slopes of the linear plots between rate k_1 and respective [sugars]. The reaction is catalyzed by mineral acids and the rate is faster in sulfuric acid. The effect of sulfuric or perchloric acid of varying ionic strength on the reaction rate is reported in Table II. The effect of hydrogen ion at constant ionic strength is also given in Table III. The ionic strength was adjusted with sodium perchlorate or sodium hydrogen sulfate depending on the acid used. The linear plot (Figure 2) between the observed k_1 and $[H^+]^2$ with intercept on the rate axis indicates that at least one term in the rate law is independent of hydrogen ion. The rate also increased with the increase in bisulfate ion at constant concentration of the hydrogen ion. The linear plot (Figure 3) between k_1 and HSO_4^- (Table IV) is similarly interpreted. The effect of sulfate ion (Table V) was so investigated that the sum total concentrations of sodium sulfate and sodium hydrogen sulfate remained constant. The rate decreased with increasing sulfate ion, indicating that sulfate complexes of vanadium(V) are unreactive. The mechanism of the oxidation of sugars as effected by the various vanadium(V) species, viz., VO_2^+, $VO_2 \cdot HSO_4$, and VO^{3+} in sulfuric acid, and the rate law consistent with the effects of hydrogen and hydrogen sul-

Table III
The Dependence of the Observed Rate Constant k_1 on $[H^+]$ at Constant Ionic Strength

A. [Vanadium(V)] = 0.02 *M*; $[HSO_4^-]$ = 5 *M*; [Glucose] = [Mannose] = 0.3 *M*; [Galactose] = 0.375 *M*; T = 50°

$[H^+]$, *M*	1.5	2.0	3.0	4.0	4.5	5.0
$10^4 k_1$, sec^{-1} (glucose)	2.1	3.0	5.4	8.8	10.8	13.2
$10^4 k_1$, sec^{-1} (mannose)	3.8	5.0	8.0	12.7	15.4	19.5
$10^4 k_1$, sec^{-1} (galactose)	7.2	9.2	14.7	22.6	27.4	32.8

B. [Vanadium (V)] = 0.02 *M*; $[ClO_4^-]$ = 6 *M*; [Glucose] = 0.26 *M*; [Mannose] = 0.3 *M*; [Galactose] = 0.3 *M*

$[H^+]$, *M*	1.0	2.0	3.0	4.0	5.0
$10^4 k_1$, sec^{-1} (glucose)	2.3	3.8	5.7	8.9	13.2
$10^4 k_1$, sec^{-1} (mannose)	2.2	3.9	6.2	10.2	18.2
$10^4 k_1$, sec^{-1} (galactose)	6.1	8.8	13.3	19.6	28.2

Table IV
The Dependence of the Observed Rate Constant k_1 on $[HSO_4^-]$ at Constant Acidity[a]

$[HSO_4^-]$, *M*	1.0	2.0	3.0	4.0	5.0
$10^4 k_1$, sec^{-1} (glucose)	8.9	10.0	11.0	12.1	13.2
$10^4 k_1$, sec^{-1} (mannose)	11.1	13.2	15.2	17.2	19.5
$10^4 k_1$, sec^{-1} (galactose)	21.8	24.6	27.4	30.0	32.8

[a] [Vanadium(V)] = 0.02 *M*; [glucose] = 0.3 *M*; [galactose] = 0.375 *M*; [mannose] = 0.3 *M*; $[H^+]$ = 5 *M*; T = 50°.

Table V
The Dependence of the Observed Rate Constant k_1 on [Sodium Sulfate] When the Sum Total Concentrations of Sodium Sulfate and Sodium Hydrogen Sulfate Are Constant[a]

$[Na_2SO_4]$, *M*	0.0	0.25	0.5	0.75	1.0	1.35
$10^4 k_1$, sec^{-1}	1.9	1.7	1.6	1.5	1.4	1.2

[a] [Vanadium(V)] = 0.02 *M*; $[NaHSO_4]$ + $[Na_2SO_4]$ = 1.35 *M*; [sulfuric acid] = 2 *M*; [glucose] = 0.3 *M*; T = 50°.

fate ions on the rate is available as supplementary material (see paragraph at end of paper).

Rate of Mutarotation. The rate of mutarotation is known to be catalyzed by an acid or a base. The rate of mutarotation, k_m (min^{-1}), of glucose in the presence of an acid at 25° can be calculated[9] from eq 3. The value so calculated in 2 *M* acid is 0.00876 sec^{-1}.

$$k_m = 0.0096 + 0.258[H^+] \quad (3)$$

Assuming that the equilibrium constant K for the mutarotation equilibrium, shown in eq 4, has a value of 1.77 at

$$\alpha\text{-glucose} \underset{k''}{\overset{k'}{\rightleftharpoons}} \beta\text{-glucose} \quad (4)$$

$$\log k^1 - \log k^2 = \frac{E}{4.576}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \quad (5)$$

25°, the value of k' calculated from the known value of k_m ($k' + k''$) in 2 *M* sulfuric acid is 0.005605 sec^{-1}. Its value, 0.1055 sec^{-1}, at 50° is calculated from eq 5, as the activation energy for the mutarotation of glucose[10] is 23 kcal mol^{-1}.

Here k^1 and k^2 are the rate constants at absolute temperatures T_1 and T_2, respectively.

Oxidation Rate with Respect to Glucose. Since the reaction has a first-order dependence in vanadium(V) and glucose, the rate of disappearance of vanadium(V) is expressed by eq 6, where k_2 is the second-order rate constant.

$$\frac{-d[V(V)]}{dt} = k_2[V(V)][\text{glucose}] \quad (6)$$

Since 1 mol of glucose reduces 2 mol of vanadium(V), one can write the relation shown in eq 7.

$$\frac{-d[V(V)]}{dt} = 2\frac{-d[\text{glucose}]}{dt} \quad (7)$$

Table VI
The Percentage Concentrations of Free Aldehyde Sugars[a] and α and β Sugars[b] in Aqueous Solution

Sugar	[α-Pyranose sugar], %	[β-Pyranose sugar], %	[Free aldehyde sugar], %
D(+)-Glucose	36	64	0.024
D(+)-Mannose	64	36	0.064
D(+)-Galactose	35	65	0.082
D(+)-Xylose	29	71	0.17
D(+)-Arabinose	63	37	0.28

[a] Reference 11. [b] Reference 12

The value of the first-order rate constant with respect to glucose, k_g, at a given [vanadium(V)] can be calculated by proper substitutions in eq 8, which is derived from eq 6 and

$$k_g = \frac{k_1[\text{vanadium(V)}]}{2[\text{glucose}]} \quad (8)$$

7. The values of k_g thus calculated are 0.376×10^{-5} and 0.32×10^{-5} sec^{-1} in solutions of 2 *M* sulfuric and perchloric acid, respectively.

Attainment of Mutarotation Equilibrium. Since in 2 *M* sulfuric acid solution the rate of mutarotation k' (0.1055 sec^{-1}) is about 28,000 times faster than the rate of oxidation of glucose with respect to glucose, $k_g = 3.76 \times 10^{-6}$ sec^{-1}, it is clear that the mutarotation equilibrium is immediately attained. The rate of oxidation of glucose is therefore not affected by the mutarotation of glucose. Thus the observed rate k_1 is the sum total of the rates contributed by each of the α and β anomers together with the contribution from the very small concentration of the sugar present as free aldehyde in the aqueous solution. The intermediate existence of the aldehyde sugar is well established in the mutarotation and its concentration has been determined on a percentage scale.[11] Therefore any experimental separation of the rates contributed by individual anomers is difficult, especially if the reaction is to be studied in a minimum 2 *M* acid solution and at 50° to have a measurable speed.

Correlation of Second-Order Rate k_2 and [Aldehyde Sugar]. It is interesting to note (Figure 4) that the plot of the second-order rate constant k_2, defined as $-d[V(V)]/(dt[\text{sugar}][\text{vanadium(V)}])$ against [aldehyde sugar] is linear with an intercept on the rate axis. This plot is consistent with eq 9, which is based on the consideration of reac-

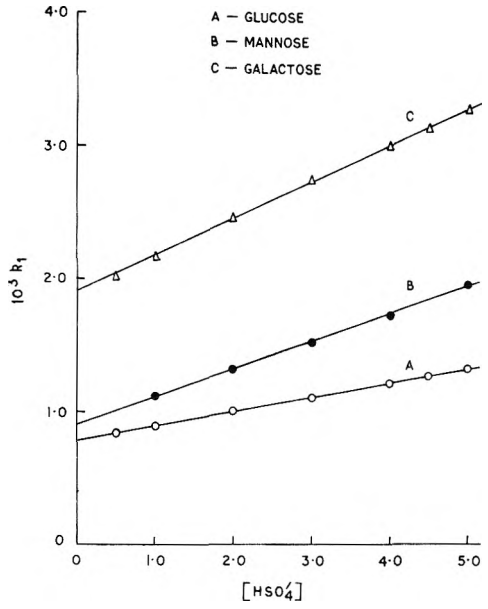

Figure 3. The linear plot between observed rate constant k_1 and $[HSO_4^-]$ at constant $[H^+]$: [vanadium(V)] = 0.02 *M*; [glucose] = 0.3 *M*; [mannose] = 0.3 *M*; [galactose] = 0.375 *M*; *T* = 50°.

$$k_2 = 2(k_{10}[G] + k_a[\text{aldehyde sugar}]) \quad (9)$$

$$\text{vanadium(V)} + G \xrightarrow{k_{10}} \text{free radical} + \text{V(IV)} + H^+ \quad (10)$$

$$\text{vanadium(V)} + \text{aldehyde sugar} \xrightarrow{k_a} \text{free radical} + \text{V(IV)} + H^+ \quad (11)$$

$$\text{vanadium(V)} + \text{free radical} \xrightarrow{\text{fast}} \text{products} + \text{V(IV)} + H^+ \quad (12)$$

tions 10–12, where G represents the sugar concentration present in pyranose form. It is to be further noted that no experimental support for vanadium(V)–glucose complex in 2 *M* sulfuric acid solution could be adduced from the spectrometric measurements. The spectrometric measurements were recorded on a Beckman DU spectrophotometer with cells of unit path length. There is a very small but definite increase in the optical density of vanadium(V)–glucose solution, but surprisingly enough, the optical density is not much affected by the increase in sugar concentration.

The oxidation products are formic acid and arabinose and the formation of a free radical during the reaction is confirmed by the induced polymerization of acrylonitrile, whereas neither vanadium(V) nor sugar solution alone induced the polymerization.

The ratio of the rates of oxidation of the free aldehyde sugar and pyranose sugar as calculated from the ratio of slope and intercept of the linear plot in Figure 4 is nearly 2900 in 2 *M* perchloric acid and 7900 in 2 *M* sulfuric acid at 50°. This would mean that most of the sugar is oxidized as aldehyde sugar.

This linear correlation helps to explain the observed reactivity of the different sugars (Table I), which is in the order xylose > arabinose > galactose > mannose > glucose. On the other hand, if sugars are oxidized in their pyranose form only, then the rates of oxidation of these sugars are expected to be of the same magnitude because of the almost identical percentage of the α and β forms (Table VI) of these sugars present at equilibrium,[12] which is not the case as is evident from the rate constants reported in Table I.

Acid Catalysis. The reaction has shown a dependence on the second power of hydrogen ion. The dependence of

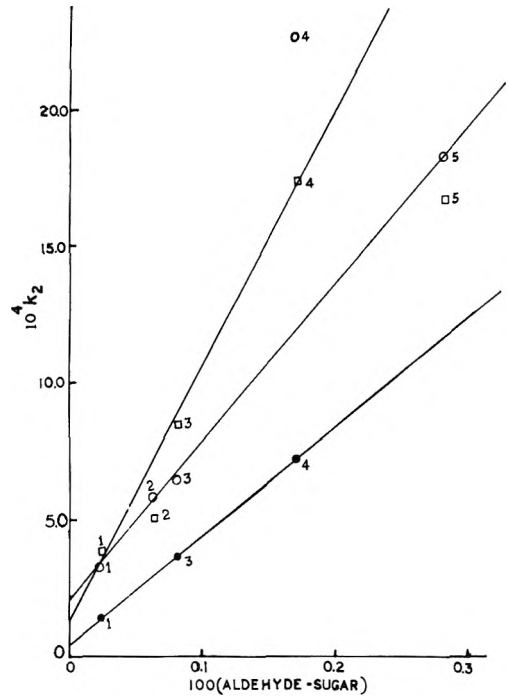

Figure 4. The linear plot between the second-order rate constant k_2 ($(-d[V(V)]/dt)/[V(V)][sugar]$) and [aldehyde sugar]: 1, glucose; 2, mannose, 3, galactose; 4, xylose; 5, arabinose; ●, sulfuric acid, 40°; □, sulfuric acid, 50°; ○, perchloric acid, 50°.

the rate on acidity has been further examined in accordance with the suggestions of Hammett and Bunnett. The plot between log k_1 and $-H_0$, the Hammett acidity function,[13] is linear but the slope values for glucose, mannose, and galactose are 0.5, 0.7, and 0.5, respectively, which are much less than the expected ideal slope of unity in the presence of perchloric acid of constant ionic strength. However, the slope values are much nearer to unity for the reaction in the presence of sulfuric or perchloric acid of varying ionic strength. These values are 0.8, 0.6, and 0.74 in sulfuric acid and 0.66, 0.75, and 0.6 in perchloric acid for glucose, mannose, and galactose, respectively. The H_0 values are those due to Paul and Long.[14]

The plot of (log k_1 + H_0) against log a_{H_2O}, suggested by Bunnett,[15] is linear with "w" values equal to 0.66, 2.4, and 1.0 in sulfuric acid and 2.7, 3.6, and 2.2 in perchloric acid for glucose, mannose, and galactose, respectively. It is felt desirable[6] not to attach any mechanistic significance to the "w" value as has been discussed by Bunnett[15] except that a water molecule participates in the mechanism.

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Registry No.—Vanadium(V), 7440-62-2.

Supplementary Material Available. The kinetic data involving the variation in the concentrations of vanadium(V), aldo sugars, dependence of the rate on glucose concentration in 4 *M* sulfuric and perchloric acid, effect of ionic strength on the rate, and the mechanism of oxidation as effected by the various vanadium(V) species in sulfuric acid will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1248.

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Rapid Separation of Organic Mixtures by Formation of Metal Complexes

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A convenient and efficient technique for resolving alcohol mixtures by preferential complexation by calcium chloride or manganese chloride with one alcohol of the mixture is reported. Isolation of the complex formed and regeneration of the alcohol allows purification of certain alcohols. Catalytic amounts of ethanol enhance the complexing ability of the metal halides. The separation of commercial mixtures of *cis*- and *trans*-4-*tert*-butylcyclohexanol, technical geraniol, and contrived mixtures of cyclododecanol–cyclododecanone were investigated and optimum conditions for these systems were determined.

Often the most difficult and time-consuming aspect of a synthetic procedure is the process of separating the desired compound from a crude product mixture containing similar compounds. The rapid pace at which modern synthetic chemistry is advancing is in large measure due to the development of powerful chromatographic methods for resolving mixtures. However, chromatographic procedures work best on a small scale and become exceedingly difficult to perform as the quantity of materials to be separated increases.

By contrast, the classical chemical methods for separation are not as limited by scale; these methods usually involve making a derivative of a functional group which can be separated from impurities by nonchromatographic means (e.g., recrystallization). Derivative formation requires an extra step and once purified the derivative is often difficult to decompose.

We have for several years been purifying mixtures of organic alcohols by complex formation with calcium chloride and other anhydrous metal halides. The literature contains only isolated reports on the use of such complexes to purify mixtures.[1] The original procedure of Jones and Woods for purification of commercial geraniol exemplifies the simplicity of the general method.

The geraniol–citronellol[2] mixture (~60:40) is dissolved in hexane and stirred with finely ground anhydrous calcium chloride. Although calcium chloride is completely insoluble in hexane, it is quickly digested by the alcohol to form a solid complex. The complex is filtered, washed with hexane, and dissolved in water, whereupon essentially pure geraniol is liberated. The whole procedure is easily carried out in several hours on a kilogram scale if necessary. Although only 35% of the geraniol is recovered in this way, it is difficult to imagine a more convenient means of isolating it from this mixture.

We have now established that this separation technique is applicable to many alcohol mixtures. A large number of mixtures containing other coordinating functional groups (e.g., amines, amides, esters, epoxide, ketones, aldehydes, acids, and nitriles) were also examined. However, for unknown reasons, the various metal complexing agents were generally less effective in separating mixtures containing functional groups other than alcohols. Before elaborating on specific applications, it will be helpful to discuss the properties of the complexes which are formed with alcohols.

Chart I

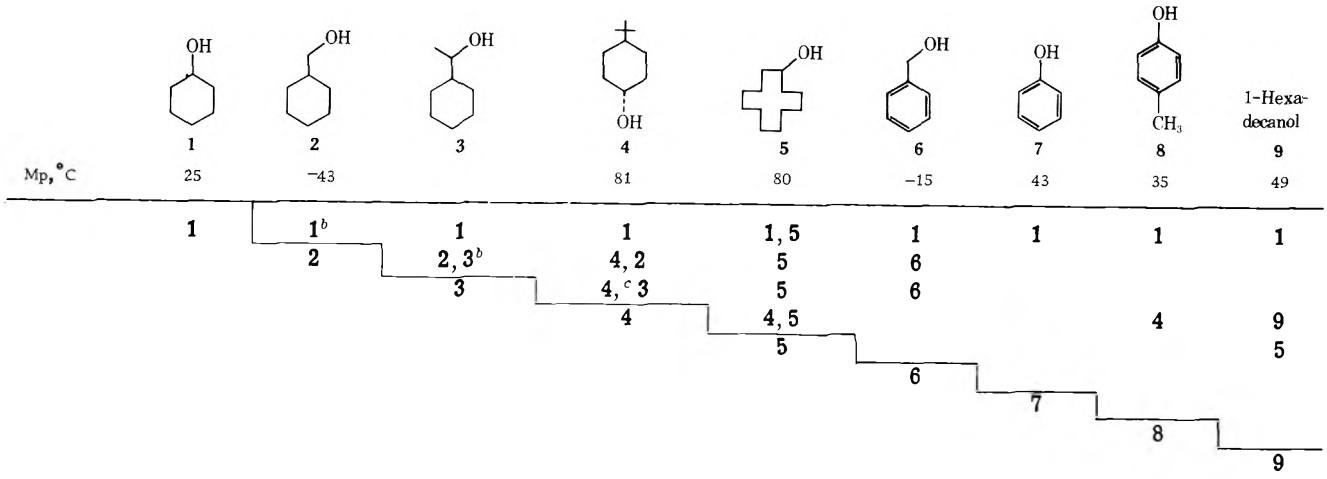
Salt	Alcohol	Alcohol/salt
$CaCl_2$	Geraniol	1.9
$CaCl_2$	α-Phenethyl alcohol	1.3
$CaBr_2$	Menthol	2.2
$MnCl_2$	Menthol	1.0
$MnCl_2$	α-Phenethyl alcohol	1.4

Nature of Alcoholates. The formation of alcoholates of anhydrous metal halides is well precedented and the stoichiometry $MX_2(ROH)_2$ is common for divalent metal ions (e.g., Mn, Ni, Ca, Zn, and Mg).[3] Since these complexes were of only small alcohols (i.e., MeOH, EtOH), we prepared and analyzed several larger complexes. As shown in Chart I, the stoichiometry of the complexes varies between one and two alcohols. These complexes were formed in the presence of a large excess of the alcohol.

An early clue about the course of complex formation and the reason for its specificity was provided by the observation that the hexane filtrate obtained during isolation of the solid complexes contained dissolved calcium chloride. In fact, alcohols such as oleoyl alcohol and citronellol, which did not form solid complexes with $CaCl_2$, dissolved large quantities of the salt in hexane. Similarly, complex mixtures of alcohols which, when pure, formed solid complexes in the standard procedure (i.e., stirred in hexane with the anhydrous salt) resulted in complete dissolution of the anhydrous salt in the hexane. Thus, although most alcohols form complexes, some crystallize more readily than others from the nonpolar solvents employed.

Another important aspect of complex formation is that the alcohols in the solid complexes stirring in hexane exchange rapidly with the alcohols in solution. This exchange process was demonstrated by isolating the $CaCl_2$ complex of 1-decanol and then stirring it in a hexane solution containing cyclohexanol (ca. 1.5 equiv). After stirring for 0.5 hr

Table I
Competitions between Pairs of Alcohols for Complex Formation with $MnCl_2$ in Hexane[a]



[a] Each of the competitions was carried out by stirring overnight an equimolar mixture of the two alcohols dissolved in hexane with 1.5 molar equiv (based on total alcohol) of finely ground anhydrous $MnCl_2$. A catalytic amount of ethanol (0.05 equiv) was added in each case. The complexes were isolated by filtration and the alcohols were released by addition of water. The ratio of alcohols in the complex was then determined by GLC. This work was done several years ago and recently we have found that the above conditions are not optimum. [b] A single entry means ~100% selection of that alcohol. A double entry means about equal selection. [c] Alcohol was favored but not selected 100%.

the solid complex contained only cyclohexanol. Whatever the cause of this facile exchange of ligands, in what appears to be a heterogeneous system, it is obviously of paramount importance to selective complex formation. The system simply equilibrates until it has optimized whatever thermodynamic factors favor solid complex formation. These features probably explain why this purification technique is capable of some of the subtle discriminations described later.

Some alcohols, especially large and/or hindered ones, when stirred with anhydrous $CaCl_2$ in hexane formed complexes very slowly. This was not surprising considering the heterogeneous nature of the process. Having already noted that an alcohol in solution could rapidly displace a weaker complexing alcohol from the solid complex (see above), it seemed likely that a small alcohol might catalyze complex formation in slower cases by aiding in digestion of the $CaCl_2$. In support of this concept we have found that catalytic quantities (1–10%) of *n*-aliphatic alcohols dramatically accelerate the rate of complex formations, especially in difficult cases. Although we now use anhydrous ethanol as the catalyst, propanol and butanol work equally well. In addition to reducing the time required for complex formation, this effect enables one to form complexes of many alcohols which fail to form any complex at all in the absence of the catalyst. For example, *l*-menthol readily formed a solid complex with anhydrous manganous chloride when 5% ethanol was present; in the absence of ethanol, under otherwise identical conditions, no complex was formed. Interestingly, *l*-menthol failed to form a complex with calcium chloride even when ethanol catalysis was employed. As will be seen later, the amount of ethanol catalyst is best kept to about 1–2% or less, since in certain sensitive separations the selectivity falls off as the amount of ethanol increases.

Factors Which Affect the Selectivity of Complex Formation. Our current understanding of the factors which determine selectivity is very limited. In general one must simply try this purification technique on the alcohol mixture in question to learn what the outcome will be. The empirical nature of this method should diminish as its use increases. In any case, we have observed certain effects which are worth pointing out. While discussing these factors individually, it is important to realize that although trends can be discerned for isolated factors, the actual effect on the selectivity is a complex function of all the factors. Thus, most of the following statements should be prefaced by the phrase "other things being equal".

The highest melting ligand is preferentially selected, as revealed in Table I, for various pairs of alcohols competing for complexation with manganous chloride ($MnCl_2$). However, exceptions are easy to find. Cyclohexanol was superior to all contenders, and phenols formed poorer complexes, probably because they are weaker bases, than alcohols of comparable melting point.

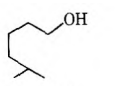
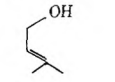
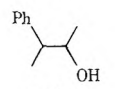
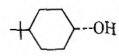
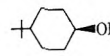
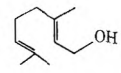
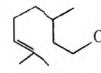
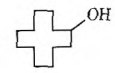
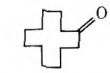
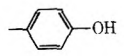
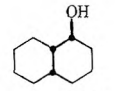
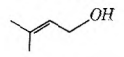
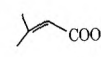
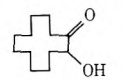
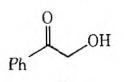
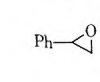
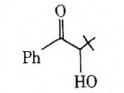
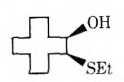
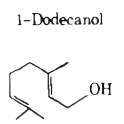
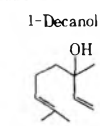
In competitions between two alcohols, both of which form solid complexes, the major component has the advantage. However, when one alcohol forms much better complexes than the other it tends to be selected even when it is the minor component. In these and other respects this purification procedure resembles fractional crystallization.

For a given carbon skeleton one generally finds that complexing ability decreases in the order primary > secondary > tertiary alcohol. Thus, 1-decanol is vastly superior to its 2, 3, 4, and 5 isomers.[5]

Actual Applications and Optimization of Variables. In addition to the separation of the contrived mixtures outlined in Table I, we have found that these purification techniques were successful in separating a variety of mixtures which arose during the course of other research problems (see Table II). Most all of the examples in Table II were carried out in a very crude manner; an undetermined amount (usually a large excess, 2+ molar equiv) of anhydrous calcium chloride was used and a "squirt" of anhydrous ethanol was added as catalyst. It is to the credit of this method of separation that even this qualitative approach was usually successful on the first try. In Table III are listed some of the mixtures for which no or only partial purification was observed. In general we have found this method to be effective on better than 50% of the alcohol-containing mixtures to which it has been applied.

More recently we have sought to establish an optimum set of reaction conditions to be tried first on any new mixture. The factors to be optimized are, of course, selectivity[6] and recovery—the product of these two determines the yield of the desired component isolated from the mixture. Unfortunately, this has not been easy, since each mixture seems to respond differently to the controllable variables.

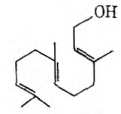
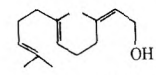
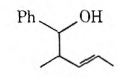
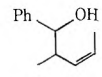
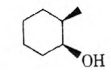
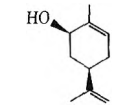
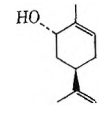
Table II
Isolation of Alcohols from Mixtures by Means of Metal Complexes[a]

Component which complexed	Component(s) which did not complex
	
	
 erythro	 threo
a 	
b 	
c 	
	
	The other three decahydro-1-naphthols
	
	
	
	PhCHO
	
 1-Dodecanol	 1-Decanol
	

[a] These separations were carried out under variable conditions. Generally, an undetermined amount (usually a large excess, 2+ molar equiv) of anhydrous calcium chloride was used, along with a variable but small amount of ethanol as catalyst. Hexane was used as solvent.

In approximate order of decreasing importance these variables are (1) mole ratio of anhydrous salt to alcohol; (2) percent of anhydrous ethanol catalyst; (3) anhydrous salt ($CaCl_2$, $CaBr_2$, $MnCl_2$, $CoCl_2$, etc.); (4) length of time stirred at room temperature; (5) solvent (hexane, CH_2Cl_2). The first two variables are the most important and we have studied in detail the effect of these variables on three cases (a, b, and c) from Table II. As can be seen from examination of the data presented in Table IV, these three

Table III
Alcohol Mixtures Not Successfully Purified by $CaCl_2$ Complexation

	
	
	
	
 Commercial oleyl alcohol	

mixtures (a, b, and c) respond differently to variables 1 and 2. Case a (*trans*-4-*tert*-butylcyclohexanol–*cis*-4-*tert*-butylcyclohexanol) is quite sensitive to both the mole ratio of anhydrous salt to alcohol and to the amount of ethanol catalyst used, whereas case b (geraniol–citronellol) is quite insensitive to these same two variables. Fortunately, most of the alcohol mixtures we have studied resemble case b more than case a. Case c (cyclododecanol–cyclododecanone) is even less sensitive to the above-mentioned variables than is case b. In fact, we have found this type of separation (of an alcohol from a nonalcohol) to be one of the most reliable applications of this purification procedure.

The results in Table IV reveal that only case a is very sensitive to the $CaCl_2$/alcohol ratio and to the amount of ethanol catalyst. The optimum selectivity[6] is obtained when 0.5 mol of $CaCl_2$ is used per mole of *trans*-4-*tert*-butylcyclohexanol in the starting mixture and when only 1% of ethanol catalyst is present. The use of 10% ethanol catalyst increases the recovery and rate of complex formation but at great expense to the selectivity. When no ethanol is present the selectivity is very high but the yields are low. Fortunately, most alcohol mixtures we have encountered resemble the geraniol purification (case b) in sensitivity to conditions. However, since the best procedure for case a also gives reasonable yields for case b, we recommend that it be adopted as the *optimum procedure: use 0.5 mol of finely ground anhydrous $CaCl_2$ per mole of alcohol to be complexed in the starting mixture and 1% (based on total moles of mixture) of absolute ethanol catalyst; these ingredients are then vigorously stirred in hexane or CH_2Cl_2 solution (~0.6 M based on moles of mixture) for 4–12 hr.*

In the case of more hindered alcohols, where the ratio of metal salt to alcohol in the complex approaches 1 (see Chart I), it may be better to employ up to 1 mol of $CaCl_2$ per mole of alcohol to be complexed. As already pointed out, in most cases this concern over the $CaCl_2$/alcohol ratio is unnecessary and in much of our earlier work we used a large excess of $CaCl_2$ and still obtained good results. Of course, as the amount of $CaCl_2$ employed approaches the stoichiometric value it becomes necessary to ensure strictly anhydrous conditions. Thus, it may be desirable to use excess $CaCl_2$ when possible to avoid these difficulties.

On the other hand, when one is dealing with mixtures of an alcohol and other components containing weaker ligands (e.g., ketones, esters, epoxides) such as in case c of

Table IV[a]

Case a (4-*tert*-Butylcyclohexanols)

Molar equiv[b] $CaCl_2$	Ethanol,[c] %	Selectivity,[d] % trans isomer	Yield,[e] % trans isomer	Time, hr
0.35	1	>99	84	10
0.5	1	91	84	10
0.7	1	88	85	10
0.35	0	>99	15	10
0.35	1	>99	84	10
0.35	2	97	90	7
0.35	10	90	81	10

Case b (Geraniol + Impurities)

Molar equiv[b] $CaCl_2$	Ethanol,[c] %	Selectivity,[d] % geraniol	Yield,[e] % geraniol	Time, hr
0.35	1	97	48	9.5
1.0	1	96	59	10.5
2.0	1	96	56	10
0.35	10	96	48	10.5
0.7	10	93	51	11

Case c (Cyclododecanol + Cyclodecanone)

Molar equiv[b] $CaCl_2$	Ethanol,[f] %	Selectivity,[d] % alcohol	Yield,[e] % alcohol	Time, hr
0.25	1	>99	34	5
0.5	1	>99	51	5
1.0	1	>99	64	5
2.0	1	>99	71	5
4.0	1	>99	69	5
0.5	1	>99	51	5
0.5	10	>99	54	5

[a] All reactions were performed with vigorous magnetic stirring in hexane as solvent (60 ml) on 5 g of the mixtures. The 4-*tert*-butylcyclohexanol (case a) used was 70% trans and 30% cis; the technical grade geraniol (case b) contained 65% geraniol, 30% citronellol, and 5% of other impurities; the cyclododecanol–cyclododecanone (case c) consisted of an equimolar mixture of the alcohol and the ketone. [b] This figure is based on total alcohol available and thus the first entry of 0.35 means that there was enough $CaCl_2$ available to complex with all the *trans*-4-*tert*-butylcyclohexanol in the mixture (70%) if two molecules of the trans alcohol are bound to each calcium ion. In case c this figure is based on total alcohol and ketone available. [c] Based on total alcohol. [d] See ref 6. [e] See ref 8. [f] Based on total alcohol and ketone.

Table IV, it appears that the yield can be increased by going to high $CaCl_2$/alcohol ratios with little loss in selectivity. It also appears that the rate of complex formation can be increased in these instances (case c) by using more (5–10%) of ethanol catalyst without a deleterious effect on selectivity.

At this point it is worth discussing briefly the other three variables (3, 4, and 5) mentioned above. We have explored a variety of anhydrous alkaline earth and transition metal halides, but $CaCl_2$ seems to be the best general reagent and also the least expensive.

The length of time required for complex formation varies dramatically depending on the alcohol involved, the efficiency of stirring (since the reactions are heterogeneous), and the amount of ethanol catalyst employed (the more ethanol the faster the complex formation). The only solvents we have used are hexane and CH_2Cl_2. For a given mixture both solvents afford similar selectivities but hexane seems to result in better recoveries; the calcium chloride alcoholates are probably more soluble in CH_2Cl_2 than in hexane.

As an example of the preparative utility of these purification procedures 100 g of commercial 4-*tert*-butylcyclohexanol (67% trans, 33% cis) afforded 56.1 g (83% yield based on trans alcohol available) of 99% pure *trans*-4-*tert*-butylcyclohexanol. The literature procedure[4] for purifying the same quantity of a sample of this alcohol slightly richer in the trans isomer (~75% trans, 25% cis) involves formation and two recrystallizations of the acid phthalate followed by saponification to give 29.8 g (~40%) of the pure trans alcohol. Thus the $CaCl_2$ method proceeds in one step, requires no time-consuming recrystallizations, and affords twice the yield of the classical derivatization approach.

As already mentioned, the purification of the epimeric 4-*tert*-butylcyclohexanols by this procedure is more sensitive to conditions than any other mixture in our experience. Although yields of 75–85% were reproducible on a small scale (5 g of crude alcohol), the yields on the larger scale (100 g) varied between 65 and 85%. The responsible variable was found to be the stirring. Surprisingly, too vigorous stirring in this case was deleterious. Thus, stirring in a Morton flask for 20 hr gave only 84% selectivity[6] for the trans epimer but the yield remained high at 81%. The optimum conditions for this case appeared to be stirring for 10 hr in a normal flask. Stirring for shorter periods gave lower yields although the selectivity remained high, whereas with longer stirring the selectivity began to fall off rapidly. This dependence of selectivity on time was noticed only in the 4-*tert*-butylcyclohexanol system.

Since we have recently found that $MnCl_2$ also works quite well for this purification, it would be interesting to see if its selectivity also exhibited this time dependence. If it did not, then $MnCl_2$ would clearly be preferred over $CaCl_2$ in this instance.

In conclusion, it should be emphasized that although we feel we have established reasonable guidelines for the purification of alcohol mixtures by formation of metal complexes, the technique is clearly still highly empirical. Each new mixture will probably require optimization of the variables, especially if one is concerned about yields and not just rapid access to a pure component. This method of purifying alcohol mixtures by formation of metal complexes has already served us well in many research problems. We feel that through wider use many new applications will be discovered.

One would hope that this concept could be extended to purification of mixtures containing other functional groups capable of coordination as Lewis bases. We have had some success in separating mixtures of ketones and esters using stronger Lewis acids (e.g., $ZrCl_4$ and $FeCl_3$) in CCl_4.[5] We were surprised to find that even $CaCl_2$ forms complexes with esters, aldehydes, and ketones as evidenced by the shifts in the carbonyl absorption of the derived complexes shown in Table V;[5] unfortunately, in the presence of

Table V[a]

Shift of Carbonyl Absorption upon Complexing with $CaCl_2$

Ligand	Metal halide	Ir shift cm^{-1}
Methyl nonyl ketone	$CaCl_2$	−95
Cyclohexanone	$CaCl_2$	−90
Methyl laurate	$CaCl_2$	−115
Lauraldehyde	$CaCl_2$	−110
trans-Decalin-1,5-dione	$CaCl_2$	−95

[a] The complexes were obtained by stirring anhydrous $CaCl_2$ with the appropriate carbonyl compound in hexane. Ir spectra of the solid complexes were obtained as Nujol mulls.

mixtures of such carbonyl compounds the $CaCl_2$ complexes which form are also mixtures and show little selectivity in choice of ligand. Other functional groups which $CaCl_2$ complexed with but failed to purify mixtures containing such moieties include amides, acids, nitriles, epoxides, and amines. Thus, among the numerous mixtures containing polar functional groups, alcohol mixtures appear to be unique in their tendency to form selective complexes with $CaCl_2$ and related Lewis acids. This is perhaps due to a favorable balance between the stability of such alcoholates and their rates of exchange with free alcohols in solution. Understanding of this useful purification phenomenon might be facilitated if structures of the complexes could be determined. In this regard it is interesting that when competitions for $CaCl_2$ complexation were performed[5] between various pairs of straight-chain alcohols ranging from 1-butanol to 1-eicosanol the alcohol with the longer chain was clearly favored, and the degree of selection increased as the difference in the length of the competing alcohols increased. Thus these complexes have no trouble incorporating large hydrocarbon residues and it would probably be very informative to learn why this is so.

Experimental Section

General. Commercial samples of all reagents were employed. 4-*tert*-Butylcyclohexanol, cyclododecanol, cyclododecanone, and 1-dodecanol were obtained from Aldrich Chemical Co. Technical grade geraniol and 1-decanol were obtained from Eastman Organic Chemicals. The anhydrous calcium chloride (8 mesh) used was obtained from Mallinckrodt Chemical Works, anhydrous calcium bromide (powder) was obtained from Merck and Co., Inc., and anhydrous manganese(II) chloride was obtained from Ventron Corp., Alfa products. The technical grade geraniol was found to contain approximately 65% geraniol, 30% citronellol, and 5% other impurities.

The commercial 4-*tert*-butylcyclohexanol consisted of a mixture of isomers, with the trans isomer generally ranging from 67 to 80% of the total mixture. Pure samples of the cis and trans isomers, for comparison purposes, were obtained by column chromatography of 1.5 g of the commercial sample on 140 g of silica gel packed in a 3.2 cm diameter column. The axial (cis) isomer was eluted with 10% EtOAc in hexane and the equatorial (trans) isomer was eluted with 20% EtOAc in hexane.

All GLC analyses were performed on a Perkin-Elmer 990 instrument using either 3% FFAP on Gas-Chrom Q (80/100 mesh) packed in a 6 ft × 0.125 in. glass column, or 3% OV-17 on Gas-Chrom Q (80/100 mesh) packed in a 6 ft × 0.125 in. glass column. On 3% FFAP, retention times were as follows: *cis*-4-*tert*-butylcyclohexanol, 4.5 min (105°); *trans*-4-*tert*-butylcyclohexanol, 5.6 min (105°); 4-*tert*-butylcyclohexanone, 3.4 min (105°); cyclododecanol, 5.6 min (145°); cyclododecanone, 2.8 min (145°). On 3% OV-17, retention times were as follows: geraniol, 5.8 min (115°); citronellol, 4.6 min (115°); 1-dodecanol, 7.5 min (130°); 1-decanol, 2.7 min (130°).

All organic solutions were dried with anhydrous magnesium sulfate unless otherwise indicated.

I. Separation of *trans*-4-*tert*-Butylcyclohexanol from the Commercial Alcohol. A. Large Scale (Optimum Conditions). Commercial 4-*tert*-butylcyclohexanol (100 g, 640 mmol) (67% trans, 33% cis), ethanol (0.29 g, 0.37 ml, 6.4 mmol), and 1 l. of hexane were placed in a 2-l. three-necked flask fitted with a mechanical stirrer and a gas inlet tube. A stream of nitrogen was slowly passed through the apparatus. The freshly powdered anhydrous calcium chloride (23.8 g, 214 mmol) was added to the stirred solution all at once, and vigorous stirring was continued at 25° for 10 hr. The heterogeneous reaction mixture was filtered and the residue was washed with pentane (3 × 200 ml). The complex was then added to a separatory funnel containing 400 ml of ice-cold water and 400 ml of ether, and shaken vigorously until it dissolved. Some heat was evolved during this process. The ether layer was separated and the aqueous layer was washed with 200 ml of ether. The combined ether extracts were washed with 300 ml of water and then dried and concentrated to give 56.1 g (83%)[8] of alcohol. Analysis by GLC showed the regenerated alcohol to contain 99% of *trans*- and 1% of *cis*-4-*tert*-butylcyclohexanol.

B. Small Scale (Optimum Conditions). To a solution of 4-*tert*-butylcyclohexanol (5.0 g, 32 mmol) (70% trans, 30% cis) and a catalytic amount of ethanol (14.7 mg, 18.6 μl, 0.32 mmol) in 50 ml of hexane was added anhydrous calcium chloride (1.25 g, 11.2 mmol) which was freshly powdered in a mortar and pestle. After the resulting mixture had been stirred at 25° for 10 hr, the solvent was filtered off and the solid complex was washed with pentane (2 × 15 ml). The white complex was shaken in a separatory funnel containing 70 ml of water and 70 ml of ether until it dissolved. The ether layer was separated and the aqueous layer was washed once with 70 ml of ether. The combined ether extracts were dried and concentrated to give 2.91 g (84%)[8] of alcohol. This alcohol was shown by GLC to contain 99.5% *trans*- and 0.5% *cis*-4-*tert*-butylcyclohexanol.

C. Methylene Chloride as Solvent. Procedure B with 50 ml of methylene chloride instead of hexane afforded 1.70 g (42%)[8] of alcohol. Analysis by GLC showed the alcohol to contain 99.5% *trans*- and 0.5% *cis*-4-*tert*-butylcyclohexanol.

D. Calcium Bromide as Complexing Agent. Procedure B with anhydrous calcium bromide (2.24 g, 11.2 mmol) powder instead of calcium chloride afforded 3.83 g (67%)[8] of alcohol. The alcohol was shown by GLC to contain 87% *trans*- and 13% *cis*-4-*tert*-butylcyclohexanol.

E. Manganous Chloride as Complexing Agent. Procedure B with anhydrous manganous chloride (1.61 g, 12.8 mmol) instead of calcium chloride afforded 3.18 g (80%)[8] of alcohol. The alcohol was shown by GLC to contain greater than 99% *trans*-4-*tert*-butylcyclohexanol.

II. Separation of *trans*-4-*tert*-Butylcyclohexanol from 4-*tert*-Butylcyclohexanone. To a solution of *trans*-4-*tert*-butylcyclohexanol (2.34 g, 15 mmol), 4-*tert*-butylcyclohexanone (2.33 g, 15 mmol), and a catalytic amount of ethanol (13.8 mg, 17.5 μl, 0.3 mmol) in 50 ml of hexane was added anhydrous calcium chloride (1.67 g, 15 mmol) which was freshly powdered in a mortar and pestle. After stirring at 25° for 10 hr, the solvent was filtered off and the white complex was washed with pentane (3 × 15 ml). The complex was then added to a separatory funnel containing 70 ml of water and 70 ml of ether, and it was shaken until the complex dissolved. The ether layer was separated and the aqueous layer was washed with 70 ml of ether. The combined ether extracts were dried and concentrated to yield 2.09 g (89%)[8] of a white solid. The solid was shown by GLC analysis to contain 99.2% alcohol and 0.8% ketone.

III. Purification of Technical Geraniol. A. Via $CaCl_2$ Complex. To a solution of technical geraniol (3.08 g, 20 mmol) and a catalytic amount of ethanol (9.2 mg, 11.6 μl, 0.2 mmol) in 70 ml of hexane was added calcium chloride (3.33 g, 30 mmol) which was freshly powdered in a mortar and pestle. After the heterogeneous mixture was stirred at 25° for 10 hr, the solvent was filtered off and the white complex was washed with pentane (2 × 25 ml). The complex was then added to a separatory funnel containing 70 ml of water and 70 ml of ether and it was shaken until the solid dissolved. The ether layer was separated and the aqueous layer was washed once with 70 ml of ether. The combined ether extracts were dried and concentrated to give 1.21 g (60%)[8] of colorless oil. The oil was shown by GLC to contain 96% geraniol and 4% citronellol.

B. Via $MnCl_2$ Complex. Procedure A with anhydrous manganous chloride (2.52 g, 20 mmol) instead of calcium chloride afforded 1.32 g (58%) of colorless oil. The oil was shown by GLC to contain 90% geraniol and 10% citronellol.

IV. Separation of Cyclododecanol from Cyclododecanone. To a solution of cyclododecanol (2.76 g, 15 mmol), cyclododecanone (2.74 g, 15 mmol), and a catalytic amount of ethanol (13.8 mg, 17.5 μl, 0.3 mmol) in 70 ml of hexane was added freshly powdered anhydrous calcium chloride (6.68 g, 60 mmol). After stirring at 25° for 5 hr, the solvent was filtered off and the white complex was washed with pentane (3 × 25 ml). The complexed alcohol was regenerated by shaking the complex in a separatory funnel containing 70 ml of water and 70 ml of ether. The ether layer was separated and the aqueous layer was washed once with 70 ml of ether. The combined ether extracts were dried and concentrated to give 1.95 g (71%)[8] of white solid. This solid was shown by GLC to contain 99.8% alcohol and 0.2% ketone.

V. Separation of 1-Dodecanol from a 70:30 Mixture of 1-Dodecanol and 1-Decanol. To a solution of 1-dodecanol (3.92 g, 21 mmol), 1-decanol (1.43 g, 9 mmol), and a catalytic amount of ethanol (13.8 mg, 17.5 μl, 0.3 mmol) in 100 ml of hexane was added freshly powdered anhydrous calcium chloride (3.34 g, 30 mmol). After stirring at 25° for 13 hr, the solvent was filtered off and the white complex was washed with pentane (3 × 30 ml). The complex

was then shaken in a separatory funnel containing 70 ml of water and 70 ml of ether until it dissolved. The ether layer was separated and the aqueous layer was washed once with 70 ml of ether. The combined ether extracts were dried and concentrated to yield 3.34 g (80%)[8] of colorless oil. Analysis by GLC showed the oil to contain 94% 1-dodecanol and 6% 1-decanol.

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Registry No.—*cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; geraniol, 106-24-1; citronellol, 106-22-9; cyclododecanol, 1724-39-6; cyclododecanone, 830-13-7; 1-dodecanol, 112-53-8; 1-decanol, 112-30-1; calcium chloride, 10043-52-4; calcium bromide, 7789-41-5; manganous chloride, 7773-01-5; 4-*tert*-butylcyclohexanone, 98-53-3.

References and Notes

(1) (a) Purification of geraniol: E. Gilderneister and F. Hoffman, "Die Aetherischen Oele", Springer-Verlag, West Berlin, 1899, p 192; H. A. Jones and J. W. Woods, *Ind. Eng. Chem.*, **34**, 488 (1942). (b) Purification of sterols and wool fat alcohols: E. V. Truter, "Wool Wax. Chemistry and Technology", Wiley-Interscience, New York, N.Y., 1956. (c) Purification of phytosterols: M. V. Vasileva and A. M. Khaletskii, *Zh. Obshch. Khim.*, **34**, 1400 (1964).
(2) The contaminant in commercial geraniol was long believed by us, and apparently by many others, to be nerol. However, we have recently shown that the minor (~40%) component is citronellol.
(3) R. C. Osthoff and R. C. West, *J. Am. Chem. Soc.*, **76**, 4732 (1954).
(4) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).
(5) K. B. Sharpless and J. A. Scott, unpublished results.
(6) Our use of the word "selectivity" is not in the conventional sense. Rather, we use the word here and subsequently to represent the percent of desired alcohol in the mixture obtained from decomposition of the complex.
(7) Camille and Henry Dreyfus Teacher-Scholar Grant recipient; Alfred P. Sloan Fellow, 1973–1975.
(8) The percent yield given is based on original amount available of desired alcohol. For example, in case IA, the amount of *trans*-4-*tert*-butylcyclohexanol available is 3.5 g (70% of 5.0 g). The yield of the purified trans epimer is 2.91 g or 84% of 3.5 g.

Diborane as a Reducing Agent. The Novel Reduction of *N*-Formylindoles and Electrophilic Substitution in Indoles

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Attempted reduction of *N*-formyl-3-methylindole (**1a**) and 2,3-dimethyl-*N*-formylindole (**1b**) with complex metal hydrides leads to skatole and 2,3-dimethylindole, respectively. Diborane reduction of indole derivatives has furnished interesting results.[1,2] Further studies with this reagent are now reported. Diborane reduction of **1a** gives 1,3-dimethylindole (**4a**, 49.4%) and 1,3-dimethyl-3-(3′-methylindolyl-1′-methyl)indoline (**6a**, 35.8%). Similarly, reduction of **1b** with diborane affords 1,2,3-trimethylindole (**4b**, 52.4%) and two diastereoisomeric 1,2,3-trimethyl-3-(2′,3′-dimethylindolyl-1′-methyl)indolines (**6b**, 36.7%, and **6c**, 6.8%). This appears to be the first report on the successful reduction of an *N*-acylindole to the corresponding *N*-alkyl derivative. The formation of the indolylmethylindolines (**6**) in the diborane reduction of *N*-formylindoles (**1**) implies that electrophilic substitution takes place primarily at the 3 position of 3-substituted indoles. These results are discussed in the light of the mechanisms of diborane reduction and electrophilic substitution in 3-substituted indoles.

Indoles,[3] oxindoles,[3d,4,5] isatins,[5] indole-2-, and indole-3-carbonyl derivatives[3a,d,6-10] including indole-3-glyoxamides,[3a,f,9,11] and their *N*-methyl analogs have been reduced with diborane. However, to our knowledge, there is no report in the literature on the reduction of *N*-acylindoles with any reducing agent.[12] In the present communication a simple method is presented for the reduction of *N*-formylindoles with diborane, partly from an interest in its synthetic implications and partly to compare the reducing properties of diborane with those of lithium aluminum hydride ($LiAlH_4$).

Jackson and his coworkers demonstrated that electrophilic substitution takes place primarily at the 3 position of 3-substituted indoles.[10,13] However, recently Wolinsky and Sundeen[14] and Casnati, Dossena, and Pochini[15] claimed to have obtained evidence in favor of direct electrophilic substitution at the 2 position of 3-alkylindoles. The work reported in the present communication was undertaken also with a view to throwing further light on this subject.

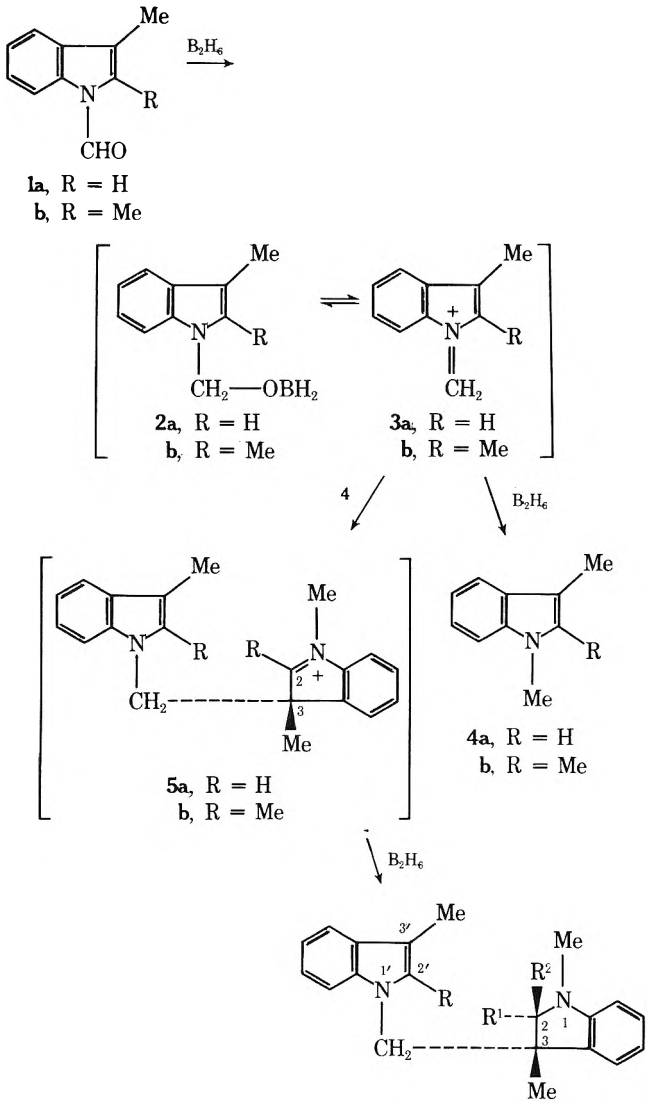
It has been observed that complex metal hydrides are unsuitable for the reduction of *N*-acylindoles,[12] presumably because of the tendency of the acyl groups of the latter to undergo cleavage under basic conditions.[12a,c,16] However, *N*-acylindoles are generally more stable in acidic than in basic media (cf. preparations of **1** by Vilsmeier–Haack method[17]). These facts and the pronounced aldehydic character of the *N*-formyl groups of **1**[17] led us to assume that diborane would be the reagent of choice for their reduction, particularly because the danger of hydrolytic cleavage would be minimum, since the reaction medium would be acidic because of the Lewis acid character of both diborane and boron trifluoride (BF_3).[18]

While attempted reduction of the *N*-formylindoles (**1**) with $LiAlH_4$ or potassium borohydride (KBH_4) under a variety of conditions always resulted in the formation of skatole and 2,3-dimethylindole, respectively,[12a] reduction of **1a** with diborane afforded 1,3-dimethylindole (**4a**) and 1,3-dimethyl-3-(3′-methylindolyl-1′-methyl)indoline (**6a**) (Scheme I). Similarly, diborane reduction of **1b** gave 1,2,3-trimethylindole (**4b**) together with two diastereoisomeric 1,2,3-trimethyl-3-(2′,3′-dimethylindolyl-1′-methyl)indolines (**6b** and **6c**). In this connection, it may be pointed out that this appears to be the first report on the successful reduction of an *N*-acylindole.[12]

The origin of both the mono- and dimeric products in the diborane reduction of **1** may be rationalized by assuming that the intermediate (**3**) may undergo further reduction with excess diborane to give **4** (Scheme I). **3** may also undergo nucleophilic attack by the initially formed indoles (**4**) to afford the indoleninium cation (**5**), which is then reduced by excess diborane to the dimers (**6**).

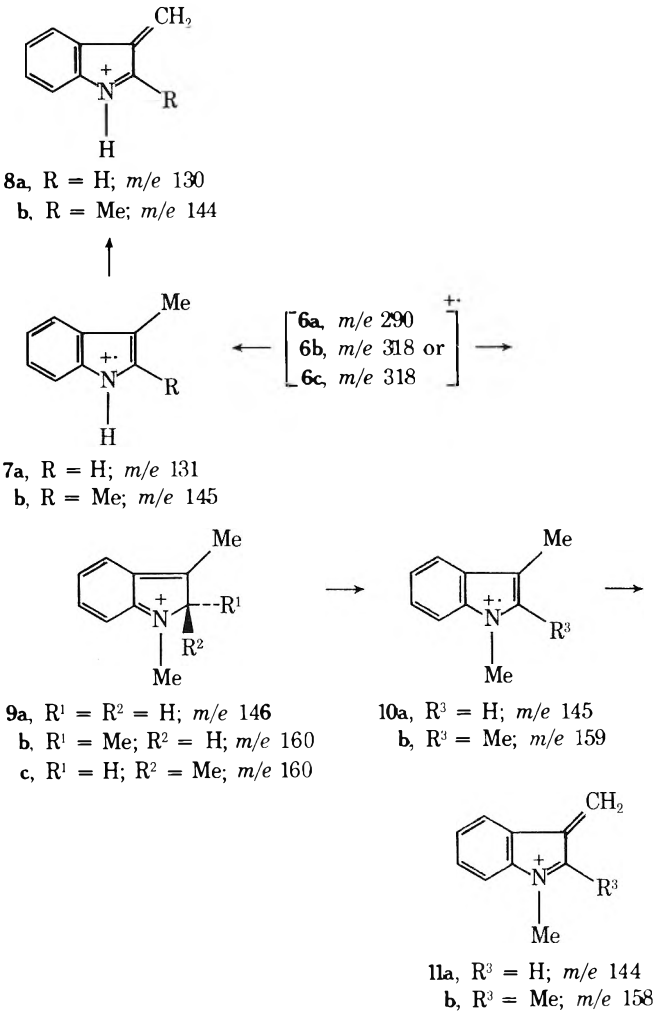
The major dimeric product was assigned the trans configuration (**6b**) on the assumption that reduction of **5** by the addition of a hydride ion at the 2 position takes place

Scheme I



predominantly trans to the bulky 3-indolylmethyl substituent.[19] Confirmation of these stereochemical assignments was obtained by examining their Dreiding models and NMR spectra. The methyl protons at the 2′ position of the cis isomer (**6c**) resonate at δ 2.00 whereas those of the trans isomer (**6b**) resonate at an unusually high field (δ 1.44). Owing to greater interaction between the two methyl groups at the 2 and 2′ positions, the trans isomer (**6b**) may preferentially exist on the average in a spatial arrangement in which the methyl protons at its 2′ position experience the shielding effect of the benzene ring of the indoline moiety, resulting in the observed upfield shift (δ 1.44). The methyl protons at the 2 position of **6b** resonate at a lower field (δ 1.44) than those of **6c** (δ 0.92). From Dreiding models it appears that the methyl protons at the 2 position of only **6b** can exist in the plane of the ring current of its indole moiety, and experience a deshielding effect, thus resulting in the observed downfield shift. On the other hand, the same protons of **6c** are shielded by the indole moiety and resonate at a higher field (δ 0.92). The methine proton at the 2 position of **6c** resonates at δ 3.52, whereas the corresponding proton of **6b** resonates at δ 3.01. Further, it appeared from the models that the methine proton at the 2 position of only **6c** lies close to the plane of the ring current

Scheme II
Mass Spectral Fragmentation Pattern of the Dimeric Products (6) Obtained in the Diborane Reduction of *N*-Formylindoles (1)

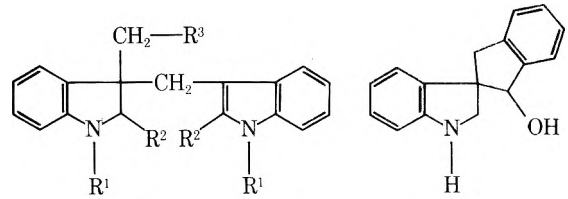


of its indole moiety. It thus experiences a deshielding effect and resonates at a lower field.

The uv spectral data and broad mass spectral fragmentation pattern of the dimeric products (**6**), which confirm their structures, are presented in the Experimental Section and Scheme II, respectively.

In this connection, it may be pointed out that, although indole,[3a–d] N-unsubstituted alkylindoles,[3d,e] oxindole,[3d,4] *N*-methyloxindole,[4] and N-unsubstituted and *N*-methylindole-3-glyoxamides[3f] were reported to give indolines on reduction with diborane, we failed to observe any indolines, either in our present work or in our earlier studies with indole-3- and indole-2-carbonyl derivatives.[3a,6,8–11]

The electrophilic attack at the 3 position of the 3-substituted indoles (**4**) by **3** and trapping of the 3,3-disubstituted indolenines (**5**) by diborane reduction follow essentially the same mechanism as is involved in the formation of the indolylmethylindolines (**12**) in the diborane reduction of in-



12, R^1, R^2 = H or Me
R^3 = H or OH

13

dole-3-carboxaldehydes[19] and indole-3-carboxylic acid,[3f] and the spirocyclic indoline (13) in the diborane reduction of 3-(o-carboxybenzyl)indole.[10] Thus, our present results, though limited and not sufficient to make any firm conclusion, tend to provide support to the theory of Jackson and his coworkers.[13] Jackson's more recent observations[20] and those of others[3e,21,22] also support this theory.[13]

Experimental Section

Light petroleum refers to the fraction boiling between 60 and 80°, if not indicated otherwise. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$, if not otherwise mentioned, chemical shifts are given in δ values relative to Me_4Si, and s, d, q, and m indicate singlet, doublet, quartet, and multiplet, respectively. Mass spectra were recorded on an AEI MS-9 spectrometer. Tetrahydrofuran (THF), BF_3OEt_2, and diglyme were dried and redistilled before use.

Attempted Reduction of *N*-Formylindoles (1) with Complex Metal Hydrides. A solution of **1a**[23] (223 mg, 0.0014 mol) in dry THF (2 ml) was added dropwise to a suspension of $LiAlH_4$ (210 mg, 0.0055 mol) in dry THF (4 ml), and the mixture was refluxed for 4 hr and then left at 25° overnight. After usual work-up and crystallization of the product from light petroleum, skatole (180 mg), mp 96–97°, was obtained. Its identity was confirmed by mixture melting point determination and TLC comparison with an authentic sample. Attempted reduction of **1a** with KBH_4 in boiling absolute EtOH and of **1b**[23] with $LiAlH_4$ or KBH_4 also resulted only in the formation of skatole and 2,3-dimethylindole, respectively.[12]

Hydrolysis of *N*-Formylindoles (1). **1a**[23] (160 mg) was treated with alcoholic NaOH (42 mg in 1 ml) for 45 min at 25°. After removal of EtOH, the residue was extracted with ether to give skatole (105 mg). The ether-insoluble fraction afforded sodium formate as colorless, shining needles, mp 252–253° (lit.[24] mp 253°) from absolute EtOH. Similar treatment of **1b** gave 2,3-dimethylindole and sodium formate.[25]

1,3-Dimethylindole (4a) and 1,3-Dimethyl-3-(3′-methylindolyl-1′-methyl)indoline (6a). Diborane (0.015 mol), generated externally by the dropwise addition of a solution of $NaBH_4$ (0.85 g, 0.0225 mol) in dry diglyme (20 ml) to a magnetically stirred solution of BF_3–OEt_2 (4.47 g, 0.0312 mol) in dry diglyme (13 ml) over 35 min, was passed into a solution of **1a** (0.95 g, 0.006 mol) in dry THF (50 ml) at 0° in a slow stream of dry nitrogen. The apparatus was initially flushed with dry nitrogen, and after completion of the addition, the generator flask was heated at 60–65° for 2 hr for driving out the residual diborane into the reaction vessel. The reaction mixture, which formed a white, gelatinous precipitate within 30 min, was left overnight at 25°, and excess diborane was destroyed carefully with MeOH. After addition of a further 25 ml of MeOH, the mixture was refluxed for 2 hr, the solvents were removed, and the residue was taken up in $CHCl_3$ (50 ml). The solution was washed successively with aqueous $NaHCO_3$ (5%) and H_2O and dried ($MgSO_4$), and the solvent was distilled off under reduced pressure to give an almost colorless oil (0.94 g). TLC examination of the oil revealed it to be a mixture of two components, which were separated by chromatography on a silica gel column. Elution with light petroleum afforded 1,3-dimethylindole (**4a**, 0.43 g, 49.4%) as a colorless liquid. The picrate was obtained as pink needles (from EtOH), mp 143–144° (lit.[26] mp 142.5–143.5°). The 1,3,5-trinitrobenzene charge-transfer complex was obtained as orange-red needles (from absolute EtOH): mp 169–170° (lit.[27] mp 169°); NMR (60 MHz) δ 7.30 (m, 1, 7-H), 6.90–7.20 (m, 3, 4-, 5-, 6-H), 6.70 (s, 1, 2-H), 3.64 (s, 3, NCH_3), 2.20 (d, 3, 3-CH_3, J = 1.2 Hz), 9.03 (s, 3, ArH).

Further elution of the column with a mixture of light petroleum and ether (17:3 v/v) gave the dimer **6a** as a soft, colorless mass (0.31 g, 35.8%): ir (Nujol mull) 3000 (m), 2888 (s), 2813 (s), 2788 (s), 1610 (s, C=C), 1480 (s), 1120 (m, 1020 (m), 765 (s), 750 cm^{-1} (s); uv λ_{max} (EtOH) 223, 230, 258, 289, and 295 nm (log ϵ 4.30, 4.31, 3.80, 3.70, and 3.71); λ_{max} (concentrated H_2SO_4) 238, 243, and 294 nm (log ϵ 3.64, 3.63, and 3.70); NMR (Varian A-60) δ 7.60 (m, 1, 7-H), 6.66–6.90 (m, 3, 4-, 5-, 6-H), 2.81 (d, 1, 2-H_A, J_{AB} = 9 Hz), 3.39 (d, 1, 2-H_B, J_{AB} = 9 Hz), 2.75 (s, 3, NCH_3), 1.38 (s, 3, 3-CH_3), 7.10–7.35 (m, 4, 4′-, 5′-, 6′-, 7′-H), 6.53 (s, 1, 2′-H), 2.32 (d, 3, 3′-CH_3, J = 1.2 Hz), 4.12 (s, 2, N′CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 290 (54, M·+), 147 (59), 146 (beyond chart), 145 (beyond chart), 144 (79), 131 (100), 130 (59); mass measurement by high-resolution mass spectrometry *m/e* 290.17947 (calcd for $C_{20}H_{22}N_2$, *m/e* 290.17829); also see Scheme II. The 1,3,5-trinitrobenzene charge-transfer complex was obtained as pink needles with a metallic lustre (from MeOH), mp 133–134°.

Anal. Calcd for $C_{20}H_{22}N_2 \cdot 2C_6H_3N_3O_6$: C, 53.65; H, 3.93; N, 15.64. Found: C, 53.40; H, 3.65; N, 15.56.

1,2,3-Trimethylindole (4b) and Diastereoisomeric 1,2,3-Trimethyl-3-(2′,3′-dimethylindolyl-1′-methyl)indolines (6b and 6c). **1b**[23] (1.038 g, 0.006 mol) was reduced for 4 hr with externally generated diborane (0.015 mol) following the foregoing procedure. The colorless, oily product, which indicated the presence of three components on TLC examination, was chromatographed on a column of silica gel (60–120 mesh, Chemo Synthetics). Elution with a mixture of light petroleum and benzene (17:3 v/v) afforded 1,2,3-trimethylindole (**4b**, 0.5 g, 52.4%) as a colorless oil. The picrate was obtained as dark-red needles (from benzene), mp 148–149° (lit.[28] mp 150°). The 1,3,5-trinitrobenzene charge-transfer complex was obtained as blood-red needles (from absolute EtOH): mp 170–171°; NMR (HA 100 MHz, CCl_4 + $CDCl_3$) δ 2.04 (s, 3, 3-CH_3), 2.22 (s, 3, 2-CH_3), 3.48 (s, 3, NCH_3), 6.75–7.06 (m, 4, 4-, 5-, 6-, 7-H), 8.80 (s, 3, ArH).

Further elution of the column with more polar solvents gave only a mixture of two components, which was rechromatographed on a column of silica gel (60–100 mesh, Gouri Chemicals) in light petroleum. The first 12 fractions contained a mixture of two components (0.30 g), while the subsequent 24 fractions gave a pure compound (175 mg), which on crystallization first from light petroleum and finally from MeOH, afforded the trans dimer (**6b**) as colorless prisms: mp 123°; uv λ_{max} (EtOH) 224, 232, 260, 288, and 293 nm (log ϵ 4.36, 4.36, 3.86, 3.78, and 3.77); λ_{max} (concentrated H_2SO_4) 238, 242, and 287 nm (log ϵ 3.74, 3.71, and 3.80); NMR (Varian HA-100) δ 7.43 (m, 1, 7-H), 6.40–6.60 (m, 3, 4-, 5-, 6-H), 3.01 (q, 1, 2-H, J = 8 Hz), 2.75 (s, 3, NCH_3), 1.40 (s, 3, 3-CH_3), 1.44 (d, 3, 2-CH_3, J = 8 Hz), 6.95–7.10 (m, 4, 4′-, 5′-, 6′-, 7′-H), 1.44 (s, 3, 2′-CH_3), 2.12 (s, 3, 3′-CH_3), 3.99 (d, 1, N′CH_A, J_{AB} = 14 Hz), 4.22 (d, 1, N′CH_B, J_{AB} = 14 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 318 (28, M·+), 161 (45), 160 (beyond chart), 159 (100), 158 (84), 145 (68), 144 (73); see also Scheme II.

Anal. Calcd for $C_{22}H_{26}N_2$: C, 82.94; H, 8.23; N, 8.80. Found: C, 83.16; H, 8.15; N, 8.78.

The residue (0.3 g) of the first 12 fractions was rechromatographed on a column of silica gel (60–100 mesh, Gouri Chemicals) in light petroleum, bp 40–60°. The first seven fractions furnished the cis dimer (**6c**) as a colorless, thick liquid (40 mg): uv λ_{max} (EtOH) 223, 231, 260, 288, and 294 nm (log ϵ 4.35, 4.37, 3.86, 3.78, and 3.78); λ_{max} (concentrated H_2SO_4) 238, 242, and 286 nm (log ϵ 3.74, 3.72, and 3.79); NMR (Varian HA-100) 7.48 (m, 1, 7-H), 6.43–6.80 (m, 3, 4-, 5-, 6-H), 3.52 (q, 1, 2-H, J = 8 Hz), 2.79 (s, 3, NCH_3), 1.32 (s, 3, 3-CH_3), 0.92 (d, 3, 2-CH_3, J = 8 Hz), 7.06–7.36 (m, 4, 4′-, 5′-, 6′-, 7′-H), 2.00 (s, 3, 2′-CH_3), 2.23 (s, 3, 3′-CH_3), 4.15 (d, 1, N′CH_A, J_{AB} = 15 Hz), 4.32 (d, 1, N′CH_B, J_{AB} = 15 Hz); mass spectral data are recorded in Table I; see also Scheme II.

Continued elution of the column wih the same solvent gave mainly **6b** (150 mg), mp 123°, together with an approximately 1:1 mixture (50 mg) of **6b** and **6c**. Yield: **6b**, 36.7%; **6c**, 6.8% (approximate).

Table I
Mass Measurement of the Dimer 6c by High-Resolution Mass Spectroscopy

Fragment	Found, *m/e*	Calcd, *m/e*	For	Rel intensity
6c M·+	318.21241	318.20959	$C_{22}H_{26}N_2$	4.36
9c	160.1123	160.1123	$C_{11}H_{14}N$	100
10b	159.1046	159.1048	$C_{11}H_{13}N$	15.60
11b	158.0969	158.0969	$C_{11}H_{12}N$	10.71
	157.0885	157.0891		2.03
	156.0820	156.0813		1.25
7b	145.0884	145.0891	$C_{10}H_{11}N$	12.70
8b	144.0802	144.0813	$C_{10}H_{10}N$	10.91
	143.0730	143.0735		2.76
	142.0642	142.0656		1.18
	130.0654	130.0656		1.41

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NMR spectra, and Professor G. W. Kenner, University of Liverpool, for high-resolution mass spectra.

Registry No.—**1a,** 31951-33-4; **1b,** 41601-98-3; **4a,** 875-30-9; **4a** 1,3,5-trinitrobenzene charge-transfer complex, 54383-93-6; **4b,** 1971-46-6; **4b** 1,3,5-trinitrobenzene charge-transfer complex, 54383-94-7; **6a,** 54383-95-8; **6a** 1,3,5-trinitrobenzene charge-transfer complex, 54383-96-9; **6b,** 54384-25-7; **6c,** 54384-26-8; skatole, 83-34-1; diborane, 19287-45-7.

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Synthesis of 4-Keto-4,5,6,7-tetrahydroindoles via Munchnone Intermediates[1]

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The amino acids, proline and pipecolinic acid, have been converted into the 4-keto-4,5,6,7-tetrahydroindoles, **5a** and **5b,** respectively, in three steps. This sequence involved the preparation of the corresponding *N*-(4-carbomethoxybutyroyl)amino acids and their subsequent reaction with acetic anhydride and dimethyl acetylenedicarboxylate, thereby yielding the pyrrole triesters, **4a** and **4b.** This latter transformation employed a 1,3-dipolar cycloaddition reaction of bicyclic munchnone derivatives generated in situ. The final step in this sequence involved a Dieckmann condensation of **4a** and **4b** using sodium hydride. The application of the sequence to acyclic amino acids was also investigated and with phenylglycine and sarcosine, the tetrahydroindoles, **15** and **16,** respectively, were obtained.

Munchnones (mesoionic oxazolium 5-oxides) have been successfully used in the preparation of pyrroles bearing simple alkyl, aryl, and/or carboalkoxy substituents.[2,3] This paper will describe the synthesis of pyrrole derivatives possessing a functionalized alkyl side chain capable of undergoing further reaction to yield 4-keto-4,5,6,7-tetrahydroindoles. In particular, this involves the reactions of *N*-(4-carbomethoxybutyroyl)amino acids with acetic anhydride and dimethyl acetylenedicarboxylate. The concept of utilizing functionalized 1,3-dipoles has recently been described by Lown and Landberg.[4]

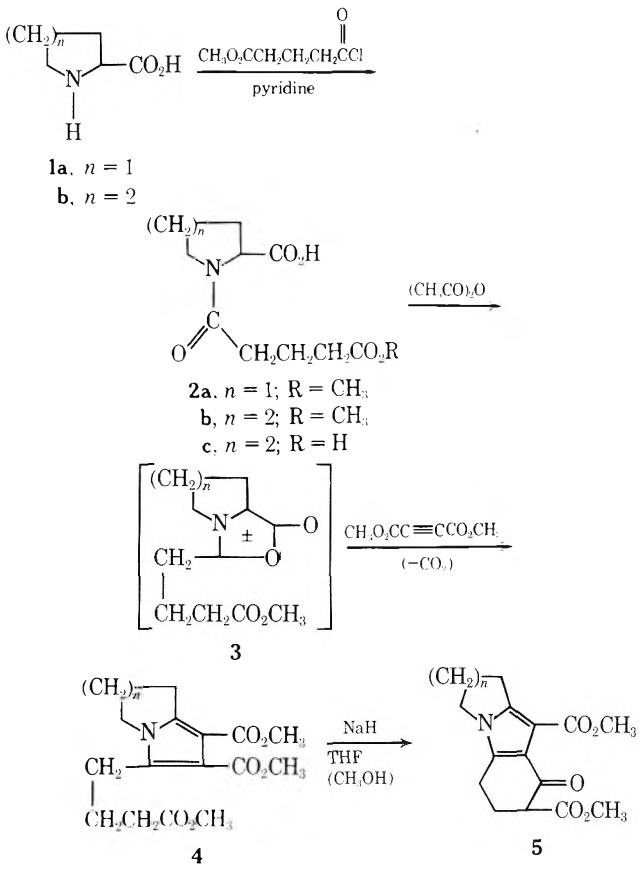
Results and Discussion

Initially, the amino acids, proline and pipecolinic acid, were used in this study, and the reactions involving these compounds are listed in Scheme I.

Treatment of these amino acids with methyl (4-chloroformyl)butyrate in refluxing pyridine afforded the *N*-acyl amino acids, **2a** and **2b,** respectively. Attempts to carry out this acylation reaction under Schotten–Baumann conditions failed to give the desired *N*-(4-carbomethoxybutyroyl)amino acids. When pipecolinic acid was treated with methyl 4-(chloroformyl)butyrate in dilute sodium hydroxide solution, a low yield of the *N*-acyl diacid, **2c,** was obtained. **2a** and **2b** were isolated as viscous oils and were used in the next step without extensive purification, although **2b** was converted into a crystalline dicyclohexylamine salt for the purposes of characterization.

Reaction of **2a** and **2b** with acetic anhydride and dimethyl acetylenedicarboxylate furnished the tetrahydropyrrolizine **4a** and tetrahydroindolizine **4b,** respectively, as oils. The formation of these products involve the intermediacy

Scheme I

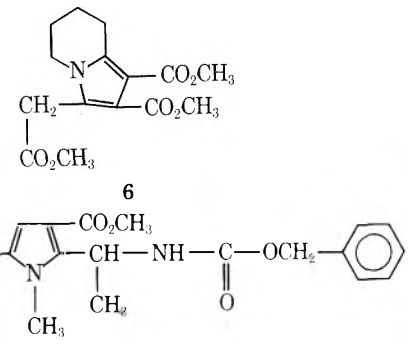


of bicyclic munchnone derivatives (**3a** and **3b**), possessing a functionalized substituent at C-2. Surprisingly, the bicyclic munchnone (**3b**) appears to be formed more readily than munchnones derived from acyclic, *N*-acyl secondary amino acids (vide infra), since carbon dioxide evolution, an indication that the 1,3-dipolar cycloaddition of the munchnone to the acetylenic dipolarophile has occurred, was observed in this case on simply mixing the reactants at room temperature. Reactions involving the acyclic, *N*-acyl amino acids required the use of elevated temperatures (45–60°).

Both the tetrahydropyrrolizine **4a** and the tetrahydroindolizine **4b** possess the requisite spectral characteristics to substantiate their structural assignments. In particular, the ultraviolet spectra of **4a** and **4b** are in good agreement with the reported uv spectrum (λ_{max} (CH_3OH) 268 mμ (log ϵ 3.97) of the homologous tetrahydroindolizine **6,** prepared by Acheson and Taylor.[5]

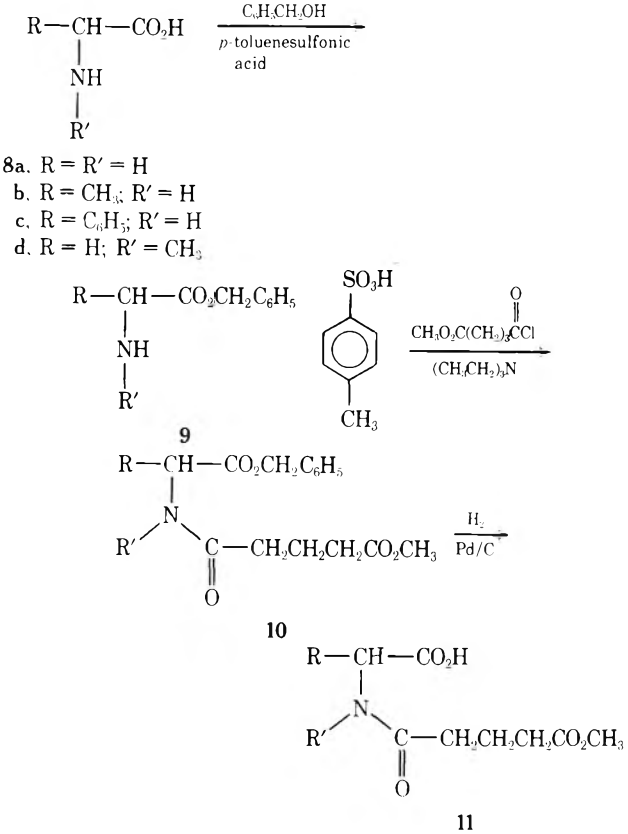
Conversion of **4a** and **4b** into the corresponding 4-keto-4,5,6,7-tetrahydroindoles, **5a** and **5b,** respectively, was accomplished by a Dieckmann condensation using sodium hydride in tetrahydrofuran containing a trace of methanol. In this manner, compound **5a,** a heterocycle which possesses three of the four rings contained in the mitomycin skeleton, was readily made.

Since it appeared that munchnones bearing a functionalized side chain at C-2 could be used in the preparation of complex pyrroles, a study of this reaction with acyclic *N*-acyl amino acids was then made in order to establish the synthetic scope of this approach. An example of such a reaction, somewhat related to the present study, has been recently reported. McDermott and Benoiton have found that treatment of Z-Ala-MeLeu with dicyclohexylcarbodiimide in THF followed by addition of methyl propiolate resulted in the formation of the crystalline pyrrole **7** in 85% yield.[6] The formation of this particular product involves the intermediacy of a mesoionic oxazolium 5-oxide which possesses a functionalized alkyl side chain (aminoalkyl group) at C-2.



In the present study, four amino acids, glycine, alanine, phenylglycine, and sarcosine (*N*-methylglycine), **8a–d,** respectively, were converted into their *N*-(4-carbomethoxybutyroyl) derivatives **11a–d,** by first preparing the benzyl ester, then acylating the benzyl ester with methyl (4-chloroformyl)butyrate in the presence of triethylamine, and finally removing the benzyl ester by hydrogenolysis (Scheme II). Once formed, the *N*-(4-carbomethoxybutyroyl) amino

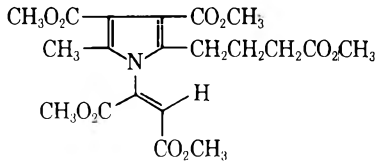
Scheme II



acids, **11a–d,** were dissolved in acetic anhydride containing dimethyl acetylenedicarboxylate and the reaction mixture was heated until carbon dioxide evolution was observed to occur (system vented through a barium hydroxide trap).

The results of the reactions studied here are consistent with earlier findings by Huisgen,[7] namely, reactions involving *N*-acyl amino acids which are derived from amino acids possessing a primary amine group usually fail to give the desired pyrrole products. In our case, reaction of *N*-(4-carbomethoxybutyroyl)glycine (**11a**) with acetic anhydride yielded the corresponding azlactone, which does not appear

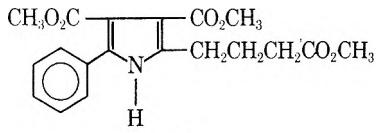
to exist in any appreciable equilibrium with the requisite mesoionic munchnone. No carbon dioxide evolution was observed even up to the reflux temperature of acetic anhydride, and only a small amount of monomethyl glutarate was obtained from the reaction mixture, indicating that hydrolysis of the azlactone had occurred on work-up. Reaction of **11b,** the amide derived from alanine, did furnish a small amount of the pyrrole **12.** This is also consistent with



12

Huisgen's finding that dimethyl 2,5-dialkylpyrrole-3,4-dicarboxylates react with dimethyl acetylenedicarboxylate in a Michael addition fashion.[7]

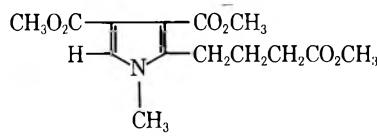
The pyrrole **13** obtained from **11c,** however, does not possess the dimethyl maleate substituent on the pyrrole



13

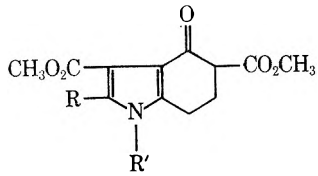
ring nitrogen. Apparently, the presence of the aromatic phenyl substituent at one of the α positions of the pyrrole ring inhibits this further reaction of 1-unsubstituted pyrroles with dimethyl acetylenedicarboxylate. In this particular example, carbon dioxide evolution was observed to occur when the temperature of the reaction mixture reached 45°. This is due to the charge stabilization of the phenyl substituent at C-4 of the munchnone, thereby facilitating the formation of this highly reactive 1,3-dipole.

The use of an *N*-aryl secondary amino acid such as **12d** was uneventful and afforded the desired pyrrole, **14,** in 57%



14

yield. Both **13** and **14** were subsequently converted into the corresponding 4-keto-4,5,6,7-tetrahydroindoles, **15** and **16,** by means of a Dieckmann condensation using conditions just described.



15, R = C_6H_5; R′ = H
16, R = H; R′ = CH_3

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt capillary apparatus which was calibrated against known standards. Ultraviolet spectra were recorded in CH_3OH solutions on a Beckman DK-2A spectrometer; infrared spectra were determined in $CHCl_3$ solutions on a Beckman IR-12 spectrometer; ^1H NMR spectra were obtained on a Varian Associates A-60 or T-60 spectrometer from $CDCl_3$ solutions using tetramethylsilane as an internal standard; mass spectra were run on an AEI MS-30. Microanalyses were performed by the Searle Laboratories Microanalytical Department. Mallinckrodt silica gel (CC7) was used in the column chromatographic work-ups.

***N*-(4-Carbomethoxybutyroyl)proline (2a).** A solution of L-proline (23.0 g, 0.2 mol) in anhydrous pyridine (300 ml) was treated with methyl (4-chloroformyl)butyrate (32.9 g, 0.2 mol) and the mixture was heated to reflux for 3 hr. The reaction mixture was cooled and poured into a slurry of concentrated hydrochloric acid (400 ml) and ice (400 ml). The resultant aqueous acidic mixture was extracted with chloroform (3 × 250 ml); the combined chloroform extract was washed with water (250 ml), then dried (Na_2SO_4), and the solvent was removed in vacuo. A thick, orange oil (42.75 g) was isolated: μ_{OH} 3300–3000, $\mu_{C=O}$ 1735 and 1645 cm^{-1}. This product, **2a,** was used without further purification in the next step (synthesis of **4a**).

***N*-(4-Carbomethoxybutyroyl)pipecolinic Acid (2b).** Using the procedure just described, a reaction of pipecolinic acid (25.8 g, 0.2 mol) and methyl (4-chloroformyl)butyrate (32.9 g, 0.2 mol) in anhydrous pyridine (300 ml) furnished **2b** as a brown viscous oil (37.10 g): μ_{OH} 3300–3000, $\mu_{C=O}$ 1735, 1720 (shoulder), and 1645 cm^{-1}. In addition to using this material for the preparation of **4b,** a small portion (1.2 g) of this oil was dissolved in anhydrous ether (50 ml) and a solution of dicyclohexylamine (1.0 g) in ether (10 ml) was added. A colorless, crystalline solid was obtained (0.9 g), mp 139–141°.

Anal. Calcd for $C_{24}H_{42}N_2O_5$: C, 65.72; H, 9.65; N, 6.39. Found: C, 65.95; H, 9.99; N, 6.36.

Dimethyl 2,3-Dihydro-5-(3-carbomethoxypropyl)-1*H*-pyrrolizine-6,7-dicarboxylate (4a). A mixture consisting of **2a** (42.75 g, assumed to be 0.176 mol), dimethyl acetylenedicarboxylate (28.4 g, 0.2 mol), and acetic anhydride (250 ml) was stirred and heated to 65°. At this temperature an exothermic reaction ensued, and the temperature quickly rose to 115°. This temperature was maintained for 18 hr by means of a heating bath. After the blackened reaction mixture was cooled, the solvents were removed in vacuo, and the black tarry residue that remained was dissolved in methylene chloride (250 ml). This solution was washed with brine (6 × 150 ml), dried (Na_2SO_4), and the solvent removed in vacuo. The black tar that remained was chromatographed on a silica gel column (1800 g). Elution of the column with 1% ethanol–99% chloroform furnished **4a** as a brown oil (25.42 g): λ_{max} 266 mμ (log ϵ 3.77); $\mu_{C=O}$ 1735 cm^{-1}. Bulb-to-bulb distillation of a small sample of this material afforded a light orange, viscous oil.

Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: 59.08; H, 6.50; N, 4.01.

Dimethyl 3-(3-Carbomethoxypropyl)-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylate (4b). A solution of **2b** (23.5 g, assumed to be 0.09 mol), dimethyl acetylenedicarboxylate (21.3 g, 0.15 mol), and acetic anhydride (400 ml) was stirred at room temperature overnight. The reaction mixture was evaporated to dryness in vacuo and the residue obtained was dissolved in ether (300 ml). The ether solution was filtered, washed with water (200 ml), 10% K_2CO_3 solution (200 ml), and water (200 ml), then dried ($MgSO_4$) and evaporated to dryness. The brown oil that was obtained (28.60 g) was divided into two equal portions and each portion was chromatographed on a silica gel column (1000 g). Elution of these columns with 10% ethyl acetate–90% benzene afforded **4b** as a light brown oil (12.12 g). Distillation of a small sample of the brown oil furnished a light yellow, viscous oil: bp 223–224° (0.9 mmHg); λ_{max} 267 mμ (log ϵ 3.82); $\mu_{C=O}$ 1730 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.74; H, 7.07; N, 3.86.

Dimethyl 2,3,5,6,7,8-Hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-7,9-dicarboxylate (5a). Sodium hydride dispersion in mineral oil (57%, 8.2 g, 0.2 mol) was washed twice with pentane, the pentane washings were carefully decanted, and distilled THF (250 ml) containing 1 ml of methanol was added. A solution of **4a** (25 g, 0.077 mol) in distilled THF (100 ml) was added in dropwise portions over a 1-hr period to this NaH suspension under a nitrogen atmosphere with stirring at reflux. Heating of the reaction mixture at reflux was continued for an additional 90 min; then it was cooled and cautiously acidified by adding concentrated hydrochloric acid (20 ml). The acidified mixture was then dissolved in water (300 ml) and the resultant solution was extracted with chloroform (2 × 250 ml). After the combined chloroform extract was washed with brine (500 ml), the organic solution was dried (Na_2SO_4) and the solvent was removed in vacuo. Trituration of the residue with ether afforded a brown solid (17.4 g) which was re-

crystallized from ethyl acetate to give a light-tan, powdery solid (5.25 g, 23%): mp 139–141°; λ_{max} 283 mμ (log ε 4.02), 263 (3.94), 225 (3.90); $\mu_{C=O}$ 1740 and 1680 cm^{-1}; in addition to δ 3.73 and 3.81 (s, OCH_3) and 3.90 (t, CH, J = 7 Hz), a series of multiplets are present between δ 2.00 and 3.60, integrating for ten protons.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.73; H, 5.95; N, 4.83.

Dimethyl 1,2,3,4,6,7,8,9-Octahydro-1-oxopyrido[1,2-*a*]indole-2,10-dicarboxylate (5b). Using the procedure described for the synthesis of **5a**, reaction of **4b** (16.08 g, 0.047 mol) with sodium hydride dispersion (57%, 4.20 g, 0.10 mol) in distilled THF (200 ml) containing 1 ml of methanol afforded a light brown solid (11.55 g, 81%), mp 142–146°. A slightly modified work-up was employed here and involved the use of acetic acid in place of concentrated hydrochloric acid during the acidification. Recrystallization of the brown solid from water and decolorization using Darco furnished **5b** as colorless plates: mp 153–157°; λ_{max} 285 mμ (log ε 3.92), 265 (3.85), 229 (3.93); $\mu_{C=O}$ 1735 and 1680 cm^{-1}; a series of multiplets between δ 1.70 and 3.95 with two singlets at δ 3.75 and 3.81 (OCH_3 protons).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.10; H, 6.42; N, 4.43.

Preparation of Amino Acid Benzyl Ester *p*-Toluenesulfonates (9). The synthesis of sarcosine benzyl ester *p*-toluenesulfonate (**9d**) will serve as an example of the synthetic method used in this reaction. A mixture consisting of sarcosine (22.3 g, 0.25 mol), *p*-toluenesulfonic acid monohydrate (48.5 g, 0.255 mol), benzyl alcohol (100 ml), and anhydrous benzene (50 ml) was heated to reflux overnight beneath a Dean-Stark trap. After 19 hr had elapsed, 10.5 ml of water had collected in the trap. The reaction mixture was cooled, ether (300 ml) was added, and the resultant mixture was refrigerated for several days. A colorless solid (58.6 g) was obtained and addition of ether (150 ml) to the mother liquor provided a second crop of solid (76.3 g). The solids were combined and recrystallized from acetone, yielding a colorless solid (63.85 g, 73%), mp 99–102°.

Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99. Found: C, 57.75; H, 6.09; N, 3.78.

In a similar manner, alanine benzyl ester *p*-toluenesulfonate (**9b**) was prepared in 65% yield, mp 112–114° (lit.[8] mp 113–114°), and phenylglycine benzyl ester *p*-toluenesulfonate (**9c**) was synthesized in 80% yield, mp 192–194.5° (CH_3CN).

Anal. Calcd for $C_{22}H_{23}NO_5S$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.87; H, 5.75; N, 3.12.

Preparation of *N*-(4-Carbomethoxybutyroyl)amino Acid Benzyl Esters (10). The synthesis of **10a** will serve as an example of the experimental procedures used for this reaction. A mixture of glycine benzyl ester *p*-toluenesulfonate[9] (**9a**, 16.85 g, 0.05 mol) in chloroform (300 ml) was cooled to 5° and triethylamine (10.0 g, 0.1 mol) was added. After stirring for a few minutes, a solution of methyl (4-chloroformyl)butyrate (8.25 g, 0.05 mol) in chloroform (25 ml) was added in dropwise portions over a 45-min period. The reaction mixture was allowed to stand overnight at room temperature, and was then washed with dilute hydrochloric acid (2 × 200 ml) and water (300 ml) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification by bulb-to-bulb distillation provided **10a** as a light yellow oil (13.15 g, 90%): μ_{NH} 3440 cm^{-1}, $\mu_{C=O}$ 1740 and 1680 cm^{-1}; δ 1.80–2.70 (m, six protons), 3.63 (s, OCH_3), 4.06 (d, CH_2, J = 5.5 Hz), 5.16 (s, OCH_2), 6.25 (broad s, NH), 7.33 (s, phenyl protons).

Anal. Calcd for $C_{15}H_{19}NO_5 \cdot \frac{1}{2}H_2O$: C, 59.58; H, 6.68; N, 4.63. Found: C, 59.39; H, 6.72; N, 4.76.

The following *N*-(4-carbomethoxybutyroyl)amino acid benzyl esters were prepared in an analogous manner.

***N*-(4-Carbomethoxybutyroyl)alanine benzyl ester (10b)** was a colorless oil obtained in 85% yield; μ_{NH} 3440, $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 1.40 (d, CH_3, J = 7 Hz), 1.80–2.60 (m, six protons), 3.65 (s, OCH_3), 4.71 (q, CH, J = 7 Hz), 5.16 (s, OCH_2), 6.25 (broad s, NH), 7.33 (s, phenyl protons).

Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.23; H, 6.89; N, 4.58.

***N*-(4-Carbomethoxybutyroyl)phenylglycine benzyl ester (10c)** was a colorless solid, mp 68–72° (benzene–hexane), obtained in 90% yield: μ_{NH} 3440, $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 1.80–2.60 (m, six protons), 3.56 (s, OCH_3), 5.16 (s, OCH_2), 5.63 (d, CH, J = 7 Hz), 6.66 (broad d, NH), 7.10–7.40 (m, phenyl protons).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.58; H, 6.25; N, 3.81.

***N*-(4-Carbomethoxybutyroyl)sarcosine benzyl ester (10d)** was a colorless oil isolated in quantitative yield: $\mu_{C=O}$ 1730 and 1650 cm^{-1}; δ 1.80–2.60 (m, six protons), 3.06 (s, CH_3N), 3.61 (s, OCH_3), 4.18 (s, CH_2), 5.16 (s, OCH_2), 7.40 (s, phenyl protons).

Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.37; H, 6.93; N, 4.49.

Preparation of *N*-(4-Carbomethoxybutyroyl)amino Acids (11). The following description of the experimental procedures used in preparing **11a** is representative of the method used in this debenzylation reaction. A solution of **10a** (12.3 g, 0.041 mol) in ethyl acetate (200 ml) was treated with 5% palladium on carbon (1.2 g) and the mixture was hydrogenated using a Parr Shaker apparatus at room temperature and atmospheric pressure. Once the theoretical amount of hydrogen had been taken up (this usually occurred within 3 hr), the mixture was filtered and the filtrate was evaporated to dryness in vacuo. **11a** was isolated as a light yellow oil (7.75 g, 93%), which crystallized on standing at room temperature: mp 62–66°; μ_{NH} 3440, μ_{OH} 3300–3000, $\mu_{C=O}$ 1730 and 1675 cm^{-1}; δ 1.80–2.65 (m, six protons), 3.65 (s, OCH_3), 4.03 (d, CH_2, J = 6 Hz), 6.85 (t, NH, J = 6 Hz), 9.30 (s, CO_2H).

Anal. Calcd for $C_8H_{13}NO_5$: C, 47.28; H, 6.45; N, 6.89. Found: C, 46.95; H, 6.55; N, 7.00.

The following *N*-(4-carbomethoxybutyroyl)amino acids were prepared in an analogous manner.

***N*-(4-carbomethoxybutyroyl)alanine (11b)** was obtained as a light yellow oil in 89% yield, which crystallized into a colorless solid: mp 137–140° (EtAc–hexane); μ_{OH} 3690 and 3300–3000, μ_{NH} 3440, $\mu_{C=O}$ 1740 and 1680 cm^{-1}; δ 1.43 (d, CH_3, J = 8 Hz), 1.80–2.60 (m, six protons), 3.65 (s, OCH_3), 4.66 (d of q, CH, J = 8 Hz), 6.80 (d, NH, J = 8 Hz), 8.33 (s, CO_2H).

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.72; H, 6.66; N, 6.83.

***N*-(4-Carbomethoxybutyroyl)phenylglycine (11c)** was isolated as colorless needles, mp 102–105° (benzene), in 88% yield: μ_{OH} 3690 and 3300–3000, μ_{NH} 3440, $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 1.70–2.60 (m, six protons), 3.60 (s, OCH_3), 5.57 (d, CH, J = 7 Hz), 7.06 (d, NH, J = 7 Hz), 7.33 (s, phenyl protons), 9.68 (s, CO_2H).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.16; H, 6.14; N, 5.01.

***N*-(4-Carbomethoxybutyroyl)sarcosine (11d)** was obtained as a colorless oil in quantitative yield: μ_{OH} 3690 and 3300–3000, $\mu_{C=O}$ 1730 and 1650 cm^{-1}; δ 1.80–2.80 (m, six protons), 3.00 and 3.08 (s, CH_3N),[10] 3.70 (s, OCH_3), 4.10 and 4.16 (s, CH_2N),[10] 9.16 (s, CO_2H).

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.94; H, 6.63; N, 6.50.

Reaction of 11b with Acetic Anhydride and Dimethyl Acetylenedicarboxylate. 11b (7.2 g, 0.033 mol) was dissolved in acetic anhydride (125 ml) containing dimethyl acetylenedicarboxylate (5.7 g, 0.04 mol), and the solution was heated to 120° for 24 hr. After the solution was cooled and the acetic anhydride was removed in vacuo, the residue was dissolved in ether (200 ml), filtered, and washed with dilute hydrochloric acid (2 × 100 ml), then water (2 × 100 ml). The ether solution was dried ($MgSO_4$) and evaporated to dryness, leaving a brown oil (10.05 g). This oil was chromatographed on a silica gel column (1200 g) and elution with 5% ethyl acetate–95% benzene afforded **12** as a light brown oil (2.2 g, 15%): λ_{max} 258 mμ (log ε 3.90); $\mu_{C=O}$ 1735 and 1710 (shoulder), $\mu_{C=C}$ 1660 cm^{-1}; δ 2.18 (s, CH_3), 1.55–2.90 (m, six protons), 3.65, 3.70, 3.83, 3.86 (s, five OCH_3), 7.36 (s, vinyl proton).

Dimethyl 2-Phenyl-5-(3-carbomethoxypropyl)pyrrole-3,4-dicarboxylate (13). A solution comprised of **11c** (5.6 g, 0.02 mol), dimethyl acetylenedicarboxylate (4.25 g, 0.03 mol), and acetic anhydride (150 ml) was warmed to 45–55° for 6 hr, then cooled and evaporated to dryness in vacuo. The residue was dissolved in ether (100 ml) and the ether solution was washed with dilute (5%) acetic acid (100 ml), 2% $NaHCO_3$ solution (100 ml), and water (100 ml). After drying ($MgSO_4$), the solution was evaporated to dryness and the residue was triturated with hexane. **13** was obtained as a viscous orange oil (6.85 g) and this material was used without further purification in preparing **15**. A small sample of **13** was purified by bulb-to-bulb distillation and afforded a light yellow oil which had the following spectral characteristics: μ_{NH} 3470 and 3340, $\mu_{C=O}$ 1735 cm^{-1}; δ 1.70–2.50 (m, four protons), 2.93 (t, CH_2, J = 7 Hz), 3.66; 3.80, 3.83 (s, three OCH_3), 7.20–7.57 (m, phenyl protons), 9.50 (broad s, NH).

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.11; H, 5.81; N, 3.46.

Dimethyl 1-Methyl-5-(3-carbomethoxypropyl)pyrrole-3,4-dicarboxylate (14). Using the procedures described for the synthesis of **13**, reaction of **11d** (15.55 g, 0.072 mol), dimethyl acetylenedicarboxylate (12.8 g, 0.09 mol), and acetic anhydride (200 ml)

furnished **14** as a yellow oil: bp 196–198° (0.6 mmHg) (12.25 g, 57%); λ_{max} 258 mμ (log ε 3.90); $\mu_{C=O}$ 1735 cm^{-1}; δ 1.70–3.10 (m, six protons), 3.61 (s, CH_3N), 3.66, 3.78, 3.83 (s, three OCH_3), 7.08 (s, pyrrole ring proton).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.52; H, 6.24; N, 4.42.

Dimethyl 2-Phenyl-4-oxo-4,5,6,7-tetrahydroindole-3,5-dicarboxylate (15). To a suspension of sodium hydride (57% dispersion in mineral oil, 2.1 g, 0.05 mol, washed with pentane to remove the mineral oil) in distilled THF (50 ml) containing 0.2 ml of methanol, a solution of **13** (6.85 g, 0.019 mol) in distilled THF (25 ml) was added in dropwise portions over a 30-min period. The reaction mixture throughout this addition was kept under a nitrogen atmosphere and was stirred while the mixture was heated to reflux. Upon completion of the addition of **13**, the mixture was refluxed for an additional 3 hr, then cooled to 5° and acidified with acetic acid (20 ml) and water (200 ml). The aqueous mixture was extracted with chloroform (2 × 100 ml), and the combined organic extract was washed with brine (200 ml), dried (Na_2SO_4), and evaporated to dryness in vacuo. The brown tarry residue (6.05 g) was then chromatographed on a silica gel column (1000 g) and elution with 20% ethyl acetate–80% benzene furnished a brown semisolid (2.23 g) which was recrystallized from benzene–ether to give **15** as a colorless powder (0.93 g, 15%): mp 121–123°; μ_{NH} 3440 and 3300, $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 2.10–3.10 (m, four protons), 3.45 (t, CH, J = 6 Hz), 3.65 and 3.68 (s, two OCH_3), 7.30–7.50 (m, phenyl protons), 10.13 (broad s, NH).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28. Found: C, 66.11; H, 5.15; N, 4.25.

Dimethyl 1-Methyl-4-oxo-4,5,6,7-tetrahydroindole-3,5-dicarboxylate (16). Following the procedure described for the synthesis of **15**, reaction of **14** (4.5 g, 0.015 mol) with sodium hydride (57% dispersion, 2.1 g, 0.05 mol) in distilled THF (50 ml) containing 0.2 ml of methanol furnished a dark orange oil (5.20 g) which was chromatographed on a silica gel column (500 g). Elution of the column with 5% ethanol–95% benzene afforded **16** as a tan solid (1.85 g, 46%): mp 95–100°; $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 2.30–3.00 (m, four protons), 3.50 (t, CH, J = 7.5 Hz), 3.56 (s, CH_3N), 3.71 and 3.78 (s, two OCH_3), 7.23 (s, indole ring proton).

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.95; H, 5.85; N, 4.88.

Acknowledgment. The author wishes to thank Ms. Mary Anne Oram for technical assistance, Mr. Michael Scaros for carrying out the catalytic hydrogenation reactions, and the Searle Laboratories column chromatography group.

Registry No.—**1a**, 147-85-3; **16**, 535-75-1; **2a**, 54384-27-9; **2b**, 54383-97-0; **2b** dicyclohexylamine salt, 54383-98-1; **4a**, 54383-99-2; **4b**, 54384-00-8; **5a**, 54384-01-9; **5b**, 54384-02-0; **8a**, 56-40-6; **8b**, 56-41-7; **8c**, 69-91-0; **8d**, 107-97-1; **9a**, 1738-76-7; **9b**, 42854-62-6; **9c**, 54384-04-2; **9d**, 54384-06-4; **10a**, 54384-07-5; **10b**, 54384-28-0; **10c**, 54384-08-6; **10d**, 54384-09-7; **11a**, 54384-10-0; **11b**, 54384-29-1; **11c**, 54384-11-1; **11d**, 54384-12-2; **12**, 54384-13-3; **13**, 54384-14-4; **14**, 54384-15-5; **15**, 54384-16-6; **16**, 54384-17-7; methyl (4-chloroformyl)butyrate, 1501-26-4; dicyclohexylamine, 101-83-7; dimethyl acetylenedicarboxylate, 762-42-5; *p*-toluenesulfonic acid, 104-15-4; benzyl alcohol, 100-51-6.

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(3) Recent examples of this reaction include the following: J. W. ApSimon, D. G. Durham, and A. H. Rees, *Chem. Ind. (London)*, 275 (1973); M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, **39**, 731 (1974).
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(10) The presence of two signals for both the CH_3N and CH_2N protons is due to the restricted rotation of the tertiary amide group; H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970).

Rearrangement of Pyruvates to Malonates. Synthesis of β-Lactams

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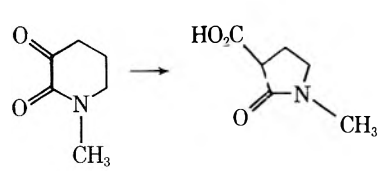
The oxidative rearrangement of α-ketoacyl derivatives to malonates has been extended to include a synthesis of β-lactams by oxidative (periodate) ring contraction of α-keto-γ-lactams. The rearrangement introduces a carboxyl group at the α carbon of the β-lactam and is capable of converting β-substituted α-keto-γ-lactams to the α,α-disubstituted ring-contracted derivatives. The application of the reaction to several simple mono- and bicyclic lactams is presented.

The fortuitous observation that periodate treatment of the δ-lactam 1-methyl-3-hydroxy-3-hydroxymethyl-2-piperidinone led to the formation of γ-lactam **2** was followed by the determination that the actual precursor of **2** was the α-keto-δ-lactam **1**.[1] The possibility that related acyclic derivatives might undergo a similar rearrangement was realized with the demonstration that α-keto esters and amides can be rearranged to malonates.[1] Rearrangement of the δ-lactam **1** to the ring-contracted derivative **2** also suggested



1 **2**

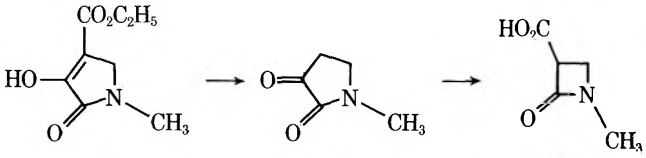
the possibility of extending the reaction to provide a synthesis of β-lactams. Formation of β-lactams by this ring-contraction reaction represents a potential synthesis of β-lactams containing either mono- or difunctionality at the α carbon, and the rearrangement conditions of periodate at room temperature and neutral pH suggested compatibility of the approach with the presence of a variety of substituents.

Examination of the numerous methods currently available for β-lactam synthesis[2] reveals that nearly all approaches require ring closure directly to the four-membered ring. Of the few methods utilizing ring expansion or ring contraction,[3] only the photolytic Wolff rearrangement of 3-diazo-2,4-pyrrolidinediones appears to have received more than passing attention.[3d,e] The potential advantages of β-lactam formation by ring contraction under mild and

selective conditions prompted the synthesis of several model compounds, and we now report application of the oxidative rearrangement to the monocyclic α-keto-γ-lactam **4** and to the bicyclic derivatives **14**, **15**, and **16**.[4]

Results and Discussion

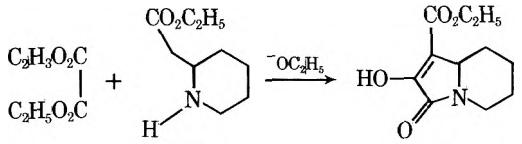
The first γ-lactam examined was 1-methyl-2,3-pyrrolidinedione (**4**), which is the γ-lactam most analogous to the δ-lactam **1**. An unsuccessful attempt has been reported[5a] to obtain **4** from the 4-ethoxycarbonyl derivative **3** by chloroform extraction after hydrolysis in hydrochloric acid, and subsequently the isolation of **4** as its 4-benzylidine derivative was reported.[10] Using the reaction conditions employed previously but with isolation by continuous extraction followed by sublimation, we have obtained **4** in 63% yield.



3 **4** **5**

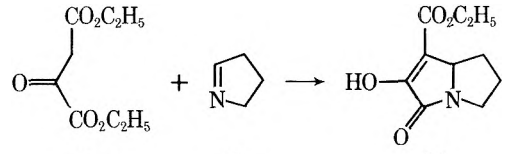
The oxidation of **4** with sodium periodate in an aqueous buffer at pH 7.0 was carried out in the manner used for oxidation of the δ-lactam **1**. The resulting carboxy-β-lactam **5** was obtained in 30% yield, without any attempt at optimization. We then turned from this monocyclic example to examine bicyclic models which would be analogous with the β-lactam antibiotics.

Preparation of Azabicyclo[4.3.0]nonane-8,9-diones. The required precursor of a β-lactam which can lead to a simple bicyclic analog of the cephalosporin antibiotics is the α-keto-γ-lactam **14**. In turn, **14** could be obtained from the bicyclic ester **7** in the same manner used for the conversion of **3** to **4**. Two approaches have been applied successfully to the synthesis of bicyclic esters such as **7**. One approach, an extension of the method used to synthesize the monocycle, is illustrated by the synthesis of **7** from the β-amino ester **6** and diethyl oxalate.[11] The other approach is



6 **7**

an extension of the imine-addition method,[6a] illustrated by the synthesis of **10** from 1-pyrroline (**9**) and diethyl oxalacetate (**8**).[12] Although **10** has also been obtained by condensation of ethyl 2-pyrrolidinylacetate with diethyl oxalate,[11] the synthesis of **7** from 2,3,4,5-tetrahydropyridine (**12**) has not been reported.

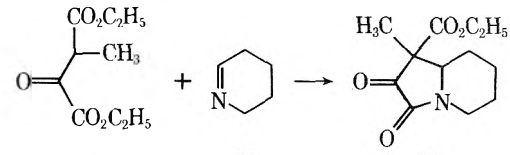


8 **9** **10**

Initially **7** was obtained according to the published procedure.[11] We then planned to make 7-substituted derivatives, e.g., **13**, by alkylation of **7** with methyl iodide, but alkylation under a variety of conditions (sodium hydride in tetrahydrofuran or dimethylformamide, thallous ethoxide in benzene) gave exclusively the O-alkylated product. Similar resistance to C-alkylation was apparently encountered and circumvented by condensation of substituted pyruvic acids or oxalacetates with an imine.[8]

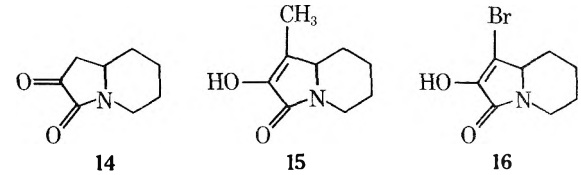
Application of the imine-addition approach to the synthesis of **13** required use of imine **12** (Δ[1]-piperideine), which is an elusive species. No attempt was made to isolate it as the monomer. Instead, a solution of **12** in ethanol–ether was prepared by dehydrohalogenation of *N*-chloropiperidine according to the method used for the preparation of 1-pyrroline,[13] which in turn is based on the procedure for the preparation of a trimer of **12**, α-tripiperideine.[14] The preparation of *N*-chloropiperidine by treatment of piperidine acetate with hypochlorite was replaced by the more convenient procedure employing direct formation from piperidine with *N*-chlorosuccinimide.[15]

Before attempting the condensation reaction with a substituted ester, we carried out the condensation of **12** with diethyl oxalacetate. Refluxing the ethanol–ether solution of **12** with a benzene solution of diethyl oxalacetate produced the desired ester **7** in 48% yield, thus providing **7** more conveniently than by the published procedure.[11] The analogous condensation of **12** with the substituted ester **11** required a longer reaction time and produced **13** in 30% yield.



11 **12** **13**

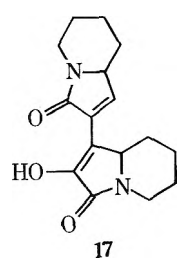
Acid-catalyzed hydrolysis and decarboxylation of ethyl ester **7** was carried out in refluxing 10% hydrochloric acid, resulting in a 60% yield of **14**. A similar procedure applied to **13** gave **15** in 74% yield. The bromo analog **16** was obtained in 80% yield from **14** by bromination at room temperature either in a heterogeneous mixture with copper(II) bromide in methylene chloride or by homogeneous bromination with copper(II) bromide in methanol.



14 **15** **16**

The properties of these bicyclic analogs of 2,3-pyrrolidinediones parallel the properties of the monocyclic compounds. The infrared spectra of **4**, **13**, and **14** all show ketone absorptions between 1767 and 1783 cm^{-1} and amide absorptions between 1700 and 1720 cm^{-1}. In contrast, **15** exhibits a broad band at 1662 cm^{-1} and **16** gives a similar band at 1680 cm^{-1}. Neither **4** nor **14** give a positive test with ferric chloride, whereas the ethyl ester **7** and the enols **15** and **16** display deep colors of burgundy or indigo.

The similarity of **14** with its monocyclic analogs is further illustrated by its self-condensation to **17**, a conversion



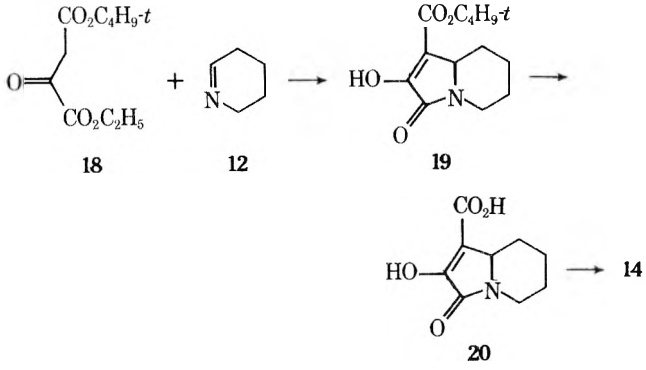
17

sufficiently facile to preclude chromatography on silica gel or storage (even at 0°) for more than several days. Infrared and ultraviolet absorption data are consistent with an enolized structure, and the NMR spectrum confirms the indicated structure by exhibiting a vinyl doublet at δ 6.6 and two sharp singlets for the enolic proton at δ 12.9. The simi-

lar aldol condensation products from monocyclic lactams[5a] are reported to produce a green to green-blue color with ferric chloride; **17** gives a green color.

2,3-Pyrrolidinediones with no substituents at C-4 invariably appear to be obtained from 4-alkoxycarbonyl precursors,[5] and the conversion of these precursors to the C-4 unsubstituted derivatives is usually quite troublesome. Our own experience with the conversion of the ethyl ester **7** to the C-7 unsubstituted derivative **14** has indicated that the time required for complete conversion is also sufficient to allow for significant side reactions. Numerous variations in the procedure resulted in no improvement in yield. Basic hydrolysis to an acid such as **20**, generally expected to be easy, has repeatedly proved to be impossible,[8,16,17] as was the case with **7**. However, if the acid could be obtained by a nonhydrolytic procedure, then decarboxylation could perhaps be achieved under conditions milder than those required for hydrolysis of the ester.

Accordingly, we prepared such 7-carboxyl derivatives from their *tert*-butyl esters, and these acids were found to decarboxylate readily at room temperature in the presence of kieselgel or powdered glass. Application of these observations to an improved synthesis of **14** required the acid **20**, which was obtained conveniently and quantitatively from the *tert*-butyl ester **19** by treatment with acetic acid saturated with HBr. The *tert*-butyl ester **19** was obtained from **12** in the same manner used for the synthesis of ethyl ester **7**. Condensation of the ester **18**[18] with **12** gave **19** in 60% yield.



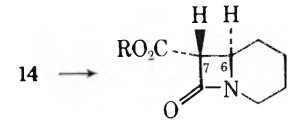
18 12 19 20

The acid **20** decarboxylated with such ease that only spectral characterization was possible. A dilute aqueous sample of **20** prepared for ultraviolet characterization decarboxylated rapidly at room temperature, giving a uv absorbance corresponding exactly with the absorbance of **14**.

Preparative decarboxylation of **20** can be carried out under a variety of conditions. Shaking **20** as a solution in methanol–acetone and a small amount of acetic acid in the presence of powdered Pyrex leads to decarboxylation at room temperature within ~2 hr. Decarboxylation in refluxing methanol–acetone is complete after about 1 hr, whereas the same conditions in the presence of powdered Pyrex lead to total decarboxylation in less than 7 min. Progress of the conversion can be followed in the uv, and the uv spectra of these solutions indicate the complete absence of **17**, the product of self-condensation. The conversion of **19** to **14** thus is quantitative, and sublimation results in a 90% yield of **14**, the residue being a mixture of **14** and **17** as seen from its infrared spectrum.

Periodate Oxidation of Bicyclic α-Ketolactams 14, 15, and 16. The rate of oxidation of **14** was determined conveniently by monitoring the uv absorbance of periodate at 223 nm. A constant value corresponding to uptake of approximately 100 mol % of periodate was obtained within 15–20 min. Comparable rates of periodate uptake were observed during the oxidation of the bicyclic analogs **15** and **16**. Phosphate buffers with sodium as the cation were used initially, but the heterogeneous reaction mixtures which frequently resulted frustrated attempts to follow the oxidation. Buffering solutions prepared by titrating phosphoric acid with lithium hydroxide proved satisfactory, but are limited by extensive precipitation above pH ~7.7.

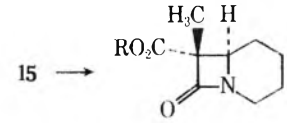
Oxidation of **14** proceeded smoothly to give **21**[19] in 70% yield. Neither the 60- nor the 100-MHz NMR spectra of **21**,



21, R = H
22, R = CH_3

or its methyl ester **22**, in deuteriochloroform revealed H-7 resolved from other downfield absorptions. However, use of pyridine instead of chloroform gave rise to substantial differential effects on the chemical shifts of the downfield protons, and a 220-MHz spectrum completely resolved H-7 from the other two absorptions. The 1.8-Hz coupling constant establishes the C-6 and C-7 protons as trans;[20] no absorption corresponding to the cis isomer was observed. Samples of ester **22** were obtained from both crude and recrystallized **21** and subjected to gas chromatographic conditions which successfully resolved esters **27** and **28**.[21] Both samples gave a single symmetrical peak, indicating the absence of the cis isomer.

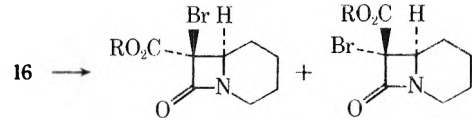
Methyl analog **15** was chosen as a simple example for determining the effect on ring contraction of an alkyl substituent at the β carbon of an α-keto-γ-lactam. Oxidation of **15** produced in 50% yield only one of the two possible β-lactam isomers, **23**, which was subsequently shown by X-ray



23, R = H
24, R = CH_3

crystallography[22] to have the carboxyl group located trans to the fused ring. The crude oxidation product was esterified and chromatographed[21] in the same manner as the unsubstituted β-lactam **21**. No peak corresponding to the other isomer was observed.

The bromo analog **16** was viewed as a potential intermediate for the synthesis of other α-keto-γ-lactams and as a compound which could give a β-lactam amenable to a variety of synthetic manipulations. Oxidation of **16** led to a 40% yield of β-lactam, subsequently shown to be a mixture of the stereoisomers **25** and **26**. Gas chromatography[21] of the



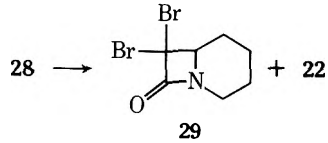
27, R = H **26**, R = H
25, R = CH_3 **28**, R = CH_3

product obtained by esterification with diazomethane gave two peaks which corresponded in molecular formula with the desired methyl ester. The ratio of peak areas was approximately 9:1. Complete separation of the isomers was then achieved by column chromatography on kieselgel, and the isomer ratio determined from gas chromatography was confirmed.

The separated isomers were hydrolyzed in nearly quantitative yield to the acids **25** and **26** with 1 equiv of potassi-

um hydroxide in 50% aqueous dioxane. X-Ray crystallographic studies[22] of these acids indicated that the carboxyl group of the major isomer, **25**, is located in the same manner as the carboxyl group of **21** and **23**, that is, trans to the fused ring.

Neither the NMR spectrum nor TLC of the original 9:1 mixture of esters **27** and **28** indicated the presence of other materials, but gas chromatography of the mixture led to several peaks in addition to those corresponding to **27** and **28**. The minor ester **28** initially was isolated by gas chromatography of mixtures enriched in this isomer, and these enriched mixtures gave relatively much greater amounts of the other materials. It was then found that stepwise lowering of the injection port temperature increased the peak area due to **28** at the expense of the combined peak areas due to the other materials; peak area due to **27** always remained the same. Injection of pure **27** gave a single peak; injection of pure **28** gave the peak corresponding to **28** plus previously observed peaks, thus indicating that these contaminating materials are due to decomposition of **28**, but not **27**, in the metal injection port of the gas chromatograph. The decomposition products were collected and gave R_f values on TLC distinctly different from the values for either **27** or **28**, confirming that they were not present initially but were formed during gas chromatography. The structures of the two major decomposition products were established as **22** and the α,α-dibromo-β-lactam **29**. The ir spectrum of **29** revealed a single carbonyl absorption at



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1782 cm^{-1}, and the NMR spectrum retained all of the absorptions characteristic of these bicyclic β-lactams.

Further studies of the scope of the oxidative ring contraction reaction of α-keto-γ-lactams are continuing and will be the subject of a subsequent report.

Experimental Section[23]

1-Methyl-2,3-pyrrolidinedione (4).[24] 4-Ethoxycarbonyl-3-hydroxy-1-methyl-2-oxo-3-pyrroline (**3**, 10.0 g, 0.054 mol)[5a] was heated for 50 min in refluxing 2.9 *M* HCl (500 ml). Continuous extraction with CH_2Cl_2 for 48 hr gave, after evaporation of solvent, a brown solid which was purified by sublimation at 90° (10 μ) to give 3.88 g (63%) of off-white solid: ir (film) 1767, 1701 cm^{-1}; NMR δ 2.75 (2 H, t, *J* = 5.5 Hz), 3.13 (3 H, s), 3.74 (2 H, t, *J* = 5.5 Hz). Alternatively, the crude solid was recrystallized from ether, giving **4** with spectral properties (ir, NMR) identical with the above, mp 89–91°.

Anal. Calcd for $C_5H_7NO_2$: C, 53.1; H, 6.2; N, 12.4. Found: C, 52.8; H, 6.0; N, 12.3.

7-Ethoxycarbonyl-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (7) from 2,3,4,5-Tetrahydropyridine (12). Ethyl sodioethoxalylacetate (52.5 g, 0.25 mol) was stirred with a mixture of water (125 ml), benzene (250 ml), and 6 *N* H_2SO_4 (42 ml). The benzene layer was separated, washed with water (2 × 150 ml), and dried (Na_2SO_4). An ether–ethanol solution of **12** was prepared from piperidine (21.5 g, 0.25 mol)[13] and the solutions of **12** and diethyl oxalacetate were combined and refluxed for 3 hr, then washed with brine (2 × 50 ml), dried (Na_2SO_4), and evaporated. The remaining dark oil was dissolved in 30 ml of ether. On standing, crystals were formed in 48% yield. Spectral (ir and NMR) properties and the melting point (115–116°) were identical with those of an authentic sample.[11]

7-Ethoxycarbonyl-7-methyl-8,9-dioxo-1-azabicyclo[4.3.0]-nonane (13). Diethyl methyloxalacetate (**11**, 12.8 g, 0.063 mol)[25] was dissolved in benzene (125 ml) and refluxed for 18 hr with a solution of **12** prepared from piperidine (0.125 mol) as described previously. The solution was washed with brine (2 × 50 ml) and dried (Na_2SO_4) and the solvents were evaporated. The remaining dark oil was dissolved in ether)~20 ml) and allowed to stand overnight, giving crystals in 30% yield. Recrystallization from hexane–$CHCl_3$ gave colorless prisms: mp 92–93°; ir 1777, 1727 cm^{-1} (br); NMR δ 0.9–2.2 (6 H, m), 1.23 (3 H, t, *J* = 7 Hz), 1.4 and 1.5 (3 H, two singlets), 2.93 (1 H, m), 3.3–4.6 (2 H, m), 4.17 (2 H, q, *J* = 7 Hz); mass spectrum *m/e* (rel intensity) 239 (M^+, 11), 211 (10), 166 (100).

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.2; H, 7.2; N, 5.9. Found: C, 60.1; H, 7.0; N, 6.0.

7-*tert*-Butoxycarbonyl-8-hydroxy-9-oxo-1-azabicyclo-[4.3.0]non-7-ene (19). A mixture of piperidine (2.72 g, 0.032 mol), *N*-chlorosuccinimide (7.45 g, 0.56 mol), and ether (165 ml) was stirred at room temperature for 0.5 hr and filtered, and the precipitate was rinsed with ether (10 ml). The filtrate was washed with water (4 × 100 ml) and brine (50 ml) and then dried ($MgSO_4$). Just before use in the next step the extract was filtered and concentrated to about 20 ml.

The ether solution of *N*-chloropiperidine was added over a period of 7 min to a stirred solution of absolute ethanol (16 ml) containing 85% KOH (2.11 g, 0.032 mol of KOH). The internal temperature of the ethanol solution was kept between 5 and 10° during addition. After addition was complete the cooling bath was replaced with a large water bath at room temperature and the ethanol–ether mixture was stirred in this bath for 2 hr. After filtration of the mixture and rinsing of the precipitate with absolute ethanol, a filtrate with a volume of 32 ml was obtained.

To 30 ml of the above solution was added freshly distilled ethyl 3-*tert*-butoxycarbonyl-2-oxopropionate[18] (3.24 g, 0.015 mol) in benzene (15 ml). The resulting solution was refluxed for 3.5 hr, then allowed to stand overnight at room temperature. With the internal temperature of the reaction mixture <25°, 2.9 *M* HCl was added until the aqueous layer gave pH ~1. The mixture was then diluted with water (50 ml) and extracted with benzene (2 × 100 ml). The combined extracts were washed with brine (30 ml), dried ($MgSO_4$), filtered, and evaporated to give a yellow solid which was chromatographed on silica gel (40 g) with $CHCl_3$. Recrystallization from $CHCl_3$–hexane gave after collection of three crops 2.28 g (60%) of colorless crystals: mp 142–146°; ir 1701 (s), 1675 (s), 1631 cm^{-1} (m); NMR δ 0.7–2.2 (5 H, m), 1.58 (9 H, s), 2.2–3.2 (2 H, m), 3.92 (1 H, dd, *J* = 11, 4 Hz), 4.35 (1 H, br dd, $J_{\alpha,kb}$ mgr = 13 Hz), 9.2 (1 H, broad hump); uv (95% EtOH) λ_{max} 245 nm (ε 8820), 304 (5500); uv (H_2O, pH 4.6) 247 (9500), 304 (4250); uv (H_2O, pH 6.0) 240 (6850), 304 (10,300); mass spectrum *m/e* (rel intensity) 253 (M^+, 1), 197 (3), 180 (7), 153 (18), 152 (14), 124 (6), 123 (5), 59 (100).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.6; H, 7.6; N, 5.5. Found: C, 61.8; H, 7.6; N, 5.9.

8,9-Dioxo-1-azabicyclo[4.3.0]nonane (14). Ester **7** (300 mg, 1.33 mmol) was heated for 2.5 hr in refluxing 2.9 *M* HCl (15 ml). Continuous extraction with CH_2Cl_2 gave, after drying ($MgSO_4$) and evaporation of solvent, a crude solid which was purified by sublimation at 57° (20 μ) to give 124 mg (60%) of solid: mp 62–66°; ir 1783, 1708 cm^{-1}; nmr δ 1.1–2.3 (6 H, m) 2.4–3.2 (2 H, m), 2.92 (1 H, m), 3.80 (1 H, m), 4.35 (1 H, br dd, $J_{\alpha,\beta}$ = 13 Hz); uv (water, acidic or neutral) λ_{max} 256 nm (ε 4000); mass spectrum *m/e* (rel intensity) 153 (M^+, 85), 125 (66), 41 (100).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.1. Found: C, 62.7; H, 7.1; N, 9.3.

7-Carboxy-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (20). To the *tert*-butyl ester **19** (146 mg, 0.58 mmol) in acetic acid (0.7 ml) was addec acetic acid saturated with HBr (11.5 ml). After being stirred at room temperature for 10 min the solution was evaporated at room temperature, resulting in a solid which was redissolved without heating in methanol. Evaporation of this solution gave 113 mg (100%) of solid: mp 142–144° dec; ir (Nujol mull) 1661 cm^{-1} (broad); NMR (DMSO-d_6) δ 0.7–2.0 (5 H, m), 2.2–3.2 (2 H, m), 3.7–4.3 (2 H, m); uv (H_2O, pH 6.3) λ_{max} 245 nm (ε 7700), shoulder at ~295 (3200); mass spectrum *m/e* (rel intensity) no observable M^+, 153 ($M^+ - 44$, 72), 125 (26), 124 (40), 41 (100).

Decarboxylation of Acid 20. Powdered Pyrex was prepared by taking granular Pyrex of minimum 80 mesh and grinding it with mortar and pestle. The amount of glass initially used was arbitrary, but relative amounts were always the same and taken from the same batch.

A. Decarboxylation at Room Temperature. The acid **20** (13 mg, 0.07 mmol) was dissolved in methanol (1.6 ml) and acetone (1.6 ml). After addition of 2 drops of acetic acid and 0.22 g of powdered Pyrex the mixture was shaken on a mechanical shaker at room temperature. Aliquots were periodically removed and their uv spectra indicated the presence only of **14** within 1.5–3.5 hr.

B. Decarboxylation at Reflux and Isolation of 14 by Sublimation. The *tert*-butyl ester **19** (166 mg, 0.65 mmol) was converted to the acid **20** as described previously. After **20** was dissolved at

room temperature in methanol (16 ml) and acetone (16 ml), powdered Pyrex (2.15 g) was added and the stirred mixture was refluxed for 7 min. Examination of the uv spectrum of an aliquot indicated the presence only of **14**. The mixture was cooled to room temperature, filtered through Celite, and evaporated at room temperature to give a residue which was immediately taken up in CH_2Cl_2 (50 ml) and dried ($MgSO_4$) for ca. 15 min. After filtration through Celite and evaporation of solvent, the residue was transferred with CH_2Cl_2 to a sublimer, evaporated, and sublimed at a bath temperature of 57° (10 μ), yielding 89 mg (90%) of **14** identical with authentic material by ir and melting point comparison. An ir spectrum of the residue after sublimation (7 mg) indicated an approximately 1:1 mixture of **14** and **17**.

Aldol Condensation Product from 14 (17). A sample of crude **14** was allowed to stand overnight at room temperature and closed to the atmosphere. Warming the solid to 70° did not result in melting. Recrystallization from hexane–$CHCl_3$ gave a cream-colored, amorphous solid: mp 219–224° dec; ir 1690, 1649, 1580 cm^{-1}; NMR δ 0.9–2.5 (12 H, m), 2.90 (2 H, m), 3.7–4.5 (4 H, m), 6.59 (1 H, d, J = 2 Hz), 12.80 (0.2 H, s), 12.93 (0.8 H, s); uv (95% C_2H_5OH) 249 nm (ϵ 12,300), 297 (14,200); mass spectrum m/e (rel intensity) 288 (M^+, 77), 270 (89), 242 (25), 214 (11), 41 (100).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.6; H, 7.0; N, 9.7. Found: C, 66.6; H, 6.9; N, 9.7.

7-Methyl-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (15). Ester **13** (1 g, 4.2 mmol) was heated for 1.5 hr in refluxing 2.9 M HCl (47 ml). Continuous extraction with CH_2Cl_2 gave, after drying ($MgSO_4$) and evaporation of solvent, a yellow solid which was recrystallized from benzene as prisms (520 mg, 74%): mp 191–193°; ir 3548 (shoulder), 3207 (br), 1662 cm^{-1} (br); NMR δ 0.7–2.4 (6 H, m), 1.85 (3 H, s), 2.82 (1 H, m), 3.50 (1 H, dd, J = 11, 4 Hz), 4.23 (1 H, br dd, $J_{\alpha,\beta}$ = 13 Hz), 8.5 (1 H, broad s); mass spectrum m/e (rel intensity) 167 (M^+, 100), 152 (94).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.6; H, 7.8; N, 8.4. Found: C, 64.6; H, 7.9; N, 8.5.

7-Bromo-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (16). Ketone **14** (1.2 g, 7.8 mmol) copper(II) bromide (3.50 g, 15.7 mmol, pulverized) and CH_2Cl_2 (109 ml) were mechanically stirred in the dark for 22 hr. After filtration through Celite and evaporation of solvent the residue was chromatographed on silica gel (20 g) with $CHCl_3$, giving 1.46 g (80%) of solid which was recrystallized from hexane–$CHCl_3$: mp 121–122° dec; ir 3451 (shoulder), 3078 (br), 1680 cm^{-1}; NMR δ 0.9–2.5 (6 H, m), 2.87 (1 H, m), 3.78 (1 H, dd, J = 11, 4 Hz), 4.29 (1 H, br dd, J = 13 Hz), 9.25 (1 H, s); mass spectrum m/e (rel intensity) 233, 231 (M^+, 33), 152 (100), 124 (37).

Anal. Calcd for $C_8H_{10}BrNO_2$: C, 41.4; H, 4.3; N, 6.0. Found: C, 41.6; H, 4.3; N, 6.1.

3-Carboxy-1-methyl-2-azetidinone (5).[24] A mixture of the pyrrolidinedione **4** (452 mg, 4.0 mmol), sodium periodate (5.14 g, 24.0 mmol), and a sodium–phosphate buffer (0.2 M, 150 ml) of pH 7.0 (before addition of periodate) was stirred in the dark for 24 hr. With ice-bath cooling, the periodate was destroyed by slow addition of aqueous $NaHSO_3$ (2 M, 60 ml) while keeping the pH near 7 by addition of saturated K_2CO_3 solution. The resulting pH 7 solution was reduced to ca. half volume by lyophilization, adjusted to pH 4 with phosphoric acid, and continuously extracted with CH_2Cl_2 for 7 days. The resulting light amber oil (220 mg) was chromatographed on silica gel (15 g) with $CHCl_3$–CH_3OH–HCO_2H (10:1:0.05), yielding 153 mg (30%) of colorless oil: ir (neat) 1745 cm^{-1} (br); NMR δ 2.86 (3 H, s), 3.50 (2 H, m), 4.10 (1 H, m), 9.2 (1 H, s); mass spectrum m/e (rel intensity) 129 (M^+, 15), 101 (100), 84 (10), 73 (30), 72 (21), 58 (37), 55 (80).

Anal. Calcd for $C_5H_7NO_3$: C, 46.5; H, 5.5; N, 10.9. Found: C, 46.3; H, 5.6; N, 10.9.

Oxidation with Sodium Periodate. General Procedure. A 0.2 M buffer was prepared by titrating phosphoric acid with aqueous LiOH. A volume of buffer was chosen such that the concentration of starting material was 0.02 M, sodium periodate was added, and the pH was adjusted to the desired value. Depending on its rate of solution in water, starting material was added all at once as a fine powder, or was added with vigorous stirring over a period of several minutes as a solution (volume ~5% of volume of buffer) in CH_3OH or tetrahydrofuran (THF). Aliquots were removed periodically and examined in the uv. Periodate and iodate were destroyed by addition of an approximately stoichiometric amount of $NaHSO_3$ dissolved in a minimum of water while keeping the pH near 7 by the addition of 2 M NaOH. Following extraction of the neutral solution with CH_2Cl_2, the pH was adjusted to 2.0 with phosphoric acid and the solution was continuously extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and evaporated.

7-Carboxy-8-oxo-1-azabicyclo[4.2.0]octane (21). The ketone **14** (3.34 g, 0.022 mol) was oxidized with $NaIO_4$ (0.044 mol) at pH 6.3 as described above to give **21** in 70% yield. The product was recrystallized from hexane–acetone: mp 145–146° dec; ir 1753, 1722 cm^{-1}; NMR δ 1.2–2.3 (6 H, m), 2.81 (1 H, m), 3.5–4.1 (2 H, m), 3.75 (1 H, d, J = 1.8 Hz), 9.2 (1 H, s); mass spectrum m/e (rel intensity) 169 (M^+, 12), 141 (100), 125 (11), 124 (32), 123 (31), 97 (42).

Anal. Calcd for $C_8H_{11}NO_3$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.9; H, 6.8; N, 8.3.

7-Methoxycarbonyl-8-oxo-1-azabicyclo[4.2.0]octane (22). The acid **21** in ether–methanol (5:1, v/v) was treated with excess CH_2N_2 in ether. After destruction of the excess with acetic acid, evaporation of solvents left **15** as an oil; ir 1760, 1730 cm^{-1}; NMR (CCl_4) δ 1.1–2.3 (6 H, m), 2.75 (1 H, m), 3.4–4.0 (2 H, m), 3.55 (1 H, d, J = 1.8 Hz), 3.70 (3 H, s); mass spectrum m/e (rel intensity) 184 (M^+ + 1, 92), 183 (M^+, 31), 156 (100), 155 (82), 124 (89), 97 (55), 96 (47). An analytical sample was prepared by preparative GC.

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.1; N, 7.6. Found: C, 59.0; H, 7.1; N, 7.6.

7-Carboxy-7-methyl-8-oxo-1-azabicyclo[4.2.0]octane (23). The methyl analog **15** (500 mg, 3.0 mmol) was oxidized with sodium periodate (2.60 g, 12.1 mmol) at pH 6.3 as described above. The resulting solid was recrystallized from hexane–acetone, yielding 285 mg (53%) of colorless prisms: mp 179–181°; ir 1743, 1713 cm^{-1}; NMR δ 1.2–2.1 (6 H, m), 1.52 (3 H, s), 2.76 (1 H, m), 3.6–4.0 (m, 2 H), 10.6 (1 H, s); mass spectrum m/e (rel intensity) 183 (M^+, 4), 155 (68), 41 (100).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.1; N, 7.6. Found: C, 59.0; H, 6.8; N, 7.6.

7-Methoxycarbonyl-7-methyl-8-oxo-1-azabicyclo[4.2.0]octane (24). A solution of the acid **23** (50 mg) in THF (15 ml) was treated with excess CH_2N_2 in ether. The solution was stirred for 18 hr and the solvents were evaporated to yield **17** as an oil: ir 1756, 1725 cm^{-1}; NMR δ 1.0–2.0 (6 H, m), 1.45 (3 H, s), 2.85 (1 H, m), 3.6–4.0 (2 H, m), 3.72 (3 H, s); mass spectrum m/e (rel intensity) 197 (M^+, 6), 169 (69), 166 (32), 138 (66), 137 (66), 41 (100). An analytical sample was prepared by preparative GC.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.9; H, 7.7; N, 7.1. Found: C, 60.9; H, 7.6; N, 7.2.

7-Bromo-7-methyoxycarbonyl-8-oxo-1-azabicyclo[4.2.0]octane (27 and 28). The bromo analog **16** (500 mg, 2.15 mmol) was oxidized with $NaIO_4$ (920 mg, 4.3 mmol) as described above to yield 215 mg (40%) of **19** and **20** as a light yellow oil. A solution of this oil in ether was treated with excess CH_2N_2 in ether. After destruction of the excess with acetic acid and evaporation of solvent, the residue was chromatographed on silica gel (10 g) to give the esters **27** and **28** as a colorless oil. A portion of this oil (166 mg) was chromatographed on kieselgel (23 g) with ether–petroleum ether (bp 30–60°) (3:1 v/v). The major isomer (**27**) was eluted first, and mixed portions containing 11 mg were recycled.

27: 139 mg; ir 1776, 1738 cm^{-1}; NMR (CCl_4) δ 1.2–2.1 (6 H, m), 2.85 (1 H, m), 3.5–4.0 (2 H, m), 3.82 (3 H, s); mass spectrum m/e (rel intensity) 263, 261 (M^+, 2), 235, 233 (20), 182 (100), 154 (14).

28: 15 mg; ir 1776, 1749 cm^{-1}; NMR (CCl_4) δ 1.1–2.2 (6 H, m), 2.82 (1 H, m), 3.5–4.0 (2 H, m), 3.82 (3 H, s); mass spectrum m/e (rel intensity) 263, 162 (M^+, 0.07), 235, 233 (1), 203, 201 (0.5), 182 (7), 154 (1.5), 43 (100).

7-Bromo-7-carboxy-8-oxo-1-azabicyclo[4.2.0]octane (25 and 26). Potassium hydroxide in 50% aqueous dioxane (0.10 M, 4.24 ml) was added to a solution of **28** (111 mg, 0.42 mmol) in 50% aqueous dioxane (2.4 ml). After standing for 12 hr, the solution was added to ice water (20 ml) and extracted with CH_2Cl_2 (3 × 15 ml). The combined extracts were dried ($MgSO_4$) and evaporated to yield 6 mg of unreacted **28** (by TLC comparison).

The aqueous solution was buffered to pH 2.0 with $NaH_2PO_4 \cdot H_2O$ (450 mg) and 3.0 M H_3PO_4. Continuous extraction with CH_2Cl_2 gave **26** (94 mg, 95%) as a solid which was recrystallized from hexane–$CHCl_3$ as colorless needles: mp 180–182° dec; ir 1777, 1719 cm^{-1}; NMR ($CDCl_3$, CD_3OD) δ 1.1–2.3 (6 H, m), 2.84 (1 H, m), 3.6–4.1 (2 H, m); mass spectrum m/e (rel intensity) 249, 247 (M^+, 14), 231, 229 (23), 221, 219 (80), 205, 203 (70), 177, 175 (79), 168 (88), 82 (100).

Anal. Calcd for $C_8H_{10}BrNO_3$: C, 38.7; H, 4.1; N, 5.7. Found: C, 39.0; H, 4.1; N, 5.7.

The major isomer, **25**, was obtained similarly and it crystallized both as a hydrate, mp 97° and 119–120°, and as the anhydrous compound: mp 124–126°; ir 1772, 1724 cm^{-1}; NMR ($CDCl_3$, CD_3OD) δ 1.2–2.2 (6 H, m), 2.87 (1 H, m), 3.6–4.1 (2 H, m); mass spectrum m/e (rel intensity) 231, 229 (M^+ − 18, 4), 221, 219 (3), 168 (14), 41 (100).

Anal. Calcd for $C_8H_{10}BrNO_3$: C, 38.7; H, 4.1; N, 5.7. Found: C, 38.8; H, 4.2; N, 5.6.

7,7-Dibromo-8-oxo-1-azabicyclo[4.2.0]octane (29). A mixture of decomposition products (94 mg) collected by preparative GC of the esters **27** and **28** was chromatographed on kieselgel (11 g) with ether–petroleum ether (3:1 v/v), giving **29** (25 mg), intermediate fractions (16 mg) shown by GC to contain **22** to the extent of ~30%, then **22** (35 mg), identical with an authentic sample by ir, NMR comparison, and GC coinjection. **29** was recrystallized from hexane–$CHCl_3$: mp 73–74°; ir 1782 cm^{-1}; NMR (CCl_4) δ 1.2–2.3 (6 H, m), 2.82 (1 H, m), 3.5–4.0 (2 H, m); mass spectrum *m/e* (rel intensity) 285 (M^+, 1.7), 283 (M^+, 3.2), 291 (M^+, 1.7), 257 (<1), 255 (1), 253 (<1), 212 (46), 210 (80), 208 (50), 204, 202 (93), 176, 174 (86), 123 (82), 95 (27), 44 (100).

Anal. Calcd for $C_7H_9Br_2NO$: C, 29.7; H, 3.2; N, 4.9. Found: C, 30.0; H, 3.3; N, 4.9.

Registry No.—**3**, 4450-97-9; **4**, 42599-26-8; **5**, 42599-27-9; **7**, 54409-76-6; **11**, 759-65-9; **12**, 505-18-0; **13**, 42599-33-7; **14**, 35620-54-3; **15**, 54409-78-8; **16**, 54409-79-9; **17**, 42599-30-4; **19**, 54409-80-2; **20**, 54409-81-3; **21**, 42599-31-5; **22**, 53618-26-1; **23**, 40876-98-0; **24**, 54409-85-7; **25**, 54409-86-8; **26**, 54409-87-9; **27**, 42599-40-6; **28**, 42599-41-7; **29**, 42599-42-8; ethyl sodioethoxalylacetate, 54409-82-4; piperidine, 110-89-4; *N*-chlorosuccinimide, 128-09-6; ethyl 3-*tert*-butoxycarbonyl-2-oxopropionate, 54409-83-5.

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(23) Solvent evaporations were carried out in vacuo using a Berkeley rotary evaporator. All melting points are uncorrected. Infrared (ir) spectra were measured in chloroform (unless otherwise indicated) on a Perkin-Elmer 137 or 337 spectrometer; ultraviolet (uv) spectra were measured using a Cary Model 14 spectrometer; and nuclear magnetic resonance (NMR) spectra were taken in $CDCl_3$ (unless otherwise indicated) on a Varian T-60 spectrometer and are reported as δ values relative to Me_4Si (δ 0). NMR line shape abbreviations include: dd, double doublet, br dd, broad double doublet. Mass spectra were obtained on a CEC 103 instrument. All reactions and continuous extractions were carried out in a nitrogen atmosphere. Chromatography was performed on Merck silica gel (70–230 mesh) or Camag kieselgel (>250 mesh) without binder as specified. Kieselgel chromatography was generally carried out in quartz columns using General Electric manganese-activated zinc silicate, Type T-1 (1%, w/w) as a short-wavelength uv indicator. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.
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Fumaric Acid Formation in the Diels–Alder Reaction of 2-Methylfuran and Maleic Acid. A Reexamination[1]

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The exo-cis Diels–Alder adduct of 2-methylfuran and maleic acid in water slowly reverts to maleic acid, 2-methylfuran, endo-cis adduct, and fumaric acid. Fumaric acid formation in this system has previously been cited to support a nonconcerted [2 + 4] cycloaddition. Present kinetic measurements, however, show that fumaric acid is formed in a very minor side reaction. The sum of the rates of cycloaddition between maleic acid and 2-methylfuran and cycloreversion of exo-cis and endo-cis [2 + 4] adducts is at least 1000 times as fast as fumaric acid formation and suggests that the main reaction proceeds by a concerted path. Possible mechanisms of direct isomerization of the maleic acid in equilibrium with adduct have been tested. Other possible mechanisms leading to fumaric acid are discussed.

The retrodiene reaction,[2] exhibited by the exo-cis adduct (I) from maleic acid and 2-methylfuran, has been asserted to be a nonconcerted reaction.[3] Gagnaire et al.[3] reported that in aqueous solution adduct I undergoes cycloreversion to yield fumaric acid along with maleic acid and 2-methylfuran (eq 1). Fumaric acid, along with exo- and endo-cis adducts, were also reported to form if maleic acid and 2-methylfuran were mixed in aqueous solution. If, however, furan or 2,5-dimethylfuran was used instead of 2-methylfuran, no fumaric acid was observed to form from the maleic acid initially present under similar conditions. On this basis the authors concluded that reversion of I to its ad-

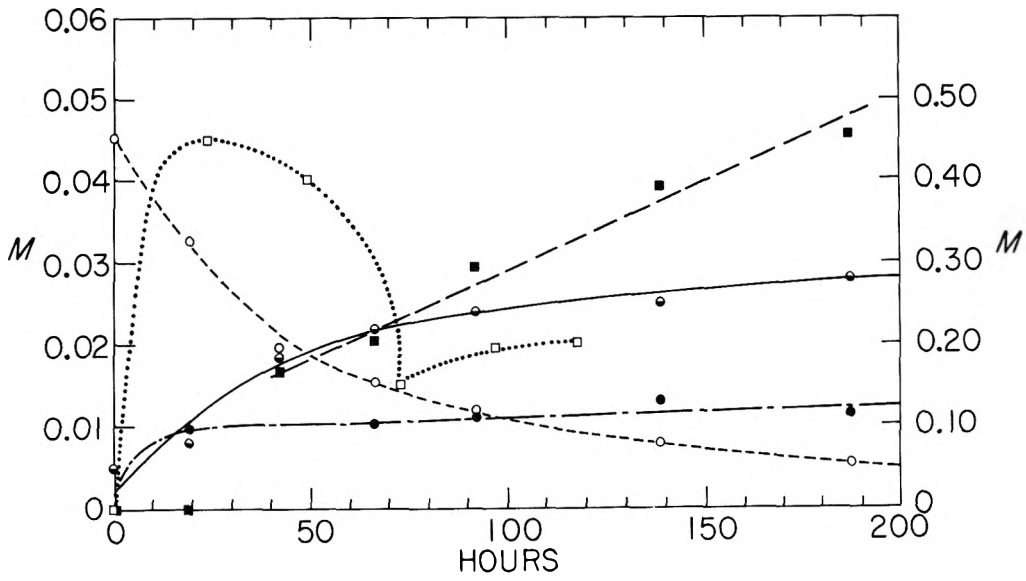
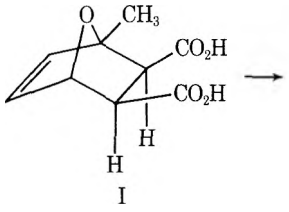


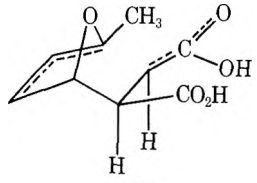
Figure 1. Concentration of products found in the aqueous layer as a function of time from decomposition of I in D_2O. Circles, use right ordinate; squares, use left ordinate. Reactants and product are designated as follows: I, open circles; maleic acid, half circles; endo-cis adduct, solid circles; 2-methylfuran, open squares; fumaric acid, solid squares. The aqueous solution becomes supersaturated in 2-methylfuran which, after a period of time, forms a second layer.



I

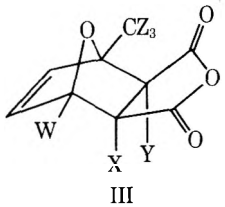
maleic acid + fumaric acid + 2-methylfuran (1)

dends involved rupture of the two bonds in separate steps. Cis–trans isomerization was presumed to occur in an intermediate such as II.



II

This conclusion, concerning the timing of bond rupture, appears to contradict that derived from earlier studies on adduct III; III is the anhydride of I. The results of extensive studies utilizing secondary deuterium isotope effects in III are in accord with a concerted and equal rupture of the



III

a, W = X = Y = Z = H
b, W = D; X = Y = Z = H
c, W = Z = H; X = Y = D
d, W = X = Y = H; Z = D
e/f, (W = X = Z = H; Y = D) / (W = Y = Z = H; X = D) (1 : 1)

two bonds during retrodiene reaction.[4] Since the mechanism for two such similar compounds undergoing reverse cycloaddition appears not to be the same, the usefulness of the methods used to investigate these reactions is weakened. Consequently we have repeated the experiments of Gagnaire et al. and examined them in greater detail.

In this report we show that fumaric acid is a very minor product and consequently the products of decomposition of I are consistent with a concerted two-bond rupture. Further experiments aimed toward the determination of the genesis of fumaric acid have been carried out and described below.

Results and Discussion

The NMR spectrum of a relatively concentrated aqueous solution of I initially exhibits resonances attributed to the protons of I but shortly after mixing there appear peaks that can be assigned to maleic acid, 2-methylfuran, and the corresponding endo-cis adduct formed from the diene and dieneophile generated from decomposition of I. After standing at ambient temperature for 100 hr, however, a new vinyl singlet, due to fumaric acid, begins to appear. At further extended reaction times fumaric acid precipitates from solution. A typical plot of the percent composition of the aqueous phase vs. time is shown in Figure 1. With an initial exo-adduct concentration (~0.5 *M*) suitable for NMR measurements, a pseudo-steady state is reached after about 150 hr. At this concentration the bulk of the 2-methylfuran formed is immiscible with water and forms a second phase. The amount of diene in the aqueous phase reaches a plateau of 0.02 *M* after about 70 hr. It is readily apparent that maleic acid appears long before and in greater quantity than fumaric acid. The question arises: Does fumaric acid form solely from free maleic acid or is it generated as a direct consequence of the formation and decomposition of cycloadducts?

Since a pseudo-steady state is reached at about the time that fumaric acid is first detected, it was of interest to determine the rate constant for decomposition of the exo-cis adduct in aqueous solution. 2-Methylfuran and maleic acid both absorb strongly at 215 nm while the adduct absorbs only weakly. The kinetics of formation of addends were thus followed. The results of such a run are shown in Figure 2. The average rate constant for decomposition at 22° is 4.84×10^{-5} sec^{-1} ($t_{1/2}$ = 3.9 hr). The apparent slow rate of exo-adduct disappearance shown in Figure 1 is thus due to the reversibility of the reaction, which becomes important at the high concentrations used by Gagnaire and Payo-Subiza to observe continuous wave NMR spectra. Under these conditions a true equilibrium between exo adduct, maleic acid, and 2-methylfuran is never reached because fumaric acid is continually being formed at the expense of maleic acid but this latter reaction is slow enough that an

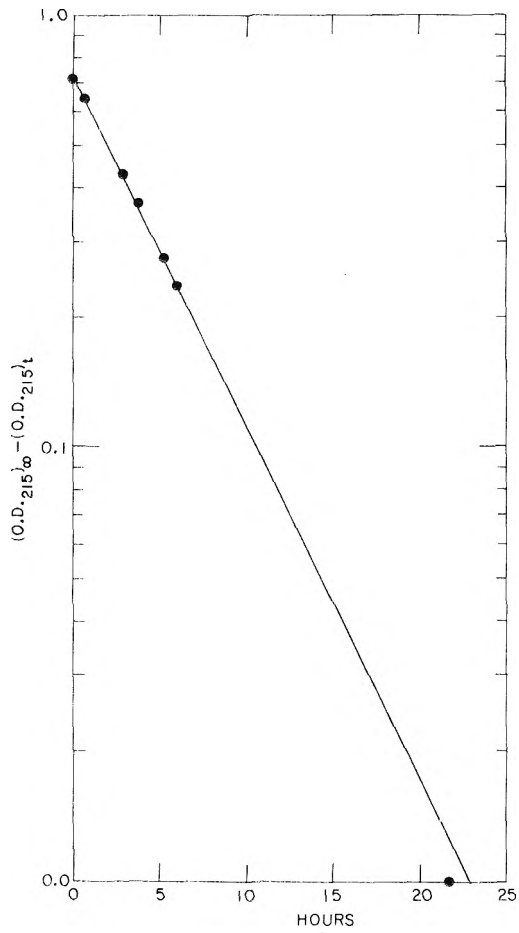


Figure 2. Kinetics of decomposition of I in ethanol–water (5:95) followed at 215 nm. $[I]_0 = 5 \times 10^{-5}$ *M*.

approximate dissociation equilibrium constant (K'_{eq}) can be calculated at t = 250 hr: K'_{eq} (aqueous phase) = [maleic acid][2-methylfuran]/[exo adduct] = 0.028 *M*. From the approximate equilibrium constant, the relatively constant concentration of diene in the aqueous phase, and the rate constant for exo-adduct decomposition, a pseudo-first-order rate constant for exo-adduct *formation* in the aqueous phase can be determined. This turns out to be 3.7×10^{-5} sec^{-1}.

Each time the adduct decomposes to addends or the addends combine to yield adduct, an intermediate and/or transition state is formed. It is interesting to compare the number of passes which yield maleic to the number which yield fumaric acid. Using the rate constants obtained above for the forward and backward reaction it can be calculated that only 2.8 per 1000 yield fumaric acid. This is a maximum value, since the number of passes over the energy surface leading to the formation and decomposition of the endo adduct has not also been included. Similar kinetic studies on decomposition of the endo adduct are precluded because of its greater instability with respect to I. NMR experiments at ambient temperature, however, show that starting with maleic acid and 2-methylfuran, endo adduct forms about twice as fast as the exo adduct. Moreover, if I is allowed to decompose in aqueous medium the endo to exo concentration ratio steadily climbs, reaching the value of about 2 after about 150 hr. Consequently, the rate of endo decomposition is about the same but formation is about twice as fast as the exo adduct. Thus a fumaric acid molecule is really formed about once per 1000 passes through the transition states leading to either formation or decomposition of Diels–Alder adducts.

Further proof that fumaric acid is only a minor product

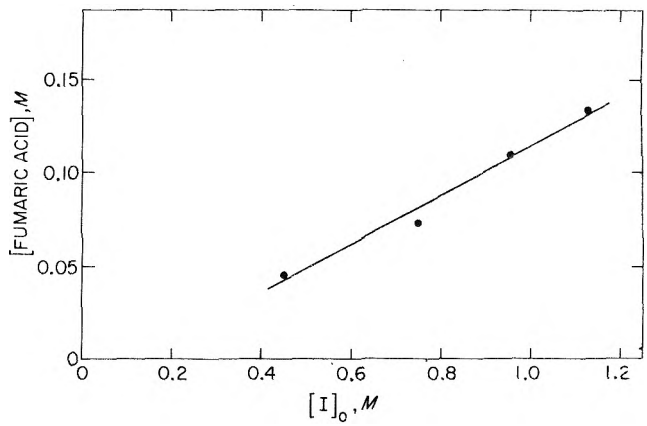


Figure 3. Fumaric acid formed from different initial concentrations of I in D_2O after 187 hr.

during apparent exo-adduct decomposition comes from direct examination of the product under conditions where the reaction is not reversible. Decomposition of I in aqueous solution at high dilution (4×10^{-5} *M*) followed by freeze drying yields maleic acid as product with no detectable fumaric acid as determined by averaging 200 NMR scans. In a control experiment, 2 l. of an aqueous solution, containing maleic and fumaric acids in a ratio of about 10:1 and a total concentration of 2.5×10^{-3} *M*, was subjected to the same isolation procedure. Fumaric acid was easily visible in an NMR spectrum of the residue in D_2O. Thus if fumaric acid were formed in the high-dilution experiment it would have been detected.

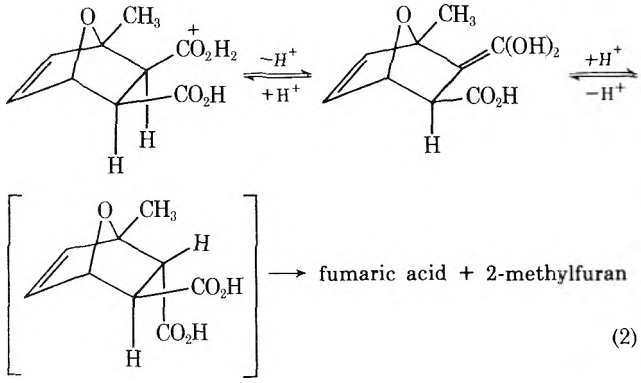
When decomposition of I is carried out in acetone-d_6 or dimethyl sulfoxide-d_6 at NMR concentrations, no fumaric acid is observed. In these solvents the equilibrium between adduct and addends lies completely to the side of addends. The first-order rate constant for disappearance of adduct in acetone-d_6 was found by NMR to be 4.8×10^{-5} sec^{-1} (22°), essentially the same as in dilute aqueous solutions. Thus the decomposition rate is about the same but the cycloaddition rate is substantially reduced in these solvents as compared to water.

The rate of appearance of fumaric acid was also examined as a function of initial exo-diacid concentration. In several parallel runs where the initial adduct concentration varied between 0.45 and 1.3 *M*, the concentrations of fumaric acid generated at various reaction times were measured by NMR. Data obtained well after the system reached pseudoequilibrium (t = 187 hr) are shown in Figure 3 and demonstrate that the rate of formation of fumaric acid is first order in exo-diacid concentration.

These results suggest two broad ways in which fumaric acid can be generated. (1) At NMR concentrations and for the period of observation (i.e., t > 100 hr) the ongoing reversible [2 + 4] cycloaddition reactions provide numerous passes through an intermediate and/or transition state. If [2 + 4] cycloaddition can be accomplished by either of two paths, one requiring a higher energy than the other, then the very large number of traverses across the lower energy path will be accompanied by a few across the higher energy path. The higher energy path could be identified with a two-step cycloaddition reaction (to be discussed below). The lower energy path is the concerted cycloaddition mechanism. (2) Alternatively, the rate of fumaric acid formation could be dependent on the product of the concentrations of free 2-methylfuran and maleic acid or in some other way on the concentration of a species, other than cycloadduct, derived from reaction of these addends. The concentration of 2-methylfuran in either phase is relatively

constant and the kinetic pattern exhibited by reactions in categories 1 and 2 would be similar, and therefore other criteria must be used to establish the genesis of fumaric acid. In the latter category reasonable mechanisms can be suggested to account for the generation of fumaric acid. These have been tested and are discussed below.

Possible Reversible Enolization. If a 0.5 *M* solution of I and its reaction products were sufficiently acidic to protonate a substantial fraction of carbonyl oxygens a reversible enolization of the adduct with concomitant isomerization could take place (eq 2).[5] Fumaric acid, obtained from



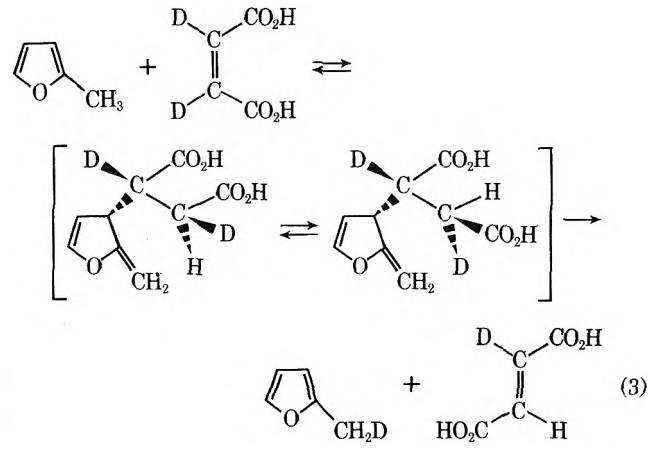
(2)

decomposition of the adduct in D_2O and then recrystallized from water, contained no excess deuterium as indicated by NMR and mass spectrometry. Thus isomerization by eq 2 is ruled out.

Catalyzed Isomerization of Maleic Acid by Reversible Radical Addition Has Been Known for Some Time.[6] This is an important path to consider, since Schenck[7] had reported previously that 2-methylfuran forms a peroxide in the presence of oxygen. Indeed, freshly distilled 2-methylfuran exposed to air quickly develops a yellow color which fails to form in the absence of oxygen. The peroxide decomposes rapidly at 70–80° and could possibly supply oxy radicals which might be effective in catalyzing cis–trans isomerization. Several experiments carried out to see if oxy radical formation is important on the time scale of fumaric acid appearance indicate that it is not. Neither the presence of *N,N,N′,N′*-tetramethylphenylenediamine in the aqueous phase nor 2,4,6-tri-*tert*-butylphenol in the 2-methylfuran phase had any effect on the ability of the reaction mixture to generate fumaric acid. Moreover, bubbling oxygen into a dimethyl sulfoxide-d_6 solution of I, allowing cycloreversion of the aqueous solution to take place in the dark, or degassing an aqueous solution of adduct prior to decomposition neither increased nor retarded the rate of fumaric acid formation. These results suggest that radicals are not responsible for the isomerization. Neither does the isomerization appear to take place in the 2-methylfuran phase.

Possible Reversible Ene Reaction. The reversible ene reaction[8] was investigated as a possible path for formation of fumaric acid. Maleic acid-2,3-d_2 was mixed with an excess of 2-methylfuran in D_2O. As shown for an exo arrangement of ene and eneophile in eq 3, vinyl-proton exchange would be expected for such a pathway. The fumaric acid collected after an extended reaction time was crystallized from a 250-fold excess of water. The dried fumaric acid, examined by NMR, showed no evidence of vinyl-protium incorporation.

Possible Nucleophilic Catalysis. Cis–trans isomerization of carbonyl-conjugated olefins by nucleophiles is well known.[9] To see whether the small quantity of carboxylate anion in equilibrium with I might possibly be catalyzing cis–trans isomerization of maleic acid,[5] 5,6-dihydro-I was prepared and added to an aqueous solution of maleic acid.



(3)

Use of 5,6-dihydro-I instead of I allows inspection of this type of pathway without the possibility of isomerization via reverse cycloaddition taking place. No fumaric acid could be detected by NMR, however, after a D_2O solution of maleic acid (0.38 *M*) and 5,6-dihydro-I was kept at ambient temperature for 7 days.

Conclusions

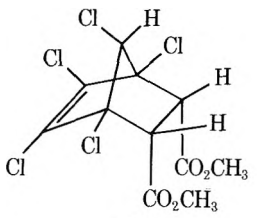
Fumaric acid formation is a minor side reaction during reversible cycloaddition of 2-methylfuran and maleic acid. For every 1000 journeys along the normal path leading to formation or decomposition of adduct, about one molecule of fumaric acid is formed. Several possible mechanisms for its formation have been tested. The results suggest that it is unlikely that carboxylate anions present, nor oxy radicals that may be formed from the expected presence of 2-methylfuran peroxide, cause maleic acid to isomerize. Neither a reversible ene reaction (eq 3) nor a reversible enolization (eq 2) appear to be responsible for the isomerization.

Fumaric acid appears to be generated in aqueous solution only when there is a substantial steady-state concentration of exo and/or endo adduct present at ambient temperature over periods of days. Adduct decomposition, of course, is a first-order reaction while cycloaddition is second order. When the initial exo-adduct concentration is low enough the cycloaddition rate is substantially reduced without affecting the cycloreversion rate; fumaric acid cannot be detected under these conditions although the reaction is carried out in water. Fumaric acid does not form in either acetone or dimethyl sulfoxide solution even when the initial concentration of exo adduct in these solvents would have been sufficient to generate fumaric acid in aqueous medium. In acetone or dimethyl sulfoxide, the adduct at these concentrations reverts completely to maleic acid and 2-methylfuran in a clean first-order reaction; the cycloaddition rate here is much reduced. Conditions which allow continuous forward and backward reactions provide an amplification of an irreversible side reaction. Several possible mechanisms have been tested and discarded. Reasonable mechanisms which remain to be considered are reversible nonconcerted [2 + 2] and [2 + 4] cycloaddition.

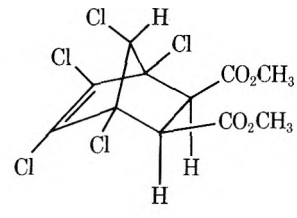
One striking observation is that fumaric acid only appears to be generated in those systems capable of supporting a substantial steady-state concentration of endo and exo [2 + 4] cycloadducts. It seems reasonable, therefore, to attribute the fumaric acid to an uncommon stepwise [$_{\pi}2_s$ + $_{\pi}4_s$] cycloaddition reaction. The stepwise path would be expected to require a higher activation energy than the symmetry-allowed concerted reaction. The intermediate would have a strong driving force for internal rotation provided by the steric crowding resulting from the proximity of the two carboxyls. An indication of the magnitude of this driving force is provided by the relative stabilities of cis and

trans pairs. In aqueous solution, maleic is 5 kcal/mol less stable than fumaric acid.[10]

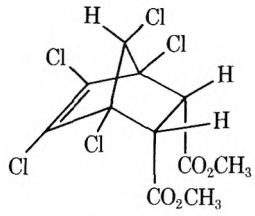
The conclusions derived from the studies of Williamson et al.[11] also suggest that *cis*-5,6-dicarboxyl groups in a bicyclo[2.2.1]-2-heptene skeleton suffer from steric crowding. Williamson and coworkers treated 1,2,3,4,5-pentachlorocyclopentadiene with dimethyl maleate and observed the formation of approximately equal quantities of IV, V, and VI,



IV

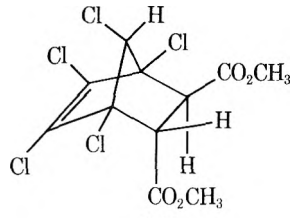


V



VI

the relative amounts presumably determined by kinetic control. The reaction of the same diene with dimethyl fumarate, however, gives a single adduct, VII. No adduct having both chlorine in the 7-anti position and an exo carbomethoxy group was detected. It is most noteworthy that when each of the four adducts was treated with sodium methoxide in methanol, VI and VII were unchanged but both IV and V yielded a product containing only VII and devoid of adduct reactant. These studies clearly demonstrate the strong driving force for the relief of steric crowding experienced by the endo-cis (IV) and exo-cis (V) 5,6-dicarbomethoxy groups.



VII

NMR spectra taken of an aqueous solution of I at successive reaction times indicates the appearance of one and only one additional adduct. The new adduct has been assigned the endo-cis configuration.[3] The spectrum which it exhibits is in agreement with coupling constants measured in similar bicyclo[2.2.1]-2-heptene systems.[12] The assignment also agrees with the ability of this compound to yield maleic acid. Therefore, for this stepwise path to be important, predominant reversion of the intermediate to fumaric acid and diene must result in spite of the expectation that formation of the second bond would result in a trans [2 + 4] adduct of greater stability than that of the cis-exo or cis-endo compound.[11] If it is assumed that the fate of every intermediate formed from stepwise addition results in internal rotation and reversion, then $\Delta\Delta G^{\ddagger}$ between concerted and stepwise [2 + 4] reaction is about 4 kcal/mol.[13]

Bartlett and coworkers[14] have shown that in the cycloaddition reactions of 1,1-dichloro-2,2-difluoroethylene to either 2,4-hexadienes or 1,4-dichloro-1,3-butadiene, recovered diene is isomerized to the extent of 3–7%. The concerted [$_{\pi}2_s + {}_{\pi}2_s$] reaction is symmetry forbidden and thus the diradical intermediate which is initially formed in the stepwise reaction can undergo internal rotation. Internal rotation competes with formation of the second bond as shown by substantial amounts of isomerized adduct along with nonisomerized product. However, another reaction competes with formation of the second bond and that is the rupture of the first bond to give recovered diene of retained and isomerized structures. In these systems formation of the second bond is three to four times faster than cleavage of the first.

If 2-methylfuran and maleic acid were able to enter into the path of [2 + 2] cycloaddition, internal rotation would be expected to compete strongly with any subsequent reaction. No [2 + 2] adduct is observed to form, however, in any of the solvents used in this study. Consequently the diradical would have to undergo bond rupture many times faster than second bond formation in order to satisfy the present observations.

Several examples of parallel [2 + 2] and [2 + 4] cycloaddition reactions progressing under one set of conditions are known.[15] In two of the systems amenable to stereochemical analysis, the results suggest that the [2 + 4] cycloadducts are formed by a concerted mechanism while the parallel [2 + 2] addition is a stepwise reaction[15c,f] and a common intermediate is ruled out.[16]

In the absence of cycloaddition products having a trans diacid structure, it is at present impossible to choose between a reversible [2 + 2] and a reversible stepwise [2 + 4] cycloaddition as the reaction responsible for generating fumaric acid.

Experimental Section

Preparation of 4-Methyl-7-oxabicyclo[2.2.1]-2-heptene-*exo-cis*-5,6-dicarboxylic Acid (I). The anhydride of the title compound was prepared as described previously.[4] Finely divided anhydride (10 g) was stirred in 50 ml of water for 2.5 hr at ambient temperature. Water was removed from the solution on a rotary evaporator at ambient temperature and the wet diacid was dried in vacuo: yield 10 g; mp 136–138° dec; NMR (D_2O, external TMS) δ 1.65 (s, 3 H), 3.06 (s, 2 H), 5.34 (d, J = 1.5 Hz, 1 H), 6.34, 6.60 (split AB quartet, J = 1.5, 5.6 Hz, 2 H).

Preparation of 4-Methyl-7-oxabicyclo[2.2.1]heptane-*exo-cis*-2,3-dicarboxylic Acid (5,6-Dihydro-I). 4-Methyl-7-oxabicyclo[2.2.1]-2-heptene-*exo-cis*-5,6-dicarboxylic acid anhydride[4] (1.74 g) in 30 ml of ethyl acetate was hydrogenated at atmospheric pressure and ambient temperature using 490 mg of 5% palladium on charcoal catalyst. Reduction was complete in about 20 min, thereby avoiding extensive reversion. The catalyst was removed by filtration whereupon the product began to precipitate out. The solution was cooled and the product was removed by filtration: NMR ($CDCl_3$) δ 1.67, 1.77 (s, m, respectively, 7 H), 3.07, 3.30 (AB quartet, J = 7.5 Hz, 2 H), 4.92 (d, J = 4.5 Hz, 1 H). The anhydride (1.1 g) was stirred with 15 ml of water at 35–50° for 1.5 hr, whereupon all the solid dissolved. The solution was concentrated in vacuo and dried in a vacuum desiccator: mp 153.6–155°; NMR (D_2O) δ 1.72 (s, 3 H), 1.97 (m, 4 H), 3.47 (s, 2 H), 5.17 (m, 1 H), 4.93 (internal HDO).

Kinetics of Decomposition of I and Formation of Fumaric Acid. Most of the kinetic studies were followed by proton NMR with a Varian A-60 instrument. Generally 1 ml of solution ranging in concentration from about 0.4 to 1.5 M in I were prepared and stored in NMR tubes. Studies were carried out in room light and in darkness, at ambient and elevated temperatures. Spectra and integrated peak areas were obtained at various times. The identifications of products (2-methylfuran, maleic and fumaric acids) peaks were made by adding authentic samples to parallel runs. Endo-cis adduct (4-methyl-7-oxabicyclo[2.2.1]-2-heptene-*endo-cis*-5,6-dicarboxylic acid) was identified by the similarity of its NMR spectrum to that of I: NMR (D_2O) δ 1.71 (s, CH_3), 3.50, 3.74 (AB quartet, H-5 and H-6, J = 10 Hz, lower half split into doublet of doublets, J = 4.6 and ~2 Hz), 5.21 (dd, J = 1.5, 4.5 Hz, H-1), ~6.35 and 6.60 (AB quartet, J = 5.5 Hz, H-2 and H-3, further splitting was obscured because of the presence of maleic acid).

Kinetics of decomposition of I were measured in a Beckman DU spectrophotometer. Solutions of I in 5% alcohol–water, ranging in concentration between 4.4×10^{-5} and 2.2×10^{-4} *M*, were prepared and the reaction was followed by measuring the optical density at 215 nm due to the appearance of maleic acid and 2-methylfuran at various times until no further increase was observed. The cell compartment was at ambient temperature (22°).

The effect of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine on the rate of appearance of fumaric acid from I was measured. A solution of I (1.0 *M*) in D_2O was prepared and the kinetics of fumaric acid formation at ambient temperature were followed by NMR and compared to the observed rate when the solution also contained *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine dihydrochloride.

In another run 1.0 ml of a 1.0 *M* solution of I in D_2O was placed in an NMR tube together with a 1.0 *M* solution of 2,4,6-tri-*tert*-butylphenol (recrystallized twice from ethanol) in 1.0 ml of $CDCl_3$. A control contained 1.0 ml of $CDCl_3$ and 1.0 ml of a 1.0 *M* solution of J. After 6 days the layers were separated and the quantity of fumaric acid was measured in each D_2O phase.

The relative rates of endo- and exo-adduct formation from 2-methylfuran and maleic acid were measured by NMR. To 1 ml of a 1.5 *M* solution of maleic acid in D_2O, 0.5 ml of 2-methylfuran was added. NMR spectra were recorded periodically. The relative quantities of endo and exo adducts were measured by comparison of their methyl peak heights at δ 1.71 and 1.65.

Effect of 5,6-Dihydro-I on Maleic Acid. Maleic acid (30.8 mg) and 49.8 mg of 5,6-dihydro-I were mixed and dissolved in 0.7 ml of D_2O. The solution was added to an NMR tube and the tube was sealed. Spectra were recorded periodically for 7 days from the time of mixing and stored at room temperature during that time.

Product Studies with Deuterated Reactions. Maleic acid-2,3-d_2 was prepared as previously described.[18] Maleic acid-2,3-d_2 (1.0354 g, 96.4% vinyl deuteration by NMR) was dissolved in 3.0 ml of D_2O in an ampoule. To this was added 1.50 ml of freshly distilled 2-methylfuran. The ampoule was cooled, flushed with nitrogen, and sealed at atmospheric pressure. The ampoule was maintained at 56° for 16 hr. Fumaric acid crystallized upon cooling. It was dried in vacuo at 100°, yield 0.264 g (~25% conversion). The fumaric acid was recrystallized from 10 ml of boiling water and dried in vacuo at 100°. A solution of known concentration of the product fumaric acid in DMSO-d_6 was prepared and its NMR spectrum compared to that for a solution of natural fumaric acid of the same concentration. The integrals for the vinyl and carboxyl protons were compared internally and between the two solutions.

In another study 2.93 g of I was dissolved in 10 ml of D_2O in an ampoule. The system was flushed with nitrogen and sealed at atmospheric pressure. The contents were heated at 56° for 5.5 hr. Upon cooling, fumaric acid precipitated and was collected. It was recrystallized and dried as described above. The recovered fumaric acid (50.81 mg) was mixed with 43.04 mg of maleic anhydride and dissolved in 0.4 ml of DMSO-d_6. The ratio of vinyl proton peak intensities (maleic anhydride/fumaric acid) for the two compounds was found to be 1.02 as compared to 1.003 for 0% exchange.

The fumaric acid product was examined by mass spectroscopy.

Registry No.—I, 54384-22-4; 5,6-dihydro-I, 54384-23-5; 4-methyl-7-oxabicyclo[2.2.1]-2-heptene-*exo-cis*-5,6-dicarboxylic acid anhydride, 54422-97-8; 2-methylfuran, 534-22-5; maleic acid, 110-16-7; fumaric acid, 110-17-8; 4-methyl-7-oxabicyclo[2.2.1]-2-heptene-*endo-cis*-5,6-dicarboxylic acid, 54384-24-6.

References and Notes

(1) Research carried out at Brookhaven National Laboratory under contract with the U.S. Atomic Energy Commission.
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(13) Alternatively, a referee has suggested, [2 + 4] cycloadditions in the present system proceeds in stepwise fashion and $\Delta G^{\ddagger}$ for internal rotation in the intermediate is 4 kcal/mol larger than that for cleavage or formation of the second bond. While this scheme can also account for the kinetics, the stereochemistry of the products is more consistent with the proposition that the major reaction (99.9%) proceeds by a concerted mechanism.
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(16) (a) Concertedness is inferred from the stereochemistry of the product and is based on the assumption that internal rotation of a biradical intermediate in a stepwise [2 + 4] cycloaddition would compete effectively with formation of the second bond as it does in the [2 + 2] cycloaddition. (b) Recently Mark[17] in a communication reported that the reaction of hexachlorocyclopentadiene and several trans-disubstituted olefins led to considerable 1,2,3,4,7,7-endo-cis 5,6-disubstituted bicyclo[2.2.1]-2-heptenes. This would suggest that these [2 + 4] cycloadditions are stepwise and internal rotation occurs in the intermediate. Before this conclusion is firmly accepted, however, appropriate control experiments must be carried out to show that chlorine atoms, capable of isomerizing the dieneophile prior to cycloaddition, are absent from the system during reaction.
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Reactivity of Thiazole Derivatives. IV.[1] Kinetics and Mechanisms of the Reaction of 2-Halogeno-4(5)-X-thiazoles with Methoxide Ion

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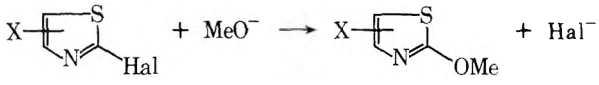
4(5)-X-2-Chlorothiazoles react with sodium methoxide in a normal aza-activated nucleophilic substitution reaction. The reactivity is influenced by substituents in positions 4 and 5. When X is 5-NO_2, the 2-methyl ether is obtained in good yields only when the amount of methoxide ion is less than that of the halo derivative; moreover, the 5-nitro-2-methoxythiazole reacts with sodium methoxide to give a mixture of two σ-anionic complexes. These Meisenheimer-like adducts rapidly decompose to a mixture of derivatives, among which the 5-nitro-2-hydroxythiazole was identified. The structural variations in comparison with those observed in thiophenoxy dehalogenation are discussed.

The reactivity of position 2 in the thiazole ring toward nucleophiles has been investigated[2,3] and the results indicate that the concept of "aza activation" can be extended to these pentatomic heterocyclic compounds, even if their peculiar structural characteristics, such as ring geometry, heterocyclic sulfur, and pronounced aza-group basicity, make their behavior different from that of the six-membered aza-activated derivatives. In fact, the reactivity of halogenothiazoles toward nucleophiles is observed also when the halogen is linked to the 4 or 5 position of the ring.[4]

With the purpose of obtaining further information on the quantitative aspects of the reactivity of chlorothiazoles, we have studied the reaction between 2-chloro-4(5)-X-substituted thiazoles (X = H, 4-CH_3, 4-Cl, 4-C_6H_5, 5-Cl, 5-CH_3, 5-NO_2) and methoxide ion in methanol at 50°.

Results and Discussion

2-Halogeno-4(5)-X-thiazoles react with sodium methoxide, quantitatively yielding the corresponding 2-methyl ethers. The stoichiometry of the reaction follows the scheme below.



In cases of 2,4-dichloro- or 2,5-dichlorothiazole, using more than 1 equiv of methoxide ion, halogen in position 4 or 5 can also be partially displaced. The displacement of the halogen atom in position 4 or 5 is also proved by independent experiments carried out on 4- and 5-halogenothiazoles;[4] nevertheless, using equimolar concentrations of thiazole and methoxide, the only product obtained is the 4(5)-chloro-2-methoxythiazole, as shown by TLC, GLC, and NMR analysis of the reaction mixture checked until 70–80% conversion: the titrimetric determinations of the halide ion coincide with appearance of 4-chloro-2-methoxythiazole (or 5-chloro-2-methoxythiazole) revealed by GLC analysis.

All reactions follow a second-order kinetic law, first order with respect to each reactant; the results are summarized in Table I.

The 5-nitro-2-methoxythiazole has been obtained (by reaction between 5-nitro-2-chlorothiazole and methoxide ion in large excess) in a poor yield (30%) as reported by Metzger,[5] who suggests preparing it by nitration of 2-methoxythiazole. However, it is possible to obtain 5-nitro-2-methoxythiazole in higher yields (85%) using the thiazole derivative and the sodium methoxide in equimolecular quantities.

Table I
Reaction between 2-Chloro-4(5)-X-thiazoles and MeO^- in MeOH at 50°

Registry no.	X	10^5 k, sec^{-1} mol^{-1} l.
	H	0.81[a]
33342-65-3	5-CH_3	0.18
26847-01-8	4-CH_3	0.24
1826-23-9	4-C_6H_5	1.3
16629-14-4	5-Cl	61
4175-76-2	4-Cl	104
3034-47-7	5-NO_2	2,960,000

[a] From ref 3.

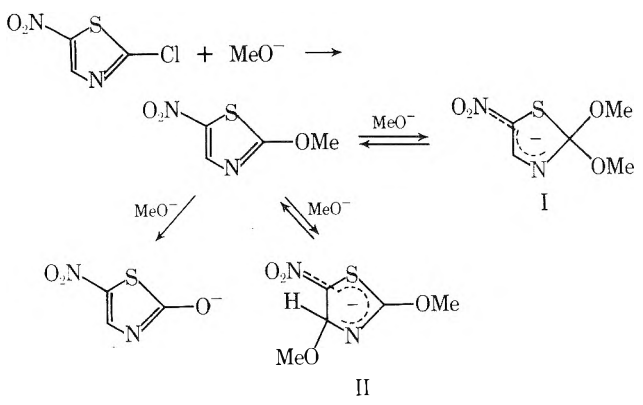
Table II
Reaction rate of the 5-Nitro-2-chlorothiazole in MeOH with MeO^-

Temp, °C	k, sec^{-1} mol^{-1} l.	$\Delta E^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
−21.0	0.031		
0.0	0.33		
10.4	1.0		
50	29.6[a]	15.7	−5.50
2-Chlorothiazole[b]			
50	0.81×10^{-5}	18.5	−27.1

[a] Extrapolated value. [b] From ref 3.

The kinetic data of Table II are obtained under these conditions. If 5-nitro-2-methoxythiazole in methanol is mixed with an equimolecular quantity (or slightly less) of sodium methoxide and the solvent is evaporated, a mixture of crystalline products, very soluble in water, but only slightly soluble in the usual organic solvents, can be obtained. By means of NMR analysis we have demonstrated the presence in this reaction mixture of two σ-like anionic complexes. These adducts are unstable and decompose into unidentified products. If the methoxydechlorination of 2-chloro-5-nitrothiazole is carried out with excess of methoxide, the 2-methoxy-5-nitrothiazole initially produced reacts with a second equivalent of methoxide ion to give complexes I and II (see Scheme I), which decompose. Also, the uv and visible spectrophotometric analysis (in the range of λ 600–250 nm) show that the first step is the methoxydehalogenation.

Scheme I



The NMR analysis (in DMSO-d_6, internal reference Me_4Si) of the mixture of I and II has been carried out and from the chemical shifts it was possible to assign structures I and II reported in Scheme I.

In both adducts the nuclear protons signals are shifted upfield with respect to 5-nitro-2-methoxythiazole [τ_{H_4} 1.48 (1 H), $\tau_{C_2OCH_3}$ 5.80 (3 H)]; the lower field signal (τ 1.92) is assigned to the ring proton of adduct I, and that at higher field (τ 4.19) is attributed to the H_4 of adduct II; this larger shift is consistent with the sp^2 to sp^3 change in the hybridization of the carbon atom[6] at position 4 of the thiazole derivative, subsequent to attack of methoxide ion on this position. Moreover, while for adduct I a singlet at τ 6.84 is found, corresponding to six equivalent methoxy protons, two peaks of three equivalent protons each are observed at τ 6.13 and 6.76, respectively, and assigned to the two nonequivalent methoxy groups of adduct II.

Adduct II has been independently observed by Illuminati and Stegel (VI Symposium of Organic Chemistry, Taormina, Italy, May 1972). In the reactions of 5-nitro-2-chlorothiazole with aliphatic amines, Ilvespää[7] found, in addition to the normal substitution products, some acyclic compounds shown by the NMR spectra in which the H-4 peak is sharply shifted downfield (τ 1.3–1.1). Such products are derived, as reported by the above-mentioned author, from a preliminary attack of the base on position 4, followed by release of halide from position 2 and by the concerted ring opening.

When NMR spectra are recorded in the presence of increasing quantities of methanol in addition to the DMSO-d_6, a slight increase of the amount of I can be observed (the intensity of the peak at τ 1.92 is increased if compared with a known quantity of benzene added as inert reference), while the amount of isomer II rapidly decreases to a value lower than that of I.

It must be emphasized that appearance of I does not quantitatively follow disappearance of II: when the DMSO/MeOH ratio is 1:1, I reaches 50%. Moreover, under these conditions the NMR spectrum is complicated by the presence of several unidentified signals, probably due to decomposition products; nevertheless it is possible to recognize a peak at τ 1.41, which has been assigned to the ring proton of 5-nitro-2-hydroxythiazole by comparison with a sample of 5-nitro-2-hydroxythiazole obtained by the method of von Babo and Prjis.[8] All attempts to isolate complexes I and II failed. The presence in methanol of isomer II to a larger extent (80%) with respect to isomer I (20%) may be justified by a kinetic control on the methoxide ion attack (more relevant steric hindrance being offered by the already alkoxy-bearing position). On the other hand, the impossibility of using resonance structures in which the negative charge is localized on the heterocyclic nitrogen

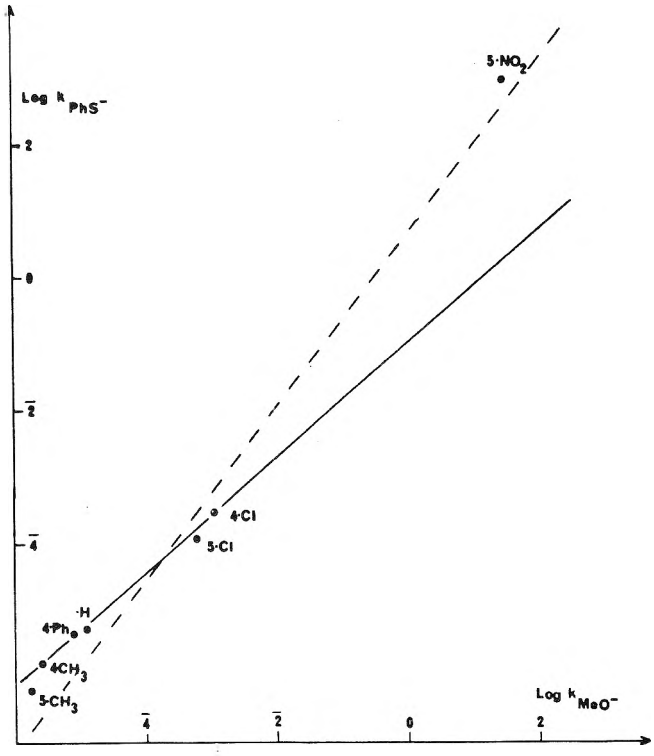


Figure 1. Dashed line, calculated by least-squares analysis for all substituted derivatives; full line, calculated only for 4-substituted derivatives.

seems to indicate that the thermodynamic stability of isomer II is due to the charge delocalization afforded by the heterocyclic sulfur atom.[9] However, the reactivity scheme of 5-nitro-2-chlorothiazole can be represented as in Scheme I.

Formation of 5-nitro-2-hydroxythiazole and instability of adducts I and II (which probably leads to the presence in the reaction medium of ring-opening products not yet identified) must be taken into account to explain the low yield in methoxydechlorination of the 5-nitro-2-chlorothiazole (at least for reactions carried out with an excess of sodium methoxide), and the incomplete conversion of adduct II to I.

The kinetic effects produced by structural variations on the methoxydechlorination of 2-chloro-X-thiazoles are very large, as the 5-nitro-2-chlorothiazole is more reactive than the 5-methyl-2-chlorothiazole by a factor of 1.6×10^7. The observed log k values of the reactions are roughly correlated with the analogous data obtained for benzenethiolate dehalogenation of the same substrates,[2] as shown in Figure 1.

The correlation coefficient is unsatisfactory (0.990). A more careful examination of the plots in Figure 1 reveals that the groups in position 4 correlate well (r = 0.998) while the groups in position 5 deviate from linearity.

Position 4 in thiazole can be thought of as "meta"-like and position 5 as "para"-like with respect to position 2. In fact, the reaction requires delocalization of negative charge in the transition state and appropriate groups in position 5 can provide strong resonance stabilization. This assumption seems reasonable, while it is not in fully agreement with the observed reactivities of 4- or 5-halogenothiazoles[4] and recent data of Noyce and Fike[10] for conjugation phenomena between position 2 and 4 in thiazole systems.

In the series of 1-halogeno-2-nitro-X-benzenes, Brieux[11] and coworkers have pointed out that the resonance contribution depends on the type of nucleophile and on the kind of substituents. Experimental σ values for substituents in

position 5 can be obtained by ρ values calculated from kinetic data of 4-X-2-chlorothiazoles. If σ(experimental) = $\sigma_I + \sigma_R$, σ_R can be evaluated, as reported in Table III.

Table III
Hammett–Taft Parameter Calculated for Nucleophilic Substitution Reactions of Some 2-Chloro-X-thiazoles[a]

Reaction	ρ_4	r	$(\sigma_R)_{exp}$ 5-CH_3	5-Cl	5-NO_2
Methoxy substitution	5.88	0.998	−0.06	−0.15	+0.49
Thiophenoxy substitution	5.14	0.995	−0.11	−0.19	+0.98

[a] See text.

Values of σ_R experimentally determined here for thiophenoxy or methoxy substitution do not substantially differ from the normal σ_R values for the donor groups CH_3 and Cl (respectively −0.12 and −0.24), in agreement with the normal application of Hammett-type correlation. Analogous values are also reported by Brieux for a homocyclic aromatic system.[11]

The case of the 5-nitro derivative is peculiar; in fact we found for the benzenethiolate substitution a $\sigma_R \sim 1$, while in the methoxy substitution, for which one can expect an analogous strong activation, the observed σ_R value is only 0.49, not different from that observed in reactions of six-membered homocyclic aromatic derivatives.[11] Therefore the exceptional nitro activation in the thiazole derivatives previously reported[2] is a specific fact of the thiophenoxy substitution. It is interesting to observe that only for 5-nitro-2-chlorothiazole is benzenethiolate more reactive than methoxide ion, while for all other substituents we observe the opposite trend. This fact can be interpreted considering that also in homocyclic aromatic systems the benzenethiolate ion is more reactive than methoxide in the strongly activated systems such as 1-halogeno-2,4-dinitrobenzenes, while with poorly activated systems, such as *p*-fluoronitrobenzene, methoxide and thiophenoxide ions react with comparable rates. We previously observed[12] that in the case of 2-halogenobenzothiazoles the benzenethiolate ion is less reactive than methoxide while the 2-halogeno-6-nitrobenzothiazoles show the opposite trend.[17]

An interesting remark can be made about the reactivity of the dichloro derivatives; previously[4] it was pointed out that the halogen at position 5 is more reactive than that at position 2. For reactions with sodium methoxide the sequence 5 > 2 > 4 was observed, so that the halogen in position 5 would be expected to be more reactive than that in position 2, at least for reaction of 2,5-dichlorothiazole. On the contrary, the experimental data show that (under our reaction conditions) the 2-methoxy dehalogenation is always favored.

This fact can be related to the different activation due to the substituent effect, less important from position 2 to 5 than from position 5 to 2.

Similarly we have observed other cases of different sensitivity to substituent effects, for example, measuring the acidity constants of 2-carboxy-6-X-benzothiazoles[13] (ρ 1.4) and 6-carboxy-2-X-benzothiazoles[14] (ρ 0.9).

Experimental Section

Physical Measurements. The NMR spectra were recorded with a Varian 100-MHz instrument, using tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in τ values and are approximated to ±0.02 ppm.

The uv spectra were recorded with a Zeiss DMR 21 spectrophotometer.

Materials. Methanol, sodium methoxide, and thiazole substrates were prepared and/or purified by methods previously described.[2] DMSO-d_6 was used without further purification (minimum deuteration 99%).

Kinetic measurements were made by usual procedures. Kinetic experiments on 2,4-dichlorothiazole and 2,5-dichlorothiazole were performed by following both the appearance of the chloride ion (Volhard) and the formation of 4(5)-chloro-2-methoxythiazole by GLC using a Hewlett-Packard instrument (6-ft column SE-30). The rate constants determined by the two analyses were within experimental error (5%).

Procedures of preparation and characterization of 2-methoxy-4(5)-chlorothiazoles and 2-methoxy-5-nitrothiazole are reported. The melting points and boiling points are uncorrected.

5-Chloro-2-methoxythiazole and 4-Chloro-2-methoxythiazole. A 20-ml portion of sodium methoxide solution in methanol (1 *N*) was added to a methanolic solution of 1.53 g of 2,5-dichlorothiazole, and the mixture was kept at 50°. After about 3 hr the titrimetrical chloride ion analysis revealed that the reaction had occurred at 74%. The mixture was poured onto ice, neutralized with HCl (1:1), and extracted with diethyl ether. The oil obtained after evaporation of the solvent was analyzed by GLC, TLC, and NMR and was found to be a mixture of two products, one of which was the starting substrate. Separation was made by silica gel column chromatography (petroleum ether–diethyl ether, 5:2). 2,5-Dichlorothiazole eluted first and then 0.91 g of an oil, bp 166–167° (760 mmHg), was obtained in 83% yield and identified by NMR analysis as 5-chloro-2-methoxythiazole.

Anal. Calcd for C_4H_4ClNSO: Cl, 23.71. Found: Cl, 23.4.

In a similar way 4-chloro-2-methoxythiazole was obtained in 86% yield as an oil, bp 185–188° (760 mmHg).

Anal. Calcd for C_4H_4ClNSO: Cl, 23.71. Found: Cl, 23.6.

Table IV reports NMR data.

Table IV
Chemical Shifts for the Reaction Product of 2,4(5)-Dichlorothiazoles and MeO⁻Na⁺ in MeOH at 50°[a]

Substrate	τH_4	τH_5	τ Me	Registry no.
2,5-Dichlorothiazole	2.69 (s)			
2-Methoxy-5-chlorothiazole	3.16 (1 H)		5.99 (3 H)	54166-43-7
2,4-Dichlorothiazole		3.13 (s)		
2-Methoxy-4-chlorothiazole		3.68 (1 H)	5.94 (3 H)	54166-44-8

[a] In τ values in CCl_4, internal reference Me_4Si.

5-Nitro-2-methoxythiazole. A 17.5-ml (2.0×10^{-2} mol) portion of sodium methoxide solution (1.15 *N*) was added dropwise under cooling to a solution of 3.5 g (2.1×10^{-2} mol) of 5-nitro-2-chlorothiazole in the minimum amount of anhydrous methanol. After a few minutes the reaction was practically complete. The solvent was partially removed under vacuum from the yellow solution and the crude residue was chromatographed on silica gel (hexane–diethyl ether, 4:1). After some unreacted material, a pale yellow solid, mp 56–59°, was obtained in 86% yield. After recrystallization from hexane this compound melted at 58–59°, and was identical with an authentic sample of 5-nitro-2-methoxythiazole obtained by nitration of 2-methoxythiazole with 86% nitric acid in sulfuric acid at 0°.[15]

Anal. Calcd for $C_4H_4N_2O_3S$: S, 20.02. Found: S, 19.7.

The yield of 5-nitro-2-methoxythiazole is decreased to 30% when the reaction is carried out in the presence of an excess of sodium methoxide.

Isolation and Characterization of the Adducts I and II. The reaction was carried out in a manner similar to that described by Illuminati[16] for isolation of the adduct of 2-methoxy-3,5-dinitrothiophene.

2-Methoxy-5-nitrothiazole (70 mg) was dissolved in the minimum amount of methanol; 0.42 ml (1 equiv) of methanolic sodium methoxide solution (1.07 *N*) was slowly added. The yellow solution immediately turned deep red. The solvent was removed under vac-

uum. The residue, a red, crystalline solid, was collected and washed with anhydrous benzene and dried at 0.1 mmHg (oil pump).

The adducts were characterized by their NMR spectra (Table III) as reported in the Results and Discussion. Small amounts of some other unidentified products are present. This fact and the instability of I and II give a discrepancy in the elemental analysis of the mixture.

Acknowledgment. This work was carried out with the financial aid of the C.N.R., Roma.

Registry No.—I, 54166-45-9; II, 54166-46-0; 5-nitro-2-methoxythiazole, 26245-61-4; methoxide ion, 3315-60-4.

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(17) Note Added in Proof. The observed lower reactivity of sodium methoxide, with regard to sodium benzenethiolate, can also be due to the formation of a σ anionic complex arising from attack of the methoxide in position 4 of the 2-chloro-5-nitrothiazole in a concurring competitive reaction, which occurs in more concentrated solutions (illuminati and coworkers, private communication). Nevertheless we have not found any evidences of such a process in our experimental conditions.

Chlorination of Disulfoxides

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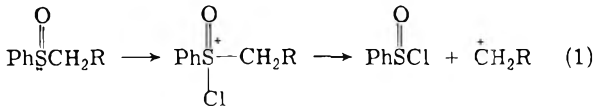
Chlorination of (±)- and *meso*-bis(phenylsulfinyl)methane (**1a** and **1b**) with sulfuryl chloride under a variety of conditions gives α-chloro sulfoxides **2a** and **2b** + **2c**, respectively, in high yield with no change in stereochemistry at the sulfur centers. With excess sulfuryl chloride, **1a** is dichlorinated to (±)-bis(phenylsulfinyl)dichloromethane (**3a**), which can be reduced, in succession, to α-chloro sulfoxide **2a** and then to **1a** with either chromous ion or tri-*n*-butylphosphine. The role of base (pyridine or sodium bicarbonate) in the chlorination of sulfoxides **1a**, **1b**, and **2a** and phenylsulfinylphenylsulfonylmethane (**4**) is fundamentally different from the role played by pyridine in the halogenation of bis(phenylsulfonyl)methane.

Recently, α-halo sulfoxides have generated a good deal of interest from both synthesis and mechanism viewpoints.[1] Earlier, we[2] reported on the syntheses and reductions of α,α-dichloro sulfoxides. We[2] as well as others[3] have commented on the problems associated with chlorination of sulfoxides where the intermediate chlorosulfoxium ion is likely to cleave and yield a relatively stable carbenium ion (eq 1). In view of this, a study has been made on the α-chlo-



(1)

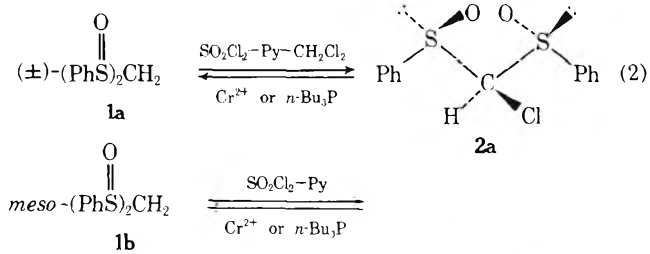
rination of sulfoxides bearing the electron-withdrawing (and carbenium ion destabilizing) sulfinyl and sulfonyl groups. Not only should cleavage (eq 1) be precluded in such systems, but with two sulfinyl groups present, the stereochemistry of the reaction at the chiral sulfur could be ascertained, since potentially one diastereomer series could be epimerized over to the other diastereomer series during the chlorination (vide infra).

Results and Discussion

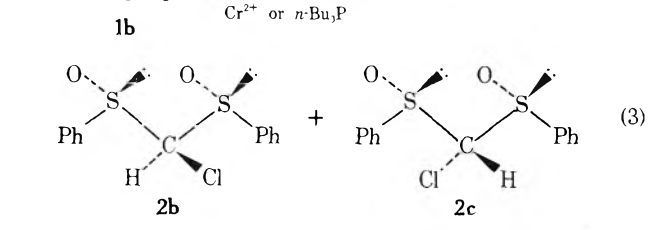
Bis(phenylsulfinyl)methane was synthesized by oxidation of bis(phenylthio)methane with 2 equiv of *m*-chloroperoxybenzoic acid (MCPBA). The two diastereomers were separated by fractional crystallization and characterized by their known melting points and ^{1}H NMR spectra.[4]

Several halogenating agents were studied, but *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and molecular bromine all proved unreactive toward **1**.[5] Chlorination with iodobenzene dichloride[6] produced α-chloro derivatives only in low yields, whereas chlorination with sulfuryl chloride took place readily and in good yields. Therefore, only the reactions of this chlorinating agent were examined in detail.

The reaction of **1a** with sulfuryl chloride in dichloromethane in the presence of either pyridine or powdered sodium bicarbonate yielded the single monochloride **2a**. Reduction of **2a** with either chromous ion[2] or tri-*n*-butylphosphine[2] gave only **1a** (eq 2). Chlorination of *meso*-**1b** gave a



(2)



(3)

50:50 mixture of **2b** and **2c**. Reduction of this mixture or reduction of the separated diastereomers with chromous ion or tri-*n*-butylphosphine gave only **1b** (eq 3). If excess

sulfuryl chloride was used, **1a** gave the dichloride **3a**, which upon reduction (Cr^{2+} or n-Bu_3P) gave **2a** (eq 4).

$$2a \underset{Cr^{2+}\text{ or }n\text{-}Bu_3P}{\overset{SO_2Cl_2\text{-}Py\text{-}CH_2Cl_2}{\rightleftharpoons}} (\pm)\text{-}(PhS)_2CCl_2 \quad (4)$$

3a

All these chlorination reactions proceeded in high yields, and little if any cleavage products were observed. This supports the earlier suggestion[2,3] that chlorination of sulfoxides will lead to C–S bond cleavage if a stabilized carbenium ion is formed (eq 1). The presence of a second sulfinyl group (R = PhSO) would be clearly a destabilizing factor for the incipient carbenium ion and thus preclude its formation.

Other workers[6,7] have shown that halogenation α to the sulfinyl group in optically active sulfoxides followed a particular pattern depending upon the specific sulfoxide studied. They observed that during halogenation the sulfur and α-carbon atoms underwent stereospecifically one of the following combinations: inversion–inversion, retention–retention, retention–inversion, or inversion–retention. The particular mode observed depended upon the sulfoxide and the conditions of halogenation; e.g., the presence of silver ion encouraged the double inversion process.[6b] We observe no change in the stereochemistry at the sulfur centers in **1** resulting from chlorination with sulfuryl chloride or iodobenzene dichloride. Chlorination of **1** with sulfuryl chloride in acetonitrile in the presence or absence of silver nitrate[6] still led to chlorination with no change in stereochemistry at the sulfur centers.

The chlorination of phenylsulfinylphenylsulfonylmethane (**4**) with sulfuryl chloride proceeds smoothly in the presence or absence of pyridine. Under the same conditions, molecular bromine gave no reaction. However, treatment of bis(phenylsulfonyl)methane (**7**) with sulfuryl chloride or bromine in dichloromethane in the absence of base gave no reaction, but in the presence of pyridine, **7** reacted with excess sulfuryl chloride and excess bromine to give the dihalides **8** and **9**, respectively.[8] The function of pyridine in this latter reaction is to first remove the α proton to generate an α-sulfonyl carbanion, which is subsequently halogenated.[9] In the reactions of sulfoxides with sulfuryl chloride, the base (pyridine or bicarbonate ion) either reacts with the intermediate chlorosulfoxium ion and/or simply reacts with the hydrogen chloride generated to prevent acid decomposition of the sulfoxides.[10]

$$PhSCH_2SO_2Ph \xrightarrow[Py\text{-}CH_2Cl_2]{SO_2Cl_2} PhSCHClSO_2Ph \xrightarrow[Py\text{-}CH_2Cl_2]{SO_2Cl_2} PhSCCl_2SO_2Ph \quad (5)$$

4 5a + 5b 6

$$(PhSO_2)_2CH_2 \xrightarrow[Py\text{-}CH_2Cl_2]{SOCl_2} (PhSO_2)_2CCl_2 \quad (6)$$

8

$$(PhSO_2)_2CH_2 \xrightarrow[Py\text{-}CH_2Cl_2]{Br_2} (PhSO_2)_2CBr_2$$

9

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-20 spectrometer at ambient temperature. The spectra were taken in deuteriochloroform with tetramethylsilane (δ 0.00) as an internal standard. Ir spectra were taken in chloroform on a Beckman IR-8 instrument. Elemental analyses were performed by Dr. Franz Kasler of the Department of Chemistry, University of Maryland.

Bis(phenylsulfinyl)methane (1a and 1b). Bis(phenylthio)methane (2.32 g, 0.01 mol) was dissolved in 20 ml of anhydrous ether. To this solution was added 3.46 g (0.02 mol) of 85% MCPBA in 15 ml of anhydrous ether. After 1 hr, 80 ml of dichloromethane was added to dissolve the precipitate, and the solution was washed three times with 10% aqueous sodium carbonate. The organic layer was dried ($MgSO_4$) and removed by rotary evaporation. A ^1H NMR spectrum of the crude reaction mixture showed it to consist mainly of **1a** and **1b** (50:50) with a small amount of unreacted starting material and sulfone **5** present. Crystallization from dichloromethane–hexane gave **1a**, mp 188–190° (lit.[4] mp 182–183°), in 40% yield. Repeated fractional crystallizations gave **1b**, mp 118–119° (lit.[4] mp 118–120°), in ca. 10% yield.

Chlorination of 1. To a solution of 1.0 g (3.8 mmol) of **1a** dissolved in 18 ml of dry dichloromethane and 2 ml of pyridine was added dropwise 0.55 g (4.1 mmol) of sulfuryl chloride in 3 ml of dichloromethane at room temperature. The course of the reaction could be followed conveniently by TLC (10% ethyl acetate in ether, silica gel) and more sulfuryl chloride added if needed. After 30 min, the solution was washed with 5% hydrochloric acid and dried ($MgSO_4$) and the solvent was removed by rotary evaporation. A ^1H NMR spectrum of the crude reaction mixture showed the presence of **2a** (ca. 90%) and unreacted **1a** (ca. 10%). Crystallization from dichloromethane gave 850 mg (75%) of **2a**: mp 137–138°; ir $\nu_{S=O}$ 1092 cm^{-1}; ^1H NMR δ 4.93 (s, 1 H) and 7.3–7.9 (m, 10 H).

Anal. Calcd for $C_{13}H_{11}ClO_2S_2$: C, 52.25; H, 3.71. Found: C, 52.42; H, 3.63.

In the same manner, **1b** gave a 50:50 mixture of **2b** and **2c** as shown by ^1H NMR spectroscopy. Fractional crystallization from dichloromethane–pentane gave one diastereomer: mp 148–150°; ir $\nu_{S=O}$ 1085 cm^{-1}; ^1H NMR δ 5.58 (s, 1 H) and 7.3–7.8 (m, 10 H).

Anal. Calcd for $C_{13}H_{11}ClO_2S_2$: C, 52.25; H, 3.71. Found: C, 52.19; H, 3.58.

The second diastereomer isolated exhibited the following physical characteristics: mp 125–126°; ir $\nu_{S=O}$ 1090 cm^{-1}; ^1H NMR δ 5.32 (s, 1 H) and 7.3–7.9 (m, 10 H).

Anal. Calcd for $C_{13}H_{11}ClO_2S_2$: C, 52.25; H, 3.71. Found: C, 52.38; H, 3.78.

When these reactions were run without pyridine but in the presence of anhydrous sodium bicarbonate (heterogeneous reactions), essentially the same results were observed.

In acetonitrile containing 5 ml of pyridine and 1.29 g (7.6 mmol) of silver nitrate, **1a** (1.0 g, 3.8 mmol) reacted with 0.785 g (5.7 mmol) of sulfuryl chloride in 2 ml of acetonitrile for 1 hr at room temperature to give ca. a 20% yield of **2a** and ca. 0.5 g (50%) of recovered **1a** (separated by thick layer chromatography, 10% ethyl acetate–ether, silica gel). The yield of **2a** was greatly improved in the absence of silver nitrate.

(±)-Bis(phenylsulfinyl)dichloromethane (3a). To a solution of 0.60 g (2.0 mmol) of **2a** dissolved in 10 ml of dichloromethane and 1 ml of pyridine was added dropwise 340 mg (2.5 mmol) of sulfuryl chloride in 2 ml of dichloromethane. The usual work-up and crystallization from dichloromethane–ethanol gave 510 mg (76%) of **3a**: mp 174–176° dec; ir $\nu_{S=O}$ 1092 cm^{-1}; ^1H NMR δ 7.3–8.2 (m).

Anal. Calcd for $C_{13}H_{10}Cl_2O_2S_2$: C, 46.71; H, 3.02. Found: C, 46.68; H, 2.86.

Reductions of the Chloro Sulfoxides. A. Chromous Ion. To a solution of 0.20 g (0.60 mmol) of dichloro sulfoxide **3a** dissolved in 10 ml of acetone and 2 ml of water (deoxygenated by bubbling nitrogen through the solution) was added via syringe 1 ml of ca. 1 *M* chromous chloride solution (Fischer Scientific). The solution was stirred under nitrogen for 2 hr and then poured into 50 ml of water. This solution was extracted with 2 × 30 ml of dichloromethane. The organic extracts were combined, dried ($MgSO_4$), and removed by rotary evaporation. A TLC (20% ethyl acetate in ether on silica gel) showed a trace of **3a** and **1a** and a major spot which corresponded to monochloro sulfoxide **2a**. Crystallization from dichloromethane–hexane gave 130 mg (72%) of **2a**, mp 135–137°, undepressed with authentic **2a**.

In the same manner, (±)-monochloro sulfoxide **2a** (0.20 g, 0.67 mmol) in a deoxygenated solution of 8 ml of acetone and 2 ml of water was allowed to react with 2 ml of ca. 1 *M* chromous chloride solution under nitrogen. The reaction was followed by TLC and was essentially complete after 24 hr. The solution was poured into 50 ml of water and extracted with 2 × 30 ml of dichloromethane. The extracts were combined, dried ($MgSO_4$), and removed by rotary evaporation. Crystallization from dichloromethane–hexane gave

170 mg (96%) of (±)-disulfoxide **1a**, mp 185–189°, undepressed with authentic **1a**.

Treatment of 0.65 mg of a 2:1 mixture of meso:(±)-disulfoxides (**1b** and **1a**, respectively) under the above reaction conditions gave no discernible change in the distribution of diastereomers.

B. Tri-n-butylphosphine. A solution of 0.20 g (0.60 mmol) of dichloro sulfoxide **3a** and 0.13 g (0.60 mmol) of tri-*n*-butylphosphine in 8 ml of methanol (under nitrogen) stood at room temperature for 30 min. Work-up (water–dichloromethane extraction) gave 0.125 (68%) of **2a**, mp 134–136°.

A solution of 0.20 g (0.67 mmol) of **2a** and 140 mg (0.67 mmol) of tri-*n*-butylphosphine in 5 ml of methanol (under nitrogen) stood at room temperature for 2 hr. The crystals that formed were filtered and washed with cold ether (3 ml) to give 115 mg of (±)-**1a**, mp 191–193°. The mother liquor yielded an addition 0.04 g of *1a*, total yield 0.165 g (90%).

Treatment of meso disulfoxide **1b** with dilute HCl in methanol in the presence or absence of tri-*n*-butylphosphine or tri-*n*-butylphosphine oxide gave no sign of epimerization to diastereomer **1a**.

Chlorination of Phenylsulfinylphenylsulfonylmethane (4). To a solution of 0.50 g (1.8 mmol) of **4**[11] and 0.50 g of sodium bicarbonate in 12 ml of dichloromethane was added dropwise 0.26 g (1.9 mmol) of sulfuryl chloride in 2 ml of dichloromethane. The reaction mixture was treated as in the analogous case of the chlorination of (±)-**1a**. An NMR spectrum of the crude reaction mixture showed a trace of unreacted **4** and two singlets (4:1 ratio) at δ 5.2 and 5.4, respectively. Crystallization from dichloromethane–hexane gave 310 mg (58%) of the major isomer (**5a**): mp 115–116°; ir ν_{SO_2} 1333 and 1142, $\nu_{S=O}$ 1095 cm^{-1}; ^{1}H NMR δ 5.25 (s, 1 H) and 7.3–8 (m, 10 H).

Anal. Calcd for $C_{13}H_{11}ClO_3S_2$: C, 49.59; H, 3.52. Found: C, 49.57; H, 3.47.

Further crystallization yielded 50 mg (9%) of the other diastereomer **5b**: mp 124–126°; ir ν_{SO_2} 1340 and 1135, $\nu_{S=O}$ 1092 cm^{-1}; ^{1}H NMR δ 5.43 (s, 1 H) and 7.3–8 (m, 10 H).

Anal. Calcd for $C_{13}H_{11}ClO_3S_2$: C, 49.59; H, 3.52. Found: C, 49.44; H, 3.60.

A similar result to the above was obtained when chlorination was run in the presence of pyridine instead of sodium bicarbonate.

Phenylsulfinylphenylsulfonyldichloromethane (6). To a solution of 0.300 g (1.07 mmol) of **4** in 12 ml of dichloromethane and 1 ml of pyridine was added 0.40 g of sulfuryl chloride in 2 ml of dichloromethane at room temperature. The solution stood for 1 hr and was worked up as usual. Crystallization from dichloromethane–hexane gave 0.315 g (90%) of **6**: mp 135–136° (from dichloromethane–ethanol); ir ν_{SO_2} 1152 and 1350, $\nu_{S=O}$ 1100 cm^{-1}; ^{1}H NMR δ 7.3–8.2 (m).

Anal. Calcd for $C_{13}H_{10}Cl_2O_3S_2$: C, 44.58; H, 2.88. Found: C, 44.49; H, 2.82.

Halogenation of Bis(Phenylsulfonyl)methane (7). To a solution of 0.90 g (3.0 mmol) of **7** in 10 ml of dichloromethane and 3 ml of pyridine was added 0.80 g of sulfuryl chloride in 2 ml of dichloromethane. After 1 hr, the mixture was diluted with 50 ml of dichloromethane, washed with 5% sodium bicarbonate (100 ml), and dried ($MgSO_4$) and the solvent was removed by rotary evaporation. Crystallization of the resulting oil gave 1.0 g (85%) of bis(phenylsulfonyl)dichloromethane (**8**), mp 157–159° (lit.[12] mp 159°).

In a similar manner, **7** treated with excess bromine gave an 80% yield of bis(phenylsulfonyl)dibromomethane (**9**), mp 156–158° (lit.[12] mp 159°). This dibromide was converted back to **7** quantitatively by sodium thiosulfate in aqueous acetone.

Registry No.—**1a**, 27995-61-5; **1b**, 27995-60-4; **2a**, 54384-32-6; **2b**, 54423-03-9; **2c**, 54423-04-0; **3a**, 54384-33-7; **4**, 54384-18-8; **5a**, 54384-34-8; **5b**, 54384-35-9; **6**, 54384-19-9; **7**, 3406-02-8; sulfuryl chloride, 7791-25-5; bis(phenylthio)methane, 3561-67-9.

References and Notes

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(4) J. L. Greene, Jr., and P. B. Shevlin, *Chem. Commun.*, 1092 (1971). These authors observed that in the presence of a europium shift reagent, the diastereotopic protons in **1b** have different chemical shifts and therefore give rise to a set of doublets. We find that simply adding a drop of acetic acid to the ^{1}H NMR tube accomplishes the same thing.
(5) These attempted halogenations were run in dichloromethane at temperatures varying from 0° to reflux in the presence and absence of pyridine. No attempt was made to initiate these reactions with acid; see F. Jung, K. C. Tin, and T. Durst, *Int. J. Sulfur Chem.*, **8**, 1 (1973).
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(8) Attempted iodination with molecular iodine failed under these conditions.
(9) Attempts to extend this reaction as a general method for halogenation of sulfones failed. For example, treatment of *p*-nitrobenzyl phenyl sulfone with sulfuryl chloride in dichloromethane in the presence of pyridine at 0° gave recovered unreacted sulfone. Sulfuryl chloride itself reacts slowly with pyridine to give an amorphous red polymer.
(10) The regioselectivity and stereochemistry of some halogenations of sulfoxides are affected by the presence of base; see (a) K. C. Tin and T. Durst, *Tetrahedron Lett.*, 4643 (1970); (b) G. Tsuchihashi, K. Ogura, S. Iriuchijima, and S. Tomisawa, *Synthesis*, 89 (1971); (c) G. Tsuchihashi and K. Ogura, *Bull. Chem. Soc. Jpn.*, **44**, 1726 (1971).
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Substituent Effects on the Efficiency of Hydrogen Migration vs. Electrocyclic Ring Closure in 1,2-Benzotropilidenes

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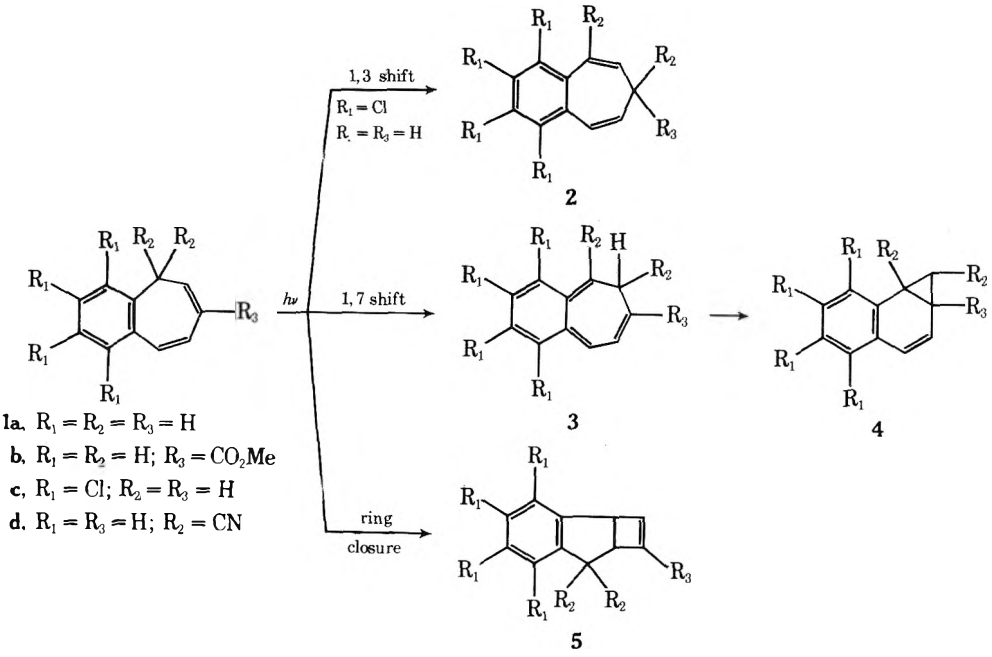
The photochemistry of 5-carbomethoxy- (**1b**), 5-cyano- (**1g**), 5-methyl- (**1e**), and 5-vinyl- (**1f**) 1,2-benzotropilidenes has been studied. Two major processes arise from the singlet excited state of these molecules: (1) production of benzonorcaradienes via a formal 1,7-hydrogen shift followed by tautomerization, and (2) electrocyclic ring closure to produce 6-substituted 2,3-benzobicyclo[3.2.0]hepta-2,6-dienes. While the overall quantum efficiency for the compounds is high (Φ = 0.53–0.85), the relative importance of the two processes is markedly substituent and modestly solvent dependent. The 5-cyano- and 5-carbomethoxy-1,2-benzotropilidenes give major amounts of electrocyclic ring closure while the remaining compounds give primarily hydrogen migration. The increased efficiency of the hydrogen shift process in going from cyclohexane to acetonitrile suggests a polar character in the transition state for this reaction.

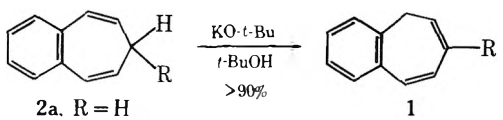
The photochemistry of cycloheptatrienes has been subject to extensive study over the past 10 years.[2] While electrocyclic ring closure of cycloheptatrienes to bicyclo[3.2.0]hepta-2,6-dienes was apparently noted first,[2a] later work established that photochemical 1,7-hydrogen shift occurs some 500 times faster than cyclobutene formation.[2e]



Since the characterization of this process, further examples of hydrogen shifts[2] as well as cases for alkyl[3,4] and phenyl migrations[6] have been reported. More recently the effect of substituents in directing the course of 1,7 shifts[7] and electrocyclic ring closure of substituted cycloheptatrienes has been reported.[8]

In contrast to the extensive investigations in cycloheptatriene photochemistry, only little work has been performed on the photochemistry of its 1,2-benzo derivatives, 1,2-benzotropilidenes. For this system three basic processes have been noted: (1) 1,3-hydrogen shift in **1c**,[9] (2) 1,7-hydrogen shift in **1a**[10] and **1b**,[11] and (3) electrocyclic ring closure in **1a**,[10] **1b**,[11] and **1d**.[12] Interestingly, the ratio of 1,7 shift to electrocyclic ring closure is markedly substituent dependent. For **1a** the 1,7 shift is virtually the exclusive process, while for **1b** the ring-closure reaction is highly favored. In our study of substituent effects on benzonorcaradiene photochemistry, it became important to know the basic photochemical reactions of substituted 1,2-benzotropilidenes. In this connection we have studied the photochemistry of several 5-substituted 1,2-benzotropilidenes. Since we have completed our work in this area and the photochemistry of the compounds is of interest in its own right, we report here details of the ancillary investigation.

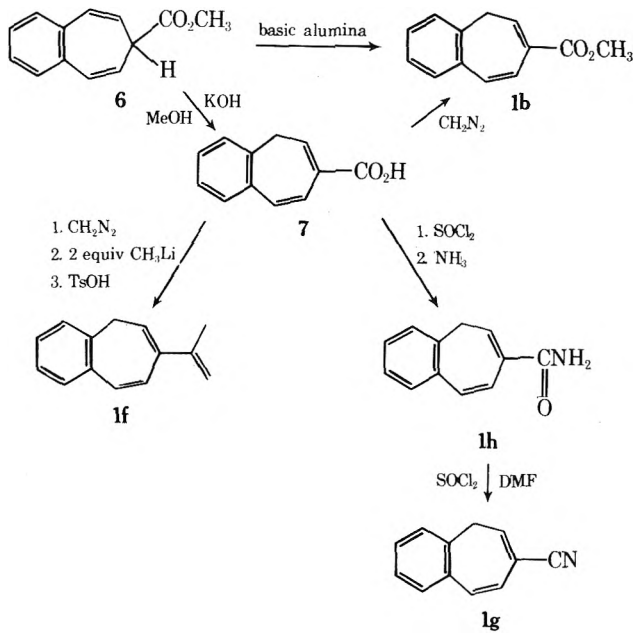
Synthesis of 5-Substituted 1,2-Benzotropilidenes. The synthesis of pure 1,2-benzotropilidenes was based on the higher thermodynamic stability of the 1,2 isomer vs.



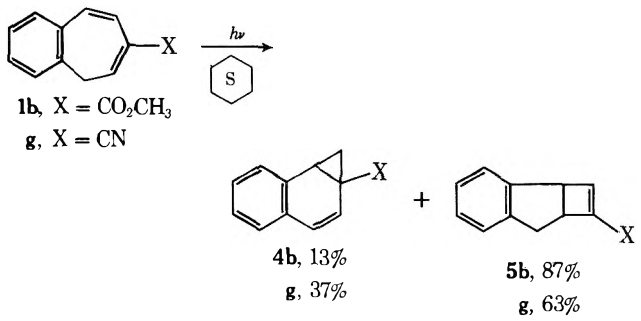
the readily available 3,4-benzotropilidenes.[13] For the unsubstituted and 5-methyl compounds, base-catalyzed isomerization of the 3,4 isomers afforded the corresponding 1,2 isomers in >90% yield. The more substituted systems were prepared from the 7-carbomethoxy-3,4-benzotropilidene as outlined in Scheme I.

Preparative Irradiation of 1,2-Benzotropilidene. The products and mechanism of 1,2-benzotropilidene irradiation were extensively studied by Pomerantz and Gruber,[10] who established by deuterium labeling that a formal 1,7 shift occurred, producing benzonorcaradiene as a primary product. Since the approximate quantum yield they reported seemed low relative to the values we had measured for similar systems (vide infra), we briefly investigated the products of the irradiation and redetermined the quantum efficiency for the process. Our reinvestigation was essentially in agreement with the results reported except that the quantum efficiency for benzonorcaradiene formation was found to be substantially higher ($\Phi = 0.79$) than the ca. 0.1 previously reported.

Scheme I
Synthesis of 5-Substituted 1,2-Benzotropilidenes

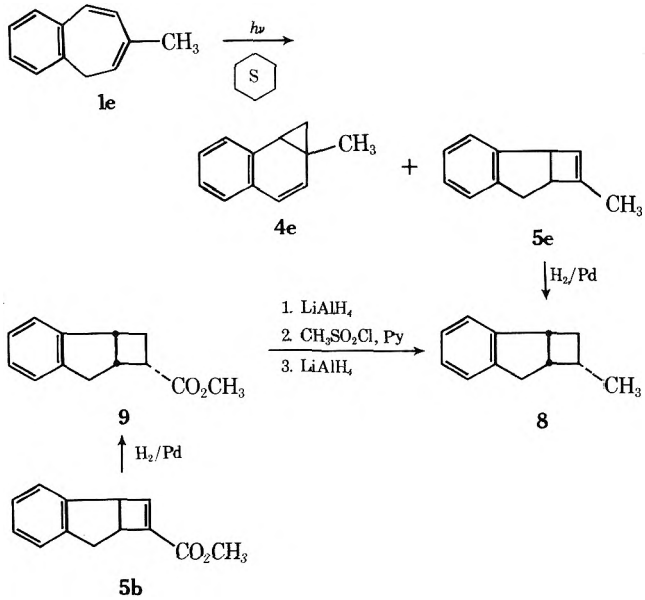


In contrast to the parent hydrocarbon, irradiation of the 5-carbomethoxy compound, **1b**, afforded only minor amounts of benzonorcaradiene, the major process being electrocyclic ring closure. The structures of the products were established by NMR and ir comparison with the known compounds.[13a] In view of the large alteration in product ratio between **1a** and **1b**, a modest number of systems were examined to establish the nature of substituent as it affected the product ratio. Irradiation of the 5-cyano compound, **1g**, produced a mixture of two products in yields of 37 and 63%, the structures **4g** and **5g** being as-



signed to these products on the basis of their spectroscopic properties. Thus, in the NMR **4g** showed the aromatic hydrogens as a multiplet at τ 2.94 and the vinyl hydrogens as a clean AB quartet [τ 3.80 (d, J = 10 Hz, 1 H), 4.03 (d, J = 10 Hz, 1 H)]. The benzylic cyclopropyl [τ 7.08 (J = 11, 7 Hz)], the exo cyclopropyl [τ 8.09 (J = 11, 4 Hz)], and the endo cyclopropyl [τ 9.79 (J = 7, 4 Hz)] appeared as clean doublets of doublets. The NMR spectrum of **5g** was equally informative, showing 1-vinyl hydrogen as a singlet at τ 3.21, one bridgehead as a multiplet at τ 5.75–5.85, a second bridgehead as a multiplet centered at τ 6.29, and the methylene group as a doublet at τ 7.03 (J = 6 Hz). The 5-cyano group then, while showing an altered ratio from the parent system, is less selective than the 5-carbomethoxy group.

While it was originally felt that alkyl substitution at the 5 position would have virtually no effect on product distribution, the availability of the 5-methyl compound dictated an examination of its photochemistry. Irradiation of **1e** at 350 nm led to a time-invariant mixture of two products in an 80:20 ratio. The major product was established as **4e** by spectroscopic comparison with the known compound.[13b] Spectroscopic data suggested **5e** as the structure of the minor product but did not rigorously exclude an alternate structure, 7-methyl-2,3-benzobicyclo[3.2.0]hepta-2,6-diene. However, the minor product was rigorously established as **5e** by relating it to the known compound, **5b**, as shown.

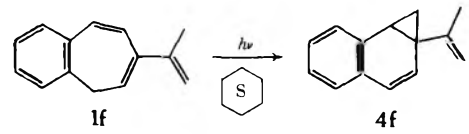


The increased amount of cyclobutene in the cases of **1b**, **1g**, and **1e** prompted us to examine a compound having a substituent which would stabilize the double bond in the cyclobutene product, yet one with much less electron-withdrawing character than a nitrile or carbomethoxy moiety. Irradiation of **1f** at 300 nm through Pyrex afforded up to 70% conversion of a single product. Preparative VPC of the reaction mixture afforded a 68% isolated yield of a compound assigned as **4f** on the basis of its spectroscopic properties. Thus, the NMR showed the aromatic protons as a broad multiplet at τ 3.0, the conjugated vinyl protons as a clean AB [τ 3.72 and 3.93 (J = 10 Hz)], the vinyl methylene as a multiplet at τ 5.2, the methyl group as a multiplet at τ 8.25, and the benzylic cyclopropyl, exo cyclopropyl, and endo cyclopropyl as doublets of doublets centered at τ 7.63 (J = 10, 5.5 Hz), 8.38 (J = 10, 3.5 Hz), and 10.02 (J = 5.5, 3.5 Hz).

Table I
Quantum Yields for Irradiation of Substituted 1,2-Benzotropilidenes in Cyclohexane

Compd	Φ disappearance	Φ cyclobutene	Φ norcaradiene
1a parent	0.85	*a*	0.79
1b 5-carbomethoxy	0.62	0.61	0.088
1e 5-methyl	0.65	0.11	0.42
1f 5-isopropenyl	0.53	*a*	0.54
1g 5-cyano	0.59	0.37	0.21

[a] Product not detected.



Quantum Yields of 1,2-Benzotropilidene Systems. To establish the effect of the substituent on the overall efficiency of the 1,2-benzotropilidene system, quantum yield determinations were made. As is evidenced by the data of Table I, the quantum yields for reaction in the substituted systems all fall in the range 0.53–0.65, with the parent system undergoing the most efficient reaction (Φ = 0.85). Thus, the substituents are not dramatically promoting some nonreactive decay process in the excited state, but simply altering the rates of the two photochemical processes.

Quantum Yields as a Function of Solvent. In the course of these studies a modest solvent effect on the ratio of the products formed from the 1,2-benzotropilidene irradiations was noted. Thus, the quantum efficiencies for the irradiation of **1b**, **1e**, and **1g** were examined in nonpolar media (cyclohexane) and polar media (acetonitrile). As evidenced by the data of Table II, the efficiency of the benzonorcaradiene formation increases by a factor of 1.6–2.0 while that of ring closure behaves less regularly. The overall effect is that the efficiency of the reaction increases in the polar acetonitrile relative to cyclohexane, and this increase is primarily due to a higher efficiency for the benzonorcaradiene formation.

Multiplicity Studies. The change in product ratio as a function of substituent and solvent might be due to excited states of different multiplicity being responsible for the two different photochemical processes. The idea of a triplet state being responsible for cyclobutene formation did not appear unreasonable, since cis–trans isomerization of a 1,2-benzotropilidene would produce a highly strained isomer which might easily undergo thermal electrocyclic ring closure to afford the cyclobutene product. Sensitization studies were only performed on the 5-methyl- and 5-cyano-1,2-benzotropilidenes, since these systems showed appreciable amounts of both types of products; thus a change in product ratio upon sensitization could be readily discerned.

The triplet energies of the 5-substituted 1,2-benzotropilidenes are unknown to our knowledge. However, a reasonable upper limit for their triplet energy would be β-methylstyrene, 59.8 kcal mol^{-1}.[14a,b] One would expect the triplet energy for the 1,2-benzotropilidene system to be in fact

Table II
Quantum Yields for Irradiation of the 5-Carbomethoxy-, 5-Methyl-, and 5-Cyano-1,2-Benzotropilidene in Cyclohexane and Acetonitrile

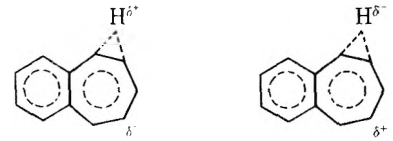
Compd	Solvent	$\Phi_{cyclobutene}$	$\Phi_{norcaradiene}$	$\Sigma\Phi$	$\Phi_{cyclobutene}/\Phi_{norcaradiene}$
1b 5-carbomethoxy	Cyclohexane	0.61	0.088	0.70	6.9
	Acetonitrile	0.64	0.17	0.81	3.7
1e 5-methyl	Cyclohexane	0.11	0.42	0.53	0.26
	Acetonitrile	0.006	0.81	0.82	0.007
1g 5-cyano	Cyclohexane	0.37	0.21	0.58	1.7
	Acetonitrile	0.28	0.44	0.72	0.64

much lower owing to the additional conjugation of a second double bond. Sensitization experiments in these systems encountered difficulties. Thus, we initially hoped to use benzophenone as a sensitizer, since energy transfer to the 1,2-benzotropilidene could be readily established by the quenching of its photoreduction to benzpinacol.[15] However, attempted sensitization of the reaction by benzophenone (E_T = 68.5 kcal mol^{-1}) led to disappearance of the starting compounds but no appearance of products. Since the products **1e** and **1g** were not stable under the sensitization conditions, thioxanten-9-one, Michler's ketone, and 2-acetonaphthone were tried as sensitizers. Only in the case of 2-acetonaphthone (E_T = 59 kcal mol^{-1}) were the products sufficiently stable under the sensitization conditions to make the reaction meaningful. For 2-acetonaphthone a direct irradiation of **1e** was made simultaneously with a sensitized run at 350 nm and the reaction progress followed by VPC. In the time that 60% coversion had been reached in the direct irradiation, less than 2% of products were formed in the sensitized reaction. A similar series of experiments were performed with **1g**, again affording no evidence for a triplet reactant being responsible for products in this system.

Discussion

The results presented here establish that the relative importance of the two major photochemical processes observed for 5-substituted 1,2-benzotropilidenes, namely electrocyclic ring closure or hydrogen shift to eventually produce a benzonorcaradiene, may be strongly altered by the nature of the 5 substituent. We have not detected the 1,3-hydrogen shift in our studies; thus, this process would appear to be of only minimal importance. The inability to sensitize the production of cyclobutene or benzonorcaradiene formation strongly suggests that these processes are originating from an excited singlet state and is in agreement with multiplicity studies on the parent 1,2-benzotropilidene.[10]

An explanation of the manner in which the substituents alter the product ratio in this system is of some interest. Of course, one might argue that the carbomethoxy and cyano groups so alter the electronic character of the 1,2-benzotropilidene excited state that a consistent interpretation for the entire group of substituents would not be expected. On the other hand, several generalizations can be noted. First, the electron-withdrawing conjugating carbomethoxy and nitrile groups favor the cyclobutene formation, while all the other substituents give major amounts of benzonorcaradienes. It is obvious that the increased amount of cyclobutene formation is not simply due to the substituent stabilizing the double bond in the product.[16] Had this been the case, then the methyl group should have been as effective as carbomethoxy, and the 5-vinyl system should certainly have given rise to appreciable amounts of electrocyclic ring closure. The increased efficiency of the benzonorcaradiene formation with increasing solvent polarity suggests that some stabilization for this transition state operates in the more polar medium. With these observations in mind, a possible rationale for the substituent effects should be noted. The increased efficiency of the benzonorcaradiene formation with increasing solvent polarity could be accommodated by either a proton-like migration in a "benzotropilium anion-like" π system, **10**, or a hydride-like migration in a "benzotropilium cation-like" π system, **11**.[17] A transition state of the latter type would readily accommodate the low efficiency of the 1,7-hydrogen migration in the 5-carbomethoxy and 5-cyano systems, since a positively charged π system would be destabilized by these moieties.[18] Thus, for this limited number of substituents, invoking a transition state such as **11** would rationalize both the substituent and solvent effect data. Obviously much additional work remains to be done before a clear interpretation of the substituent effect is at hand.



10 **11**

Experimental Section

Melting points were taken in a Thomas-Hoover Unimelt apparatus and are corrected. Infrared spectra were taken as neat films or KBr pellets with a Perkin-Elmer Model 137 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60A or a Jeolco MH-100 instrument in chloroform-*d* or carbon tetrachloride and are reported in τ units using tetramethylsilane as internal standard. Mass spectra were obtained with an AEI-MS-9 instrument with an ionizing potential of 70 eV. Preparative irradiations were performed with a Rayonet photochemical reactor equipped with 16 RPR-3000 Å lamps or 16 RPR-3500 Å lamps. Gas chromatographic analyses were performed on a Varian Aerograph Model 1200 or 1400 flame ionization instrument using the following columns: column A, 25 ft × 0.125 in., 5% SE-30 on DMCS-treated 60/80 Chromosorb G; column B, 12 ft × 0.125 in., 5% PDEAS on 60/80 Chromosorb W; column C, 10 ft × 0.25 in., 10% PDEAS on 60/—] Chromosorb W; column D, 5 ft × 0.125 in., 3% SE-30 on 100/120 Varaport 30; column E, 25 ft × 0.375 in., 5% SE-30 on DMCS-treated 60/80 Chromosorb G; column F, 10 ft × 0.25 in., 5% SE-30 on 60/80 Chromosorb; column G, 13 ft × 0.125 in., 5% SE-30 on DMCS-treated 60/80 Chromosorb G. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. NMR spectra were obtained at 60 MHz unless otherwise noted.

1,2-Benzotropilidene (1a). A solution of 0.6 *M* potassium *tert*-butoxide in *tert*-butyl alcohol (20 ml) was added to 200 mg of **5a**[13a] in 5 ml of *tert*-butyl alcohol and refluxed for 3 hr on a steam bath. The cooled solution was diluted with water and extracted with ether. Removal of the ether yielded an orange oil which was chromatographed on neutral Woelm alumina (2 × 10 cm column, slurry packed with hexane). One fraction was collected, 150 ml, 180 mg (90%) of **1a** which was greater than 99% pure by VPC analysis (column A).[20]

5-Methyl-1,2-benzotropilidene (1e). To an ethereal solution containing 0.298 g of **2e**[13a] was added 25 ml of 0.6 *M* potassium *tert*-butoxide in *tert*-butyl alcohol. The mixture was refluxed in a steam bath for 1.5 hr under nitrogen; the cooled reaction mixture was diluted with water and extracted with ether. The organic layer was washed with water, then with saturated sodium chloride solution, dried over calcium sulfate, and concentrated, yielding 0.290 g of an orange oil. The oil was chromatographed on Alcoa alumina (0.25 × 10 in., 2% ether–hexane). One fraction was collected (50 ml), yielding 0.267 g (90%) of **1e** greater than 99% pure by VPC (column A): ir (neat) 3.27 (m), 3.36 (s), 6.75 (m), 6.90 (s), 7.05 (m), 11.88 (m), 12.71 (s), 13.34 (s), 13.64 (m), and 13.85 μ (m); NMR (CCl_4) τ 2.93 (s with shoulder at 2.99, 4 H), 3.13 (d, J = 11 Hz, 1 H), 3.78 (d, J = 11 Hz, 1 H), 4.60 (t, broad, J = 7 Hz, 1 H), and 7.12 (d, J = 7 Hz, 2 H).

Anal. Calcd for $C_{12}H_{12}$: C, 92.31; H, 7.69. Found: C, 92.45; H, 7.73.

5-Carbomethoxy-1,2-benzotropilidene (1b). A solution of 0.473 g of **6**[13b] in 2 ml of 4% ether–hexane was passed through a column of Woelm activity III basic alumina (2 × 23 cm column, slurry packed with 4% ether–hexane). Elution proceeded as follows: 4% ether–hexane, 100 ml, nil; 4% ether–hexane, 150 ml, 0.424 g (89%) of **1b** as a colorless oil homogeneous by NMR and VPC (column B) analysis: ir (neat) 3.43 (w), 5.80 (s), 6.13 (m), 6.26 (m), 6.98 (s), 7.95 (s), 9.28 (s), 12.41 (s), 13.36 (s), and 13.93 μ (s); NMR (CCl_4) τ 2.61–3.28 (m, 7 H), 6.30 (s, 3 H), and 6.98 (d, J = 7 Hz, 2 H).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. Found: C, 78.24; H, 6.16.

1,2-Benzotropilidene-5-carboxylic Acid (7). A potassium hydroxide–methanol solution (6.0 g of potassium hydroxide, 24 ml of methanol, and 40 ml of water) was added to a solution of 4.2 g (0.021 mol) of **6** in 20 ml of ether at room temperature. The solution immediately turned blood red and gradually faded to a pale yellow. The ether layer was distilled and the remaining mixture refluxed at 90° for 4 hr. The cooled hydrolysis solution was extracted with 30 ml of ether. The aqueous layer was decolorized with Norit, acidified to a pH of 2 with concentrated hydrochloric acid, and extracted with a hot benzene–methylene chloride solution. The organic layer was washed with saturated brine solution, dried over calcium sulfate, and concentrated in vacuo, yielding 3.77 g (96%) of **7**, mp 196–198.5°. Two recrystallizations from ethyl acetate–hexane yielded the analytical sample: mp 203.8–204.8°; NMR (Me_2SO-d_6) τ 2.75 (broad s, 4 H), 2.90–3.35 (five-line multiplet, 3 H), and 6.98 (d, J = 7 Hz, 2 H); ir (KBr) 3.2–3.5 (m), 3.7–3.9 (m), 5.9 (s), 7.0 (m), 7.55 (m), 7.85 (s), 11.1 (m), 12.42 (s), 12.87 (s), 13.13 (s), 13.40 (m), and 13.9 μ (s).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.41; H, 5.38. Found: C, 77.20; H, 5.40.

1,2-Benzotropilidene-5-carboxamide (1h). A three-molar excess of thionyl chloride was added to a refluxing mixture of 3.38 g (0.0182 mol) of **7** in 20 ml of dry benzene. When the acid completely dissolved, ir analysis showed that there was complete conversion to the acid chloride. The solvent and excess thionyl chloride were removed in vacuo, yielding a brown oil which was taken up in 100 ml of anhydrous ether. Dry ammonia was bubbled through the solution until the mixture showed pH 10. The mixture was diluted with water and extracted with methylene chloride; the organic layer was washed with saturated sodium chloride, dried over calcium sulfate, and concentrated in vacuo, yielding 2.53 g (77.5%) of the amide, mp 155–165°. Two recrystallizations from ethanol–water yielded the analytical sample: mp 161–162°; ir (KBr) 2.94 (m), 3.10 (m), 6.01 (s), 6.18 (s), 6.30 (m), 7.00 (m), 7.11 (m), 8.95 (m), 9.06 (m), 12.36 (m), and 13.35 μ (s).

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.84; H, 5.95; N, 7.57. Found: C, 77.37; H, 6.00; N, 7.57.

5-Cyano-1,2-benzotropilidene (1g). Thionyl chloride, 4.05 ml (0.0563 mol), dissolved in approximately 1 ml of *N,N*-dimethylformamide was added dropwise over 1 min to a stirred solution of 2.61 g (0.0141 mol) of the amide in 10 ml of *N,N*-dimethylformamide maintained at 0° in the dark under a nitrogen atmosphere. The solution was allowed to warm to room temperature and stirred for 48 hr. The solvent was distilled from the reaction mixture and the remaining oil was diluted with water and extracted with 50% ether–benzene. The organic layer was washed with water (2 × 30 ml) and saturated sodium chloride, dried over calcium sulfate, and concentrated, yielding 2.5 g of a brown oil. The oil was chromatographed on silica gel (2.3 × 60 cm column, slurry packed in 5% ether–hexane). Elution proceeded as follows: 5% ether–hexane, 250 ml, nil; 5% ether–hexane, 525 ml, 1.52 g (64.5%) of **1g**, mp 64–65°. Two recrystallizations from ether–hexane yielded the analytical sample: mp 65.9–66.8°; ir (KBr) 4.50 (m), 6.35 (m), 6.77 (m), 11.15 (m), 11.35 (m), 12.30 (w), 12.60 (s), 13.16 (s), 13.4 (m), and 13.84 μ (m); NMR (CCl_4) τ 2.81 (broad singlet with shoulder at 2.9, 5 H), 3.5–3.8 (three lines, broad, 2 H), and 6.90 (d, J = 7.5 Hz, 2 H).

Anal. Calcd for $C_{12}H_9N$: C, 86.22; H, 5.39; N, 8.38. Found: C, 85.90; H, 5.46; N, 8.38.

5-Isopropenyl-1,2-benzocycloheptatriene (1f). An ethereal diazomethane solution was added dropwise to a partial solution of 0.4 g (0.215 mol) of **7** in 2 ml of dry ether. When the acid had dissolved the solution was concentrated, dissolved in 25 ml of dry tetrahydrofuran, and cooled to −78° by an acetone–Dry Ice bath. To this solution was added 2.35 ml (0.514 mmol) of a 2.2 *M* methyllithium solution over a 10-min period and the reaction mixture was stirred for 1 hr. The reaction mixture was then quenched with 75 ml of water and extracted with ether. The organic layer was washed with water (2 × 20 ml) and saturated sodium chloride, dried over calcium sulfate, and concentrated. The ir of the oil indicated incomplete conversion; so the reaction was executed a second time with the same amount of reagents. After another hour of reaction time, the reaction was worked up as before. The crude alcohol, a clear oil, was dissolved in 50 ml of dry benzene to which was added 15 mg of *p*-toluenesulfonic acid and the mixture was heated at 50° for 2 hr. The reaction mixture was concentrated to an oil which was dissolved in ether and washed with water (2 × 20 ml) and saturated sodium chloride, dried over calcium sulfate, and concentrated, yielding 385 mg of a dark oil. The oil was chromatographed on Alcoa alumina (1 × 30 cm column, hexane). One fraction of 500 ml was taken, yielding 250 mg (64%) of **1f**, mp 65–70°. Two recrystallizations from ethanol–hexane yielded the analytical sample: mp 77.5–78.5°; ir (KBr) 6.22 (m), a series of three medium bands between 6.71 and 7.3 with a fourth strong band at 6.9, 11.25 (s), 11.40 (m), 11.6 (m), 12.5 (s), 13.3 (s), 13.6 (m), and 14.4 μ (m); NMR (CCl_4) τ 2.91 (m, 5 H), 3.35 (d, J = 12 Hz, 1H), 4.2 (broad t, J = 7.5 Hz, 1 H), 5.09 (broad d, J = 6 Hz, 2 H), 7.0 (d, J = 7.5 Hz, 2 H), and 8.12 (d, J = 1 Hz, 3 H).

Anal. Calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 91.93; H, 7.56.

Irradiation of 5-Carbomethoxy-1,2-benzotropilidene (1b). A solution of 252 mg of **1b** in 70 ml of cyclohexane was degassed for 15 min with purified nitrogen, then irradiated in a stoppered quartz test tube for 57 min with a bank of 16 RPR-3500 Å lamps in a merry-go-round apparatus. By VPC two products were produced, one major and one minor. The irradiation mixture was separated by preparative VPC (column C at 130°). The major product had ir and NMR spectra identical with those of 6-carbomethoxy-2,3-benzobicyclo[3.2.0]hepta-2,6-diene. The minor product had ir and NMR spectra identical with those of 6-carbomethoxy-2,3-benzonorcaradiene.

In a similar experiment, a solution of 168.0 mg of 5-carbomethoxy-1,2-benzotropilidene and 24.5 mg of eicosane in 45 ml of cyclohexane was prepared. The solution was degassed for 30 min with purified nitrogen, and 20 ml of it was irradiated in a Pyrex test tube with a bank of 16 RPR-3500 Å lamps in a merry-go-round apparatus for 65 min. By VPC analysis the total product yield was quantitative: 6-carbomethoxy-2,3-benzobicyclo[3.2.0]hepta-2,6-diene, 85.7%; 6-carbomethoxy-2,3-benzonorcaradiene, 14.3%.

Irradiation of 5-Cyano-1,2-benzotropilidene (1g). A solution containing 0.7 g of **1g** in 150 ml of purified cyclohexane was irradiated in the Rayonet with 350-nm light. Periodic analysis of the reaction by VPC (column D at 150°) showed that two products were formed at a constant ratio of 60:40. After 148 min of irradiation, VPC analysis indicated complete consumption of starting material. The reaction mixture was concentrated to afford a light yellow solid which was chromatographed on silica gel (1.7 × 88 cm column, slurry packed, 3% ether–hexane). Elution proceeded as follows: 3% ether–hexane, 250 ml, nil; 5% ether–hexane, 190 ml, nil; 5% ether–hexane, 330 ml, 0.309 g (44%) of **5g**, mp 69–71°.

Recrystallization of this material from ether–hexane yielded the analytical sample: mp 71.5–72.5°; NMR (CCl_4) τ 2.95 (s, 4 H), 3.21 (s, 1 H), 5.75–5.85 (broad s, 1 H), 6.29 (five-line multiplet, 1 H), and 7.03 (d, J = 6.0 Hz, 2 H); ir (KBr) 3.39 (m), 4.5 (s), 6.35 (m), 6.8 (s), 7.02 (m), 8.15 (s), 10.2 (m), 10.45 (m), 11.1 (m), 11.4 (m), 11.65 (m), 12.15 (m), 12.69(m), and 13.35 μ (s).

Anal. Calcd for $C_{12}H_9N$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.65; H, 5.42; N, 8.23.

Continued elution with 325 ml of 7% ether–hexane yielded 0.183

g (26%) of **4g**. Recrystallization of this material from 10% ether–hexane yielded the analytical sample: mp 59–60°, NMR (CCl_4) τ 2.94 (m, 4 H), 3.8 (d, J = 10 Hz, 1 H), 4.03 (d, J = 10 Hz, 1 H), 7.08 (d of d, J = 11, 7 Hz, 1 H), 8.09 (d of d, J = 11, 4 Hz, 1 H), and 9.79 (d of d, J = 7, 4 Hz, 1 H); ir (KBr) 4.5 (s), 6.79 (m), 6.93 (m), 9.51 (s), 12.31 (s), 12.71 (s), 13.0 (s), 13.50 (m), and 13.95 μ (m).

Anal. Calcd for $C_{12}H_9N$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.49; H, 5.34; N, 8.12.

Preparative Irradiation of 5-Methyl-1,2-benzotropilidene (1e). A solution of 0.179 g of **1e** in 20 ml of purified cyclohexane was degassed for 10 min with nitrogen and irradiated for 2 hr in a Pyrex test tube with a 400-W Hanovia lamp. The solvent was removed in vacuo and the resulting oil was purified by preparative vpc (column E at 160°). Peak 1, **5e** (28%): ir (neat) 6.12 (m), 6.75 (s), 6.95 (s), 8.0 (s), 10.25 (m), 12.5 (s), and 13.40 μ (s); NMR (CCl_4) τ 3.00 (s, 4 H), 4.07 (m, 1 H), 6.0 (m, 1 H), 6.60 (m, 1 H), 7.15 (broad d, J = 6.0 Hz, 2 H), and 8.31 (m, 3 H).

Anal. Calcd for $C_{12}H_{12}$: C, 92.31; H, 7.69. Found: C, 92.00; H, 7.97.

The second peak, isolated in 53% yield, was identified as **4e** by ir and NMR comparison with the known compound.[13b]

6-*endo*-Carbomethoxy-2,3-benzobicyclo[3.2.0]hept-2-ene (9). A solution of 5-carbomethoxy-1,2-benzotropilidene (**1b**) in 200 ml of purified cyclohexane in a Pyrex vessel was inrradiated for 3 hr with a bank of 16 RPR-3500 Å lamps. After removal of the cyclohexane in vacuo the residue was dissolved in 100 ml of ethyl acetate, 20 mg of 5% Pd/C was added, and the mixture was hydrogenated for 2 hr on a Parr hydrogenation apparatus. The residue from the hydrogenation was chromatographed on 120 g of silica gel (2.3 × 36 cm column slurry packed in 2% ether–hexane). Elution proceeded as follows: 0.2 l., 2% ether–hexane, nil; 0.1 l., 5% ether–hexane, nil; 0.5 l., 5% ether–hexane, 0.48 g (48%) of **9** as a clear oil: ir (neat) 3.40 (m), 5.76 (s), 6.76 (m), 6.86 (m), 6.97 (m), 7.40 (m), 8.33 (br), 8.49 (br), and 13.30 μ (s); NMR (CCl_4) τ 2.72 (s, 4 H), 6.0–6.75 (m, 3 H), 6.38 (s, 3 H), 6.75–7.00 (m, 2 H), and 7.2–7.7 (m, 2 H). The material was hydrolyzed to its carboxylic acid: mp 101.5–104°; ir (KBr) 2.7–4.3 (br, s), 5.83 (s), 7.03 (m), 7.43 (m), 8.08 (s), 8.13 (s), 10.60 (m), 13.22 (s), and 13.50 μ (m).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.43; H, 6.30.

6-*endo*-Hydroxymethyl-2,3-benzobicyclo[3.2.0]hept-2-ene. A solution of **9** (0.566 g, 2.78 mmol) in 15 ml of anhydrous ether was added dropwise over 0.5 hr to a slurry of 0.200 g (5.27 mmol) of lithium aluminum hydride in 15 ml of anhydrous ether. Following addition, the mixture was refluxed for 10 hr. Subsequently the excess hydride and reduction complex were decomposed by cautious addition of water (2.4 ml). The organic portion was decanted and the alumina salt was dissolved in 5% HCl (20 ml). The aqueous acid solution was extracted with ether (2 × 20 ml), and the combined organic layers were washed with saturated sodium chloride solution (30 ml) and dried over anhydrous calcium sulfate. After removal of the ether by distillation, the remaining light yellow oil was chromatographed on deactivated silica gel (2.0 × 28 cm column slurry packed with 30% ether–hexane). Elution with 30% ether–hexane proceeded as follows: 50 ml, 0.0110 g of mixture of an unidentified oil and a small amount of unreacted ester; 100 ml, 0.432 g (89%) of 6-*endo*-hydroxymethyl-2,3-benzobicyclo[3.2.0]-hept-2-ene: ir (neat) 2.93 (s), 3.38 (s), 3.46 (m), 6.80 (m), 9.47 (m), 9.66 (m), 9.83 (m), 10.03 (m), and 13.39 μ (s); NMR ($CDCl_3$) τ 2.88 (s, 4 H), 6.0–7.1 (series of overlapping m, 6 H), 7.1–7.7 (m, 1 H), and 8.2–8.7 (m, 2 H).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.69; H, 8.20.

6-*endo*-Methyl-2,3-benzobicyclo[3.2.0]hept-2-ene (8). To an ice-cooled solution of 0.306 g (1.76 mmol) of 6-*endo*-hydroxymethyl-2,3-benzobicyclo[3.2.0]hept-2-ene in 10 ml of dry, freshly distilled pyridine, 0.5 ml of freshly distilled methanesulfonyl chloride was added dropwise over 0.25 hr. After stirring for 5 hr, the reaction mixture was poured onto 30 g of ice in 30 ml of water and extracted with ether (2 × 50 ml). The organic layer was washed with 5% hydrochloric acid (3 × 30 ml) and saturated sodium chloride solution (30 ml), and dried over anhydrous calcium sulfate. The ether was removed in vacuo to give ca. 450 mg (100%) of the mesylate. Infrared spectroscopic analysis showed that no alcohol remained. The mesylate was then dissolved in anhydrous ether (10 ml) and added slowly to an ice-cooled slurry of 0.200 g of lithium aluminum hydride in 10 ml of ether. Following addition, the ice bath was removed and the mixture was refluxed for 14 hr. After cooling to room temperature, the excess hydride was decomposed by cautious addition of water. The organic portion was removed by filtration and the alumina salt was dissolved in 5% hydrochloric acid (20 ml). The aqueous acid solution was extracted with ether (2 × 20 ml) and the combined organic layers were washed with saturated sodium chloride solution (30 ml) and dried over anhydrous calcium sulfate. After removal of ether by distillation, there remained 247 mg of liquid. Vapor phase chromatography (column F at 110°) gave pure 6-*endo*-methyl-2,3-benzobicyclo[3 2.0]hept-2-ene: ir (CS_2) 3.26 (m), 3.38 (s), 7.34 (m), 7.63 (m), 8.10 (m), 8.36 (m), 8.70 (m), 9.36 (m), 9.82 (m), 10.26 (m), 10.35 (m), 13.55 (s), and 14.16 μ (m); NMR (CCl_4) τ 2.98 (s, 4 H), 6.0–7.5 (aliphatic absorption with broadened s at τ 6.98, 6 H), 8.52 (m, 1 H), and 9.04 (d, J = 6.5 Hz, 3 H); mass spectrum m/e (rel intensity) 158 (M, 6), 115 (20), 116 (B, 100), 117 (10), 128 (8), and 129 (9).

Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.67; H, 8.83.

Hydrogenation of 6-Methyl-2,3-benzobicyclo[3.2.0]hepta-2,6-diene (5e). An 8-mg sample of **5e** was dissolved in 10 ml of ethyl acetate containing 2 mg of 5% Pd/C and the mixture was hydrogenated for 8 hr at atmospheric pressure. After filtration through Celite, the ethyl acetate was removed by distillation and the hydrogenation product was isolated by preparative VPC (column F at 130°). The purified material showed a VPC retention time and ir spectra (CCl_4 and CS_2) identical with those of the synthesized authentic sample.

2-Acetonaphthone Sensitized Irradiation of 5-Methyl-1,2-benzotropilidene (1e). Stock solutions of 0.2 M 2-acetonaphthone in benzene and 0.02 M **1e** in benzene were prepared. For a typical run 1.5 ml of 0.2 M 2-acetonaphthone and 0.2 ml of 0.0016 M **1e** were placed in a Pyrex test tube and diluted to 2 ml with benzene. In a matching test tube was placed 0.2 ml of 0.02 M **1e**

Table III
Quantum Yield Data for 1,2-Benzotropilidenes

Compd	Light absorbed, mE	Concn, $M \times 10^3$	% conversion	$\Phi_{disappearance}$	$\Phi_{cyclobutene}$	$\Phi_{norcaradiene}$
1a[c]	0.139	10.2	15	0.80	*a*	0.73
1a[c]	0.126	10.2	16	0.90	*a*	0.85
1b[c]	0.214	18.4	12	*b*	0.62	0.09
1b[c]	0.287	18.4	15	0.60	0.57	0.08
1b[c]	0.266	18.4	17	0.61	0.68	0.09
1b[c]	0.263	18.4	17	0.65	0.64	0.08
1g	0.0873	15.7	25	0.57	0.36	0.21
1g	0.0434	15.7	13.5	0.61	0.37	0.22
1e	0.0117	16.5	13.5	0.64	0.12	0.45
1e	0.0041	16.5	4.3	0.59	0.10	0.38
1f	0.0298	16.5	10.0	0.58	*a*	0.59
1f	0.0368	16.5	10.0	0.47	*a*	0.49

[a] Product was not detected. [b] Value was not determined. [c] This value was measured in a 65-ml actinometer cell. All other numbers determined in a 12-ml cell.

and the volume was made up to 2 ml with benzene. At these concentrations the uv absorptions of the sensitizer and substrate are such that the tropilidene can capture <0.5% of the incident light. Both solutions were degassed for 10 min with a stream of nitrogen and then irradiated simultaneously in the Rayonet with 350-nm light. The reaction was followed by VPC (column G at 125°) with the following results. In the time that the unsensitized reaction had reached 60% conversion to products the sensitized run showed ~2% products and ca. 50% loss of **1e**.[21] To the direct run was added 0.051 g of 2-acetonaphthone to bring the solution to 0.15 *M* sensitizer and the solution was irradiated again. VPC analysis showed that the products were essentially stable to the sensitizer.

2-Acetonaphthone Sensitized Irradiation of 5-Cyano-1,2-benzotropilidene (1g). The same procedure and concentrations were used as described for **1e**. This irradiation was monitored with column D at 145°, giving the following results. At a time in which the direct irradiation had gone to 94% conversion, the sensitized reaction gave <2% products. Sensitizer (0.051 g) of 2-acetonaphthone was then added to the direct reaction and irradiated again. VPC analysis showed that both photoproducts were stable to the sensitizer.

Benzophenone Sensitization of 5-Methyl-1,2-benzotropilidene (1e). Into three matched test tubes were placed the following solutions: (1) 0.15 *M* benzophenone and 0.15 *M* benzhydrol in 2 ml of benzene; (2) 0.15 *M* benzophenone, 0.15 *M* benzhydrol, and 1.7×10^{-3} *M* of **1e** in 2 ml of benzene; and (3) 1.73×10^{-3} *M* **1e** in benzene. The concentrations in tube 2 ensured that benzophenone was capturing greater than 99% of the light. Irradiation for 30 min at 3500 Å followed by VPC analysis showed that in tube 3 there was 70% conversion to products while in tube 2 no product was formed yet starting material had essentially disappeared. Uv analysis for remaining benzophenone in tube 2 using tube 1 as a standard indicated that the disappearance of benzophenone in tube 2 had been quenched by ~70%. Thus, energy transfer had occurred from benzophenone to **1e**. Unfortunately, when a reaction mixture consisting of 70% **4e** and 30% **1e** was irradiated in the presence of 0.15 *M* benzophenone and 0.15 *M* benzhydrol, VPC analysis indicated that both **4e** and **1e** disappeared with no production of volatile products.

Preparative Irradiation of 5-Isopropenyl-1,2-benzocycloheptatriene (1f). A degassed solution of 0.200 g of **1f** in 100 ml of spectral grade cyclohexane was irradiated for 4 hr in the Rayonet with 300-nm light. Periodic analysis of the reaction by VPC (column D at 150°) showed formation of one major product. When the reaction reached 60% completion the solution was concentrated and the resultant oil was purified by preparative VPC (column F at 145°). The recovered starting material was identical with the authentic material by NMR, while the photoproduct (68% yield in an extended irradiation) had the following spectral data: NMR (CCl_4) τ 3.0 (broad m, 4 H), 3.72 (d, J = 10 Hz), 3.93 (d, J = 10 Hz, 2 H), 5.2 (m, 2 H), 7.63 (d of d, J = 10, 5.5 Hz, 1 H), 8.25 (m, 3 H), 8.38 (d, J = 3.5 Hz, 1 H, the other portion of the doublet lies under the methyl absorption), 10.02 (d of d, J = 6, 3.5 Hz, 1 H); ir (neat) 6.1 (m), 6.71 (m), 6.90 (m), 11.0 (m), 12.8 (s), 13.1 (m), and 13.5 μ (s). Exact mass analysis: calcd *m/e* 182.10954440; found *m/e* 182.10978794; difference, 0.00024.

Quantum Yield Determinations. These were made as previously described[13b] using either a 12-ml or 65-ml actinometer cell. The pertinent data from these determinations are presented in Table III.

Registry No.—**1a**, 264-08-4; **1b**, 35393-09-0; **1e**, 54276-79-8; **1f**, 54276-80-1; **1g**, 54276-81-2; **1h**, 54276-82-3; **4f**, 54276-83-4; **4g**, 54276-84-5; **5a**, 18511-42-7; **5e**, 54276-85-6; **5g**, 54276-86-7; **6**, 31399-17-4; **7**, 54276-87-8; **8**, 54276-88-9; **9**, 54276-89-0; **9** free acid, 54276-90-3; **9** OH analog, 54276-91-4.

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(14) (a) A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965); (b) *trans*-1-phenylbutadiene is a better model for the triplet energy, but an exact value for this compound does not appear to have been recorded.[10]

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(17) This type of rationalization is not entirely new, since a charged transition state employing a hydride shift has been suggested to explain the increased rate of thermal isomerization of some 7-substituted tropilidenes.[2g]

(18) A referee has noted that the quantum yields for the 1,7-shift product decrease in going from the parent to the 5-methyl to the 5-vinyl system and asks if this is consistent with transition state **11**. We wish to note here that this trend is not inconsistent with our consideration of **11**, since a methyl has been considered as an electron-withdrawing group inductively[19] and vinyl is certainly electron-withdrawing inductively. However, we do not feel strongly about this point.

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Photochemical Cyclization of Olefinic N-Chloroamides

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Chlorination of olefinic N-monoalkylamide lithium derivatives with N-chlorosuccinimide provided N-chloroamides. Irradiation of these in benzene solution with a 450-W high pressure mercury arc through a Corex filter led to bridged and unbridged C-chloro-N-acylpyrrolidines and C-chloro-γ-lactams. No six-membered-ring formation was found but selectivity was shown for double bonds with increased substitution.

Intramolecular addition of amino radicals ($R_2N\cdot$) and aminium radicals ($R_2HN\cdot^+$) to double bonds is well established and has been shown to lead only to the formation of five-membered rings.[1-9] In these studies nitrogen radicals were generated by decomposition of tetrazenes, or from N-nitroso- or N-chloroamines in neutral or acidic solutions, by irradiation or by treatment with titanium trichloride. Since the analogous cyclization of olefinic carbon radicals can be diverted from a kinetically favored five-membered-ring formation to generation of six-membered rings by placing strong radical-stabilizing substituents on the acyclic carbon radical,[10-17] or by steric constraints in the cyclopentane formation,[18,19] it was of interest to see if amide radicals would show divergence from the cyclization of amine radicals. As no cyclizations of olefinic amide radicals were known until the latter part of our investigation, their demonstration as a new method for formation of lactams or N-heterocyclic amides was of particular interest as a model study for alkaloid syntheses.[20]

An electron spin resonance study has shown that the amide radical is best described with location of the radical centered on nitrogen in a 2p orbital[21] and intramolecular hydrogen abstraction[22-26] seems to take place preferentially with transfer of hydrogen to nitrogen rather than oxygen.[24] The photolysis of saturated N-chloroamides thus leads to γ- and δ-chloroamides, which usually cyclize to γ- and δ-iminolactones.[22,23] N-Alkylation has, however, been found in the generation of some bicyclic lactams, where the usual O-alkylation would require bridgehead iminolactones.[26]

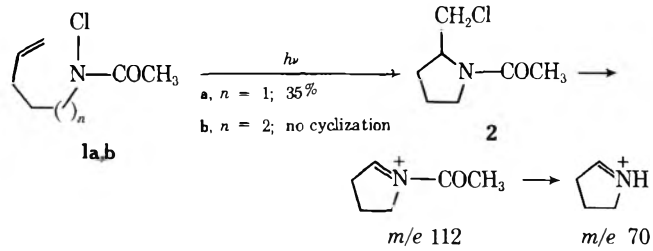
Attempted intermolecular photochemical reactions of N-alkyl-N-chloroamides with a variety of olefins had failed[23] when our intramolecular reaction studies were started but such reactions have now been described for N-chloroacetamide and chlorinated N-chloroacetamides.[20a]

The following examples demonstrate the formation of five-membered lactams or N-heterocyclic amides as main products in the photochemical reactions of olefinic N-alkyl-N-chloroamides and limitations of this new reaction. The product yields which are shown were often obtained from very small scale reactions with high percentage losses in purifications. Higher preparative yields may be possible and the isolation of minor products remains for further investigation.

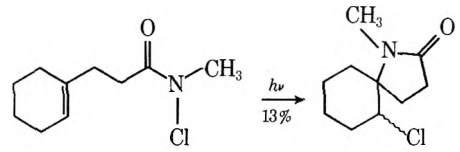
Two general types of N-chloroamides were used in this study. The compounds were either acetamides of olefinic amines or N-methylamides of olefinic acids. The N-chloro derivatives were obtained in 40–70% yields from reactions of these amides with n-butyllithium and N-chlorosuccinimide.

Irradiation of N-chloro-N-(4-n-penten-1-yl)acetamide (**1a**) in benzene solution with a 450-W high-pressure mercury arc, filtered through Corex, gave the N-acetyl-2-chloromethylpyrrolidine **2**. This product was particularly characterized by its mass spectrum, which showed a fragment at *m/e* 70 arising from an initial loss of CH_2Cl to give an *m/e* 112 ion and subsequent loss of CH_2CO, as seen from a metastable peak (*m/e* 43.8) corresponding to the *m/e* 112 to 70 fragmentation.

In contrast to this cyclization, the next higher homolog, N-chloro-N-(5-n-hexen-1-yl)acetamide (**1b**), yielded a mixture of at least seven components containing primarily the parent N–H amide when irradiated in benzene and only that major compound when irradiated in cyclohexane.

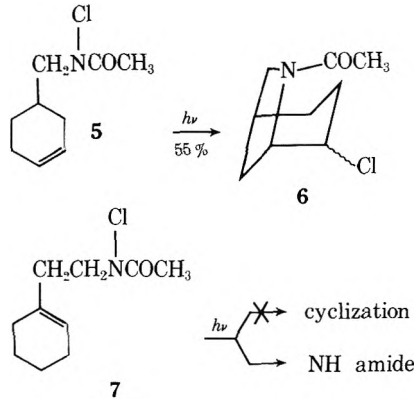


When N-chloro-N-methyl-3-(cyclohex-1-en-1-yl)propionamide (**3**) was subjected to photolysis, only the spirolactam **4** with characteristic ir absorption at 1690 cm^{-1} and an NMR multiplet at δ 4.0 for the proton adjacent to chlorine could be isolated and no perhydroquinolone was obtained.



3 **4**

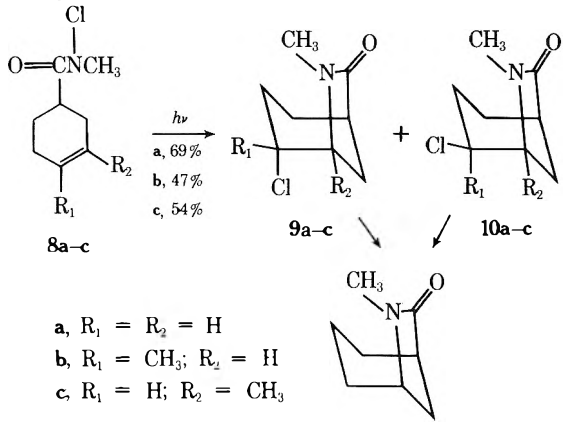
Irradiation of N-chloro-N-[(3-cyclohexen-1-yl)methyl]acetamide (**5**) gave bicyclic product **6** to which a [3.2.1] bridged structure could be assigned on the basis of the remarkable overlap of its mass spectrum with that of authentic 6-acetyl-6-azabicyclo[3.2.1]octane, prepared by reduction of *m*-aminobenzoic acid[27] and acetylation.[28] On the other hand, no monomeric cyclization product was obtained from irradiation of N-chloro-N-[2-(1-cyclohexen-1-yl)ethyl]acetamide (**7**), where only the parent amide was isolated.



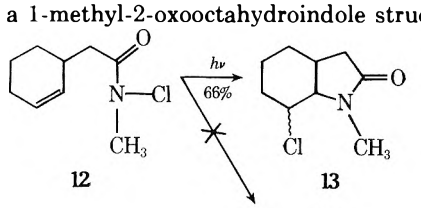
These findings are consistent with the usual preference for five-membered-ring formation and steric facilitation of olefinic radical cyclizations when the double bond and radical centers are separated by three atoms.

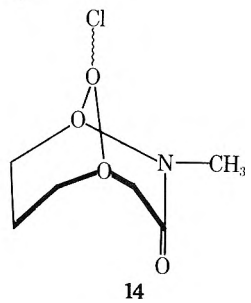
Bridged [3.2.1] bicyclic products (**9a** and **10a**) were also obtained from irradiation of *N*-chloro-*N*-methylcyclohex-3-enecarboxamide (**8a**). The product mixture, containing about equal amounts of epimeric chlorolactams, could be separated by absorption chromatography, yielding the less polar axial chloro compound **9a** with an *N*-methyl NMR signal at δ 2.96 and the more polar equatorial chloro epimer **10a** with the *N*-methyl signal at δ 3.16. Reduction of these compounds with tri-*n*-butylstannane gave the lactam **11**, which could be compared with the methylation product of 6-azabicyclo[3.2.1]octan-7-one.[27]

The presence of methyl substituents at either end of the double bond (**8b,c**) did not divert the cyclization reaction from formation of bridged γ-lactams (**9b,c, 10b,c**). Thus the 4-methyl chloroamide **8b** yielded a separable 1:1 mixture of chloro epimers **9b** and **10b**, which showed analogous NMR differences and equivalent mass spectra. Since the 3-methyl chloroamide **8c** could not be completely freed from the 4-methyl isomer **8b**,[30] a mixture of four products was obtained from that reaction. Chromatographic separation into the two sets of axial and equatorial chlorolactams and subtraction of the NMR spectra of pure isomers **9b** and **10b** gave spectra of the isomers **9c** and **10c**, showing protons on carbon bearing chlorine at δ 4.08 and 3.95, respectively.



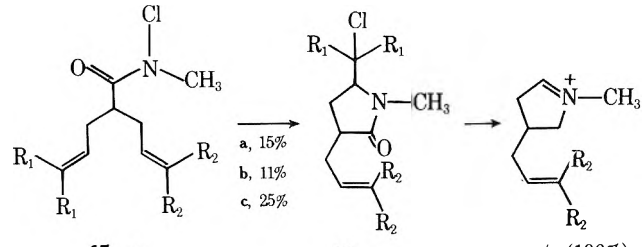
The occurrence of the perhydroindole skeleton in several alkaloid classes prompted an examination of the photochemical cyclization of *N*-chloro-*N*-methyl-2-cyclohexen-1-yl acetamide (**12**). The resultant product could be assigned a 1-methyl-2-oxooctahydroindole structure **13** with





exclusion of the alternative bicyclic lactam **14** by its NMR spectrum. The ring juncture proton next to nitrogen was seen as a triplet at δ 3.42, which collapsed to a doublet (J = 7.5 Hz) by decoupling from the proton next to chlorine at δ 3.90.

The analogous *N*-3,4-dimethoxybenzyl chloroamide did not yield any cyclization product on irradiation but gave instead the *N*-acylimine by loss of a hydrogen from the benzylic substituent. Since cyclization would have provided facile synthetic access to alkaloids with the lycorane skeleton, the alternative dimethoxyphenylacetic acid amide of 2-(cyclohex-2-en-1-yl)ethylamine was prepared, but it could not be converted to the required *N*-chloroamide.



15a–c **16a–c** *m/e* (100%)

a, R_1 = CH_3, R_2 = H — **17a**, 138
b, R_1 = R_2 = H — **b**, 138
c, R_1 = R_2 = CH_3 — **c**, 166

The above examples show that olefinic chloroamides undergo intramolecular reactions with double bonds at various levels of substitution. In order to learn if there is any selectivity associated with the degree of substitution, the allyl-3,3-dimethylallyl chloroamide **15a** was irradiated. Only the cyclization product **16a**, derived from reaction of the more substituted double bond, could be detected. A characteristic vinyl multiplet in the NMR spectrum and a mass spectral base peak **17a** at *m/e* 138 due to loss of the chloropropenyl group (with no *m/e* 166 peak from loss of chloromethylene) could be compared and contrasted with corresponding spectra derived from cyclization of the symmetric diene chloroamides **15b** and **15c**. Since the unsubstituted double bond did not react at all in the mixed diene **15a** but reacted in the diallyl compound **15b** and since highest yields were found from the fully substituted diene **15c**, selectivity for more substituted double bonds is indicated in this reaction. While this selectivity implies some stability for amide radicals, one does not, however, find formation of *N*-acylpiperidine rather than *N*-acylpyrrolidine products corresponding to cyclizations of stabilized olefinic carbon radicals. The difference may be due to a smaller compression barrier and less ring strain in formation of the intermediate *N*-acylpyrrolidine radical.

Experimental Section

Preparation of Amides. *N*-(4-*n*-Penten-1-yl)acetamide. To 1.1 g (0.029 mol) of lithium aluminum hydride in 125 ml of ether, 2.45 g (0.029 mol) of 4-pentenonitrile was added dropwise in an equal volume of ether so as to maintain a steady reflux. The mixture was refluxed overnight, then 0.28 ml of water followed by 0.28 ml of 15% sodium hydroxide followed by 0.84 ml of water was added. The ether layer was filtered and cooled, and 2.94 g (0.0288 mol) of acetic anhydride was added dropwise with stirring. The solution was stirred for 1.5 hr, then 20 ml of 15% sodium hydroxide was added and the mixture was stirred overnight. The ether layer was separated, dried over magnesium sulfate, filtered, and concentrated to yield a colorless liquid which was distilled to give 2.5 g (68%) of a colorless oil: bp 70–71° (0.02 mm); ir 1650, 1550 cm^{-1}; NMR δ 1.65 (q, 2 H), 1.98 (s, 3 H), 2.10 (m, 2 H), 3.25 (q, 2 H), 4.85–6.00 (m, 3 H), 6.65 (m, 1 H).

Anal. Calcd for $C_7H_{13}NO$: C, 66.1; H, 10.3; N, 11.0. Found: C, 66.3; H, 10.5; N, 11.1.

N-(5-*n*-Hexen-1-yl)acetamide was prepared similarly from 5-hexenonitrile,[32] giving 74% of colorless liquid: bp 84–85° (0.07 mm); ir 1550, 1650 cm^{-1}; NMR δ 1.95 (s, 3 H), 3.25 (q, 2 H), 4.8, 5.1, 5.8 (3 m, 4 H).

Anal. Calcd for $C_8H_{15}NO$: C, 68.0; H, 10.7; N, 9.9. Found: C, 68.0; H, 10.9; N, 10.1.

***N*-[(3-Cyclohexen-1-yl)methyl]acetamide.** To a slurry of 3.58 g (0.094 mol) of lithium aluminum hydride in 200 ml of ether was added 10 g (0.094 mol) of 3-cyclohexenecarbonitrile in an equal volume of dry ether. The mixture was refluxed for 24 hr and cooled, and 0.94 mol of water was added slowly, followed by 0.94 ml of 10% sodium hydroxide solution and 3 ml of water. The resulting white precipitate was removed by filtration. The ether solution was cooled to 0° and 7.8 g (0.076 mol) of acetic anhydride dissolved in an equal volume of ether was added dropwise. The resulting solution was slurried for 3 hr at room temperature; 10 ml of 10% sodium hydroxide was added and the solution was stirred for an additional 45 min. The aqueous layer was separated and the ether layer was dried over potassium carbonate, filtered, and concentrated to a colorless oil. Distillation yielded 10.7 g (75%): bp 88–95° (0.07 mm); ir 1650 cm^{-1}; NMR δ 1.9 (s, 3 H), 3.1 (t, 2 H), 5.6 (s, 2 H), 7.8 (br, 1 H).

Anal. Calcd for $C_9H_{15}NO$: C, 70.6; H, 9.9; N, 9.1. Found: C, 70.6; H, 10.0; N, 9.0.

***N*-Methyl-3-cyclohexenylcarboxamide.** A solution of 5.0 g (0.039 mol) of 3-cyclohexencarboxylic acid in 125 ml of dry benzene was cooled to 0°, and 7.0 g (0.059 mol) of oxalyl chloride was added slowly with stirring. After 3 hr at room temperature the benzene and excess oxalyl chloride were evaporated, 150 ml of dry benzene was added to the residue, and excess anhydrous methylamine was bubbled through the solution. Evaporation of the solvent, solution in ether, washing with 10% hydrochloric acid, and concentration and crystallization from pentane gave 4.8 g (89%) of white solid: mp 89–90°; ir 1660 cm^{-1}; NMR δ 2.2 (m, 6 H), 2.8 (d, 3 H), 5.7 (s, 2 H), 6.1 (br, 1 H).

Anal. Calcd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1. Found: C, 69.2; H, 9.5; N, 9.8.

3- and 4-Methyl-3-cyclohexenecarboxylic Acid. A sealed glass tube containing 11.3 g (0.166 mol) of isoprene and 12.0 g (0.166 mol) of acrylic acid was heated to 120° for 8 hr. Then the tube was cooled and the semisolid contents were washed with cold hexane to give 10.8 g (46%) of white solid: mp 88–92°,[30] 97–99°; ir 1700 cm^{-1}; NMR δ 1.64 (s, 3 H), 2.1 (m, 7 H), 5.30 (s, 1 H), 11.19 (s, 1 H). Dehydrogenation over palladium on charcoal at 215° gave *p*-toluic acid, indicating the solid acid to be the 4-methyl isomer.

The liquid portion was distilled to give 8.2 g (35%) of colorless liquid: bp 60–62° (0.01 mm); ir 1700 cm^{-1}; NMR δ 1.64 (s, 3 H), 2.1 (m, 7 H), 5.30 (s, 1 H), 11.2 (s, 1 H). This was taken to be the 3-methyl isomer.

4- and 3-Methyl-*N*-methyl-3-cyclohexenecarboxamide. In analogy to the above preparation of the cyclohexenecarboxamide, the 4-methyl-substituted compound was prepared in 93% yield: mp 111–112°, crystallized from hexane; ir 1650 cm^{-1}; NMR δ 1.60 (s, 3 H), 2.68 (d, 3 H), 5.04 (s, 1 H), 5.84 (br, 1 H).

Anal. Calcd for $C_9H_{15}NO$: C, 70.6; H, 9.9; N, 9.1. Found: C, 70.7; H, 10.0; N, 9.0.

From 2.5 g (0.017 mol) of 3-methyl-3-cyclohexenecarboxylic acid was prepared 2.3 g (86%) of *N*-methylamide, crystallized from hexane–benzene: mp 51–56°; ir 1650 cm^{-1}; NMR δ 1.56 (s, 3 H), 2.64 (d, 3 H), 5.08 (s, 1 H), 5.64 (br, 1 H).

Anal. Calcd for $C_9H_{15}NO$: C, 70.6; H, 9.9; N, 9.1. Found: C, 70.8; H, 10.0; N, 8.9.

***N*-Methyl-2-(2-cyclohexen-1-yl)acetamide.** To 50 g (0.036 mol) of 2-(2-cyclohexen-1-yl)acetic acid[33] in 12.5 ml of benzene, 0.45 g (0.035 mol) of oxalyl chloride was added at 0°. The mixture was stirred overnight at room temperature, benzene and excess oxalyl chloride were evaporated, and the crude acid chloride was added dropwise to 125 ml of benzene, saturated at 0° with methylamine. The solution was stirred for 1 hr; then water was added and the organic layer was separated, washed with 10% hydrochloric acid, and dried over magnesium sulfate. The solvent was evaporated and the residue was crystallized from pentane to give 4.5 g (80%) of white needles: mp 58–58.5°; ir 1650 cm^{-1}; NMR δ 2.72 (d, 3 H), 5.50 (m, 2 H), 6.10 (m, 1 H).

Anal. Calcd for $C_9H_{15}NO$: C, 70.5; H, 9.9; N, 9.1. Found: C, 70.4; H, 9.8; N, 9.3.

2-Allyl-*N*,5-dimethyl-4-hexenamide. To 125 ml of dry ethyl ether and 0.129 mol of sodium hydride (6.2 g, 50% dispersion in mineral oil, from which the oil was removed by washing with pentane) was added dropwise 17 g (0.086 mol) of ethyl 2-acetyl-5-methyl-4-hexenoate.[33] The slurry was stirred for 15 min; then 10.4 g (0.086 mol) of allyl bromide dissolved in an equal volume of dry ether was added dropwise. This mixture was refluxed overnight, then filtered, washed with water, and dried over magnesium sulfate. The ether solvent was evaporated to give 14.6 g (71%) of ethyl 2-acetyl-2-allyl-5-methyl-4-hexenoate: bp 67–72° (0.02 mm); ir 1650, 1720, 1750 cm^{-1}; NMR δ 1.28 (t, 3 H), 1.64 (s, 3 H), 1.72 (s, 3 H), 2.16 (s, 3 H), 2.62 (d, 4 H), 4.24 (q, 2 H), 4.78–6.00 (m, 4 H).

To a solution of 2.0 g (0.087 mol) of sodium in 150 ml of methanol, 14.6 g (0.061 mol) of ethyl 2-acetyl-2-allyl-5-methyl-4-hexenoate was added, and the solution was refluxed overnight. Half of the methanol was evaporated, water was added, and the mixture was quickly extracted with ethyl ether. The ether solution was dried over magnesium sulfate, concentrated, and the residual oil distilled to yield 7.6 g (69%) of methyl 2-allyl-5-methyl-4-hexenoate: bp 104–106° (26 mm); ir 1650, 1750 cm^{-1}; NMR δ 1.64 (s, 3 H), 1.72 (s, 3 H), 2.32 (m, 5 H), 3.76 (s, 3 H), 5.0–6.2 (m, 4 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 10.0. Found: C, 72.7; H, 10.1.

Hydrolysis of 9.2 g (0.039 mol) of methyl 2-allyl-5-methyl-4-hexenoate in 150 ml of methanol and 20 ml of water with 3.5 g (0.087 mol) of sodium hydroxide at room temperature (2 hr) was followed by removal of half of the solvent, addition of more water, and extraction with ether. To the aqueous layer 10% hydrochloric acid was added until the pH was about 4, and this solution was extracted with ether. The acidic ether extracts were dried over magnesium sulfate, concentrated, and the residual liquid distilled to give 3.66 g (58%) of colorless oil: bp 73–76° (0.05 mm); ir 1720 cm^{-1}; NMR δ 1.68 (s, 3 H), 1.72 (s, 3 H), 2.41 (m, 5 H), 5.09–6.16 (m, 4 H), 12.0 (s, 1 H).

To 125 ml of dry benzene and 3.7 g (0.023 mol) of 2-allyl-5-methyl-4-hexenoic acid, cooled in an ice bath, 4.3 g (0.034 mol) of oxalyl chloride was added dropwise. The solution was stirred overnight at room temperature. Benzene and excess oxalyl chloride were evaporated, and the crude acid chloride was added dropwise to 125 ml of dry benzene saturated with methylamine. The solution was stirred for 1 hr, water was added, and the benzene layer was separated and dried over magnesium sulfate. Concentration and distillation gave 3.6 g (82%) of colorless oil: bp 84–86° (0.02 mm); ir 1650 cm^{-1}; NMR δ 1.64 (s, 3 H), 1.72 (s, 3 H), 2.26 (m, 5 H), 2.86 (d, 3 H), 5.00–6.20 (m, 5 H).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.9; H, 10.6; N, 7.7. Found: C, 73.1; H, 10.8; N, 7.7.

2-Allyl-*N*-methyl-4-pentenamide. Following the above procedure, 19.5 g of ethyl 2-acetyl-2-allyl-4-pentenoate[34] was converted to 11.3 g (78%) of methyl 2-allyl-4-pentenoate: bp 64–66° (15 mm); ir 1630, 1730 cm^{-1}; NMR δ 2.32 (m, 5 H), 3.60 (s, 3 H), 4.80–5.88 (m, 6 H). Analogous subsequent reactions gave the *N*-methylamide in 69% yield: mp 54–55°; ir 1640 cm^{-1}; NMR δ 2.20 (m, 5 H), 2.72 (d, 3 H), 4.60–5.90 (m, 7 H).

Anal. Calcd for $C_9H_{15}NO$: C, 70.5; H, 9.9; N, 9.1. Found: C, 70.4; H, 10.0; N, 8.9.

***N*,5-Dimethyl-2-(3-methyl-2-buten-1-yl)-4-hexenamide.** Similarly, 7.74 g (0.0395 mol) of 2-(3-methyl-2-buten-1-yl)-5-methyl-4-hexenoic acid[35] was converted to 6.2 g (75%) of the *N*-methylamide: bp 95–99° (0.01 mm); ir 1670 cm^{-1}; NMR δ 1.58 (s, 6 H), 1.66 (s, 6 H), 2.20 (m, 5 H), 3.26 (s, 3 H), 4.92 (t, 2 H).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.6; H, 11.1; N, 6.7. Found: C, 74.8; H, 11.2; N, 6.6.

Preparation of *N*-Chloroamides Using Ethyl Ether as Solvent. The procedure for preparation of *N*-chloro-*N*-methyl-3-cyclohexenecarboxamide (**8a**) is representative. To 50 ml of dry ethyl ether and 1.0 g (0.0072 mol) of *N*-methyl-3-cyclohexenylcarboxamide, 4.5 ml (0.0072 mol) of 1.6 *M* *n*-butyllithium in hexane was added. A jelly-like precipitate formed rapidly and the mixture was stirred for 1 hr. To this mixture 1.44 g (0.0108 mol) of *N*-chlorosuccinimide was added all at once and the mixture was refluxed overnight. Water was added, and the ether layer was separated, washed with water, dried over magnesium sulfate, and concentrated. The residual oil was chromatographed on silica gel and eluted with ether. The first fraction gave a light yellow oil which was distilled to yield 0.96 g (76%) of a colorless oil: bp 44–47° (0.1 mm); ir 1675 cm^{-1}; uv λ_{max} (C_2H_5OH) 206 nm (log ϵ 3.66); NMR δ 2.0 (m, 6 H), 3.3 (s, 3 H), 5.78 (s, 2 H).

Anal. Calcd for $C_8H_{12}NOCl$: C, 55.3; H, 7.0; N, 8.1; Cl, 20.4. Found: C, 55.5; H, 7.1; N, 7.9; Cl, 20.4.

***N*-Chloro-*N*-[2-(1-cyclohexen-1-yl)ethyl]acetamide (7).** From 2.0 g (0.00912 mol) of *N*-[2-(1-cyclohexen-1-yl)ethyl]acetamide[36] in 100 ml of ethyl ether was prepared 1.34 g (55%) of *N*-chloro-*N*-(2-(1-cyclohexen-1-yl)ethyl)acetamide: bp 50–55° (0.08 mm); ir 1675 cm^{-1}; NMR δ 1.6 (m, 5 H), 2.0 (m, 5 H), 2.2 (s, 3 H), 3.8 (t, 2 H), 5.5 (br, 1 H).

Anal. Calcd for $C_{10}H_{16}NOCl$: C, 59.6; H, 8.0; N, 6.9; Cl, 17.6. Found: C, 59.3; H, 8.2; N, 6.9; Cl, 17.5.

Preparation of *N*-Chloro-*N*-(5-*n*-hexen-1-yl)acetamide (1b). From 1.0 g (0.0071 mol) of *N*-(5-*n*-hexen-1-yl)acetamide in 50 ml of ethyl ether was prepared 0.60 g (48%) of chloroamide: bp 60–70° (0.07 mm); ir 1675 cm^{-1}; NMR δ 1.55 (m, 6 H), 2.14 (s, 3 H), 3.72 (t, 2 H), 4.85–6.15 (m, 3 H).

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.7; H, 8.0; N, 8.0; Cl, 20.2. Found: C, 55.0; H, 8.1; N, 7.9; Cl, 20.2.

***N*-Chloro-*N*-(4-*n*-penten-1-yl)acetamide (1a).** From 1.0 g (0.0079 mol) of *N*-(4-*n*-penten-1-yl)acetamide in 50 ml of ether was prepared 0.54 g (42%) of *N*-chloroamide: bp 42–43° (0.03 mm); ir 1675 cm^{-1}; NMR δ 1.98 (m, 4 H), 2.27 (s, 3 H), 3.78 (t, 2 H), 4.89–6.00 (m, 3 H).

Anal. Calcd for $C_7H_{12}NOCl$: C, 52.0; H, 7.5; N, 8.7; Cl, 21.9. Found: C, 52.0; H, 7.6; N, 8.5; Cl, 22.0.

***N*-Chloro-*N*,5-dimethyl-2-allyl-4-hexenamide (15a).** From 0.967 g (0.00535 mol) of *N*-methyl-2-allyl-4-hexenamide in 50 ml of ethyl ether was prepared 0.523 g (45%) of *N*-chloroamide: ir 1650 cm^{-1}; NMR δ 1.68 (s, 3 H), 1.76 (s, 3 H), 2.38 (m, 5 H), 3.48 (s, 3 H), 5.04–6.24 (m, 4 H).

Preparation of *N*-Chloroamides using 1,2-dimethoxyethane as a Solvent. The procedure for preparation of *N*-chloro-*N*-[(3-cyclohexen-1-yl)methyl]acetamide (**5**) is representative. To 1.07 g (7.04 mmol) of *N*-[(3-cyclohexen-1-yl)methyl]acetamide and 50 ml of dry 1,2-dimethoxyethane under nitrogen, 4 ml (~8.0 mmol) of *n*-butyllithium in hexane was added. After stirring for 1.5 hr, 1.02 g (8.2 mmol) of *N*-chlorosuccinimide dissolved in 50 ml of dry 1,2-dimethoxyethane was added dropwise and the mixture was stirred for 3 hr at room temperature. Water was added, followed by dichloromethane. The organic layer was separated, washed with saturated sodium chloride, and dried over magnesium sulfate. Concentration and chromatography of the residual yellow oil on silica gel, eluting with ethyl ether, gave 0.48 g (36%) of *N*-chloroamide: ir 1665 cm^{-1}; NMR δ 2.22 (2, 3 H), 3.60 (d, 2 H), 5.62 (s, 2 H).

Anal. Calcd for $C_9H_{14}NOCl$: C, 57.6; H, 7.5; N, 7.5; Cl, 18.9. Found: C, 57.4; H, 7.6; N, 7.6; Cl, 18.6.

***N*-Chloro-*N*-methyl-2-(2-cyclohexen-1-yl)acetamide (12).** From 1.0 g (0.0065 mol) of *N*-methyl-2-(2-cyclohexen-1-yl)acetamide was prepared 0.80 g of *N*-chloroamide: ir 1670 cm^{-1}; NMR δ 1.60 (m, 6 H), 2.50 (m, 3 H), 3.28 (s, 3 H), 5.50 (m, 2 H).

***N*-Chloro-*N*-methyl-3-(1-cyclohexen-1-yl)propionamide (3).** From 0.319 g (1.90 mmol) of *N*-methyl-3-(1-cyclohexen-1-yl)propionamide was prepared 0.162 g (42%) of *N*-chloroamide: ir 1670 cm^{-1}; NMR δ 0.76 (m, 12 H), 3.36 (s, 3 H), 5.44 (s, 1 H).

***N*-Chloro-*N*,5-dimethyl-2-(3-methyl-2-buten-1-yl)-4-hexenamide (15c).** From 1.11 g (0.0053 mol) of *N*,5-dimethyl-2-(3-methyl-2-buten-1-yl)-4-hexenamide was prepared 0.76 g (57%) of *N*-chloroamide: ir 1670 cm^{-1}; NMR δ 1.58 (s, 6 H), 1.66 (s, 6 H), 2.20 (m, 5 H), 3.26 (s, 3 H), 4.42 (t, 2 H).

Preparation of *N*-Chloro-*N*-methyl-2-allyl-4-pentenamide (15b). From 1.0 g (0.0062 mol) of *N*-methyl-2-allyl-4-pentenamide was prepared 0.55 g (47%) of *N*-chloroamide: ir 1660 cm^{-1}; NMR δ 2.24 (m, 5 H), 3.24 (s, 3 H), 4.72–5.80 (m, 6 H).

***N*-Chloro-*N*,3-dimethyl- and *N*,4-dimethyl-3-cyclohexenecarboxamide (8c and 8b).** From 1.0 g (0.0065 mol) of *N*,3- and -4-dimethyl-3-cyclohexenecarboxamide was prepared 0.71 g (58%) of *N*-chloroamide: ir 1660 cm^{-1}; NMR δ 1.64 (s, 3 H), 2.0 (m, 6 H), 3.28 (s, 3 H), 5.24 (s, 1 H).

***N*-Chloro-*N*,4-dimethyl-3-cyclohexenecarboxamide (8b).** From 1.0 g (0.0065 mol) of *N*,4-dimethyl-3-cyclohexenecarboxamide was prepared 0.80 g (65%) of *N*-chloroamide: ir 1660 cm^{-1}; NMR δ 1.64 (s, 3 H), 2.0 (m, 6 H), 3.29 (s, 3 H), 5.23 (s, 1 H).

Photolysis of *N*-Chloroamides. *N*-Chloroamides were irradiated in benzene under a nitrogen atmosphere using a Hanovia 450-W high-pressure mercury arc with a Corex filter, unless otherwise stated. The photolysis apparatus consisted of a Pyrex cylinder (55 mm. i.d. and 298 mm long) with a 60/50 ground joint on top, into which a water-jacketed quartz lamp housing was fitted. A no. 2 stopcock 70 mm from the top of the ground joint was connected to a mercury seal gas trap during the irradiations.

Photolysis of *N*-Chloro-*N*-methyl-3-cyclohexenecarboxamide (8a). The following procedure for the photolysis of *N*-chloro-*N*-methyl-3-cyclohexenecarboxamide is representative. To 190 ml of dry benzene in the photolysis apparatus was added 0.55 g of *N*-chloroamide. Nitrogen was bubbled through the solution for 5 min, and the solution was then irradiated for 15 min. Benzene was evaporated and ether was added to the light brown oil to give a brown precipitate and colorless solution. The ether solution was separated and concentrated to yield 0.50 g of light brown oil. The oil was distilled to yield 0.38 g (69%) of colorless oil: bp 60–62° (0.01 mm); ir 1700 cm^{-1}; NMR δ 2.0 (m, 7 H), 2.92 (s, 1.5 H), 3.16 (s, 1.5 H), 3.76 (t, 0.5 H), 3.92 (d, 0.5 H), 4.16 (m, 0.5 H), 4.40 (s, 0.5 H); a mixture of isomers **9a** and **10a**.

Anal. Calcd for $C_8H_{12}NOCl$: C, 55.3; H, 7.0; N, 8.1; Cl, 20.4. Found: C, 55.1; H, 7.2; N, 7.9; Cl, 20.1.

The isomers were separated as follows. Onto a chromatographic column containing 100 g of silica gel was placed 0.168 g of the mixture and this was eluted with ethyl ether. A solvent gradient, starting with 1% ethanol and 2.5% increments using 200 ml each, was brought to 10% ethanol, when fractions were obtained.

Fraction 1 was distilled to yield 0.070 g: bp 60–61° (0.01 mm); ir 1700 cm^{-1}; NMR δ 2.0 (m, 7 H), 2.96 (s, 3 H), 3.76 (t, 1 H), 4.40 (s, 1 H).

Fraction 2 was distilled to yield 0.053 g: bp 60–61° (0.01 mm); ir 1700 cm^{-1}; NMR δ 2.0 (m, 7 H), 3.16 (s, 3 H), 3.88 (d, 1 H), 4.10 (m, 1 H).

The mass spectra of the isomers were identical: *m/e* 173 (34), 138 (48), 110 (100), 96 (57), 42 (61).

Fraction 1 was assigned as 6-methyl-4-*exo*-chloro-6-azabicyclo[3.2.1]octan-7-one (**10a**), and fraction 2 was assigned as 6-methyl-4-*endo*-chloro-6-azabicyclo[3.2.1]octan-7-one (**9a**) on the basis of the position of the methyl singlet (NMR) and polarity.

Photolysis of *N*-Chloro-*N*-[(3-cyclohexen-1-yl)methyl]acetamide (5). Irradiation of 0.476 g (2.55 mmol) of *N*-chloro-*N*-[(3-cyclohexen-1-yl)methyl]acetamide in 190 ml of dry benzene for 20 min gave 0.405 g of a light brown oil, distilled to yield 0.268 g (55%) of colorless liquid (**6**): bp 80–90° (0.01 mm); ir 1620 cm^{-1}; NMR δ 2.20 (s, 3 H), 3.52 (m, 2 H), 4.05 (m, 1 H), 4.32 (m, 1 H); mass spectrum *m/e* (rel intensity) 187 (M^+, 28), 152 (7), 145 (9), 110 (75), 68 (100).

Anal. Calcd for $C_9H_{14}NOCl$: C, 57.6; H, 7.5; N, 7.5; Cl, 18.9. Found: C, 57.8; H, 7.7; N, 7.5; Cl, 18.8.

Photolysis of *N*-Chloro-*N*-[2-(1-cyclohexen-1-yl)ethyl]acetamide (7). A solution of 1.3 g (0.0065 mol) of chloroamide in 150 ml of dry benzene was irradiated until the solution did not darken a potassium iodide solution in aqueous acetic acid (1.25 hr). The mixture was worked up as described above to yield 0.11 g of a light yellow oil which was found to be identical with *N*-[2-(1-cyclohexen-1-yl)ethyl]acetamide.

Photolysis of *N*-Chloro-*N*-(5-*n*-hexen-1-yl)acetamide (1b). An irradiated solution of 0.60 g (0.0034 mol) of the chloroamide in 150 ml of dry benzene was checked every 30 min with potassium iodide in aqueous acetic acid. After 1.5 hr the test solution no longer turned dark when added to a small amount of the photolysis mixture, indicating absence of active chlorine. The mixture was worked up as above and the oil was distilled to give 0.11 g of a material which contained seven components on TLC (Eastman silica gel sheet developed with ethyl ether). The NMR of the crude product was very similar to that of *N*-(5-*n*-hexen-1-yl)acetamide.

Irradiation of 0.213 g (0.00122 mol) of *N*-chloro-*N*-(5-*n*-hexen-1-yl)acetamide in 150 ml of dry cyclohexane for 1 hr and distillation gave 0.18 g (90%) of *N*-(5-*n*-hexen-1-yl)acetamide, bp 80–85° (0.03 mm).

Photolysis of *N*-Chloro-*N*-(4-*n*-penten-1-yl)acetamide (1a). From 0.55 g of *N*-chloroamide in 150 ml of dry benzene, irradiation for 1 hr and distillation gave 0.19 g (35%) of colorless liquid (**2**): bp 75–80° (0.03 mm); ir 1670 cm^{-1}; NMR δ 2.1 (m, 7 H), 3.6 (m, 5 H); mass spectrum *m/e* (rel intensity) 161 (M^+, 10), 126 (11), 112 (33), 70 (100), 43 (55), metastable peak at 43.8.

Photolysis of *N*-Methyl-*N*-chloro-2-(2-cyclohexen-1-yl)-acetamide (12). From 0.80 g (0.0043 mol) of *N*-chloroamide in 150 ml of benzene, 15-min irradiation, and distillation, 0.53 g (66%) of **13** was obtained as a colorless liquid: bp 70–75° (0.01 mm); ir 1690 cm^{-1}; NMR δ 1.55 (m, 7 H), 2.16 (d, 2 H), 2.54 (m, 1 H), 2.92 (s, 3 H), 3.42 (t, 1 H), 3.90 (m, 1 H); mass spectrum *m/e* (rel intensity 187 (16), 110 (100), 97 (11), 42 (16), 41 (9), 39 (8). A high-resolution spectrum was taken: *m/e* 187.067 (M^+), 110.072 (P^+).

Anal. Calcd for $C_9H_{14}NOCl$: C, 57.6; H, 7.5; N, 7.5; Cl, 18.9. Found: C, 57.6; H, 7.5; N, 7.5; Cl, 18.7.

Photolysis of *N*-Chloro-*N*-methyl-3-(1-cyclohexen-1-yl)-propionamide (3). From 162 mg (0.805 mmol) of **3** in 190 ml of benzene and irradiation for 25 min, 148 mg of a brown oil was obtained. Distillation gave 48 mg (30%) of a colorless liquid, bp 90–100° (0.01 mm). The liquid was chromatographed on silica gel in chloroform, and 25-ml fractions were collected. Fraction 14 contained, after distillation, 22 mg of **4** as a colorless liquid: bp 90–95° (0.01 mm); ir 1690 cm^{-1}; NMR δ 1.0–2.5 (m, 12 H), 2.76 (s, 3 H), 4.00 (m, 1 H); mass spectrum *m/e* (rel intensity) 201 (M^+, 19) 166 (27), 124 (100), 111 (29), 73 (29).

Photolysis of *N*-Chloro-*N*,5-dimethyl-2-allyl-4-hexenamide (15a). From 0.523 g (0.00224 mol) of *N*-chloroamide in 180 ml of

benzene and irradiation for 20 min, 0.51 g of dark oil was obtained. TLC of 100 mg on silica gel with ether gave one major fraction (R_f 0.29–0.32). This fraction was distilled to yield 15 mg (15%) of colorless liquid **16a**: ir 1630, 1680 cm^{-1}; NMR δ 1.48 (s, 3 H), 1.59 (s, 3 H), 2.99 (s, 3 H), 3.60 (t, 1 H), 4.80–5.84 (m, 3 H); mass spectrum *m/e* (rel intensity) 215 (M^+, 5), 138 (100), 110 (76), 96 (50), 81 (84), 55 (45), 39 (76), 42 (65).

Photolysis of N-Chloro-N-methyl-2-allyl-4-pentenamide (15b). From 0.55 g (0.0029 mol) of *N*-chloroamide in 190 ml of benzene and 20-min irradiation, 0.50 g of oil was obtained. TLC of 100 mg on silica gel with ethyl ether gave a fraction (R_f 0.1–0.2) which was distilled to give 11 mg (11%) of **16b** as colorless liquid: bp 60–80° (0.05 mm); ir 1680 cm^{-1}; NMR δ 2.80 (s, 3 H), 3.56 (m, 3 H), 4.80–5.84 (m, 3 H); mass spectrum *m/e* (rel intensity) 187 (M^+, 19), 138 (100), 110 (37), 96 (52), 81 (30), 42 (72), 39 (47).

Photolysis of N-Chloro-N,5-dimethyl-2-(3-methyl-2-buten-1-yl)-4-hexenamide (15c). From 0.76 g of *N*-chloroamide in 170 ml of benzene and irradiation for 15 min, 0.75 g of brown oil was obtained. TLC of 130 mg on silica gel with ethyl ether gave a fraction (R_f 0.14–0.36) which was distilled to give 32 mg (25%) of colorless oil (**16c**): bp 80–90° (0.02 mm); ir 1685 cm^{-1}; NMR δ 1.46, 1.56, 1.58, 1.66 (4 s, 12 H), 2.98 (s, 3 H), 3.58 (m, 1 H), 4.92 (m, 1 H); mass spectrum *m/e* (rel intensity 243 (M^+, 24), 166 (100), 110 (61), 98 (99), 41 (89).

Photolysis of a Mixture of N-Chloro-N,3- and -4-dimethyl-3-cyclohexenecarboxamide (8c and 8b). Irradiation of 0.63 g (0.0034 mol) of *N*-chloroamides in 180 ml of benzene for 20 min gave 0.54 g of crude photoproduct, which was distilled to give 0.334 g (54%): bp 60–70° (0.001 mm); ir 1690 cm^{-1}; NMR, a series of eight methyl singlets at δ 1.36, 1.42, 1.60, 1.70, 2.68, 2.88, 2.90, and 3.04.

The mixture was chromatographed on a high-pressure liquid chromatograph using Porasil A–chloroform, yielding two fractions. Fraction 1 was a mixture of 4-*exo*-chloro-6,4-dimethyl- and -6,5-dimethyl-6-azabicyclo[3.2.1]octan-7-one (**9b,c**): ir 1680 cm^{-1}; NMR δ 1.39 (s, 1.8 H), 1.67 (s, 1.2 H), 2.75 (s, 1.8 H), 3.00 (s, 1.2 H), 3.52 (d, 1.4 H), 4.08 (s, 0.6 H). Fraction 2 was a mixture of 4-*endo*-chloro-6,4-dimethyl- and -6,5-dimethyl-6-azabicyclo[3.2.1]octan-7-one (**10b,c**): ir 1680 cm^{-1}; NMR δ 1.52 (s, 1.8 H), 1.74 (s, 1.2 H), 2.97 (s, 1.8 H), 3.14 (s, 1.2 H), 3.65 (d, 0.4 H), 3.95 (m, 0.6 H). The mass spectra of the two fractions were identical; *m/e* 187 (M^+, 36), 124 (79), 110 (100), 56 (53), 42 (53).

Photolysis of N-Chloro-N,4-dimethyl-3-cyclohexenecarboxamide (8b). From 0.78 g (0.0042 mol) of *N*-chloroamide in 190 ml of benzene and irradiation for 20 min, 0.76 g of light brown oil was obtained and distilled to give 0.366 g (47%) of **9b** and **10b**: bp 70° (0.01 mm); ir 1700 cm^{-1}; NMR, four methyl singlets at δ 1.70, 1.76, 3.05, and 3.20.

High-pressure liquid chromatography using Porasil A–chloroform gave two fractions. Fraction 1 (**9b**) was crystallized from hexane: mp 117°; ir 1700 cm^{-1}; NMR δ 1.66 (s, 3 H), 2.98 (s, 3 H), 3.50 (d, 1 H). Fraction 2 (**10b**) was a liquid and distilled: bp 60° (0.01 mm); ir 1700 cm^{-1}; NMR δ 1.70 (s, 3 H), 3.10 (s, 3 H), 3.60 (d, 1 H). The mass spectra of the isomers were identical: *m/e* (rel intensity) 42 (100), 187 (M^+, 37), 152 (58), 110 (82), 109 (70), 42 (100).

Anal. Calcd for $C_9H_{14}NOCl$: C, 57.6; H, 7.5; N, 7.5; Cl, 18.9. Found for fraction 1: C, 57.3; H, 7.7; N, 7.7; Cl, 18.8. Found for fraction 2: C, 57.9; H, 7.7; N, 7.6; Cl, 18.6.

6-Methyl-6-azabicyclo[3.2.1]octan-7-one (11). A. A mixture of 0.44 g (0.0035 mol) of 6-azabicyclo[3.2.1]octan-7-one,[27] 0.40 g (0.0088 mol) of 90% sodium amide, and 10 ml of toluene was refluxed for 4 hr, then 2.5 ml of methyl iodide was added and the mixture was refluxed overnight. Cooling, filtration, and distillation gave 0.38 g (78%) of colorless liquid; bp 38–40° (0.1 mm). This material was identical with the compound obtained from the following dechlorination by ir and NMR.

B. A mixture of 5 ml of dry benzene, 0.42 g (0.0024 mol) of 6-methyl-4-chloro-6-azabicyclo[3.2.1]octan-7-one (**9a** and **10a**), 0.77 g (0.0026 mol) of tri-*n*-butylstannane, and a few crystals of azabisisobutyronitrile was refluxed overnight; then 10% hydrochloric acid was added followed by water. The benzene layer was separated, dried over magnesium sulfate, and concentrated, and the colorless liquid was chromatographed on silica gel with pentane to remove tri-*n*-butyltinchloride. Benzene was added to the column followed by benzene–ethyl ether followed by benzene-ethyl ether–ethanol in a 40:50:10 ratio to give a light brown oil. The oil was distilled to yield 0.122 g (37%) of colorless liquid: bp 37–40° (0.1 mm); ir 1695 cm^{-1}; NMR δ 1.65 (m, 9 H), 2.80 (s, 3 H), 3.56 (m, 1 H).

Anal. Calcd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.9; H, 9.6; N, 9.8.

6-Acetyl-6-azabicyclo[3.2.1]octane. A solution of 1.6 g (12.8 mmol) of 6-azabicyclo[3.2.1]octan-7-one[27] in 25 ml of 1,2-dimethoxyethane was added dropwise to 0.49 g (12.8 mmol) of lithium aluminum hydride in 50 ml of 1,2-dimethoxyethane. The mixture was refluxed overnight and cooled, and 0.13 ml of water was added, followed by 0.13 ml of 15% sodium hydroxide, followed by 0.4 ml of water. The slurry was stirred for 30 min, filtered, and cooled, and 3 ml of acetic anhydride was added dropwise. The solution was stirred for 3 hr; then 15 ml of 10% sodium hydroxide was added. The mixture was stirred for 1 hr. The organic layer was separated, dried over potassium carbonate, concentrated, and distilled to give 1.7 g (86%) of a colorless liquid: bp 70–75° (0.01 mm); ir 1625 cm^{-1}; NMR δ 2.04 (s, 3 H), 2.40 (br, 1 H), 3.36 (m, 2 H), 3.92 (t, 0.5 H), 4.32 (t, 0.5 H); mass spectrum *m/e* (rel intensity) 153 (M^+, 27), 110 (55), 68 (100), 43 (23).

Anal. Calcd for $C_9H_{15}NO$: C, 70.5; H, 9.9; N, 9.1. Found: C, 70.5; H, 9.8; N, 9.0.

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Registry No.—**1a,** 54385-04-5; **1b,** 54385-05-6; **2,** 54385-06-7; **3,** 54385-07-8; **4,** 54385-08-9; **5,** 54385-09-0; **6,** 54385-10-3; **7,** 54385-11-4; **8a,** 36393-98-3; **8b,** 54385-12-5; **8c,** 54385-13-6; **9a,** 36394-04-4; **9b,** 54385-39-6; **9c,** 54385-40-9; **10a,** 36394-03-3; **10b,** 54385-41-0; **10c,** 54385-42-1; **11,** 24173-53-3; **12,** 54385-43-2; **13,** 54385-14-7; **15a,** 54385-15-8; **15b,** 54385-16-9; **15c,** 54385-17-0; **16a,** 54385-18-1; **16b,** 54385-19-2; **16c,** 54385-20-5; *N*-(4-*n*-penten-1-yl)acetamide, 54385-21-6; 4-pentenonitrile, 592-51-8; *N*-(5-*n*-hexen-1-yl)acetamide, 54385-22-7; 5-hexenonitrile, 5048-19-1; *N*-[(3-cyclohexen-1-yl)methyl]acetamide, 54385-23-8; 3-cyclohexenecarbonitrile, 100-45-8; *N*-methyl-3-cyclohexenylcarboxamide, 54385-24-9; 3-cyclohexenecarboxylic acid, 4771-80-6; 3-methyl-3-cyclohexenecarboxylic acid, 54385-25-0; 4-methyl-3-cyclohexenecarboxylic acid, 4342-60-3; isoprene, 78-79-5; acrylic acid, 79-10-7; 4-methyl-*N*-methyl-3-cyclohexenecarboxamide, 54385-26-1; 3-methyl-*N*-methyl-3-cyclohexenecarboxamide, 54446-42-3; *N*-methyl-2-(2-cyclohexen-1-yl)acetamide, 54385-27-2; 2-(2-cyclohexen-1-yl)acetic acid, 3675-31-8; 2-allyl-*N*,5-dimethyl-4-hexenamide, 54385-28-3; ethyl 2-acetyl-5-methyl-4-hexenoate, 1845-52-9; allyl bromide, 106-95-6; ethyl 2-acetyl-2-allyl-5-methyl-4-hexenoate, 54385-29-4; methyl 2-allyl-5-methyl-4-hexenoate, 54385-30-7; 2-allyl-5-methyl-4-hexenoic acid, 54385-31-8; 2-allyl-*N*-methyl-4-pentenamide, 54385-32-9; ethyl 2-acetyl-2-allyl-4-pentenoate, 3508-77-8; methyl 2-allyl-4-pentenoate, 54385-33-0; *N*,5-dimethyl-2-(3-methyl-2-buten-1-yl)-4-hexenamide, 54385-34-1; 2-(3-methyl-2-buten-1-yl)-5-methyl-4-hexenoic acid, 54385-35-2; *N*-chlorosuccinimide, 128-09-6; *N*-[2-(1-cyclohexen-1-yl)ethyl]acetamide, 51072-38-9; *N*-methyl-2-allyl-4-hexenamide, 54385-36-3; *N*-methyl-3-(1-cyclohexen-1-yl)propionamide, 54385-37-4; 6-azabicyclo[3.2.1]octan-7-one, 6142-56-9; 6-acetyl-6-azabicyclo[3.2.1]octane, 54385-38-5.

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Ultraviolet Photoelectron Spectra of Some Substituted Triarylphosphines

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The photoelectron spectra of a series of triarylphosphines, containing various ring substituents, have been investigated. The spectra show a band due to ionization from the phosphorus lone pair (IP_1), followed by one or more bands assigned to ionizations of the phenyl π electrons. The values of IP_1 are sensitive to the nature of the ring substituents and reflect the influence of the substituents on the charge density at the ring position adjacent to the phosphorus. The number of observed IP's in the region assigned to the phenyl π electrons are generally the same as the number of IP's for the corresponding monosubstituted benzene. Moreover the IP values are generally close to the IP's found for the monosubstituted benzenes. The observed results are explained by a lack of substantial resonance interaction between the phosphorus and the π orbitals of the aryl system. The variation of phosphorus lone pair IP values is discussed in terms of charge stabilization in the radical cation produced by ionization of a lone-pair electron.

Several recent articles on the ultraviolet photoelectron spectra (pes) of monosubstituted benzenes have discussed the effect of substitution on ionization from the $e_g\pi$ orbitals of benzene.[1-7] The resonance effect of certain substituents (OR,[3] CH_3[4,7]) on the b_1 orbital[8] appears to raise its energy (lower ionization potential) from that of the a_2 orbital,[8] and thus the first ionization potential (IP) can be assigned to ionization from the b_1 orbital. The second ionization is then from the a_2 orbital and appears unchanged from the corresponding ionization in benzene (9.24 eV). Other substituents (F,[4] Cl[6]) show the same resonance effect, but an electron-withdrawing inductive effect is apparently also present. Thus the first two IP's are assigned as before, but the IP values are somewhat larger. In monosubstituted benzenes containing a third class of substituents (*tert*-butyl,[9] $(CH_3)_3Si$,[9] CF_3[9]) the ionizations from the a_2 and b_1 orbitals are close in energy and are either poorly resolved or not at all. The band envelopes are raised or lowered in energy from that of benzene, depending on whether the substituent is electron donating or withdrawing.

b_1 a_2

In the present study we have investigated the pes of a series of triarylphosphines containing these ring substituents. Schäfer and Schweig[10] have interpreted the pes of dimethylphenylphosphine in terms of a complete lack of interaction between the aryl group and the trivalent phosphorus atom. The energies of ionization from the phosphorus lone pair and phenyl π orbitals remain virtually the same as in $(CH_3)_3P$ and benzene, respectively. Debies and Rabalais[11] observed in the pes of $C_6H_5PH_2$ a stabilization of the phenyl π orbitals and a splitting of the a_2 and b_1 components, along with a destabilization of the phosphorus lone pair. It was suggested that this is due to delocalization of charge from phenyl π orbitals into the d orbitals on phosphorus. (The IP of the phenyl π electrons in $(C_6H_5)_3P$ is the same as in benzene, however, and no splitting of the components was observed.)

Results and Discussion

The pes of the substituted triarylphosphines (Table I) show one or more peaks in the region assigned to ionization of the phenyl π electrons in the corresponding monosubstituted benzenes (Table II). In most cases the number of IP's observed in this region corresponds to the number of IP's observed for the monosubstituted benzene. In addition to these, a low IP band is observed in each of the spectra, which is readily assigned, as by the previous authors,[10,11] to ionization from the lone pair of electrons on phosphorus.

Although the complexity of the molecules studied appears to inhibit the use of vibrational fine structure in assigning the bands in the phenyl region, it seems likely that the band assignments for the triarylphosphines generally correspond to the assignments made for the monosubstituted benzenes. The following reasons are apparent.

(1) In almost all cases, and independent of the nature of the substituent, the IP's assigned to the phenyl electrons in $aryl_3P$ correspond closely to the IP's found for the monosubstituted benzene. Particularly in the case of $aryl_3P$ substituted with methoxy and dimethylamino groups, the separation of ionizations from the a_2 and b_1 orbitals is so large that it is unlikely that the assignments could be reversed upon substitution into the phosphino system, with one energy level raised and the other lowered from the value in the monosubstituted benzene.

Table I
Vertical Ionization Potentials[a] of $(RC_6H_4)_3P$

Compd	R	IP_1[b]	IP_2[c]	IP_3[c]	IP_4
1	4-CF_3	8.65	9.8[d]	9.9	
2	4-Cl	8.18	9.16	9.63	11.40[e]
3	4-F	8.12	9.6[f]		
4	4-H	7.92	9.20		
5	4-$(CH_3)_3Si$	7.67	8.84	9.02	
6	4-CH_3	7.6	8.9[f]		
7	4-$(CH_3)_2CH$	7.53			
8	4-$(CH_3)_3C$	7.52	8.8[f]		
9	4-CH_3O	7.48	8.30	9.00	
10	4-$(CH_3)_2N$	6.9–7.0[d]	7.30[g]	8.67	9.56[h]
11	2-CF_3	8.30	9.5[d]	9.68	
12	2-CH_3	7.64	8.62	9.4[d]	
13	2-CH_3O	7.37	8.22	8.71	
14	3-F	8.32	9.2	9.6–9.7[d]	
15	3-CH_3	7.68	8.58	9.53	
16	3-CH_3O	7.72	8.35	9.03	

[a] In electron volts. [b] Phosphorus lone pair. [c] Phenyl π electrons. [d] Shoulder. [e] Chlorine lone pair. This band is accompanied by a shoulder at 11.7 eV, also assigned to a chlorine lone pair. [f] IP_2 and IP_3 are unresolved. The value listed is the maximum of the resulting peak. [g] Ionization apparently from $(CH_3)_2N$ lone pair. [h] Assigned to an ionization from a phenyl π orbital.

Table II
Vertical Ionization Potentials[a] of RC_6H_5

Registry no.	R	IP_1[b]	IP_2[b]	IP_3[b]
98-08-8	CF_3[c]	9.7		
462-06-6	F[d]	9.11(b_1)	9.82(a_2)	
108-90-7	Cl[c,e]	9.1(b_1)	9.7(a_2)	11.32[f]
71-43-2	H	9.24		
768-32-1	$(CH_3)_3Si$[c]	9.0[g]	9.3[g]	
108-88-3	CH_3[d]	8.72(b_1)	9.24(a_2)	
98-06-6	$(CH_3)_3C$[c]	9.0		
100-66-3	CH_3O[h]	8.42(b_1)	9.21(a_2)	
121-69-7	$(CH_3)_2N$[h]	7.45(b_1)[i]	9.00(a_2)	9.85(b_1)

[a] In electron volts. [b] Assignments in parentheses. [c] Reference 9. [d] Reference 4. [e] Reference 6. [f] Chlorine lone pair. Accompanied by a band at 11.7 eV also assigned to a chlorine lone pair. [g] Two components of the band envelope were attributed to IP_1 and IP_2 by R. A. N. McLean, *Can. J. Chem.*, 51, 2089 (1973). [h] Reference 3. [i] Ionization apparently correlates with $(CH_3)_2N$ lone pair.

(2) There is no great change in the phenyl IP values among the ortho, meta, or para isomers with a given substituent. The effect of substitution into the phosphino system on the relative a_2 and b_1 IP's would be expected to vary with the position of substitution.

(3) In the $aryl_3P$ containing CF_3, $(CH_3)_3C$, and $(CH_3)_3Si$ substituents, the ionizations from the a_2 and b_1 phenyl orbitals are not resolved. This is also true for the corresponding substituted benzenes. Therefore there is no evidence here that the relative energies of the a_2 and b_1 orbitals are changing much upon substitution into the phosphino system.

The phosphorus lone pair IP values appear to be a well-behaved function of the electron-donating or -withdrawing nature of the substituents. A very good correlation (correlation coefficient 0.986) is observed between the Hammett σ_p parameter[12] and the lone pair IP of phosphorus (see Figure 1) for the ten compounds with para substituents. The inductive electron-withdrawing nature of the fluorine and chlorine atoms is indicated, but the effect is apparently partially cancelled in the para derivatives by the electron-donating resonance effect, which places charge on the ring

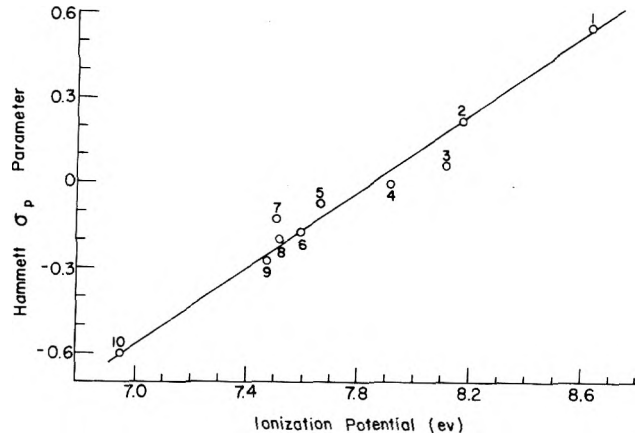

Figure 1. Correlation of ionization potential of the phosphorus lone pair with the Hammett σ_p substituent constant for $(p\text{-}RC_6H_4)_3P$. The numbers on the points correspond with the compound numbers in Table I.

position adjacent to the phosphorus, and causes some lowering of the lone pair IP. In the *m*-fluoro derivative the resonance effect is submerged, and the result is a noticeable raising of the phosphorus lone pair IP. The strong resonance effect of the *p*-dimethylamino and *p*-methoxy substituents enhances the electron density adjacent to the phosphorus, and the result is a pronounced lowering of the IP value, whereas the somewhat higher value for the *m*-methoxy derivative is consistent with the diminished resonance effect at the meta ring position. The electron-donating effect of the alkyl groups is expected, but the lack of any change in the lone pair IP's among the ortho, meta, and para methyl derivatives should be noted. Despite the inductive effect of the $(CH_3)_3Si$ group, it appears to be only a modest electron donor, poorer than the alkyl groups. This phenomenon is well documented[13] and is believed to be due to an electron-withdrawing component in the behavior of the silicon, in which charge from the aromatic ring is delocalized into the $d\pi$ orbitals of the silicon.

The results of this study show that while the effect of the substituted aryl groups on the phosphorus lone pair electrons is easily rationalized, there is little apparent effect of the phosphorus on the π orbital energies of the aryl system. This observation is independent of the nature of the aryl substituent. This would appear to rule out any substantial resonance effect between the phosphorus lone pair of electrons and the filled π orbitals of the ring, or any substantial stabilization of the phenyl π orbitals by interaction with the phosphorus d orbitals. The lack of resonance interaction is consistent with the finding of Schäfer and Schweig.[10] More generally, there is little evidence that the trivalent phosphorus acts as a significant electron donor or acceptor toward an attached aryl group.[14]

It is suggested that the correlation between the phosphorus lone pair IP values and the substituent σ_p values should be discussed in terms of the effect of the substituent on the energy difference between the ground state and the cationic state (analogous to the consideration of σ_p as measuring the effect of the substituent on the energy difference between the ground state and a charged transition state[12]). This effect is determined largely by the action of the substituent on the developing charge at the "reaction site" (here the phosphorus atom). In this case migration of electrons from the substituted aryl groups to the positive phosphorus center would result in a stabilization of the cation. Thus not only would lower lone pair IP's result than those expected from Koopmans' theorem[15] but the magnitude of the charge migration (and therefore lowering of the IP) is

related to the σ_p value of the substituent. The lack of deviation from the normal σ_p correlation, particularly on the part of the dimethylamino and methoxy substituents, argues against any enhanced resonance interaction between the substituents and the positive phosphorus center, and therefore the drift of charge would be through the P–aryl σ bond. On the other hand, the ability of the trivalent phosphorus to effect significant stabilization of the radical cation, produced by ionization from the aryl π orbitals, appears to be quite limited.

It should be noted that any correlation between phosphorus lone pair IP's and substituent σ_p values assumes no significant difference in hybridization at the phosphorus among the para-substituted aryl$_3$P. Thus the effects discussed above are not extended here to a comparison between the aryl$_3$P and other phosphines. For instance the lone-pair IP's for PH_3, $(CH_3)_3P$, and $(C_6H_5)_3P$ are 9.9,[9] 8.6,[16] and 7.9 eV, respectively, and this difference appears to reflect the difference in bond angles at the phosphorus (94°,[17] 99°,[18] and 103°,[19] respectively).[20]

Experimental Section

The spectra were obtained with a Perkin-Elmer Model PS-18 photoelectron spectrometer, using the He(I) resonance line (21.22 eV). Since elevated temperatures were necessary for proper sample vapor pressures, a direct inlet probe was used for all samples. Temperatures generally in the range of 60–130° were used in order to obtain proper count rates, but 150° was necessary for the *p*-$(CH_3)_3C$ and *p*-$(CH_3)_3Si$ derivatives, and 240° was necessary for the *p*-$(CH_3)_2N$ compound. The spectra were calibrated with Ar (15.759- and 15.937-eV lines) and Xe (12.130-eV line), used as internal standards. The values listed for IP_1 (Table I) are the band maxima. In order to obtain a comparison between the phenyl IP values for aryl$_3$P and the corresponding monosubstituted benzenes, the values of IP_2 and IP_3 (Table I) were obtained as often as possible in accordance with the method of obtaining the vertical IP's for the corresponding monosubstituted benzene (Table II).

The phosphine samples were prepared by the Grignard method.[21]

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Registry No.—**1**, 13406-29-6; **2**, 1159-54-2; **3**, 18437-78-0; **4**, 603-35-0; **5**, 18848-96-9; **6**, 1038-95-9; **7**, 29949-82-4; **8**, 54409-77-7; **9**, 855-38-9; **10**, 1104-21-8; **11**, 25688-42-0; **12**, 6163-58-2; **13**, 4731-65-1; **14**, 23039-94-3; **15**, 6224-63-1; **16**, 29949-84-6.

Supplementary Material Available. Photoelectron spectra of 1–16 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1292.

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Stereochemistry of Dihydrothiophene Formation from Vinylphosphonium Salts[1a]

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Evidence is presented which shows that the *cis*-2,5-dialkyl-2,5-dihydrothiophenes are formed in preference to the trans isomers in the reaction between vinylphosphonium salts and α-mercaptocarbonyl compounds. Substituent trends suggest a steric basis for this effect. The implications of the results for stereoselective conjugated diene preparation are discussed. Seven new examples of the synthesis of the dihydrothiophenes are reported.

One of the most active areas in organic synthesis in the past decade has been the development of methods for the construction of unsaturated compounds in stereoselective and stereospecific ways. Whereas the preparation of 1,5-dienes is an active field,[2] work on the stereoselective synthesis of 1,4- and 1,3-dienes has been limited. As we have pointed out,[3] this has greatly restricted the application of the Diels–Alder reaction to stereospecific organic synthesis.

One method of 1,3-diene synthesis which has been shown to be stereospecific is the thermal decomposition of 2,5-

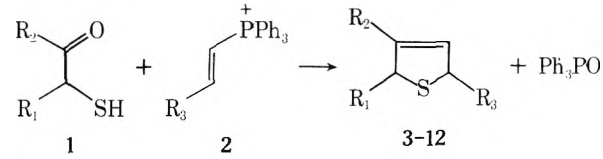
Table I
Products and Yields of 2,5-Dihydrothiophenes[a]

Carbonyl compd	Vinyl salt[b]	Product	R_1	R_2	R_3	Reaction time, hr	Yield, %
1a	2a	3[c]	Me	H	Me	18	32
1b	2a	4[d]	Et	H	Me	2	70
1b	2c	5	Et	H	*i*-Pr	3	50
1c	2a	6	Me	Me	Me	18	78
1c	2b	7	Me	Me	Et	18	60
1d	2a	8	Me	Et	Me	18	80
1d	2b	9	Me	Et	Et	18	64
1d	2c	10	Me	Et	*i*-Pr	18	64
1e	2a	11[e]	$-(CH_2)_4-$		Me	18	91
1e	2b	12	$-(CH_2)_4-$		Et	42	88

[a] Satisfactory analytical data were recorded for all new compounds in this table. [b] Prepared by in situ isomerization of the allylic isomer. [c] Reference 12. [d] Contains ca. 10% thiophene impurity. [e] Reference 3.

Results

A. Dihydrothiophene Preparations. The dihydrothiophenes were prepared by the general method previously outlined.[3] The yields, reaction times, and spectral characteristics of new materials are collected in Tables I and II. In all cases, the allylic phosphonium salt was used as the reagent and isomerized to its vinyl isomer in situ.[3]



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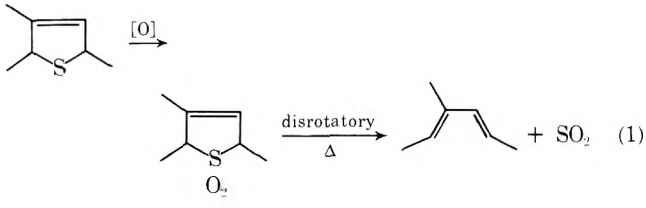
Several comments on this reaction are required. We have found that the use of *undistilled* α-mercaptocarbonyl compounds, especially in the case of α-mercaptoaldehydes, leads to much superior results. Distillation of these materials invariably leads to dehydration of their dimeric form and subsequent diminution of the yields of dihydrothiophenes. In addition, in several reactions using α-mercaptoaldehydes, the NMR spectrum of the chromatography product showed the presence of thiophene (δ 6.5–7.0). Since all reactions were performed under a blanket of nitrogen, air oxidation of the dihydrothiophene seem unlikely, and as no trace of the corresponding tetrahydrothiophene could be detected, disproportionation does not seem probable. At this time, we have no explanation for this result.

Table II
Indices of Refraction and NMR Spectra of New Dihydrothiophenes

Compd	n_D (temp, °C)	NMR spectral data[a]
5	*b*	5.75 (s, 2), 4.4–3.9 (m, 2), 2.1–1.35 (m, 3), 1.0 (t, 3, J = 7 Hz), 0.97 (d, 6, J = 7.5 Hz)
6	1.5291 (25)	5.37 (d, 1, J = 2 Hz), 4.4–3.8 (m, 2), 1.8 (d, 3, J = 0.5 Hz), 1.46 (d, 3, J = 7 Hz), 1.42 (d, 3, J = 7 Hz)
7	1.4930 (20)	5.32 (d, 1, J = 2 Hz), 4.25–3.5 (m, 2), 2.0–1.5 (m, 2), 1.78 (d, 3, J = 0.5 Hz), 1.37 (d, 3, J = 7.0 Hz), 1.0 (t, 3, J = 6.5 Hz)
8	1.4910 (25)	5.5 (s, 1), 4.55–3.95 (m, 2), 2.6–1.8 (m, 2), 1.46 (d, 3, J = 7.5 Hz), 1.42 (d, 3, J = 7.5 Hz), 1.12 (t, 3, J = 9.0 Hz)
9	1.4921 (25)	5.52 (s, 1), 4.5–3.9 (m, 2), 2.5–1.6 (m, 4), 1.48 (d, 3, J = 7.5 Hz), 1.16 (t, 3, J = 8.0 Hz), 1.01 (t, 3, J = 8.0 Hz)
10	1.5062 (20)	5.37 (d, 1, J = 1.5 Hz), 4.4–3.8 (m, 2), 2.7–1.5 (m, 3), 1.39 (d, 3, J = 7 Hz), 1.10 (t, 3, J = 8 Hz), 0.96 (d, 6, J = 8 Hz)
12	1.5221 (20)	5.25 (d, 1, J = 2.0 Hz), 4.3–3.7 (m, 2), 2.80–1.15 (m, 10), 1.00 (t, 3, J = 6 Hz)

[a] Tabulation follows the order chemical shift (δ), multiplicity, number of protons, coupling constant. Spectra run in $CDCl_3$. [b] Sample contaminated by thiophene.

dihydrothiophene sulfones,[4] which occurs in a completely regiospecific and stereospecific disrotatory[5] manner. We have recently published[3,6] a new and facile preparation of 2,5-dihydrothiophenes from vinylphosphonium salts and have shown that they can be converted to conjugated dienes in high yields through the intermediacy of the corresponding sulfones (eq 1). In view of its importance for



(1)

diene synthesis, we decided to investigate the stereochemistry of the dihydrothiophene formation.

The stereochemistry of this process is important in other ways. Thus it has been shown[5c,7] that the photochemical decomposition of the sulfones occurs in the opposite stereochemical sense and therefore a stereoselective preparation of dihydrothiophenes would allow the selective formation of either of two diene isomers at will. Further, the use of the sulfones has been illustrated in the synthesis of 1,4-dienes,[8] divinyl ethers,[8] divinyl amines,[9] and cyclobutenes.[10] In each case, the stereochemistry of the sulfone determines that of the product.

B. Separation of the Dihydrothiophenes. Initially we were unable to detect any indication of the presence of two dihydrothiophene isomers using gas chromatography. However, by utilizing a very polar column packing and low temperatures[12] we finally achieved separation of two isomers in some cases. In each case, the order of elution was *trans*- followed by *cis*-2,5-dialkyl-2,5-dihydrothiophene, as was shown by the ratios of dienes subsequently obtained (vide post). Unfortunately, in cases where the NMR spectrum showed the presence of the corresponding thiophenes as an impurity, it could not be separated and therefore the cis/trans ratio of dihydrothiophenes could not be determined directly. In Table III the cis/trans ratio derived by GLC analysis is recorded.

C. Preparation and Decomposition of the Sulfones. As already discussed, thermal elimination of sulfur dioxide is a stereospecific disrotatory process and therefore the

stereochemistry of the dienes obtained faithfully reflects that of the dihydrothiophenes from which they are derived. Specifically, *cis*-1 leads to *E,E* or *Z,Z* diene whereas *trans*-1 affords *E,Z* or *Z,E* diene on oxidation and pyrolysis. Therefore isomeric analysis of the dienes also affords the cis/trans ratio of the dihydrothiophenes and gives a check on the direct GLC analysis.

One possible problem foreseen was the rearrangement of the dienes by 1,5-hydrogen transfer.[5c,13] We chose to effect the pyrolysis of the sulfones in the injection port of a gas chromatograph to minimize the pyrolysis time and thus the chance for rearrangement. As yet we have failed to detect a rearranged diene in any of the cases studied.

The dihydrothiophenes were oxidized to the sulfones using *m*-chloroperbenzoic acid and were immediately decomposed by injection into the GLC. In every case, the only products observed were sulfur dioxide and a diene mixture. The results of the diene analysis are incorporated into Table III. Where possible, the dienes were collected separately and identified by their spectra. In several cases (**8, 9, 10**) separation on a preparative scale was not feasible and then the NMR spectrum of the diene mixture served to identify the major component and GLC analysis gave the *E,E/E,Z* ratio. In the case of **11**,[14] because of the extremely heavy bias of the diene mixture, authentic samples were prepared and compared to the pyrolysis products.

Inspection of Table III shows that the two methods of analysis give similar results when thiophenes are not present in the dihydrothiophene preparation. In all cases, the cis isomer is favored over the trans, but incorporation of increasingly bulky groups on the ring leads to a relative increase in the amount of trans isomer present.

Discussion

The accepted mechanism for the cyclization reaction involves[3] the conjugate addition of thiolate ion to the polarized double bond of the phosphonium salt, followed by an intramolecular Wittig reaction of the ylide so formed (eq 2). The first step of this sequence is known to be reversible.[15] Assuming irreversible betaine decomposition,[16] the product stereochemistry will be determined by structural influences on the transition state for this step. Models suggest that the ring is nearly planar at this point with substantial eclipsing of all substituents. Thus it is clear that to minimize the serious steric interactions, substituents at C-2 and C-5 (Figure 1) must be trans to the phosphorus atom, thus favoring the formation of the *cis*-2,5-dialkyl-2,5-dihydrothiophene. A result of this analysis is the prediction that this steric discrimination should decrease as the steric bulk of R,R′, and X increase. Inspection of Table III bears this out and lends support to the rationale.

The two dihydrothiophenes (**11, 12**) derived from α-mercaptocyclohexanone appear to be special cases. Here R′ and X constitute part of a six-membered ring and models suggest that cis fusion in these compounds should be by far the favored mode. Again the isomeric distribution supports this interpretation.

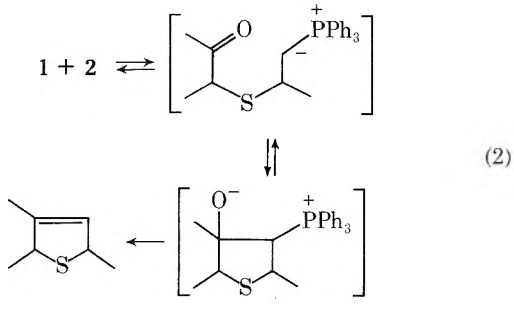


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Table III
Isomeric Distribution of Dihydrothiophene and Diene Mixtures[a]

Dihydrothiophene	GLC analysis cis:trans (%)	Sulfone pyrolysis (*E,E* + *Z,Z*):(*E,Z* + *Z,E*), %
3		92:8
4	83:17	81:19
5	*b*	75:25
6	79:21	79:21
7	67:33	69:31
8	78:22	*c*
9	78:22	*c*
10	54:46	57:43
11		96:4
12		96:4

[a] See Experimental Section for GLC conditions. [b] Direct determination impossible owing to thiophene contamination. [c] Separation of isomers not achieved.

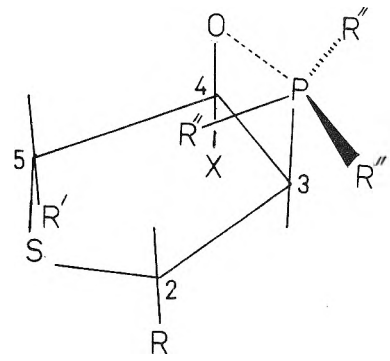

Figure 1. Stereochemical model for dihydrothiophene formation.

It is interesting to note that we have observed no case where the formation of *Z,Z* diene occurs in the sulfone pyrolyses. Apparently the well-known steric problems encountered in such a compound prevent its formation.

Conclusions

It is evident from the foregoing that the formation of dihydrothiophenes from vinylphosphonium salts is a stereoselective process, especially when the steric bulk of the substituents is not too large. Therefore the overall diene synthesis allows the regiospecific and stereoselective formation of conjugated dienes. As we have pointed out,[6b] the net effect achieved is the coupling of two vinyl moieties. This unique aspect, as well as the mildness of the conditions, the readily availability of the starting materials, and the high yields, make the method of potential use in organic synthesis.

Experimental Section

Infrared spectra were recorded on a Beckman IR-12 in carbon disulfide solution; NMR spectra were obtained on a Jeolco C60HL spectrometer in carbon tetrachloride solution unless otherwise noted and are reported in parts per million downfield from Me_4Si as internal standard. Mass spectra were obtained on a Varian MATCH5-DF instrument. GLC analyses were carried out on F & M Models 720 and 5750 gas chromatographs utilizing the following columns: A, 10 ft × 0.375 in. 20% TCEP on Chromosorb P; B, 8 ft × 0.375 in. 20% SE-30 on Chromosorb W. The flow rate of helium carrier gas was 1 ml/sec. Compositions of mixtures were determined using a disc integrator and are considered to be accurate to ±3%. Unless otherwise noted, solvents were removed at reduced pressure and chromatographies were performed using Fisher acidic alumina, Brockman activity grade I. Microanalyses were performed by A. B. Gygli, Microanalysis Laboratory, Toronto, Ontario, Canada.

Preparation of Dihydrothiophenes 3–12. These were prepared using the conditions outlined previously,[3,6] reflux times and yields being indicated in Table I. GLC analyses were performed using column A at 120° and the results are shown in Table III. Compounds 11 and 12 showed no detectable separation of isomers under any conditions. Analytical samples were collected from column B.

Mercaptocarbonyl compounds **1b**,[17] **1c**,[18] and **1e**[11c] were prepared by literature methods.

2-Bromo-3-pentanone. To a mechanically stirred slurry of 110 g (1.1 mol) of calcium carbonate and 87 g (1 mol) of 3-pentanone in 1 l. of cold chloroform was added dropwise 145 g (0.9 mol) of bromine over a period of 4 hr at 0°. After addition was complete, the mixture was stirred for 3 hr and filtered and the filtrate was washed with 300 ml of saturated aqueous sodium bicarbonate solution and dried ($MgSO_4$). Removal of the solvent gave an oil which was distilled to give the bromo ketone (80 g, 55%), bp 55° (15 mm) [lit.[19] bp 48° (12 mm)].

2-Mercapto-3-pentanone (1d). A solution of 30 g of potassium hydroxide in 150 ml of water was saturated with hydrogen sulfide at 0°. With continuous addition of hydrogen sulfide, 45 g (0.27 mol) of 2-bromo-3-pentanone in 10 ml of absolute ethanol was added dropwise with stirring over a period of 2 hr. The solution was stirred for 2 hr as it warmed to room temperature and extracted with two 75-ml portions of ether. The ether extracts were washed with water, dried, and evaporated to give 25 g (78%) of pure **1d**[20] which was used without distillation: NMR δ 3.45 (q, 11, J = 7.5 Hz), 2.9–2.4 (d of q, 2, J = 2, 7 Hz), 1.4 (d, 4, J = 7.5 Hz), 1.1 (t, 3, J = 7 Hz).

2-Mercaptopropionaldehyde (1a). To a cooled mixture of 56 g of finely pulverized sodium sulfhydrate in 250 ml of ether was added 25 g (0.18 mol) of 2-bromopropanal,[21] bp 42–50° (60 mm). The slurry was stirred vigorously overnight and filtered and the solvent was removed to afford an oil which solidified on trituration with methanol: yield 1.0 g (6%); NMR δ 5.93 (d, 2, J = 6 Hz), 4.7 (broad d, 2, J = 6 Hz), 3.63 (broad q, 2, J = 7.5 Hz), 1.06 (d, 6, J = 7.5 Hz). The material exists as the dimer,[11] as no carbonyl absorption could be detected in the infrared spectrum.

3-Methyl-2-buten-1-yltriphenylphosphonium Bromide. To a solution of 7.0 g (0.02 mol) of triphenylphosphine hydrobromide[22] in 50 ml of acetonitrile was added 3.0 g of isoprene, and the solution was stirred for 15 hr. The salt was precipitated by adding 150 ml of ethyl acetate and filtered, and the residue was dried to give 8.2 g (100%) of a solid: mp 230–234° (lit.[23] mp 233–235°); NMR δ 8.0 (m, 15), 5.5–4.5 (m, 3), 1.75 (d, 3, J = 7 Hz), 1.35 (d, 3, J = 4.5 Hz).

Refluxing a solution of this salt in pyridine containing some triethylamine for 3 hr[3] caused its isomerization into salt **2c**.

(*Z*)-1-(1-Cyclohexenyl)propene. To a suspension of 7.42 g (0.02 mol) of ethyltriphenylphosphonium bromide in 100 ml of dry tetrahydrofuran was added a solution of 2.2 g (0.02 mol) of potassium *tert*-butoxide in 25 ml of the same solvent dropwise with stirring and under nitrogen. The mixture was stirred at ambient temperature for 25 min, and 2.2 g (0.02 mol) of cyclohexenecarboxaldehyde was added slowly with stirring. The milky solution was stirred overnight and added to a mixture of 100 ml of water and 100 ml of ether, and the organic layer was separated and concentrated to 20 ml. After addition of 100 ml of pentane, the mixture was filtered, concentrated, and distilled to give 1.4 g (55%) of a mixture of dienes, bp 62–65° (12 mm). GLC analysis (column A, 130°) showed the mixture to consist of 24% *E* and 76% *Z* isomer. The latter was collected: NMR δ 5.81–4.95 (m, 3), 2.40–1.85 (m, 4), 1.84–1.40 (m, 7); ir 700 (m), 720 (s), 800 (m), 920 (s), 970 cm^{-1} (w), in agreement with the literature values.[14,24] The retention time was identical with that of the minor isomer obtained from **11** via oxidation and pyrolysis.

(*E*)-1-(1-Cyclohexenyl)propene.[14] The pure *Z* isomer was dissolved in 5 ml of petroleum ether and a crystal of iodine was added. The flask was irradiated for 16 hr with a 60-W incandescent bulb. GLC analysis showed a quantitative conversion to the *E* isomer, identical in all respects with the major isomer obtained from **11** via oxidation and pyrolysis.

General Procedure for Oxidation of 3–12. Dihydrothiophene (0.01 mol) was dissolved in 50 ml of methylene chloride and cooled in an ice bath. *m*-Chloroperbenzoic acid (0.02 mol) was added in two portions and the solution was stirred for 3 hr at 0° and overnight at ambient temperature. The filtered solution was washed with 50 ml of saturated aqueous sodium carbonate, dried, and concentrated to give a quantitative yield of sulfone, which was used directly.

Sulfone Pyrolyses. The sulfone was injected into the injection port (280°) of the gas chromatograph fitted with column A. The dienes were eluted after sulfur dioxide and were collected, individually where possible, for spectral analysis, and were compared to authentic samples where required.

2,4-Hexadiene, obtained from **5,** was separated into the *E,Z* and the *E,E* isomers, which were identified by comparison of spectra and retention times with those of authentic samples.[25]

2,4-Heptadiene,[26] obtained from **4,** was separated into the 2*E*,4*Z* isomer [NMR δ 6.41–5.05 (m, 4), 2.08 (q, 2, J = 7.5 Hz), 1.70 (d, 3, J = 6 Hz), 1.00 (t, 3, J = 7.5 Hz); ir 715 (s), 765 (m), 780 (m), 840 (m), 900 (w), 950 (s), 985 cm^{-1} (s)] and the *E,E* isomer [NMR δ 6.07–5.01 (m, 4), 2.02 (q, 2, J = 7.5 Hz), 1.65 (d, 3, J = 6 Hz), 1.00 (t, 3, J = 7.5 Hz); ir 820 (w), 895 (m), 930 (m), 950 (m), 985 cm^{-1} (vs)].

2-Methyl-3,5-octadiene, obtained from **5,** was separated into two isomers. The major one [NMR (CS_2) δ 6.0–5.12 (4, m), 2.45–1.76 (3, m), 0.96 (d, 6, J = 6.5 Hz), 0.98 (t, 3, J = 7.5 Hz); ir 700 (w), 860 (m), 900 (w), 990 cm^{-1} (s)] was identified as the 3*E*,5*E* isomer. The other isomer showed NMR δ 6.20–5.05 (m, 4), 2.37–1.78 (m, 3), 1.02 (d, 6, J = 7.0 Hz), 0.98 (t, 3, J = 7.5 Hz); ir 700 (m), 861 (s), 950 (m), 985 cm^{-1} (m). Although the 3*Z*,5*E* isomer cannot be excluded by these data, we favor 2-methyl-3*E*,5*Z*-octadiene for this compound.

Anal. Calcd for C_9H_{16}: *m/e* 124.12520 Found: *m/e* 124.12582.

3-Methyl-2,4-hexadiene[27] was obtained from **6.** The major isomer was obtained pure and its spectra showed it to be the 2*E*,4*E* isomer [NMR δ 6.07–5.05 (m, 3) which contained the low-field half of an AB quartet centered at 5.95, J_{AB} = 15 Hz, 1.86–1.55 (m, 9); ir 772 (s), 840 (m), 927 (m), 970 (vs), 1030 cm^{-1} (m)]. Not enough of the minor isomer could be obtained for NMR, but its ir spectrum [825 (m), 927 (w), 964 cm^{-1} (s)] suggested that no cis-disubstituted double bond was present and a mixture of the two isomers enriched in the minor one showed a very complex absorption at δ 5.66–5.05, strongly reminiscent of (2*E*,4*Z*)-hexadiene. On this basis we assign it the structure 3-methyl-(2*Z*,4*E*)-hexadiene.

3-Methyl-2,4-heptadiene was obtained from **7.** The major component was separated and identified as the 2*E*,4*E* isomer [NMR δ 6.06–5.01 (m, 3), 1.90 (q, 2, J = 7 Hz), 1.74–1.48 (m, 6), 0.97 (t, 3, J = 7 Hz); ir 700 (w), 795 (m), 810 (w), 860 (s), 965 cm^{-1} (s)]. Not enough of the minor isomer could be obtained pure for NMR analysis but on the basis of the infrared spectrum [700 (m), 760 (w), 865 (vs), 967 cm^{-1} (s)] we believe that the majority of the material must possess a trans-disubstituted double bond and therefore we designate it as the 2*Z*,4*E* isomer. Contamination of this material with the 2*E*,4*Z* isomer cannot be excluded.

Anal. Calcd for C_8H_{14}: *m/e* 110.10955. Found: *m/e* 110.10969.

3-Ethyl-2,4-hexadiene[28] was obtained from **9.** It could not be separated into its isomeric components, but analysis of the spectra of the mixture was done as follows. The NMR absorption for the three vinyl protons occurred between δ 6.36 and 5.00 and included the low-field half of an AB quartet (J_{AB} = 15 Hz), the intensity of which suggested that all the material contained a trans-disubstituted double bond. The absence of a strong infrared absorption below 800 cm^{-1} confirmed this. The remainder of the NMR spectrum showed δ 2.38–1.92 (q, 2, J = 7 Hz), 1.90–1.55 (m, 6), and two overlapping triplets, J = 7.5 Hz, centered at δ 1.01 and 0.98 whose relative intensities were 25:75. This is consistent with a mixture of 75% 3-ethyl-(2*E*,4*E*)-hexadiene and 25% of the 2*Z*,4*E* isomer, in good agreement with results of GLC analysis of **8.** The ir spectrum of the mixture showed 780 (w), 825 (w), 930 (w), 965 cm^{-1} (s).

3-Ethyl-2,4-heptadiene was obtained from **9.** It could not be separated into its components under any conditions. The mixture of isomers showed NMR δ 6.45–5.05 [m, 3, which contained the low-field portion of an AB quartet centered at 5.91 (J_{AB} = 15 Hz)], 2.48–1.88 (m, 4), 1.67 (d, 3, J = 6 Hz), 1.01 (t, 3, J = 7.2 Hz), 0.97 (t, 3, J = 7.2 Hz); ir 760 (w), 800 (w), 900 (w), 960 cm^{-1} (vs).

Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 86.89; H, 12.84.

3-Ethyl-6-methyl-2,4-heptadiene was obtained from **10** and was separated into the 2*E*,4*E* isomer [NMR δ 5.87–5.07 (m, 3), 2.45–1.92 (m, 3), 1.61 (d, 3, J = 7 Hz), 0.97 (d, 6, J = 6 Hz), 0.96 (t, 3, J = 6 Hz); ir 810 (m), 860 (w), 950 (m), 975 cm^{-1} (vs)] and the 2*Z*,4*E* isomer [NMR δ 6.37–5.02 (m, 3), 2.55–1.82 (m, 3), 1.66 (d, 3, J = 7 Hz), 1.03 (d, 6, J = 6 Hz), 1.00 (t, 3, J = 7.5 Hz); ir 800 (m), 945 (m), 968 cm^{-1} (s)]. This latter assignment of structure was based on the absence of any significant absorption below 800 cm^{-1}, which suggested the absence of a cis-disubstituted double bond.

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.70; H, 13.24.

1-(1-Cyclohexenyl)propene[14] was obtained from **11**. The major and minor isomers were identical with the authentic samples of the *E* and *Z* isomers, respectively.[24]

1-(1-Cyclohexenyl)butene[14] was obtained from **12**. The vinyl region of the NMR spectrum was very similar to that of the *E* isomer obtained from **11** and on that basis was assigned the same configuration: NMR δ 6.11–5.20 (m, 3, which contained the low-field half of an AB quartet, J_{AB} = 15 Hz), 2.34–1.33 (m, 10), 1.00 (t, 3, J = 6.5 Hz).

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Registry No.—**1a**, 54354-14-2; **1b**, 53101-85-2; **1c**, 40789-98-8; **1d**, 17042-24-9; **1e**, 42904-05-2; **2a**, 7301-94-2; **2b**, 54354-15-3; **2c**, 54354-16-4; *cis*-**3**, 33765-35-4; *trans*-**3**, 33765-34-3; *cis*-**4**, 54354-17-5; *trans*-**4**, 54354-18-6; *cis*-**5**, 54354-19-7; *trans*-**5**, 54354-20-0; *cis*-**6**, 54354-21-1; *trans*-**6**, 54354-22-2; *cis*-**7**, 54354-23-3; *trans*-**7**, 54354-24-4; *cis*-**8**, 54354-25-5; *trans*-**8**, 54354-26-6; *cis*-**9**, 54354-27-7; *trans*-**9**, 54354-28-8; *cis*-**10**, 54354-29-9; *trans*-**10**, 54354-30-2; *cis*-**11**, 54354-31-3; *trans*-**11**, 54354-32-4; *cis*-**12**, 54354-33-5; *trans*-**12**, 54354-34-6; 2-bromo-3-pentanone, 815-52-1; 3-pentanone, 96-22-0; 2-bromopropanal, 19967-57-8; 3-methyl-2-buten-1-yltriphenylphosphonium bromide, 1530-34-3; triphenylphosphine hydrobromide, 6399-81-1; isoprene, 78-79-5; (*Z*)-1-(1-cyclohexenyl)propene, 5680-41-1; (*E*)-1-(1-cyclohexenyl)propene, 54354-35-7; ethyltriphenylphosphonium bromide, 1530-32-1; cyclohexenecarboxaldehyde, 30326-86-4; (*E,Z*)-2,4-hexadiene, 5194-50-3; (*E,E*)-2,4-hexadiene, 5194-51-4; (*2E,4Z*)-heptadiene, 54354-36-8; (*E,E*)-2,4-heptadiene, 2384-94-3; 2-methyl-(3*E*,5*E*)-octadiene, 54354-37-9; 2-methyl-(3*E*,5*Z*)-octadiene, 54354-38-0; 3-methyl-(2*E*,4*E*)-hexadiene, 54354-39-1; 3-methyl-(2*Z*,4*E*)-hexadiene, 54354-40-4; 3-methyl-(2*E*,4*E*)-heptadiene, 54354-41-5; 3-methyl-(2*Z*,4*E*)-heptadiene, 54354-42-6; 3-ethyl-(2*E*,4*E*)-hexadiene, 54354-43-7; 3-ethyl-(2*Z*,4*E*)-hexadiene, 54354-44-8; 3-ethyl-2,4-heptadiene, 54354-45-9; 3-ethyl-6-methyl-(2*E*,4*E*)-heptadiene, 54354-46-0; 3-ethyl-6-methyl-(2*Z*,4*E*)-heptadiene, 54354-47-1.

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Stable Rotamers of 9,9′:9′,9″-Terfluorenyls at Room Temperature[1]

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The reactions and spatial structures for the stereoisomers $C_{39}H_{26}$, mp 293° dec (A) and mp 257° dec (B), which are stable at room temperature in solution were investigated. It is proposed from NMR spectra that these are conformational isomers, namely *s-cis,s-cis-* and *s-cis,s-trans*-9,9′:9′,9″-terfluorenyls occurring as the result of restricted rotation about the sp^3–sp^3 carbon–carbon single bonds. A isomerized to B by treatment with Raney nickel. Rotamers A and B were obtained simultaneously by the Michael addition of fluorene to 9,9′-bifluorenylidene.

During investigation on the self-condensation of fluorene (**1**) by treating with various bases, we have obtained 9,9′:9′,9″-terfluorenyl, mp 257° dec (B),[2] by reaction of **1** with sodamide. Pinck and Hilbert also obtained this compound but with mp 293° dec (A)[3] by the Michael addition of **1** to 9,9′-bifluorenylidene (**2**) (Scheme I).

A was isomerized to B, followed by thermolysis of the resulting B to give 9,9′-bifluorenyl (**3**) and **2**,[2] as established by ESR.[4] Isomers A and B were isolated simultaneously by reaction of 9-bromofluorene with methanolic potassium hydroxide in acetone or from other reactions.[5] Both compounds are stable at room temperature in solution, and give fluorenone by oxidation and **1** by reduction.[2,6] Previously we suggested that A and B could be rotational isomers around the C_9–$C_{9'}$–$C_{9''}$ carbon–carbon single bonds.[7]

In the preliminary communication,[8] we reported the conformations and conformational isomerizations of A and B. The present investigation gives further details on the spectral basis of the previous assignments, and is concerned with the Michael addition of **1** to **2**.

Conformations of 9,9′:9′,9″-Terfluorenyl Isomers. Mass spectra of A and B are virtually identical: the parent peak appears at *m/e* 494; the base peak at *m/e* 329 (9,9′-bifluorenyl cation) and *m/e* 165 (9-fluorenyl cation) are fragments whose origin can be interpreted by simple cleavage of $C_{9-9'}$ or $C_{9'-9''}$ bonds from the parent ion.

The ir spectra show absorption bands due to the methine hydrogen C–H stretching frequencies at 2899 cm^{-1} for **3** (9-CH, 9′-CH) and 2917 cm^{-1} for A (9-CH, 9″-CH), whereas two bands at 2883 and 2918 cm^{-1} are observed for B (9-

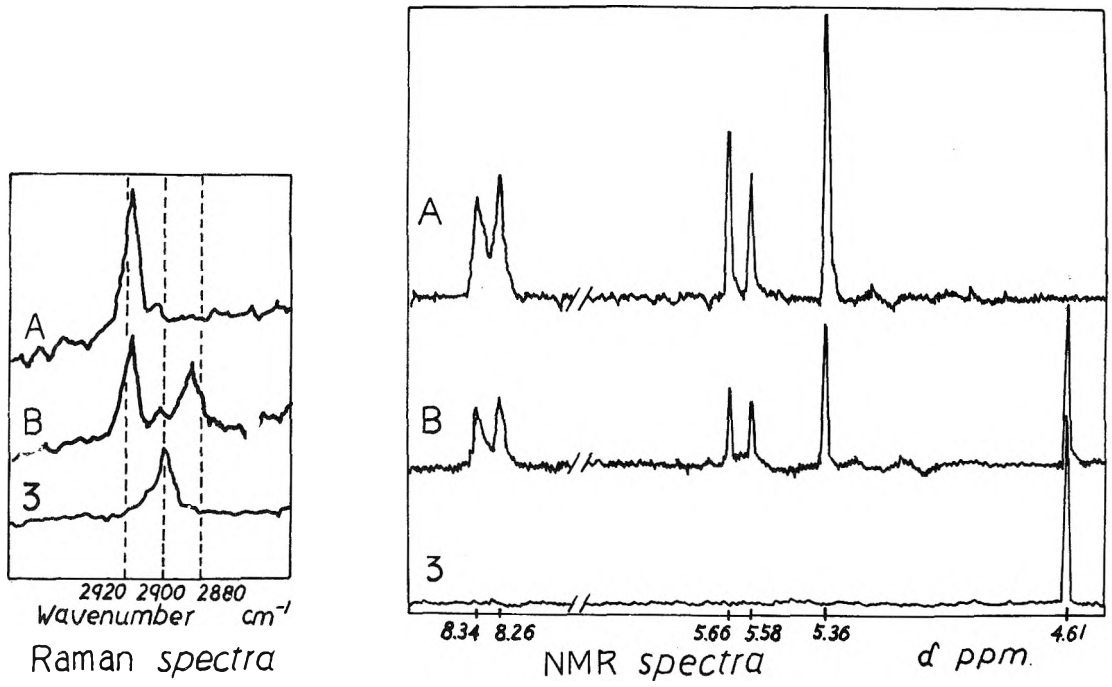
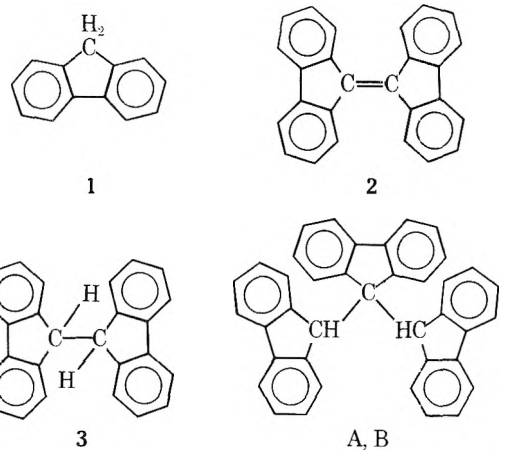


Figure 1. Partial Raman and NMR spectra of A, B, and 3.

Scheme I



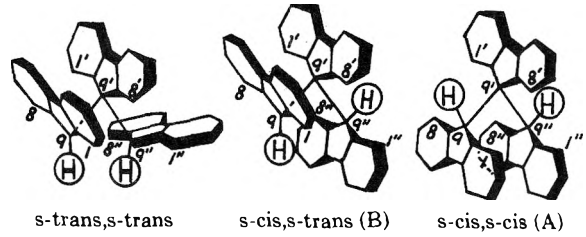


Figure 2.

CH, 9″-CH). Similarly, there are fairly strong absorptions in the Raman spectra at 2900 cm^{-1} for **3**, at 2918 cm^{-1} for A, and at 2884 and 2919 cm^{-1} for B, as Figure 1 shows. Therefore, the two methine frequencies in B would seem due to different conformational effects.

The NMR spectrum of **3** exhibits a 16-proton signal at 7.58–6.85 ppm (aromatic region) and a two-proton singlet from the 9- and 9′-methines at 4.61 ppm. Both A and B show a 24-proton signal at 8.34–5.58 ppm (aromatic region), a two-proton singlet of C_9 and $C_{9''}$ at 5.36 ppm in A, and the nonequivalent two protons at 4.61 and 5.36 ppm in B. The assignment of signals to these methine protons in **3**, A, and B was confirmed by the syntheses of the corresponding deuterated compounds.

In addition, some characteristic shifts in the NMR spectra appear at higher (5.58 and 5.66 ppm, J = 8 Hz) and lower (8.26 and 8.34 ppm) fields than would be expected as two doublets in both A and B; the extent of each doublet area is equivalent to two protons in A and one proton in B. Furthermore, signal intensities decreased in the NMR spectra of A-*1-d* (or 1-deuterio-9,9′:9′,9″-terfluorenyl, mp 293°C dec) and B-*1-d*.

An examination of the space-filling molecular models of 9,9′:9′,9″-terfluorenyls indicates that the rotation about the sp^3–sp^3 single bonds of $C_{9-9'}$ and $C_{9'-9''}$ is sufficiently restricted due to the close proximity of the hydrogen atoms at the 1, 8, 1′, 8′, 1″, 8″, 9, and 9″ positions, so the following three rotamers can exist in the ground state (see Figure 2).

(a) Three planes in the 9,9′:9′,9″-terfluorenyl, that is, 9- and 9″-fluorenyls and 9′-fluorenylidene, can be folded cis with respect to one another, so the molecule exists in the s-cis,s-cis conformation.

(b) Both the 9-fluorenyl and 9′-fluorenylidene planes may be folded cis with respect to each other, and that of 9″-fluorenyl may be oriented s-trans to those of the central 9′-fluorenylidene, leading to the s-cis,s-trans conformation.

(c) The 9- and 9″-fluorenyl planes may be s-trans and s-trans to the central plane of the 9′-fluorenylidene, yielding the s-trans,s-trans conformation. However, this conformation must be less stable owing to the severe steric repulsion between the two bulky 9- and 9″-fluorenyl groups (plane distance ca. 0.87 Å), so that the possibility of its existence may be excluded from examination of the molecular models.

Consequently, the NMR signal at 4.61 ppm in B arises from the s-trans conformation by analogy with **3**;[9] the other, at 5.36 ppm, is in agreement with that of the singlet in A, and can be assigned as due to the s-cis conformation. Accordingly, compounds A and B must be presumed to be the s-cis,s-cis and s-cis,s-trans conformations, respectively.

The anomalous shifts of aromatic proton signals (5.58, 5.66; 8.26, 8.34 ppm) in the NMR spectra are probably due to a torsional conformation about the $C_{9-9'}$ and $C_{9'-9''}$ sp^3–sp^3 bonds, so that each 9- and 9″-fluorenyl ring is twisted out from the 9′-fluorenylidene plane to remove the strain within the range of the restricted degree.

Table I
Treatment of 9,9′:9′,9″-Terfluorenyl Isomers with Raney Nickel

Material (g)	Reaction conditions				Products, g (%)			
	RNi, g	Et_3N, g	Temp, °C	Time, hr	B	3	1	Recovered, g (%)
A (1.5)	10.0	0.3	60	1	0.78 (52)		0.10 (7)	0.31 (21)
A (1.5)	10.0	0.3	60	3	1.13 (75)	0.08 (5)	0.09 (6)	0.12 (8)
A (1.5)	10.0	0.3	60	5	1.14 (76)	0.04 (3)	0.10 (7)	0.05 (3)
A (1.5)	10.0	0.3	Reflux	3	0.42 (28)	0.28 (19)	0.58 (39)	
A (1.5)	10.0		Reflux	3	0.24 (16)	0.41 (27)	0.60 (40)	
B (1.5)	10.0	0.3	60	5		0.53 (35)	0.09 (7)	0.60 (40)
B (1.5)	10.0	0.3	Reflux	3		0.55 (37)	0.45 (30)	0.26 (17)

Thus, two aromatic protons at the 1,8″ positions of the 9- and 9″-fluorenyl planes in A are actually located in the shielding zone of the π electron cloud on the central 9′-fluorenylidene ring, which shifts the signal to higher field; however, the other two protons at the 1″,8 positions are in a deshielded zone which shifts the signal to lower field, as Figure 3 shows. Likewise, the two protons at the 1 and 8 positions of the *cis*-9-fluorenyl ring, with respect to the central 9′-fluorenylidene ring in B, resonate at higher and lower fields than other aromatic protons.

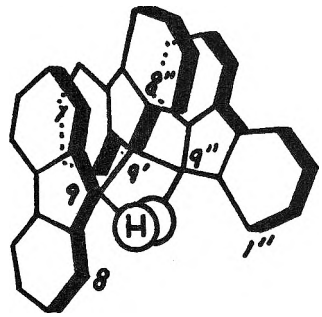


Figure 3.

Isomerization of Rotamer A to B. No isomerization of A into B except by thermolysis has been performed hitherto. A is also converted into B by treatment with Raney nickel; hydrogenolysis of the resulting B gives **3**, **1**,[10] and a small amount of hexahydrofluorene[11] as shown in Table I.

Upon treating with Raney nickel, A-*9,9″-d*$_2$ was converted into B-*9-d* by proton exchange. The terfluorenyl molecule may be adsorbed on the catalyst at the 9″-fluorenyl plane containing a 9″ deuterium atom. Thus, the reaction proceeds with inversion of the conformation to give B-*9-d* by the attack of reactive hydrogen at the back side of the 9″ carbon to which the 9″ deuterium has been attached.

Michael Addition of Fluorene (1) to 9,9′-Bifluorenylidene (2). The effect of bases on the formation of these isomers through the Michael addition of **1** to **2** are listed in Table II. The yields of A decreased and those of B increased in the order methyl, ethyl, and *n*-propyl alcohol in the presence of the sodium alkoxide. The predominant formation of A in 90% pyridine–water solution was distinct from the coformation of A and B in sodium ethoxide–dry pyridine, whereupon the ratio of the isomers depends on the polarity of the medium. In addition, the yields of the isomers were inverted as the concentration of sodium ethoxide in ethanol increased.

The Michael addition of 2,7-dibromo-(or chloro-) fluorene to **2** gave abnormal products such as 2,7,2″,7″-tetrabromo- (or chloro-) 9,9′:9′,9″-terfluorenyl by combinations of elimination and readdition steps via 2,7-dihalogeno-9,9′-bifluorenylidene.[12] Therefore, the process for the formation of A and B was investigated by using **1**-*2,7-d*$_2$ as a donor. The deuterium contents in A-*2,7-d*$_2$ and B-*2,7-d*$_2$ are of the same order. Accordingly, the isomers A and B are formed simultaneously through the different sequences, with no retro-Michael reaction occurring, as Scheme II shows.

A could be formed by cis addition involving the cis conformation of the 9-fluorenyl plane with respect to the fluorenylidene plane in **2**. There are two possible ways for the formation of B (s-cis,s-trans) by cis (or trans) addition which includes the s-trans (or s-cis) conformation of the 9-fluorenyl plane with regard to the fluorenylidene plane in **2**. Consideration of models indicates that the protonation

Scheme II

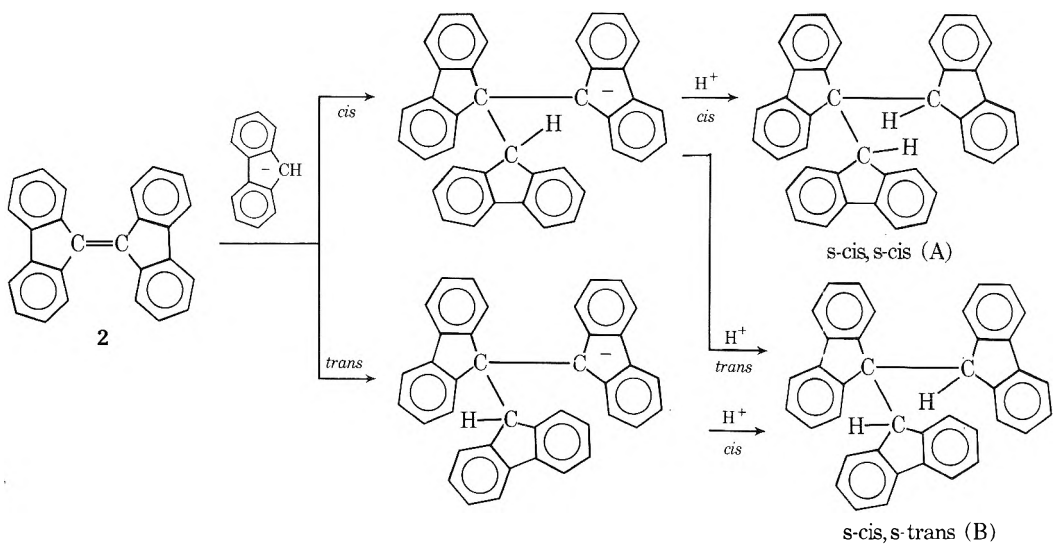


Table II
9,9′:9′,9″-Terfluorenyls by the Michael Addition of 1 to 2

Reaction conditions				9,9′:9′,9″-Terfluorenyl isomers		
				Yield of isomers,	Ratio of isomers, %	
Solvent	Base	Concn, %	Time, hr	%	A	B
EtOH	EtONa	0.1	200	78	86	14
EtOH	EtONa	1	55	81	68	32
EtOH	EtONa	5	30.5	62	59	41
EtOH	EtONa	10	9.5	87	11	89
EtOH	EtONa	15	11	84		100
EtOH	EtOK	0.5	150	50	89	11
EtOH	EtOK	10	5	87	83	17
MeOH	MeONa	1	160	43	74	26
MeOH	MeONa	10	53	72	100	
MeOH	MeOK	1	200	30	100	
MeOH	MeOK	10	51	80	100	
n-PrOH	*n*-PrONa	1	52	82	25	75
n-PrOH	*n*-PrONa	10	45	56		100
Pyridine	EtONa	1	15	74	56	44
Pyridine	KOH	5	3	80	100	

of the latter course is more hindered than those of the former resulting from the close proximity of the 9″-fluorenyl plane.

Experimental Section

All the melting points are uncorrected. The melting points of deuterio compounds in this series are identical with those of the parent hydrocarbons.

The VPC analyses were run with a JGC-1100FP gas chromatograph (Japan Electron Optics Laboratory Co., Ltd.), using a 1-m column containing 3% Silicone DC QF-1 on Chromosorb W AW (60–80 mesh). The content of each component was calculated from the peak areas as the average value of five chromatograms. Response factors used to correlate relative areas with percent yields of hexahydrofluorene and **1** were 0.84 and 1.00.

The ir spectra were obtained as KBr pellets (4000–400 cm^{-1}) or as suspensions in hexachlorobutadiene (3000–2800 cm^{-1}) using a IR-G spectrophotometer (Japan Spectroscopic Co., Ltd.).

The Raman spectra were recorded on a JRS-Ul spectrometer (Jeol) with an argon laser (5145.4 Å) and an interference filter. The experiments were run with a slit width of 160 μ and 23 A of laser output at a scanning speed of 10 Å/min.

The mass spectra were measured with a RMU-6E apparatus (Hitachi, Ltd.). The sample evaporating temperature was controlled at 160° (for monomeric fluorenes) or 200° (for dimeric and trimeric fluorenes). Calculation of incorporated deuterium into compounds was from the average value of five spectra.

The NMR spectra were obtained with a JNM-PS-100 (100 MHz) or a JNM-C60-HL (60 MHz) spectrometer (Jeol) in benzene-d_6 (for dimeric and trimeric fluorenes) or CCl_4 (for monomeric fluorenes), using TMS as internal reference. The deuterium incorporation was determined from the average value of seven peaks.

Treatment of 9,9′:9′,9″-Terfluorenyl Isomers with Raney Nickel. Typical Procedure. To a mixture of 1.5 g of A and 100 ml of dry toluene was added 10.0 g of Raney nickel (W-4), 0.3 g of triethylamine, and 10 ml of dry toluene, which was maintained at 60° for 3 hr while being stirred.

The reaction mixture was filtered and the filtrate was evaporated under reduced pressure; the residue was extracted with 100 ml of boiling ethanol, leaving a powder which was recrystallized from 200 ml of ethyl acetate to give B (1.08 g), mp 256–257° dec, recovered A (0.12 g, 8%), mp 291–293° dec, and **3** (0.06 g), mp 242–243°.

Upon standing, the alcohol extract gave 0.05 g (total 1.13 g, 75%) of B, mp 254–256° dec. The mother liquor was concentrated to dryness, and the residue was sublimed in vacuo at 130°. The sublimate was recrystallized from ethanol to yield **1** (0.09 g), mp 110–113°. **3** (0.02 g, total 0.08 g, 5%) was obtained by recrystallization of the residue. The alcohol mother liquor was submitted to VPC; **1** and 1,2,3.4,4a,9a-hexahydrofluorene were confirmed.

Treatment of Fluorene (1) with Raney Nickel. A mixture of 5.0 g of **1** and 3.0 g of triethylamine in 100 ml of dry toluene was refluxed with 25 g of Raney nickel for 5 hr. The reaction mixture was analyzed by VPC; 40% of 1,2,3,4,4a,9a-hexahydrofluorene and 60% of **1** were confirmed.

The toluene was removed in vacuo to leave a faintly colored oil which was distilled to give hexahydrofluorene as a colorless liquid: bp 128–130° (15 mm), 264° (757 mm) (the Siwoloboff method); $n^{20}D$ 1.5536; d_4^{20} 1.008; $(R_L)_D$ 54.72 (calcd, 54.61); ir (KBr sandwich) 679, 732, 748, 762, 1445, 1471, 2870, 2950, 3020, 3045, and 3070 cm^{-1}; mass spectrum *m/e* 172 (M^+), 166, 157, 143, 129, 115, 104, 91, 89, and 77; NMR δ 0.81–2.01 (m, 8 H), 2.11–3.31 (m, 4 H), and 7.03 ppm (s, 4 H).

Michael Reaction of 9,9′-Bifluorenylidene (2) with Fluorene (1). Typical Procedure. Sodium (1.7 g) was treated with 54 ml of absolute ethanol; then there was added 1.1 g ($\frac{1}{300}$ mol) of **2** and 0.6 g ($\frac{1.1}{300}$ mol) of **1**, the mixture was heated in a sealed tube at 95–98° for 9.5 hr.

After cooling, the precipitate was filtered off and recrystallized from benzene and/or ethyl acetate to give B (1.02 g), mp 256–257° dec. The filtrate was added to water, and the precipitate was separated and further purified by a combination of recrystallization, alumina column chromatography, and vacuum sublimation. Subsequently, 0.25 g (total 1.27 g, 77%) of B, mp 256–257° dec, 0.16 g (10%) of A, mp 291–293° dec, trace amounts of fluorenone, mp 80–82°, and **1**, mp 113–115°, were obtained.

In case ethanol was used as solvent, the crystals of B were contaminated by 1,4-bis(2,2′-biphenylylene)-1,3-butadiene.[13] The butadiene was removed easily as a complex with 2,4,7-trinitrofluorenone, mp 297–298.5° dec.

Anal. Calcd for $C_{28}H_{18} \cdot 2(C_{13}H_5O_7N_3)$: C, 65.86; H, 2.87; N, 8.53. Found: C, 65.79; H, 2.61; N, 8.42.

Beside 9,9′:9′,9″-terfluorenyl isomers, in some experiments, trace amounts of **3**, fluorenol, and fluorenone were separated. A minute amount of 9-methoxy-9,9′-bifluorenyl, mp 155–157°, was isolated instead of **3** in the presence of potassium methoxide.

Anal. Calcd for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 89.69; H, 5.46.

Synthesis and Reaction of A-*9,9″-d*$_2$. 1-*9,9-d*$_2$. The title compound was prepared according to the directions of Cram and Kollmeyer.[14] The extent of deuterium incorporation was 95% by NMR: mass spectrum *m/e* 167 (d_1, 12%) and 168 (d_2, 88%).

3-*9,9′-d*$_2$. **3** was deuterated in a similar manner to give the deuterio compound (98% yield). Deuterium incorporation was calculated as 100% by NMR; mass spectrum *m/e* 332 (d_2, 100%).

B-*9,9″-d*$_2$. A mixture of 1.64 g of **2** and 0.92 g of 1-*9,9-d*$_2$ in 30 ml of ethanol-*O-d* containing 3 g of sodium ethoxide was heated and gave 1.83 g (74%) of B-*9,9″-d*$_2$ and 0.14 g (6%) of A-*9,9″-d*$_2$. Deuterium content of B was accounted for as 100% on the 9 and 9″ positions (there were no peaks at 5.36 and 4.61 ppm) by NMR: mass spectrum *m/e* 494 (d_0, 0.1%), 495 (d_1, 13.9%), and 496 (d_2, 86%).

A-*9,9″-d*$_2$. **2** was treated with 1-*9,9-d*$_2$ in a mixture of sodium deuteroxide, deuterium oxide, and pyridine to give A-*9,9″-d*$_2$ (83% yield). A deuterium content of 89% at the 9 and 9″ positions (5.36 ppm) was determined by NMR: mass spectrum *m/e* 494 (d_0, 0%), 495 (d_1, 19%), and 496 (d_2, 81%).

Treatment of A-*9,9″-d*$_2$ with Raney Nickel. A-*9,9″-d*$_2$ (1.50 g) was allowed to react with Raney nickel and yielded 0.42 g (28%) of B-*9-d* and 0.80 g (53%) of A-*9,9″-d*$_2$. A 90% deuterium content at the 9 and 9″ positions (5.36 ppm) of recovered A was observed by NMR: mass spectrum *m/e* 494 (d_0, 1%), 495 (d_1, 16%), and 496 (d_2, 83%). The content of unexchanged deuterium at the 9 (ca. 94%, 5.36 ppm) and 9″ positions (ca. 25%, 4.61 ppm) of B was estimated by NMR: mass spectrum *m/e* 494 (d_0, 20%), 495 (d_1, 59%), and 496 (d_2, 21%).

Michael Reaction of 2 with 1-*2,7-d*$_2$. 1-*2,7-d*$_2$. A mixture of 12.54 g of 2,7-diiodofluorene and 9.7 g of lithium aluminum deuteride in 150 ml of dry tetrahydrofuran was refluxed for 9 hr.[15] The reaction mixture was decomposed with 9 ml of deuterium oxide in 20 ml of dry tetrahydrofuran and concentrated to dryness. The residue was sublimed in vacuo at 90° to afford 2.5 g (50%) of **1** (from *n*-hexane).

A mixture of 2.5 g of foregoing **1**, 2 g of sodium methoxide, 20 ml of water, and 80 ml of 1,2-dimethoxyethane was refluxed for 15 hr. Work-up of the resulting mixture gave 1-*2,7-d*$_2$ (2.22 g): mass spectrum *m/e* 166 (d_0, 33%), 167 (d_1, 44%), 168 (d_2, 22%), and 169 (d_3, 2%).

Michael Reaction of 2 with 1-*2,7-d*$_2$. Foregoing 1-*2,7-d*$_2$ (0.37 g) was allowed to react with **2** (0.66 g) to give B (0.54 g) and A (0.02

g). A: mass spectrum *m/e* 494 (d_0, 20%), 495 (d_1, 39%), 496 (d_2, 33%), and 497 (d_3, 9%). B: mass spectrum *m/e* 494 (d_0, 19%), 495 (d_1, 40%), 496 (d_2, 32%), and 497 (d_3, 9%).

Michael Reaction of 2 with 1-*l*-*d*. 1-Iodofluorene. A 0.9-g portion of 1-aminofluorene[16] was diazotized in the usual way and the diazonium sulfate was decomposed in the presence of potassium iodide to yield 1-iodofluorene (0.39 g, 27%), mp 40–42°, mass spectrum *m/e* 292 (M^+) and 165.

Anal. Calcd for $C_{13}H_9I$: C, 53.45; H, 3.11. Found: C, 53.66; H, 2.94.

The title compound was oxidized with sodium bichromate in acetic acid to afford 1-iodofluorenone, mp 143.5–145° (lit.[17] mp 144–145°).

1-*l*-*d*. 1-*l*-*d* was obtained from 1-iodofluorene in an analogous manner from that of 1-2,7-d_2: mass spectrum *m/e* 166 (d_0, 26%), 167 (d_1, 63%), and 168 (d_2, 11%).

Michael Reaction of 2 with 1-*l*-*d*. A mixture of 2 and 1-*l*-*d* was treated as usual and afforded A-*l*-*d* (12% yield) and B-*l*-*d* (63% yield). A-*l*-*d*: mass spectrum *m/e* 494 (d_0, 35%), 495 (d_1, 57%), and 496 (d_2, 8%). B-*l*-*d*: mass spectrum *m/e* 494 (d_0, 36%), 495 (d_1, 60%), and 496 (d_2, 4%).

Acknowledgments. The authors wish to express their thanks to Mr. K. Matsushita, Mr. M. Kunugi, and Mrs. K. Shinozaki, Japan Electron Optics Laboratory Co., Ltd., for their NMR measurements, and to Mr. H. Shino, Jeol, for his help in carrying out the Raman spectra. They also are grateful to Dr. Elizabeth K. Weisburger of the National Institutes of Health for editorial assistance.

Registry No.—1, 86-73-7; 2, 746-47-4; 3, 1530-12-7; A, 42759-04-6; B, 42759-03-5; hexahydrofluorene, 1559-97-3; 1,4-bis(2,2′-biphenylylene)-1,3-butadiene complex with 2,4,7-trinitrofluorenone, 54366-31-3; 9-methoxy-9,9′-bifluorenyl, 54366-32-4; 1-iodofluorene, 54366-33-5.

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Conformations of Vicinal Diesters

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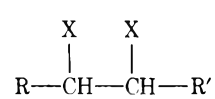
In diesters derived from 4-methyl-2,3-pentanediol, 1-phenyl-1,2-propanediol, and 3-methyl-1-phenyl-1,2-butanediol, the preference for gauche oxygen functions with respect to the ethanic backbone is nearly as large as for the diols themselves. Two reasons for the preference for gauche diester groups are possible: (a) dipolar attraction and (b) an intrinsic attraction related to electronegativity, but presently not well defined. Solvent effects and the effects of steric hindrance on conformation were studied, as well as ^{13}C chemical shifts and ^{13}C–H coupling constants. For erythro diesters, the data seem best interpreted in terms of an intrinsic attraction.

In their classic work on the application of NMR to problems in conformational analysis, Bothner-By and Naar-Colin observed rather unusual conformations for *meso*-2,3-diacetoxybutane (gauche ester functions).[1] Electrostatic attraction between the dipoles of the ester groups was considered to be a possible reason for this conformational preference. Later Schmid also reported unusual conformations for phenyl-substituted diesters.[2] However, substituted succinates show no well-defined preference for gauche carbonyl functions.[3,4]

Recent work by Abraham and Kemp showed that vicinal fluorine groups X preferred a gauche orientation despite sizable dipolar repulsion.[5] Phillips and Wray have correlated the tendency for X groups to occupy a gauche conformation with the total electronegativity of these groups.[6] However, Eliel and Kaloustian attributed the tendency for vicinal ether functions to be gauche to an attractive van der Waals interaction.[7] It is possible that electronegative X groups shrink the "size" of their respective lone pairs[8] so that the repulsions of the lone pairs is superseded by electron–nuclear attractions.[6,9] However, others have warned against too facile arguments involving the size of lone pairs.[8]

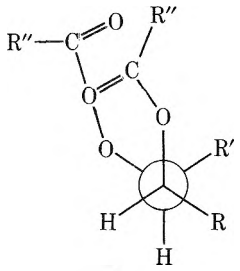


In a theoretical discussion of the reason for gauche X groups in 1,2-difluoroethane, Pople et al. considered the interaction of the two X groups to be repulsive, but this effect was counteracted by a hyperconjugative effect such that the electron withdrawal by an electronegative group X "partially empties the 2p orbital on carbon and facilitates the hyperconjugative electron delocalization by the neighboring CH_2 group".[10] On the other hand, Epiotis considers the interaction of two X groups to be attractive due to interaction of nonbonding pairs on the X groups forming antibonding and bonding combinations. The destabilizing ef-

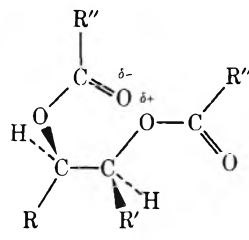
fect of the antibonding combination is ameliorated because of charge transfer from this antibonding orbital into the unfilled antibonding orbital on the ethanic skeleton.[11] This treatment did not explain why other dihalides do not necessarily prefer a gauche conformation.[12] In theoretical calculations of the conformation of certain fluorine compounds, Abraham and coworkers suggested that no special explanations were necessary to account for the conformation.[13]

The chlorine groups of 2,2′-dichlorobiphenyls lie very close to one another in space, possibly indicative of an attractive interaction.[14] However, Zefirov and coworkers have suggested that interaction between second-row elements (e.g., sulfur–sulfur interactions) are more highly repulsive than interactions between first-row elements.[15,16]

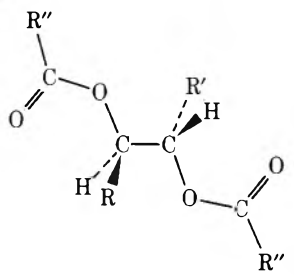
Thus, in the molecules of interest in this study, vicinal diesters **1a–c**, two explanations might be applied to explain the preference of the ester functions for a gauche conformation: (1) dipolar attraction or (2) an intrinsic preference related to the electronegativity of the groups, whose nature is not completely elucidated as yet. The alkyl oxygens of the ester groups are rendered more electronegative than oxygens of analogous diols or diethers by resonance with the carbonyl, which places a partial positive charge on the alkyl oxygens. Molecular models suggest that conformation **1a**, which has maximum dipolar attraction, suffers from steric interactions between the R″ groups, if R″ is large. This steric interaction is alleviated in **1b**, but the dipolar attraction is not as large. Models suggest that **1c** would be the preferred conformation if only steric effects were important.



1a



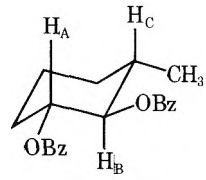
1b



1c

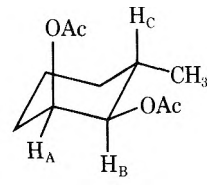
The purpose of this work is to attempt to distinguish between the two possible reasons for the presumed attraction between ester functions, and to establish the scope of the phenomenon. Solvent effects and the effect of size of R″, R′, and R will be discussed.

To attempt to establish the limiting NMR coupling constants for purely trans and purely gauche hydrogens, compounds **2–4** were investigated.[17] In **2**, near-conformational purity should be present; the coupling constant for the trans hydrogens A and B was ca. 10 Hz. This value seems rather small[18] perhaps owing to special factors present in the cyclohexane ring in this particular molecule (e.g., flattening to alleviate the sequential gauche interactions of the three equatorial groups),[1d] but this value will be taken as a rough approximation of the true value. In **3**, the relevant hydrogens are axial–equatorial in either of the major conformers; the averaged coupling contant for these gauche hydrogens is ca. 3 Hz.



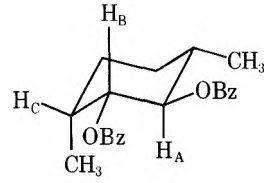
2

J_{AB} = 9.7 Hz
$J_{BC} \cong$ 9.8 Hz



3

J_{AB} = 2.9 Hz
J_{BC} = 10.2 Hz

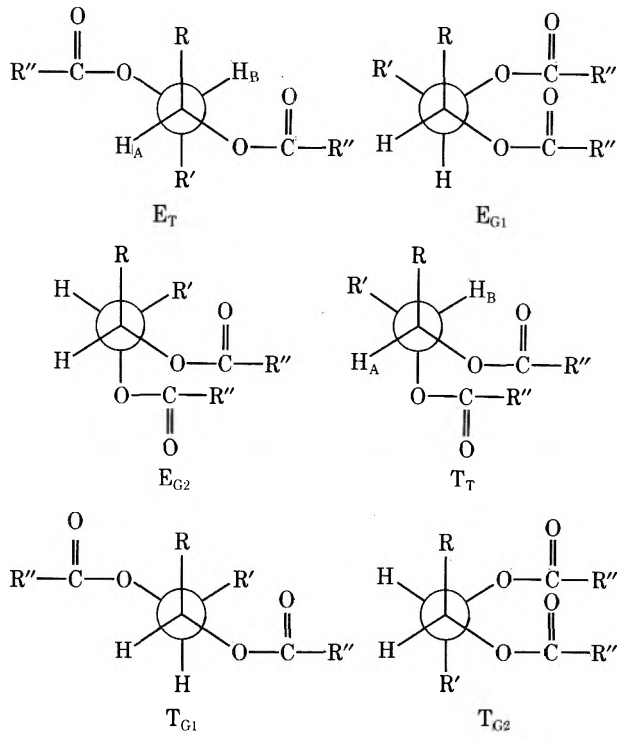


4

J_{AB} = 9.9 Hz
J_{BC} = 4.2 Hz

The NMR data for the acyclic compounds of interest are shown in Table I, in which older data on analogous diols are also included for comparison purposes.[19] These data may be interpreted in terms of the conformers shown in Scheme I (in which E_T signifies the conformer in the erythro set of isomers having trans hydrogens, etc.).

Scheme I



The conformation of the diesters (in CCl_4) is *roughly* similar to that of the diols, but the solvent effect is quite different. Intramolecular hydrogen bonding, of course, stabilizes the gauche hydroxyl groups of the diol. A sizable attractive interaction (but of somewhat smaller magnitude) must stabilize the gauche acetoxy functions (compare **5a** and **5b**, **6a** and **6b**).

The size of the ester function (specifically, R″) does not appear to have a large effect upon the conformation of the ethanic backbone.

Table I
100-MHz NMR Spectra of Vicinal Diesters

$$R-\underset{X}{CH_A}-\underset{X}{CH_B}-R'$$

Compd	R	R′	X	J_{AB} (J_{BC}^*), Hz[a] CCl_4	HOAc	CH_3CN	DMSO
Erythro 5a	CH_3	*i*-Pr	OH	3.3			6.0
5b			OAc	4.6 (7.2)		4.3 (7.5)	4.1 (7.4)
5c			OCOPh	5.5 (6.3)	4.3 (7.4)	4.0 (7.7)	4.0 (7.6)
Erythro 6a	CH_3	Ph	OH	4.0			5.3
6b			OAc	4.2	4.4	4.3	4.1
6c			OCOPh	4.1	4.2	4.3	4.3
6d			OCO-*i*-Pr	4.5			4.3
Erythro 7a	*i*-Pr	Ph	OH	5.8			7.5
7b			OAc	7.2			5.5
Threo 8a	CH_3	*i*-Pr	OH	5.9			5.3
8b			OAc	4.3 (7.2)	4.7 (7.0)	5.0 (6.7)	5.0 (6.6)
8d			OCO-*i*-Pr	4.8 (6.4)			~5.6
Threo 9a	CH_3	Ph	OH	7.5			6.4
9b			OAc	7.4	6.9	6.2	6.0
9c			OCOPh	7.7	7.5	6.5	6.6
9d			OCO-*i*-Pr	7.5		6.1	6.2
Threo 10a	*i*-Pr	Ph	OH	6.4			6.2
10b			OAc	6.0			5.8

[a] Where R′ is isopropyl, J_{BC} refers to the coupling constants of the $CH(OCOR'')CH(CH_3)_2$ fragment.

For the erythro isomers, the effect of increasing the size of R and/or R′ is to increase the population of conformer E_T (Scheme I). Conformer E_T minimizes the repulsive interaction of R and R′, but the mutual attraction of the ester functions is also eliminated. In the compounds studied, E_T is dominant only in the case of **7b**, where R = *i*-Pr and R′ = Ph, and then E_T is only slightly favored. Thus, it appears that a very large repulsion between R and R′ is necessary to overcome the attractive interaction of the ester groups.

For the threo isomers, no strong conformational preference is evident in any compound of this study. Conformer T_T is dominant by a small amount for **9**, but T_{G1} and/or T_{G2} are preferred for **8** and **10**.

The inability to distinguish between two conformers such as T_{G1} and T_{G2} has been one of the major problems in acyclic conformational analysis. This distinction can be made, in theory, with the aid of ^{13}C–H vicinal coupling constants.[3b,20,21] This technique has not been used frequently, but it is of great potential usefulness. Lemieux and coworkers have demonstrated that a Karplus type of dependence exists between dihedral angle and the ^{13}C–H coupling constant ($^3J_{CH}$). Limiting values of ca. 8 Hz were found for trans nuclei, and ca. 1 Hz for gauche nuclei in the compounds tested (certain carbohydrates).

In spectra of these natural abundance ^{13}C compounds, well-resolved splitting patterns could be obtained only for isolated methyl groups (Figure 1), or, in certain cases, for carbonyl groups. For **8b** and **8d**, the coupling constant between $^{13}CH_3$ and H_B was found to be 1.6 Hz (with a confidence level of ±0.4 Hz). For **9b** and **9d**, $^3J_{CH}$ was ca. 2 and 2.1 Hz, respectively.

For **8**, the fairly small J_{AB} values indicate a preference for a conformer having gauche hydrogens A and B. The $^3J_{CH}$ values suggest that methyl and H_B are predominantly gauche. Only conformer T_{G2} is consistent with both sets of data. For **9**, the "averaged" J_{AB} suggests that a mixture of conformers is present, whereas the $^3J_{CH}$ value suggests again a preference for conformers with gauche CH_3 and H_B groups. A mixture of T_T and T_{G2} accounts for these data. It seems reasonable that T_{G1} should not be highly populated in **8** and **9**, since R′ (phenyl or isopropyl) would be highly hindered and the ester functions would be trans.

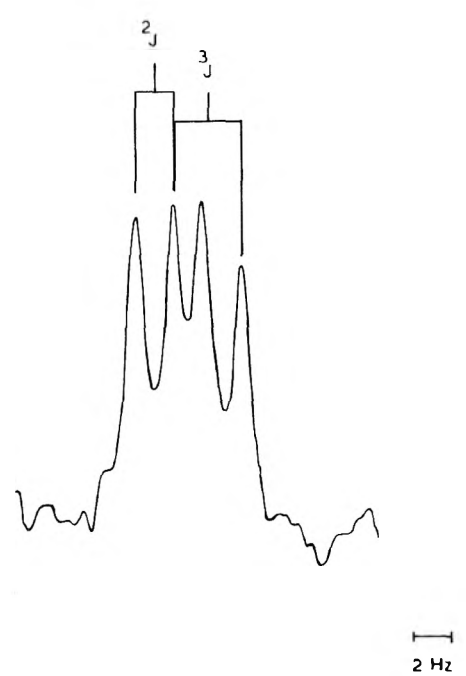


Figure 1. ^{13}C spectrum (100 Hz sweep width) of one of the center members of the quartet (^1J = 128 Hz) of the methyl group in **5c** (R = CH_3; R′ = *i*-Pr).

For the erythro compounds **5c**, **6b**, and **6d**, $^3J_{CH}$ was 3.8, 3.2, and 3.0 Hz, respectively. These values indicate that the conformer having trans $^{13}CH_3$ and H_B groups (E_{G1}) is more highly populated than its counterpart in the threo series.[22] In the alternative gauche H_A–H_B conformer, E_{G2}, phenyl or isopropyl is again highly hindered. However, $^3J_{CH}$ values have been determined in relatively few types of molecules

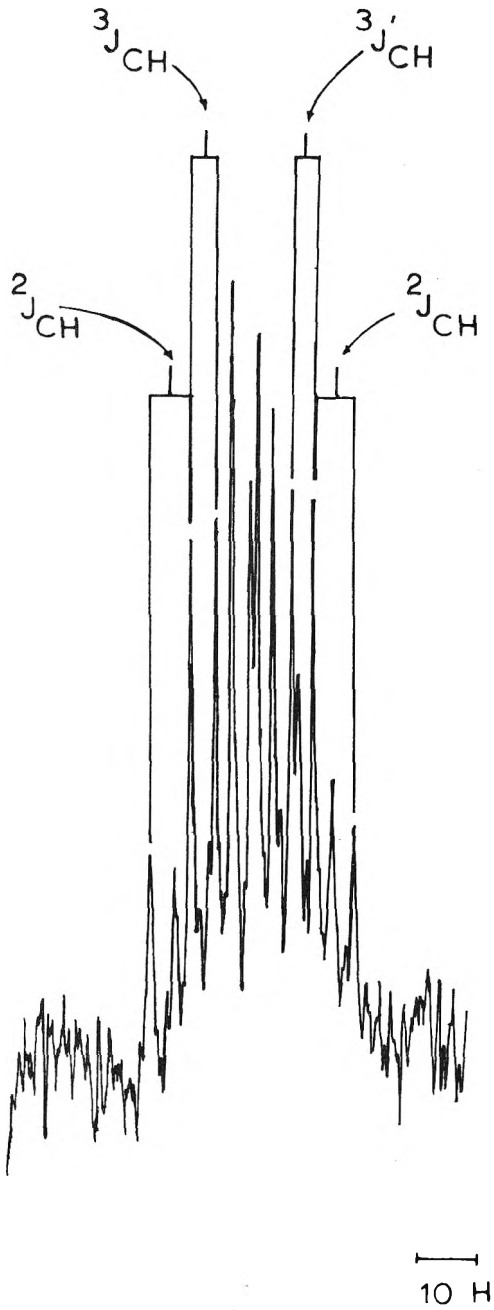


Figure 2. ^{13}C spectrum (500 Hz sweep width) of the carbonyl region for compound **8b** (R = CH_3; R' = *i*-Pr). The pattern represents partially superposed double quartets, one for each OAc group. Each quartet is formed by coupling of the carbonyl carbon to the methyl group of the acetate ($^2J_{CH}$). Each doublet in the double quartet represents the coupling of carbonyl to H_A or H_B.

of known geometry, and the implication of $^3J_{CH}$ values must be regarded as rather tentative pending additional verification.

It was possible to determine well-resolved splitting patterns for the carbonyl carbons in two cases (Figure 2). For **8b**, $^3J_{CO-H}$ values of 3.6 and 4.2 Hz were observed for the two ester groups. Compound **6c** yielded similar coupling constants. The "averaged" value of $^3J_{CO-H}$, as observed in a methyl ester, has been reported as 4.5 Hz.[23] These data suggest that considerable rotational averaging is present for one ester group in **8b**.

As Table I shows, the effect of solvent upon conformation is rather complex. For **5** and **7**, a change from CCl_4 to a more polar solvent results in a *decrease* in J_{AB}, indicating that E_T diminishes and that E_{G1} and/or E_{G2} become more important. The increase in population of these conformers which have gauche X groups is similar to findings for dihalides[21] and dinitriles,[24,25] where repulsive, not attractive, interaction of the dipoles of the X groups is present. It seems likely that an attractive dipolar interaction between the ester groups (as in **1a**) would have been diminished by the interaction of the ester and solvent dipoles, leading to a lower preference for the E_G conformers.

The threo compounds populate a more "averaged" set of conformations on moving to the more polar solvents, which is not easily correlated with any simple solvent effect. For **8b**, no change is $^3J_{CH}$ was found (1.5 Hz) on moving from CCl_4 to DMSO.[7d,26] This suggests that the change in J_{AB} reflects a conversion from T_{G2} to T_T (both have gauche CH_3 and H_B groups).[27]

Carbonyl resonances have been shown to be sensitive to the changes in electron density associated with solvation.[28,29] It seemed likely that strong dipolar interactions, such as occur in **1a**, the face-to-face conformation, would also result in chemical shift changes. However, erythro and threo isomers having the same carbon skeleton show similar chemical shifts (Table II). Erythro **6b** and **7b**, which also occupy rather different sets of conformers, have similar carbonyl shifts. In **4**, the ester groups are confined near one another, but the carbonyl shifts are rather similar to those of **2** and **5c**. Thus, either the face-to-face conformation is not important, or, if it is, no large effect on ^{13}C chemical shifts results.[30] The change from an acetate (**8b**) to an isobutyrate (**8d**) results in a large chemical shift change for carbonyl, but no large effect upon the ^{13}C resonances of the hydrocarbon backbone is evident. This suggests that no large steric interaction between R'' and the carbon backbone is present.

In summary, for the erythro isomers the lack of an effect of R'' size, the solvent effect, and the rotational averaging of carbonyl are not consistent with a conformational preference dominated by dipolar attraction (as in **1a**), although forms such as **1b** are not necessarily excluded. One alternative proposal, that hyperconjugation leads to a preference for gauche X groups, is not supported by the sizable importance of T_T compared to T_{G2} (threo isomers). Hydrogens A and B are not properly situated for hyperconjugation in T_T as they are in T_{G2}.

Experimental Section

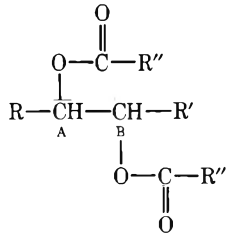
The general synthetic procedures involved the esterification of diols available from other studies,[19a] the use of the "dry" Prevost reaction, or the use of the "wet" Prevost reaction followed by esterification of the mixed half-esters.[31,32] Melting points are uncorrected.

***erythro*-4-Methyl-2,3-pentanediol Diacetate (5b). Procedure A.** Using the literature "wet" procedure,[32] a solution of 22.7 g (0.0875 mol) of iodine, 29.2 g (0.0175 mol) of silver acetate, and 7.0 g (0.0833 mol) of *cis*-4-methyl-2-pentene in 50 ml of acetic acid was converted to 9.7 g of the mixed half-esters (an oil).

Procedure B. According to literature procedures[32] the above half-esters were fully esterified: 0.58 g (3.6 mmol) of starting material was treated with 4 ml of acetic anhydride plus 0.2 g of sodium acetate, with a 20-hr reflux period. The crude product was distilled, bp 82–86° (7 mm) [lit.[33] bp 65–68° (2.5 mm)], giving 0.24 g (39%) of product: NMR (CCl_4) δ 0.88 [d, 3 $(CH_3)_2CH$], 0.95 [d, 3, $(CH_3)_2CH$], 1.1 [m, 1, $(CH_3)_2CH$], 1.90 (s, 3, OAc), 2.02 (s, 3, OAc), 4.7 [dd, 1, CHOAc), and 5.3 (dq, 1, CHOAc); ir (CCl_4) 2950, 2930, 1735, 1380, 1049, and 1025 cm^{-1}. The NMR spectrum also showed minor impurities that were not removed with repeated distillation.

***erythro*-4-Methyl-2,3-pentanediol Dibenzoate (5c). Procedure C.** Using the literature procedure for the "dry" Prevost,[32] a mixture of 5.09 g (0.22 mol) of silver benzoate [dried for 15 hr at 42° (ca. 1 mm)] and 2.82 g (0.011 mol) of *trans*-4-methyl-2-pentene in ca. 100 ml of dry benzene (distilled from calcium hydride) was refluxed for 20 hr under nitrogen with mechanical stirring. The literature work-up was used except that the product was not distilled owing to discoloration of the product. Chromatography on silica gel (Baker) using increasing amounts of ether in pentane as

Table II
^{13}C Chemical Shifts



Compd	R	R′	R″	^{13}C chemical shift, ppm[b] C=O	R″	C_A	C_B	CH_3	$(CH_3)_2CH$	
5c	CH_3	*i*-Pr	Ph	165.8		70.3	78.9	15.0	19.2	29.3
				165.5					18.0	
6b	CH_3	Ph	CH_3	169.9	21.0	71.6	75.6	14.6		
				169.5	21.0					
7b	*i*-Pr	Ph	CH_3	170.2	21.0	78.5	75.2		19.5	28.3
				169.6	20.8				16.6	
8b	CH_3	*i*-Pr	CH_3	170.5	21.4	69.4	79.0	16.6	19.0	28.7
				170.1	21.3					
8d	CH_3	*i*-Pr	*i*-Pr	176.2	*a*	69.2	78.3	16.6	19.1	28.7
				176.0	*a*				17.1	
9b	CH_3	Ph	CH_3	170.0	21.0	71.4	76.3	16.5		
				169.6	20.8					
10b	*i*-Pr	Ph	CH_3	170.0	21.1	77.7	74.3		19.5	28.7
				169.5	20.6				17.2	
2	Cyclic		Ph	166.2		75.3	78.8	17.9		
				165.8						
4	Cyclic		Ph	166.2		76.9	75.0	18.0		
				165.6				12.8		

[a] Complex nonequivalent methyl signals present. [b] Vs. Me_4Si as 0 ppm.

eluents followed by rotary evaporation gave product that appeared pure by all spectral methods and so distillation was not attempted [lit.[34] bp 153° (0.1 mm)]: yield 2.06 g (63%); NMR (CCl_4) δ 0.99 [d, 3, $(CH_3)_2CH$], 1.09 [d, 3, $(CH_3)_2CH$], 1.39 (d, 3, CH_3), 2.0 [m, 1, $(CH_3)_2CH$], 5.36 (m, 2, CH(OBz), and 7.05–8.15 (m, 10, Ar); ir (CCl_4) 3023, 3006, 2915, 1730, 1595, 1480, 1350, 1310, 1145, and 1050 cm^{-1}.

***erythro*-1-Phenyl-1,2-propanediol Diacetate (6b).** The ester was prepared by procedure B from 0.50 g (3.3 mol) of 1-phenyl-1,2-propanediol, 0.2 g of sodium acetate, and 4 ml of acetic anhydride. The crude diester was chromatographed on 185 g of silica gel using ether–pentane mixtures. The product appeared pure, and distillation was not attempted [lit.[35] bp 109° (0.4 mm)]: NMR (CCl_4) δ 1.14 (d, 3, CH_3), 1.89 (s, 3, OAc), 2.03 (s, 3, OAc), 5.13 (dq, 1, CHOAc), 5.91 (d, 1, CHPh), and 7.3 (s, 5, Ph).

***erythro*-1-Phenyl-1,2-propanediol Dibenzoate (6c).** This material was prepared by procedure C in 38% yield. Several recrystallizations from methanol gave 4.6 g (38%) of product: mp 95–96° (lit.[36] mp 96–97°); NMR (CCl_4) δ 1.38 (d, 3, CH_3), 5.57 (dq, 1, $CHCH_3$), 6.29 (d, 1, CHPh), 7.27 (s, 5, Ph), and 7.1–8.2 (m, 5, Ar); ir (CCl_4) 3110, 3085, 3050, 3007, 1760, 1748, 1604, 1453, 1160, 1120, 1100, 1075, 1060, and 760 cm^{-1}.

***erythro*-1-Phenyl-1,2-propanediol Diisobutyrate (6d). Procedure D.** A mixture of 0.52 g (0.034 mol) of the parent diol, 2 ml of isobutyryl chloride, and 10 ml of pyridine was refluxed for 24 hr. The remaining solids were washed with ethyl acetate, and the combined organic filtrates were extracted with two 15-ml portions of 10% HCl and with dilute sodium bicarbonate solution and dried ($MgSO_4$). Rotary evaporation of the solvent gave an oil which was chromatographed on ca. 150 g of silica gel using ether–hexane eluents. Certain intermediate fractions showed high purity, and distillation again was not attempted. The pure fractions weighed 0.68 g (68% yield): NMR (CCl_4) δ 0.98–1.28 (complex methyl doublets), 2.48 [m, 2, $(CH_3)_2$ CH], 5.26 (dq, 1, $CHCH_3$), 5.71 (d, 1, CHPh), and 7.29 (s, 5, Ph); mass spectrum (20 eV) *m/e* (rel intensity) 248 (54), 204 (94), 178 (16), 177 (100), 176 (7), 134 (21), 117 (8), and 71 (6); *m/e* 248 represents M^+ − isobutyric acid.

***erythro*-1-Phenyl-3-methyl-1,2-butanediol Diacetate (7b).** This material was prepared by a slight variant of procedure D in 56% yield: NMR δ 0.91 [broad d, 6, $(CH_3)_2CH$], 1.96 (s, 3, OAc), 2.00 (s, 3, OAc), 5.11 (dd, 1, CHOAc), 5.82 (d, 1, CHOAc), and 7.32 (s, 5, Ph); mass spectrum (20 eV) *m/e* (rel intensity) 212 (1), 205 (5), 204 (26), 192 (9), 162 (8), 150 (12), 149 (100), 115 (10), 107 (56), and 42 (35); *m/e* 149 and 115 represent PhCH(OAc) and *i*-C_3H_7CHOAc, respectively.

***threo*-4-Methyl-2,3-pentanediol Diacetate (8b).** This material was prepared by procedures A (35% yield) and B (39% yield), bp 89–92° (8 mm) [lit.[33] bp 81–82° (25 mm)]. Later work showed that chromatography on silica gel and film drying (no distillation) was preferable: NMR (CCl_4) δ 0.82 [d, 3, $(CH_3)CH$], 0.93 [d, 3, $(CH_3)_2CH$], 1.10 (d, 3, CH_3CHOAc), 1.0–1.4 [m, 1, $(CH_3)_2CH$], 1.95 (s, 3, OAc), 2.03 (s, 3, OAc), 4.65 (dd, 1, CHOAc), and 5.02 (dq, 1, CHOAc).

***threo*-4-Methyl-2,3-pentanediol Dibenzoate (8c).** This material was prepared by procedure D (17% yield). The oil was chromatographed on 200 g of silica gel with pentane–ether eluents, yielding 0.237 g (17%) of pure product [lit.[34] bp 143° (0.06 mm)]: NMR (CCl_4) δ 0.96 [d, 6, $(CH_3)_2CH$], 1.28 (d, 3, CH_3), 2.06 [m, 1, $(CH_3)_2CH$], 5.1 (dd, 1, CHOBz), 5.4 (dq, 1, $CHCH_3$), and 7.2–8.2 (m, 10, Bz).

***threo*-4-Methyl-2,3-pentanediol Diisobutyrate (8d).** This product was prepared by procedure D (56% yield). The resulting oil was purified by chromatography on silica gel: NMR (CCl_4) δ 0.9–2.0 (complex methyl doublets), 4.75 [dd, 1, $CHCH(CH_3)_2$], and 5.05 (dq, 1, CH_3CH); mass spectrum (70 eV) *m/e* (rel intensity) 215 (9), 171 (21), 143 (100), 142 (95), 115 (52), 100 (26), 83 (50), 72 (36), 71 (68), and 43 (86). The *m/e* 143 and 115 peaks represent cleavage of the ion at the bond joining the isobutyroxy groups.

***threo*-1-Phenyl-1,2-propanediol Diacetate (9b).** This material was prepared by procedure A (85% yield) and B (62% yield): bp 106–112° (1 mm) [lit.[35] bp 112–116° (0.7–0.9 mm)]; NMR (CCl_4) δ 1.04 (d, 3, CH_3), 1.94 (s, 3, OAc), 2.01 (s, 3, OAc), 5.20 (dq, 1, $CHCH_3$), 5.71 (d, 1, CHPh), and 7.30 (s, 5, Ph); ir (CCl_4) 3010, 1734, 1370, 1225, and 709 cm^{-1}.

***threo*-1-Phenyl-1,2-propanediol Dibenzoate (9c).** This material was prepared by procedure C (76% yield): mp 95–96° (lit.[36] mp

96–97°); NMR (CCl_4) δ 1.38 (d, 3, CH_3), 5.57 (dq, 1, $CHCH_3$), 6.29 (d, 1, CHPh), 7.27 (s, 5, Ph), and 7.1–8.2 (m, 10, Ar).

***threo*-1-Phenyl-1,2-propanediol Diisobutyrate (9d).** The parent diol (0.52 g, 2.4 mmol) was converted to the diester by procedure D, yielding 0.73 (73%) of product: NMR (CCl_4) δ 1.0–1.3 (complex series of methyl doublets), 2.5 [m, 2, $(CH_3)_2CH$], 5.25 (m, 1, $CHCH_3$), 5.71 (d, 1, CHPh), 7.31 (s, 5, Ph); mass spectrum (70 eV) *m/e* (rel intensity) 248 (7), 204 (12), 177 (46), 135 (12), 71 (100), 43 (20); *m/e* 248 represents M^+ − isobutyric acid; *m/e* 177 represents $PhCHOC(=O)C_3H_7$.

***threo*-1-Phenyl-3-methyl-1,2-butanediol Diacetate (10b).** Using procedure A, 2.0 g (0.014 mol) of *trans*-1-phenyl-3-methyl-1-butene was converted to 2.0 g (66%) of the mixed half-esters. Using procedure B, 1.0 g (4.5 mol) of the half-esters were acetylated; chromatography of the product on silica gel afforded considerable quantities of a material having only one acetoxy NMR peak, which blended with the desired product. Only 0.3 g (25%) of the desired diester could be isolated: NMR (CCl_4) δ 0.89 [d, 3, $(CH_3)_2CH$], 0.99 [d, 3, $(CH_3)_2CH$], 1.83 (s, 3, OAc), 2.00 (s, 3, OAc), 5.07 (dd, 1, CHOAc), 583, (d, 1, CHPh), and 7.27 (s, 5, Ph); mass spectrum (20 eV) *m/e* (rel intensity) 204 (30), 149 (100), 115 (10), 107 (63), 68 (21), 63 (19), and 43 (45).

3-Methyl-1,2-cyclohexanediol Dibenzoate (2). Using procedure D, the crude parent diol (mixture of isomers (0.3 g, 2.3 mmol) was esterified (20% yield of the desired isomeric product) and purified by chromatography on silica gel: NMR ($CDCl_3$, 100 MHz) δ 0.88 (d, 3, CH_3), 1.1–1.8 (broad m, 6, ring hydrogens), 2.16 (broad m, 1, ring hydrogen), 2.16 (broad m, 2, ring hydrogen), 5.01 (broad m, 2, CHOBz), 7.1–8.1 (m, 10, Ar); mass spectrum (20 eV) *m/e* (rel intensity) 321 (9), 230 (26), 227 (2), 226 (36), 131 (4), 109 (11), 108 (42), 106 (9), 105 (100), and 93 (11).

3-Methyl-1,2-cyclohexanediol Diacetate (3). Using procedure A, 10.0 g (0.10 mol) of 3-methylcyclohexene, 27.7 g (0.11 mol) of iodine, and 26.5 g (0.22 mol) of silver acetate were converted to 21.5 g of the mixed half-esters. Using procedure B, 20.5 g of the mixed half-esters was acetylated, giving 13.9 g of crude diester **3**. Distillation at 9 mm gave the following fractions: boiling at 109–113°, 3.3 g, and 113–119°, 3.93 g. Both fractions were somewhat impure, showing an additional acetoxy peak in the NMR. Chromatography of a portion of the second fraction on silica gel gave essentially pure **3**, which, however, was slightly contaminated with another isomer of the same general structure: NMR ($CDCl_3$, 100 MHz) δ 0.86 (d, 3, CH_3), 1.4–2.3 (broad m's, ring hydrogens), 1.94 (s, 3, OAc), 2.01 (s, 3, OAc), 4.47 (dd, 1, J = 2.9, 10.3 Hz, CHOAc), and 5.19 (m, 1, CHOAc); mass spectrum (20 eV) *m/e* (rel intensity) 155 (6), 154 (6), 113 (21), 112 (100), 111 (42), 97 (46), 95 (85), 94 (99), 79 (80), and 43 (72); *m/e* 155 represents M^+ − acetic acid.

3,6-Dimethyl-1,2-cyclohexanediol Dibenzoate (4). Using procedure C, 1.96 g (0.0169 mol) of 3,6-dimethylcyclohexene, 4.31 g (0.0169 mol) of iodine, and 7.96 g (0.0339 mol) of silver benzoate were allowed to react, and the crude product was chromatographed on silica gel. The early fractions contained considerable quantities of a material lacking one benzoate. A material isomeric with **4** was obtained in fraction 5, but it could not be adequately purified. The desired product was obtained in fractions 8–12 totaling 0.52 g (9%): NMR ($CDCl_3$, 100 MHz) δ 0.90 (d, 3, CH_3), 0.96 (d, 3, CH_3), 1.31–1.87 (m, 5, ring hydrogens), 2.3–2.6 (m, 1, ring hydrogen), 5.13 (dd, 1, CHOBz), 5.25 (apparent t, 1, CHOBz), 7.06–7.42 (m, 6, *m*-, *p*-Bz), 7.77–8.05 (m, 4, *o*-Bz); mass spectrum (20 eV) *m/e* (rel intensity) 216 (1), 123 (33), 122 (100), 106 (12), 105 (87), 77 (28), and 43 (3). Peaks *m/e* 122 and 105 represent C_6H_5COOH and $C_6H_5CO^+$, respectively.

NMR Spectra. These spectra were taken on a Varian XL-100 instrument or, in a few cases, on a Varian A-60D. For **5–10** the spectra were (CCl_4 solution) simulated using the LAOCOON III program adapted to provide a computer-generated plot of the input parameters. The parameters were adjusted until the computer plot was superimposible upon the spectrometer plot. Coupling constants were determined from the average of several traces of expanded spectra. The concentration of the solutions for the proton spectra of **5–10** was 2.5%, except for **7b**, **9b**, and **10b** in DMSO (5%).

The spectra listed in Table I were taken at 100 MHz, whereas the spectra listed in the Experimental Section were taken at 60 MHz, except as noted, at rather variable concentrations. The solvent for **2–4** was $CDCl_3$ (ca. 10% w/v). The spectra for **2–4** were not simulated; however, the coupling constants quoted for **3** were essentially the same at 60 and at 100 MHz as taken directly from the spectra. For **4**, the validity of the coupling constants was verified by selectively decoupling protons A and B from other intefering protons. Although the pattern changed in the decoupling experiments, the line separation resulting rom the A–B coupling was essentially invariant. For **2**, both spin decoupling and the addition of $Eu(fod)_3$ were necessary in order to attain a clear spectrum. Although several accounts of the change in conformation upon the addition of $Eu(fod)_3$ have been published, variable amounts of $Eu(fod)_3$ gave little or no change in the basic line separations quoted.

The ^{13}C spectra were determined in 12-mm tubes using as high a concentration of substrate as possible (usually 10% w/v in $CDCl_3$, if sufficient substrate was available). In a typical run, i.e., for **2**, a 5000-Hz spectral width was used, with a 0.4-sec acquisition time, and a pulse delay of 0.1 sec; 5.2 K of transients were collected using a pulse width of 30 μsec. The maximum resolution, as calculated by the computer, was 0.0992 ppm. The chemical shifts were determined from the computer listing of the peaks, with respect to the middle line of $CDCl_3$, which was taken as 76.9 ppm from TMS, the ultimate standard.

In order to determine the ^{13}C–H coupling constants, a narrower "window" (either 500 or 1000 Hz) was used in order to improve resolution. Either the gated mode of operation was used,[37] or, in some cases, the decoupler was not used. The coupling constants were determined from the average of several measurements (somewhat more variability was noted for these line separations compared to H–H couplings, perhaps owing to digitization). In practice, only measurement of coupling constants to carbons of isolated methyl groups was possible in the machine time that was available; the signals for other carbons tended to be unresolved multiplets.

In the expanded spectra such as in Figure 1, it was difficult to tell ^2J from ^3J. The constant line separation observed in all compounds, ca. 2.1 Hz, was taken as ^2J. The ^{13}C–H couplings were simulated using the LAOCOON III program. The spectra were shown to be subject to first-order interpretation in most cases, although in other cases (5 and 8) small adjustments were necessary to make the simulated spectrum fit the original.

Registry No.—**2**, 54382-87-5; **3**, 42282-50-8; **4**, 54354-06-2; **5a**, 6702-10-9; **5b**, 54354-07-3; **5c**, 4265-29-6; **6a**, 1075-04-3; **6b**, 21145-69-7; **6c**, 21759-65-9; **6d**, 54354-08-4; **7a**, 19776-13-7; **7b**, 54354-09-5; **8a**, 6464-40-0; **8b**, 54354-10-8; **8c**, 4306-97-2; **8d**, 54354-11-9; **9a**, 1075-05-4; **9b**, 21145-70-0; **9c**, 21759-66-0; **9d**, 54354-12-0; **10a**, 19776-14-8; **10b**, 54354-13-1; isobutyryl chloride, 79-30-1; acetyl chloride, 75-36-5; benzoyl chloride, 98-88-4; 3-methyl-1,2-cyclohexanediol, 23477-91-0.

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Conformational Analysis. Effect of a Vicinal Hydroxyl Group on the Methylation Rates of Cyclohexyldimethylamines and *trans*-Decalyldimethylamines

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The rates of methylation of the four 3-dimethylamino-*trans*-2-decahydronaphthols, of the *cis*- and *trans*-2-dimethylaminocyclohexanols, as well as those of the corresponding "parent" amines have been measured as a function of temperature. The rate of the *cis*-3-dimethylamino-*trans*-decahydronaphthol **2** is found to be unusually high for a compound with an axial dimethylamino group and confirms the flattened chair conformation assigned to this compound. The difference in reactivity between axial and equatorial dimethylamino groups seems to be of steric origin (a much more restricted transition state in the former case). An unusual feature of the reaction is that in cases involving an equatorial dimethylamino group the rate constant of the diequatorial isomer is significantly much lower than that of the isomer with an axial hydroxyl group.

Although the reaction of alkyl halides with tertiary amines (Menschutkin reaction) has been extensively studied,[3] there is relatively little information regarding the rates of alkylation of simple conformationally stable exocyclic amines.[4–6] In this work we report the rates of methylation in acetonitrile of the four 3-dimethylamino-*trans*-2-decahydronaphthols (**1**, **2**, **3** and **4**), of the *trans*- and *cis*-dimethylaminocyclohexanols (**5** and **6**), and of the corresponding parent amines (**7**, **8**, and **9**).

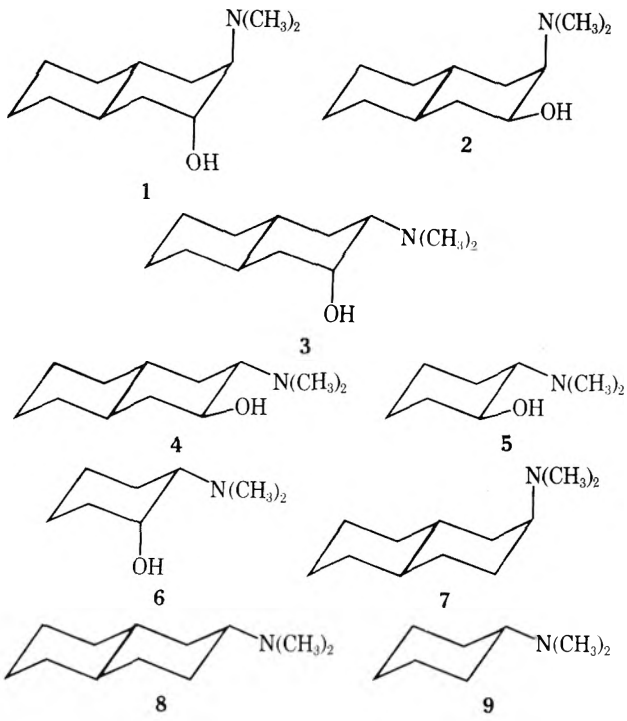
Results and Discussion

The results of the methylation of the four 3-dimethylamino-*trans*-2-decahydronaphthols (**1–4**), of the *trans*- and *cis*-dimethylaminocyclohexanols (**5** and **6**), of the *trans*- and *cis*-2-decalyldimethylamines (**7** and **8**), and of the cyclohexyldimethylamine are summarized in Table I. The kinetic measurements have been effected in acetonitrile so as to compare them with Allinger's results on *tert*-butylcyclohexylamines. Acetonitrile being in fact a good proton acceptor, it had to be checked that no competition was taking place between the intramolecular H bond and H bond with acetonitrile; to settle this point we have observed the NMR spectra in this solvent and we do not find any variation in half-width band height for the proton α to the substituent. Furthermore, for the compound **2**, deformed by a strong H bond, one finds a value of 22 Hz for the $W_{1/2}$ of the proton α to OH, this value being the same in $CDCl_3$.

The rates constants were evaluated graphically; these values are the average of at least three independant determinations.

The values of $\Delta H^{\ddagger}$ were obtained from the gradient of plots of log k/T against the reciprocal of the absolute temperature; the values of $\Delta S^{\ddagger}$ were obtained from the Eyring equation, i.e., from the gradient of T log k/T against T. The precision of the value of k_2 is of the order of 1%. The error of the $\Delta S^{\ddagger}$ value is of the order of 1 eu.

First, it may be noted that the compounds in which the dimethylamino group occupies an axial position react more slowly than those in which this group occupies an equatorial position. This is what one would expect, inasmuch as it is experimentally known that axial groups undergo reactions at reduced rates when compared to equatorial groups, in



cases in which the congestion increases in the product (and hence in the transition state) relative to the starting material.[7-10] In the case of the "parent" amines, the *trans*-2-decalyldimethylamine (**7**) reacts some 120 times more slowly than the corresponding cis isomer (**8**) at the same temperature, and this is in good agreement with the results obtained by Sicher and coworkers.[5] The difference in reactivity between axial and equatorial isomers which amounts to a free-energy difference of about 3 kcal mol^{-1} led Sicher to suggest the possibility of the axial compound reacting through a boat form transition state in which the dimethylamino group was in an equatorial position. A consideration of the activation entropies, however, casts great doubt upon such a transition state for the axial compound. Thus the activation entropy value of −41 eu for the axial compound as compared to that of −32 eu for the equatorial compound is in favor of a much more congested and restricted transition state in the former case, and this would be true only if the transition state in this compound still resembled the initial state. Since the final product in this reaction is still chair, there is no reason to think that the axial isomer undergoes reaction through a boat form transition state.

Secondly, it is observed that all the amino alcohols (with the exception of **2**) react more slowly than the corresponding "parent" amines. Thus in all of the amino alcohols (with the exception of **2**), the overall effect of the vicinal hydroxyl group is a "retarding" effect and can be expressed by the ratio k_H/k_{OH}, where k_H and k_{OH} are the rate constants of parent amine and amino alcohol, respectively. The actual magnitude of the rate retardation is, however, found to differ according to the mutual steric positions of the functional groups.

Compd	1	2	3	4	5	6
k_H/k_{OH}	3	0.8	4.2	39	32	2.5

In the discussion which follows we find it convenient to treat separately the compounds in which the dimethylamino group occupies an equatorial position from those in which this group occupies an axial position.

Compounds with an Equatorial Dimethylamino Group. We include in this class the *trans*- and *cis*- (**5** and **6**) dimethylaminocyclohexanols because in both compounds the conformational equilibrium is almost totally displaced toward the conformer with the dimethylamino group in an equatorial position.[11] It is thus found that the two trans isomers (**4** and **5**) react more slowly than the corresponding cis isomers (**3** and **6**), and that the ratio k_H/k_{OH} is different in going from the cyclohexane to the decalin series. The smaller retardation ratio in the former (**5** and **6**) case could be due either to an equilibrium not totally displaced or to a more facile deformation of the cyclohexane system. On the other hand, the variation of the ratio k_H/k_{OH} in going from the cis to the trans compounds is almost the same for the two series (2.5:32 and 4.2:39, respectively, for the cyclohexane and decalin series).

The higher reactivity of the cis compounds as compared to that of the trans compounds is difficult to predict inasmuch as it is known that intramolecular hydrogen bond formation in diequatorial compounds involves a "puckering" of the chair whereas in the cis compounds the approach of the two functional groups involves a flattening of the chair.[12] It would seem, then, in view of this fact, that the diequatorial compounds would undergo reaction more rapidly than the cis compounds, the breaking of the hydrogen bond needing less energy in the former case than in the latter.

However, similar results have been observed in the Menschutkin reaction on the 4-*tert*-butyl-2-methyldimethylcyclohexylamines for which Sicher and coworkers[5] report a higher reactivity for the cis isomer than for the trans isomer. Some findings related to those observed in this reaction are reported in the literature. Thus, Chapman and coworkers[13] have shown that the rate with an equatorial carboxyl group undergoes acid-catalyzed esterification and is much less affected by a vicinal axial group than it is by a

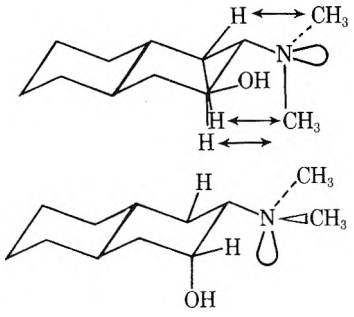
Table I
Second-Order Rates of Methylation in Acetonitrile and Activation Parameters

Compd	Temp, °C	k_2, 10^4 l. mol^{-1} sec^{-1}	$\Delta G^{\ddagger}$(273 K), kcal mol^{-1}	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
	0.0	0.685			
1	10.0	1.68	21.2	12.1	−33.4
	20.0	2.10			
	0.0	2.44			
2	10.0	5.09	20.6	11.1	−34.6
	20.0	10.1			
	0.0	62.5			
3	10.0	115.3	18.4	9.5	−32.6
	20.0	217.2			
	0.0	6.70			
4	10.0	14.0	19.9	9.3	−38.7
	20.0	25.8			
	0.0	5.64			
5	10.0	11.9	19.7	10.4	−34.3
	20.0	23.1			
	0.0	64.6			
6	10.0	128.2	18.7	9.8	−32.3
	20.0	241.9			
	0.0	1.99			
7	10.0	4.06	21.6	10.35	−41.6
	20.0	7.92			
	0.0	237.8			
8	10.0	488.6	17.9	8.9	−32.6
	20.0	895.4			
	0.0	154.5			
9	10.0	364.5	20.77	11.2	−35.2
	20.0	719.3			

vicinal equatorial group. Again, in oxime formation on the 4-*tert*-butyl-2-methyl-1-acetylcyclohexanes, analogous rate relationships have been observed by Heymes and Dvolaitzky.[14]

For all these reactions a number of interpretations have been proposed. Thus, in the Menschutkin reaction on the 4-*tert*-butyl-2-methyldimethycyclohexylamines, Sicher explains the different reactivities of the four isomers from a consideration of conformational energies (*A* values) and arranges them in the following order of stability: NMe_2(e) Me(e) > NMe_2(e) Me(a) > NMe_2(a) Me(e) > NMe_2(a) Me(a). The retarding effect due to the introduction of a vicinal methyl group seems then to increase with increasing stability in the ground state. Corresponding considerations of the transition-state energies ought to be envisaged, and according to Sicher,[5] it is probable that the transition states of the four isomers would be deformed, this deformation, or tension equivalent to it, preexisting in the ground states of the two cis and diaxial isomers whereas in the case of the diequatorial isomer the deformation energy should be added as part of the activation energy of the reaction.

This interpretation, although attractive, does not seem to explain the whole situation as regards the compounds studied in this paper. Indeed it is unlikely that the same stability order could apply to the compounds under study in this paper inasmuch as intramolecular hydrogen bonding in the cis isomers would tend to stabilize them whereas the opposite would be true in the diequatorial isomer.[12] As we have been able to show that the cis isomer **3** as well as its quaternary ammonium salt exist in a normal nondeformed chair conformation,[15] we think that the low reactivity of the diequatorial isomer **4** is most probably due to steric hindrance in the transition state. Examination of Dreiding models sheds light on this situation. In the intramolecularly hydrogen bonded conformation in this isomer, one of the methyl groups has syn-axial interactions with the two hydrogens in positions 2 and 4 and the other methyl group has a syn interaction with the equatorial hydrogen in position 4, whereas in the cis isomer **3** such syn interactions do not exist.



As the third methyl group is introduced to form the quaternary ammonium salt (which is what takes place in the transition state) a much more important steric hindrance to the free rotation of the trimethylammonium group being formed is introduced in the trans compound than in the cis compound. This state of affairs is clearly demonstrated by the calculated activation entropies. While the activation enthalpies are similar (9.54 kcal for isomer **3** and 9.34 kcal for isomer **4**), the activation entropies, on the other hand, differ considerably (−32 eu for **3** and −38 eu for **4**).

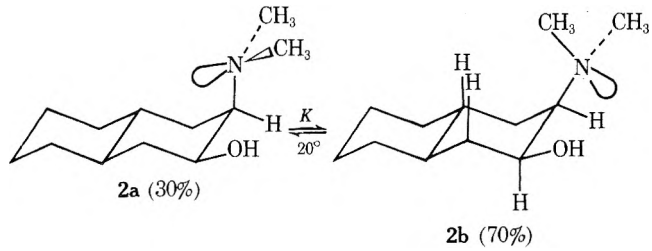
The same reasoning can also apply to the 4-*tert*-butyl-2-methyldimethylaminocyclohexanes of Sicher. Indeed, the hindrance to the free rotation of the trimethylammonium group, as a result of the presence of the vicinal methyl group, should be even greater; the methyl group being bulkier than the hydroxyl group, the retarding effect due to the introduction of a vicinal methyl group, here expressed as the ratio k_H/k_{CH_3} (10 and 227 for the cis and trans isomers, respectively) is much greater than the corresponding ratios observed for the amino alcohols (4 and 39 for the cis and trans isomers, respectively).

This interpretation can thus be rationalized to account for the differences in reactivity observed between cis and trans isomers in this group of reactions. It is evident that kinetic studies evaluating entropy factors ought to be performed to justify the validity of such a generalization.

An approximate evaluation of the steric factors intervening in the transition states of compounds **3** and **4** can be reached by assuming that the activation enthalpy of the reaction consists of two factors, viz., an electronic factor, corresponding to the breaking of the hydrogen bond, and a steric or entropy factor corresponding to the attack by the methyl iodide. Thus, taking 5.8 and 2.0 kcal/mol as the respective hydrogen bond enthalpy values in the cis and trans isomers,[16] and by assuming that the two isomers are energetically on the same level,[17] one shows that the steric factor is 7.34 kcal/mol in the trans isomer (**4**) whereas it is only 3.7 kcal/mol in the cis isomer (**3**). It is thus found that the steric factor outweighs the electronic factor in the trans isomer, clearly showing the importance of steric factors in the transition state and therefore the validity of our interpretation.[22]

Compounds with an Axial Dimethylamino Group. In the case of the diaxial isomer **1** the ratio k_H/k_{OH} is equal to 3. This small value corresponds to a very slight steric hindrance of the hydroxyl group to the attack of methyl iodide by the amine. That this is so is clearly illustrated by comparison with the retarding effect due to a vicinal methyl group in the analogous *tert*-butyl compound, where this effect, expressed as the ratio k_H/k_{CH_3}, is only 1.[5] Thus, we attribute the low activity of compound **1** compared to that of the parent amine **7** as solely arising from the inductive effect of the hydroxyl group. By virtue of its tendency to attract electrons, the hydroxyl group will tend to "pull in" the lone-pair electrons toward the nitrogen atom and thereby render it less accessible to attack by the methyl iodide.

The situation in the cis isomer **2** is of particular interest. Thus, it has been shown that compound **2** actually exists as a mixture of two conformers (**2a** and **2b**) in equilibrium,[18] conformer **2a** being in a normal chair form whereas conformer **2b** adopts a flattened chair conformation and is responsible for the bonded hydroxyl band in the infrared spectrum.



The NMR spectrum of the tetradeuterated compound[15] of this isomer shows an unusually high coupling constant between the two protons in positions 2 and 3 for an angle of 60°, this confirming the presence of conformer **2b**. The same type of flattening was observed for the quaternary ammonium salt of the diaxial isomer **1**, it being even more pronounced in the quaternary ammonium salt of isomer **2**, where it results in a "twist chair" conformation.

The ratio here observed, k_H/k_{OH} = 0.8, would tempt one

to think that the vicinal hydroxyl group had, so to speak, an "accelerating" effect on the reaction of the amine with methyl iodide. This unexpected high reactivity should, however, not come as a surprise and is in fact in agreement with the flattened chair conformation assigned to this compound. Furthermore, the presence of 30% of conformer **2a** (at 20°) should lower the rate constant of conformer **2b**, the observed methylation rate constant being that of the equilibrium mixture.[19] Thus, applying the method independently developed by Eliel[20] and Winstein[21] to this equilibrium, $k_{obsd} = (k_e K + k_a)/(K + 1)$ where k_{obsd} is the measured rate constant, k_e and k_a the rate constants of pure equatorial and axial compounds, respectively, and K the equilibrium constant = 2.3 at 20°, and, by assuming that the conformer **2a** has the same rate constant as the diaxial isomer 1,[23] the calculated rate constant for the conformer **2b** at 20° is found to be 13.6×10^{-4} l. mol^{-1} sec^{-1}. It is thus found that this conformer **2b** reacts much more quickly than compounds 1 and 7 and slower than the compounds with an equatorial dimethylamino group.

The activation enthalpies for the two isomers (1 and 2) are calculated to be 12.1 and 11.1 kcal mol^{-1}, respectively, values slightly higher than that of 10.3 kcal mol^{-1} calculated for the parent amine. The activation entropies are, however, found to be more positive for the two isomers (−33 eu for 1 and −34 eu for 2) as compared to that of −41 eu for the parent amine. The entropy value found for the diaxial compound 1 is quite surprising because, in principle, the transition state of this isomer ought to have the same degree of congestion as that of the parent amine, unless the presence of the vicinal hydroxyl group equally axial brings about a flattening of the substituted ring at the moment of attack by the methyl iodide and thereby places the trimethylammonium group being formed out of the 1,3-syn axial interactions with the axial protons in positions 1 and 10, thus resulting in a much less congested transition state. Such a transition state would indeed be compatible with the flattened chair conformation assigned to the quaternary ammonium of this isomer.[15]

The activation entropy value of −34.6 eu for the isomer 2 agrees quite well with the flattened chair conformation attributed to it; the dimethylamino group, being in a pseudoequatorial position, would be expected to be already free of the syn-1,3-axial interactions. This finding, however, would seem to be incompatible with the almost diequatorial conformation of this isomer; the angle between the amino and hydroxyl groups being smaller than the corresponding angle in the diequatorial isomer 4, one would expect a much more hindered situation and therefore a much more negative activation entropy value in this case. However, the steric environment in this isomer is different from that of isomer 4 as revealed by examination of molecular models. Thus, intramolecular hydrogen bond formation in this isomer orients the two methyl groups out and away from the syn-axial interactions present in the diequatorial isomer, and since the C–N bond is only pseudoequatorial, the free electron pair is accessible to attack by the methyl iodide. Another possibility could be that of this isomer undergoing reaction through a transition state in which the substituted ring is in a boat form (or further still a twist form). However, a comparison of the activation entropies of this isomer (−34 eu) with that of −32 eu for the other cis isomer 3 seems to render such a transition state unlikely.[24] If, however, such were the case, the entropy of activation of a boat being greater than that of a chair form,[25] other things being equal, the activation entropy of isomer 2 would be expected to become more positive than that of isomer 3, which, unfortunately, it does not. It would then

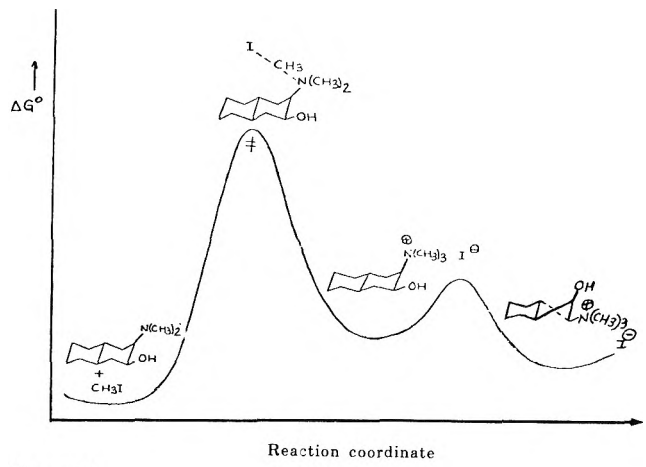


Figure 1.

seem reasonable to conclude that the observed rate constant and the activation entropy value found for this isomer are in agreement with a flattened chair conformation assigned to it and that the transition state is still flattened, the passage into the twist chair conformation of the methiodide salt taking place only after the transition state, as illustrated in Figure 1.[35]

Conclusion

The influence of the inductive effect of the hydroxyl group on the methylation rate is feeble, since in cases where the hydroxyl group has practically no steric hindrance or no hydrogen bonding (case of the diaxial isomer), the observed retarding effect is relatively small. In cases where there is hydrogen bonding, it is possible to assess the steric effects due to the bulky trimethylammonium group, these effects being more marked in the diequatorial compound 4. This reaction, very sensitive to small conformational differences around the reaction center, gives evidence for a notable deformation in compound 2.

Lastly, the study of the substitution reaction (Menschutkin reaction) of these amino alcohols helps to explain the results in elimination reactions (Hofmann,[26] Wittig, Cope[27]).

Experimental Section

Melting points were taken on a Dr. Tottoli melting point apparatus and are uncorrected. Composition and homogeneity of liquid samples were monitored by a Barber-Colman gas chromatograph series 5000 using an 8-ft Carbowax 20M over 3% Anakrom column. Microanalyses were performed by the Microanalysis Laboratories, Montpellier. The compounds used in this study were synthesized by standard stereospecific routes, from starting materials of known conformation. The pseudo-first-order rate constants for the methylation in acetonitrile with a 500-fold excess of methyl iodide were measured by means of a conductimetric bridge.[28-31] These were converted to second-order constants by the simple relation $k_2 = k_1/[CH_3I]$, where $[CH_3I]$ is the molar concentration of methyl iodide.

The enthalpies $\Delta H^{\ddagger}$ and entropies $\Delta S^{\ddagger}$ of activation were calculated directly from the experimental kinetic data by the method of least squares with the aid of the expression given by Cagle and Eyring.[32]

***trans*-Δ²-Octalin.** this compound was prepared by the diene condensation of *p*-benzoquinone and butadiene according to the method of Johnson,[33] bp 77° (14 mm) [lit.[32] bp 59° (8 mm)]. VPC showed that this compound was homogeneous.

2,3-Epoxy-*trans*-decalin was prepared by reaction of the *trans*-Δ²-octalin with *p*-nitroperbenzoic acid, bp 106° (22 mm) [lit.[32] bp 105° (21 mm)].

3(a)-Dimethylamino-*trans*-2(a)-decahydronaphthol (1). This compound was prepared directly from the epoxide by reaction with an alcoholic solution of dimethylamine, mp 76–78°. Anal.

Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10; O, 8.11. Found: C, 73.36; H, 11.36; N, 7.16; O, 8.68.[31]

3(a)-Dimethylamino-*trans*-2(e)-decahydronaphthol (2). This compound came from 3(a)-amino-*trans*-2(a)-decahydronaphthol, which was converted to the cis isomer by the usual method, i.e., via the oxazoline. Dimethylation of the amino alcohol gave the *N,N*-dimethylamino compound **2**, mp 40–41°. Anal. Calcd for $C_{12}H_{23}NO$: C, 74.04; H, 11.75; N, 7.10; O, 8.11. Found: C, 73.96; H, 11.43; N, 7.25; O, 8.30.[31]

3(e)-Dimethylamino-*trans*-2(a)-decahydronaphthol (3) was obtained by reduction of 3(e)-amino-*trans*-2-decalone chloride over platinum oxide, followed by dimethylation of the amino alcohol, mp 61–62°. Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75 ; N, 7.10; O, 8.11. Found: C, 72.91; H, 11.39; N, 7.28; O, 8.35.[31]

3(e)-Dimethylamino-*trans*-2(e)-decahydronaphthol (4). This compound was prepared from 3(e)-hydroxy-*trans*-2(e)-decalinecarboxylic acid according to a known procedure, mp 51–52°. Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10; O, 8.11. Found: C, 73.23; H, 11.31; N, 7.18; O, 8.26.[34]

***trans*-2-Dimethylaminocyclohexanol (5).** This compound was prepared from 1,2-epoxycyclohexane by a method identical with that used for compound **1**, bp 105–106° (25 mm). Anal. Calcd for $C_8H_{17}NO$: C, 67.13; H, 11.96; N, 9.79; O, 11.26. Found: C, 66.97; H, 11.92; N, 9.81; O, 11.30.

***cis*-2-Dimethylaminocyclohexanol (6).** This compound was prepared from 1,2-epoxycyclohexane by a method similar to that used for compound **2**, mp 72–73°. Anal. Calcd for $C_8H_{17}NO$: C, 67.13; H, 11.96; N, 9.79; O, 11.26. Found: C, 67.24; H, 11.99; O, 11.36.

2-*trans*-*N,N*-Dimethylamino-*trans*-decalin (7). This compound was prepared by reduction of *trans*-2-decalone oxime over platinum oxide. Dimethylation and purification via the hydrochloride salt (mp 235–236°) gave compound **7**. VPC showed that the compound was homogeneous. Anal. Calcd for $C_{12}H_{23}N$: C, 79.4; H, 12.60.

***2-cis*-*N,N*-Dimethylamino-*trans*-decalin (8)** was prepared by reaction of *trans*-decalytosylate with sodium azide, followed by dimethylation of the resulting amine (mp of hydrochloride salt 225°). VPC showed that the compound was homogeneous. Anal. Calcd for $C_{12}H_{23}N$: C, 79.6; H, 12.8.

***N,N*-Dimethylaminocyclohexane (9)** was prepared from the corresponding amine which was commercially available, bp 82° (19 mm).

Kinetic Measurements. The method used in the determination of rate constants was the same as that used by Allinger. Each compound (5×10^{-4} mol) was dissolved in 100 ml of acetonitrile (Merck purified by distillation from magnesium sulfate under nitrogen) and stored under nitrogen. Resistance measurements were made on 5-ml aliquots of the standard solution to which was added carefully weighed (approximately 0.5 ml) methyl iodide, using a Philips conductivity bridge, Model G.M. 4249. Dry nitrogen was passed through the solution during each run. The temperature control was such that no variation was greater than 0.1°. In order to better correlate the exposed results we have brought rate-constant values determined at different but close temperatures, at 0, 10 and 20°, by Arrhenius extrapolation (the experimental values are given in ref 1).

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Registry No.—**1**, 2454-63-9; **2**, 1204-73-5; **3**, 18289-82-2; **4**, 25690-15-7; **5**, 15910-74-4; **6**, 20431-82-7; **7**, 20184-40-1; **7** HCl, 38506-08-0; **8**, 19432-46-3; **8** HCl, 38506-06-8; **9**, 98-94-2; 2,3-epoxy-*trans*-decalin, 21399-51-9; 3(a)-amino-*trans*-2(a)-decahydronaphthol, 15875-02-2; 3(e)-amino-*trans*-2-decalone, 54003-43-9; cyclohexylamine, 108-91-8; 1,2-epoxycyclohexane, 286-20-4; *trans*-2-decalone oxime, 15876-37-6; *trans*-2-decalyltosylate, 54053-73-5.

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(22) As we have remarked, we have verified that there is no competition between intramolecular H bonds and H bonds with solvent, at least in the initial state. If this effect should, however, be of some importance, then the value of the activation enthalpy for the H bond would be weaker for the diequatorial compound, as the solvation of equatorial hydroxyl is greater; thus steric hindrance effects are preponderant, as suggested above.
(23) To a first approximation this assumption seems reasonable and it can be assumed that the diaxial isomer **1** and conformer **2a** will be subjected only to the inductive effect of the hydroxyl group and will thus have the same reactivity toward methyl iodide.
(24) The difference between these two values is evidently very small and goes in fact in the order of the error on the value of entropy. Thus, that difference is in good agreement with the more congested transition state in the case of the cis isomer with the amino group in pseudoaxial position; otherwise the boat transition state would be driven to a value of $\Delta S^{\ddagger}$ of approximately −27 eu.
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(35) We are thankful to a suggestion of one of the referees of this paper, who suggests that the difference in reactivity between the amine **7** and the amino alcohol **2** is coming from the difference in solvation in the transition state; the solvation would, in fact, be less due to electrostatic stabilization with the amino alcohol than with the amine. If this effect can come into play, it would, however, be difficult to measure; the authors do not think that it can explain the difference in reactivity, for it will intervene also in the case of the isomers in which $-N(Me)_2$ is equatorial, for which the $\Delta S^{\ddagger}$ values between amine and amino alcohols are not found to be so very different.

Aromatic N-Oxides. VIII. Dual Bond Cleavage of the Anhydro Base Intermediate in 4-Alkylpyridine N-Oxide–Acid Anhydride Reactions[1-3]

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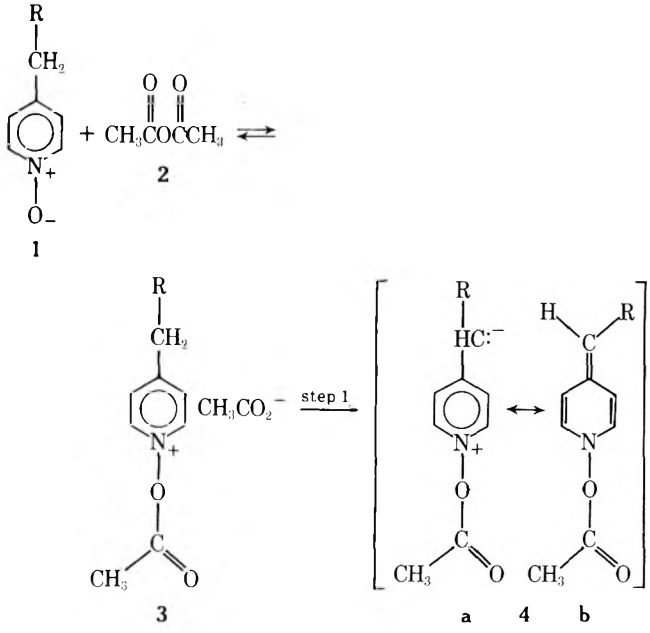
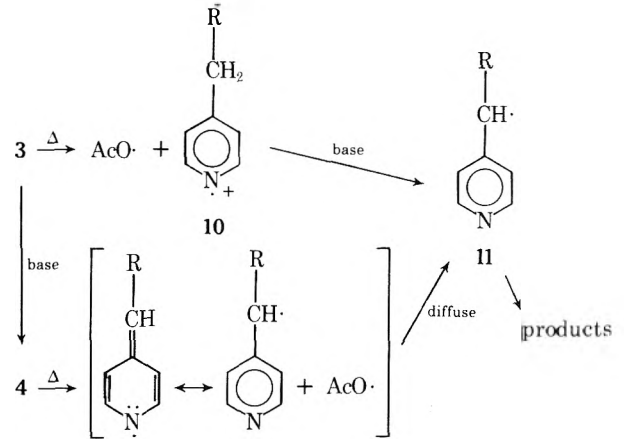
The CIDNP effect in the reaction of 4-methylpyridine N-oxide and acetic anhydride was confirmed for the partial formation of ester **5** (R = H); however, attempts to observe the CIDNP effect using 4-neopentylpyridine N-oxide or 4-benzylpyridine N-oxide proved negative. The NMR study with 4-benzylpyridine N-oxide–acetic anhydride revealed a transient intermediate assigned to anhydro base **4** (R = C_6H_5). 1-Acetoxy-4-methylpyridinium perchlorate in neutral refluxing acetonitrile was stable while addition of tri-*n*-butylamine gave ester and alkylpyridine products similar in yield to those from the reaction of 4-methylpyridine N-oxide and acetic anhydride under comparable corditions.These results are interpreted via a dual bond cleavage of anhydro base **4**.

The generally accepted mechanistic pathway for the reaction of 4-alkylpyridine N-oxides and acid anhydrides has been reviewed previously[1,5,6] and is outlined below. Step 1 has been established as rate determining[7,8] and evidence has been obtained for the intermediacy of the anhydro base **4**;[7] however, the formation of esters **5** and **6** via step 2a has been somewhat controversial. Recent evidence[1,6] favors the heterolytic fragmentation of the N–O bond of **4** producing ion pairs which on recombination form **5** and **6**. The alternate explanation entailed homolytic fission of the N–O bond forming radical pairs which can recombine to give **5** and **6** or diffuse and lead to **7**, **8**, **9**, and carbon dioxide.[9-12] Iwamura and coworkers[13] have reported the CIDNP effect in the generation of **5** (R = H) and proposed that at least a portion of ester formation occurred via recombination of radical pairs. They also observed the CIDNP effect in the formation of methane and ethylpyridine (**8**, R = H) supporting their radical origin. Although evidence for the presence of radicals in these reactions is substantial, the source of radicals has not been established. In this report we wish to describe the source of free radicals, to provide additional evidence for the intermediate anhydro base **4**, and to present some results of CIDNP studies.



A review of the mechanistic pathway reveals two intermediates that seem to be reasonable candidates for radical production: the 4-alkyl-1-acetoxypyridinium ion (**3**), as initially suggested by Boekelheide and Harrington,[14] or the anhydro base **4**. In either case homolytic N–O bond fission is required as the initial step. Fragmentation of **3** leads to radical cation **10**, which upon deprotonation forms radical **11** that proceeds to products, while N–O bond cleavage of **4** produces radical pairs which can liberate **11** via diffusion.



The reaction of 4-methylpyridine N-oxide with acetic anhydride in refluxing acetonitrile produced CO_2 (13.5%), 4-methylpyridine (**7**, R = H) (9.3%), 2,4-lutidine (**9**, R = H) (0.9%), 4-ethylpyridine (**8**, R = H) (3.1%), 4-pyridylmethyl acetate (**5**, R = H) (17%), and 4-acetoxy-4-methylpyridine (**6**, R = H) (16%). When 1-acetoxy-4-methylpyridinium perchlorate in refluxing acetonitrile was treated with tri-*n*-butylamine under the same conditions as the preceding experiment, the products formed were CO_2 (4.8%), 4-methylpyridine (4.7%), and a mixture of 4-pyridylmethyl acetate and 3-acetoxy-4-methylpyridine (15%). In this latter experiment the yields are somewhat reduced but both radical products and esters were formed in about the same ratio. However, if 1-acetoxy-4-methylpyridinium perchlo-

rate were refluxed alone in acetonitrile for the same time as in the above two experiments, no evolution of carbon dioxide was observed and upon work-up the 1-acetoxy-4-methylpyridinium ion was hydrolyzed to regenerate 86% of 4-methylpyridine *N*-oxide.

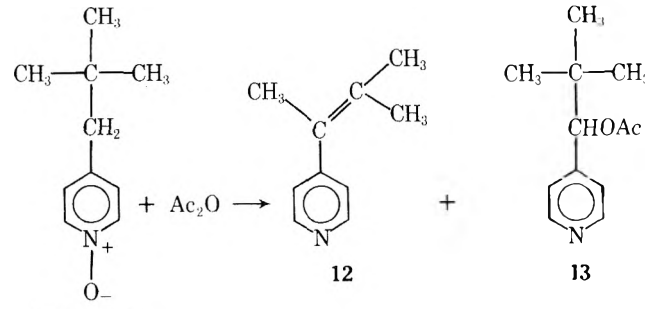
The homolytic N–O bond fragmentation of **3** under neutral conditions should be detectable by the loss of carbon dioxide from the acetoxy radical produced. No carbon dioxide was evident in the last experiment. These experiments clearly demonstrated that 1-acetoxy-4-methylpyridinium ion (**3**, R = H) is thermally stable under conditions that permit the anhydro base **4** (R = H) to fragment, producing esters and radical-originated products. Therefore, we assign the origin of radicals to the homolytic N–O cleavage of **4** followed by diffusion. Since **4** also serves as the source of esters via heterolytic fission followed by ion-pair recombination, we encounter here an example of a dual bond cleavage process (competing heterolytic and homolytic fission) for **4**. The effect of structure variation in the reactants on enhancing heterolytic N–O bond fission or homolytic fission has been summarized in a previous paper.[1]

The reaction of 4-benzylpyridine *N*-oxide and acetic anhydride was studied previously and provided spectroscopic evidence (uv) for the intermediacy of the anhydro base (**4** R = C_6H_5) in rearrangement to ester **5**, R = C_6H_5.[7] We have reexamined this reaction looking especially for radical-generated products and obtained the following results: CO_2 (2%), 4-benzylpyridine (20%), and 1-phenyl-1-(4-pyridyl)-methyl acetate (**5**, R = C_6H_5) (54%). A careful search for 1-phenyl-1-(4-pyridyl)ethane (**8**, R = C_6H_5) revealed the absence of this material. Carbon dioxide formation has been taken as a minimum measure of radical production and usually exceeds the amount of alkylpyridines formed in the reaction.[12] The low yield of carbon dioxide and absence of **8** (R = C_6H_5) is consistent with a low production of radicals; however, the unusually high yield of 4-benzylpyridine is puzzling.

During an NMR study of the 4-benzylpyridine *N*-oxide–acetic anhydride reaction a transient absorption signal (singlet) was observed at δ 5.65. This band reached a maximum intensity at about 35 sec reaction time and decayed to zero in about 100 sec reaction time. The formation of ester **5** (R = C_6H_5) was complete in 160 sec. The assignment made to the δ 5.65 band is the exocyclic proton of the anhydro base **4b** (R = C_6H_5) and we offer this observation in support of the intermediacy of the anhydro base **4** in the formation of ester **5** (R = C_6H_5). The polyolefinic structure of **4b** (R = C_6H_5) has been established as the preferred structure in classical anhydro bases which show absorption of exocyclic olefinic protons at δ 5.2–5.4.[15]

Although the evidence appears convincing[1,6] that ester **5** formation proceeds by heterolytic N–O bond fission of the anhydro base **4** followed by recombination of ion pairs, we note above that the anhydro base **4** also undergoes homolytic N–O bond cleavage. Iwamura and coworkers[13] attributed the CIDNP effect observed in the reaction of 4-methylpyridine *N*-oxide and acetic anhydride to ester **5** formation by recombination of radical pairs. We have repeated Iwamura's work to develop our technique in observing the CIDNP effect in these *N*-oxide reactions. Our results with the reaction of 4-methylpyridine *N*-oxide and acetic anhydride (studied at six different temperatures, 70–140 ± 0.5°) were essentially identical with those of Iwamura.

CIDNP studies were extended to reactions of 4-neopentylpyridine *N*-oxide and 4-benzylpyridine *N*-oxide with acetic anhydride. In the case of 4-neopentylpyridine *N*-oxide, the products of reaction with acetic anhydride were 2-(4-pyridyl)-3-methyl-2-butene (**12**, 54%) and 1-(4-pyridyl)-2,2-dimethyl-1-propyl acetate (**13**, 31%).[1] An appreciable degree of reaction was diverted by carbon skeletal rearrangement via carbonium ions followed by elimination and thus favored a substantial, if not exclusive, contribution of ion-pair formation from anhydro base **4** (R = t-Bu). A search for the CIDNP effect in this reaction was negative. Likewise an NMR study of the 4-benzylpyridine *N*-oxide–acetic anhydride reaction showed no CIDNP effect (neither emission nor enhanced absorption) for any bands associated with 1-phenyl-1-(4-pyridyl)methyl acetate (**5**, R = C_6H_5) or 4-benzylpyridine. Thus the absence of the CIDNP effect in the 4-neopentylpyridine and 4-benzylpyridine *N*-oxides reduces the prospects of ester **5** formation via radical pairs and further strengthens the ion pair mechanism.



1 (R = *t*-Bu)

Experimental Section

4-Benzylpyridine *N*-oxide, mp 104–106° (recrystallized from dry benzene, lit.[7] mp 104–105°), was prepared in 86% yield from 4-benzylpyridine[16] (50 g, 0.29 mol), glacial acetic acid (150 ml), and 30% H_2O_2 (70 ml) by the method of Hands and Katritzky.[17]

Reaction of 4-Benzylpyridine *N*-Oxide with Acetic Anhydride. The apparatus used for this reaction was described previously.[12] A solution of 4-benzylpyridine *N*-oxide (9.0 g, 48.6 mmol) and acetic anhydride (50 ml, 530 mmol) was refluxed under N_2 for 3.0 hr. Rapid titration[18] of aliquots taken from the $Ba(OH)_2$ traps showed that 0.99 mmol (2%) of CO_2 had been evolved. GLC analysis[19] of the crude reaction mixture showed the presence of acetic anhydride, 4-benzylpyridine (R_f 4.5 min), 1-phenyl-1-(4-pyridyl)methanol[20] (R_f 6.6 min), 1-phenyl-1-(4-pyridyl)methyl acetate (R_f 8.8 min), and a small amount of unidentified material (R_f 10.5 min). Addition of authentic samples to the crude mixture gave peak enhancement without distortion; however, addition of 1-phenyl-1-(4-pyridyl)ethane[21] to the reaction mixture gave a new peak (R_f 5.4 min).

The reaction mixture was treated with water (100 ml), basified (solid $NaHCO_3$), and extracted ($CHCl_3$). The extract was decolorized (Nuchar) and dried ($MgSO_4$) and the solvent was removed in vacuo to give 8.9 g of a brown liquid residue. NMR analysis of the residue[22] showed the presence of 20% 4-benzylpyridine and 80% 1-phenyl-1-(4-pyridyl)methyl acetate. The brown residue (8.8 g) was chromatographed on Fluorisil (200 g, 60–100 mesh) and elution with benzene gave 6.4 g (58%) of 1-phenyl-1-(4-pyridyl)methyl acetate. Further elution with $CHCl_3$–benzene (4:1) gave 4-benzylpyridine (1.67 g, 20%). The ir and NMR were identical with those of known samples.

Chemically Induced Dynamic Nuclear Polarization (CIDNP) Studies. A. 4-Methylpyridine *N*-Oxide with Acetic Anhydride.[13] A solution of 4-methylpyridine *N*-oxide[16] (130 mg, 1.2 mmol) in acetic anhydride (0.60 ml, 6.2 mmol) was placed in a precision NMR tube and frozen rapidly (Dry Ice–acetone). The sample was degassed by bubbling N_2 through the solution as thawing occurred, and the tube was sealed under N_2 with a pressure cap and refrozen (−70°) until used. The sample (thawed in a water bath to room temperature) was inserted into a preheated (90° ± 0.5°) NMR cavity[23] and spectrum scanning was begun immediately at a sweep rate of 500 Hz/100 sec. In 9 sec emission (E) and enhanced absorption signals (A) appeared at δ 5.13 (E) (s, 4-$CH_3CO_2CH_2C_5H_4N$); 2.86 (E), 2.73 (E), 2.60 (A), 2.46 (A) (q, 4-$CH_3CH_2C_5H_4N$); 1.33 (E), 1.21 (A), 1.08 (A) (t, 4-$CH_3CH_2C_5H_4N$);

and 0.05 (E) (s, CH_4). In addition a singlet at δ 1.91 (4-$CH_3CO_2CH_2C_5H_4N$) showed no E or A and increased steadily to a constant absorption (in ca. 180 sec), while a singlet at δ 2.36 (4-$CH_3C_5H_4N^+O_2CCH_3$) with no E or A decreased in intensity to zero (ca. 180 sec). These signal assignments were made by comparison with spectra of authentic samples.

Repetitive scans were run over selected regions of the spectrum to monitor peak intensities vs. time. The intensity of the emission singlet at δ 5.13 passed through a maximum at ca. 40 sec, decayed to an apparent zero in ca. 110 sec, and grew to a constant absorption intensity in ca. 180 sec.[24] The skewed quartet (E and A) at δ 2.86–2.46 and the triplet (E and A) at δ 1.33–1.08 passed through maximum intensity at ca. 55 sec (irrespective of sign) and reached a constant absorption value in ca. 400 sec.[24] The emission singlet at δ 0.05 was not rigorously ohsrrved as a function of time.

Additional studies of the reaction of 4-methylpyridine N-oxide with acetic anhydride was made at the following temperatures: 70, 106, 123, 134, and 140° (±0.5°). In every instance the same E and A signals were observed with slight variation of signal intensity with temperature.

B. 4-Neopentylpyridine N-Oxide with Acetic Anhydride. NMR tubes containing 4-neopentylpyridine N-oxide[1] (100 mg, 0.66 mmol) and acetic anhydride (0.50 ml, 5.14 mmol) were prepared as described above and the reaction was studied at the following temperatures: 70, 90, 106, 123, 134, and 140° (±0.5°). No indication of any CIDNP effect (E or A) was observed under any of these conditions in any region of the spectrum. The NMR spectrum of samples run at 70, 90, or 106° exhibited no change over a period of 1 hr; however runs at 123, 134, and 140° exhibited the steady growth of an absorption signal at δ 5.5 due to the methine proton of 1-(4-pyridyl)-2,2-dimethyl-1-propyl acetate. Assignment was confirmed by comparison with the spectrum of an authentic sample. Five NMR samples were combined after the CIDNP studies and analysis by GLC gave results comparable to those previously reported.[1]

C. 4-Benzylpyridine N-Oxide with Acetic Anhydride. Using the above procedure the reaction of 4-benzylpyridine N-oxide (111 mg, 0.60 mmol) and acetic anhydride (0.50 ml, 5.14 mmol) was studied over temperature ranges from ambient to 141 ± 0.5°. Below 70° an absorption band at δ 6.82 (4-$C_6H_5CH(OAc)C_5H_4N$) appeared and gradually increased in intensity while the band at δ 3.99 (4-$C_6H_5CH_2C_5H_4NO$ or 4-$C_6H_5CH_2C_5H_4N^+O_2CCH_3$) gradually decreased. Above 90° an emission band at δ 4.20 (E) and enhanced absorption band at δ 3.99 (A) appeared in 3 sec. The band intensity of the δ 4.20 (E) passed through a maximum at ca. 50 sec, decayed to zero in ca. 100 sec, and increased to a very small constant absorption band in ca. 160 sec.[24] The band intensity of δ 3.99 (A) increased to a maximum at ca. 50 sec and slowly decreased to a low-intensity band at ca. 500 sec while a band at δ 3.85 (4-$C_6H_5CH_2C_5H_4N$) slowly grew to constant intensity in ca. 500 sec.[24] A transient absorption signal was observed at δ 5.65 (4-$C_6H_5CH{=}C_5H_4NO_2CCH_3$)[14] which passed through a maximum at ca. 35 sec and decayed to zero after ca. 100 sec.[24] The band at δ 6.82 increased steadily to a constant value with no evidence of E or A at any time under all conditions studied.[24] The aromatic band at δ 7.25 (4-$C_6H_5CH_2C_5H_4NO$) decreased while δ 7.33 (4-$C_6H_5CH(OAc)C_5H_4N$) increased, reaching a constant intensity in ca. 160 sec.[24] Signal assignments were based on addition of authentic samples or by comparison with the spectra of authentic samples. Five NMR samples were combined and analysis by GLC[19] gave results comparable to those described in the earlier experiment.

Reaction of 4-Methylpyridine N-Oxide with Acetic Anhydride in Acetonitrile. The apparatus used for this experiment was described previously.[12] Acetic anhydride (5.10 g, 0.05 mol) was added dropwise over 10 min to a solution of 4-methylpyridine N-oxide[16] (3.3 g, 0.03 mol) in acetonitrile (30 ml) and the mixture was refluxed for 2.8 hr and allowed to cool. Rapid titration[18] of aliquots taken from the $Ba(OH)_2$ traps showed that 13.5% CO_2 had been evolved. After the acetonitrile was evaporated, analysis of the residue by GLC[25] showed the following composition: 4-methylpyridine (9.3%, R_f 3.0 min), 2,4-lutidine (0.9%, R_f 4.0 min), 4-ethylpyridine (3.1%, R_f 4.7 min), 4-pyridylmethyl acetate (17%, R_f 12 min), and 3-acetoxy-4-methylpyridine (16%, R_f 14.5 min). Peak identification was made by addition of authentic samples to the residue and observing peak enhancement without distortion.

Reaction of 1-Acetoxy-4-methylpyridinium Perchlorate with Base. The apparatus used for this reaction was described previously.[12] Tri-n-butylamine (7.7 g, 0.04 mol) was added dropwise over 5 min to a refluxing solution of 1-acetoxy-4-methylpyridinium perchlorate[26] (10.0 g, 0.037 mol) in dry acetonitrile (35 ml) and the mixture was refluxed for 3 hr total and cooled. Titration[18] of the excess $Ba(OH)_2$ in the traps showed that 4.8% CO_2 was evolved. Acetonitrile was distilled and analysis of the residue was achieved by GLC,[27] which showed the presence of 4-methylpyridine (4.7%, R_f 3 min) and a mixture[28] of 4-pyridylmethyl acetate (major component) and 3-acetoxy-4-methylpyridine (15%, R_f 11.5 min). Peak enhancement without distortion was observed when authentic samples were added to the residue.

Thermal Stability of 1-Acetoxy-4-methylpyridinium Perchlorate. The apparatus used was the same as in the preceding two experiments. A solution of 1-acetoxy-4-methylpyridinium perchlorate[26] (16.50 g, 0.066 mol) in acetonitrile (50 ml) was refluxed for 3 hr. No barium carbonate was formed in the $Ba(OH)_2$ traps. After the acetonitrile was distilled, the residue was treated with ca. 30% NaOH solution and extracted with $CHCl_3$. The extract was dried and the solvent was removed to give 6.14 g (86%) of 4-methylpyridine N-oxide, mp 187–188° (lit.[29] mp 185–186°). The ir spectrum was identical with that of an authentic sample.

Registry No.—1 (R = Ph), 7259-53-2; 1 (R = H), 1003-67-4; 1 (R = t-Bu), 54410-45-6; 2, 108-24-7; 3 perchlorate, 1658-37-3; 4, 55410-46-7; tri-n-butylamine, 102-82-9.

References and Notes

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(2) Presented in part before the Organic Division at the 164th National Meeting of the American Chemical Society, New York, N.Y., Aug 1972.
(3) Grateful acknowledgment is made to the National Science Foundation for a research grant (NSF GP-3858) in partial support of this work.
(4) Abstracted from a portion of the Ph.D. Dissertation submitted by J.P.K. in May 1972 and by K.Y. in Aug 1969 at West Virginia University.
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(16) The authors wish to thank Reilly Tar and Chemical Co., Indianapolis, Ind., for a generous supply of this compound.
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(18) G. J. van Nieuwenberg and L. A. Hegge, *Anal. Chim. Acta*, **5**, 68 (1951).
(19) Analysis was performed with a Victoreen Model 4000 gas chromatograph using a 0.125 in. × 6 ft copper column packed with 20% Carbowax 20M on Chromosorb W. AW. HMDS (80/100 mesh) at an oven temperature of 210° and He pressure of 70 psi.
(20) In a separate experiment pure 1-phenyl-1-(4-pyridyl)methyl acetate was placed on the above GLC column and showed partial conversion to 1-phenyl-1-(4-pyridyl)methanol. TLC analysis of the crude reaction mixture showed the absence of 1-phenyl-1-(4-pyridyl)methanol.
(21) This material was prepared by the method described in ref 1.
(22) The analysis was based on the ratio of integration areas of the benzylic protons at δ 3.85 and the ester methine proton at δ 6.92.
(23) The CIDNP studies were performed using a Varian Associates HA-60-EL proton-stabilized high-resolution NMR spectrometer (60 MHz) with H_2O proton resonance used for the lock signal. Probe temperatures in these studies ranged from 35 to 141 ± 0.5° and were calibrated with ethylene glycol before and after each experiment. All N-oxides used were analytically pure and the acetic anhydride was distilled prior to use. Repetitive spectral scans were obtained over 10–120-min time periods at intervals of 3 sec or longer dependent on the scan region or reaction rate. At least five and usually ten identical samples were prepared for each. Emission (E) and/or enhanced absorption (A) were noted in some cases and recorded as a function of time. All reported chemical shift values (δ) are relative to Me_4Si.
(24) Spectral reproductions of the repetitive scan data are recorded in the Ph.D. Dissertation[4] of J.P.K.
(25) Analysis was performed with the column and instrument described in ref 19 at an oven temperature of 162° and He flow rate of 50 ml/min.
(26) This substance was prepared by the method of C. W. Muth and R. S. Darlak, *J. Org. Chem.*, **30**, 1909 (1965).
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(28) The interval between the two peaks of the esters was too close to obtain area ratios.
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Conformational Analysis. CVII. The Contribution of a β-Axial Methyl Group to the Cotton Effect of a Cyclohexanone[1,2]

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trans-3,5-Dimethylcyclohexanone has been prepared in optically active form and with known absolute configuration. For the *R,R* configuration, the amplitude of the optical rotatory dispersion curve was found to be +37°. The trisubstituted ketone, 3,3,5(*R*)-trimethylcyclohexanone, was also prepared and found to exhibit a positive optical rotatory dispersion curve. These data are not consistent with the octant rule, and it is concluded that theoretical interpretations of optical rotatory dispersion curves which omit explicit consideration of the σ system connecting the perturbing group and the carbonyl are too crude to be reliable.

The usefulness of Cotton effect curves, obtained either by optical rotatory dispersion or by circular dichroism measurements, for assigning absolute configuration was summarized by Djerassi.[4] It was shown that the carbonyl group possessed properties that made it particularly useful as a probe for carrying out this kind of investigation. The octant rule gave a qualitative theoretical rationalization of the sign of the Cotton effect, as determined by the position of a perturbing substituent in the vicinity of the carbonyl.[5] Cyclohexanones, with their reasonably well-defined geometries, were early candidates for thorough study. It was found that an axial or equatorial group on carbon 2 (the α carbon) of a cyclohexanone, or an equatorial group on a carbon 3 (the β carbon) of a cyclohexanone, gave a Cotton effect in accord with theoretical predictions.[4]

The theory behind the octant rule was worked out on the level of the one-electron approximation for the case of a perturbing substituent and a carbonyl group interacting in space without regard to the intervening molecular structure.[6] Such a treatment indicated that the β-axial substituent should show a considerably larger Cotton effect than the β-equatorial substituent. At the time the present investigation was undertaken (1965), there were two kinds of β-axial methylcyclohexanones known for which absolute configurations and optical rotatory dispersion curves were available.[7] These were the 5α-methyl-3-keto steroids, which showed amplitudes of +18 (predicted about +50), and the corresponding 5β-methyl compounds, which showed amplitudes of +7 (predicted −50). Because these examples were somewhat complex, it was considered desirable to prepare simple molecules of known absolute configuration with β-axial methyl groups, so that the experimental data would be on a better footing. After this work was completed, additional similar examples of the failure of the octant rule were described in the literature.[8-10]

The compounds examined in the present investigation were optically active *trans*-3,5-dimethylcyclohexanone and the further methylated derivative, 3,3,5-trimethylcyclohexanone. The chair conformations in these molecules may be assumed to be close to ideal in geometry. It is at once apparent that carbons 2, 4, and 6, lying as they do in nodal planes, make no contribution to the Cotton effect curve. In addition, the contributions of C-3 and C-5 being equal and opposite, cancel; and the observed Cotton effect is therefore associated with the methyl groups. In *trans*-3,5-dimethylcyclohexanone, therefore, to the extent that the molecule is in the chair form, the amplitude of the Cotton effect would be the sum of the positive contribution of the axial methyl at C-3 and negative contribution from the equatorial methyl at C-5. In 3,3,5-trimethylcyclohexanone, the amplitude of the Cotton effect would come solely from the C-3 axial methyl group, since the contributions of the equatorial methyl groups at C-3 and C-5, being equal and opposite, would cancel.

In the present work, samples of these compounds were desired which were not only optically active, but of known absolute configuration. There are a number of methods available for the resolution of ketones, but most of them are not very general. Alcohols, on the other hand, can be resolved much more reliably.[11] In the present case, a reduction of the desired ketone to an alcohol would give a resolvable product, but at the expense of the introduction of another asymmetric center. One would then have the problem of establishing the absolute configuration.

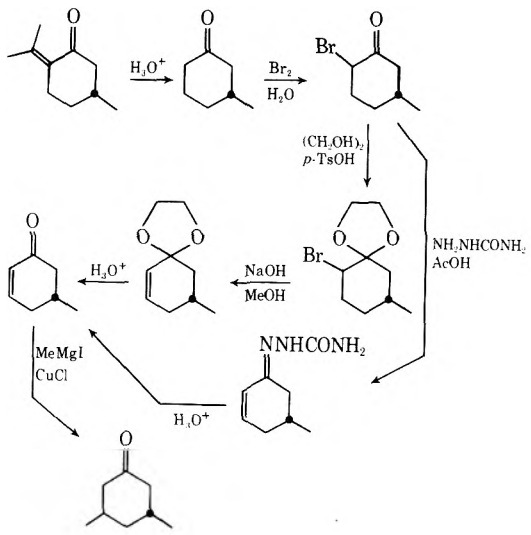
An alternative approach to obtaining the required compounds consists of beginning with an available optically active material of known absolute configuration, and transforming it to the desired compounds. The simple terpene (+)-pulegone[12] meets these requirements; it is of known[13] absolute configuration, and acid-catalyzed retroaldolization leads to (+)-3-methylcyclohexanone (see scheme).

Synthesis of *dl*-*trans*-3,5-Dimethylcyclohexanone. In connection with the synthetic work, large quantities of this compound were required. Since the cis isomer is the thermodynamically stable one, the trans isomer is not obtained in good yield by methods leading to a thermodynamic product. It had been previously obtained in two other ways at the outset of this work, both which were laborious and gave poor yields.[14-18]

Among the methods considered for the synthesis of the desired ketone was the Michael addition of methylmagnesium iodide to 5-methyl-2-cyclohexenone.[19] The 1,4 addition of a Grignard reagent to an α,β-unsaturated ketone appears to be an ordinary Michael-type addition, except that it is irreversible, and the product obtained from the reaction will be governed by kinetic control.[20,21] The Michael reaction has not been very thoroughly studied with respect to the stereochemistry of the product, which may often result from thermodynamic rather than kinetic control.[22-24] The stereochemical result of kinetic control has been explained on the basis of attack by the nucleophile perpendicular to the olefinic bond, and from the least hindered side of the molecule.

When the Michael addition of methylmagnesium iodide to 5-methyl-2-cyclohexenone was carried out with the aid of cuprous chloride,[25] *trans*-3,5-dimethylcyclohexanone was obtained in a yield of 55–68%. The purity of the product was 94–96%, with 4–6% of the cis isomer. This useful way for obtaining the *trans*-3,5-dimethylcyclohexanone has been previously described.[20]

The necessary *dl*-5-methyl-2-cyclohexenone is a known compound, its synthesis and physical properties having been described in the literature by Blanchard and Goering.[19] The present synthesis followed their method, and



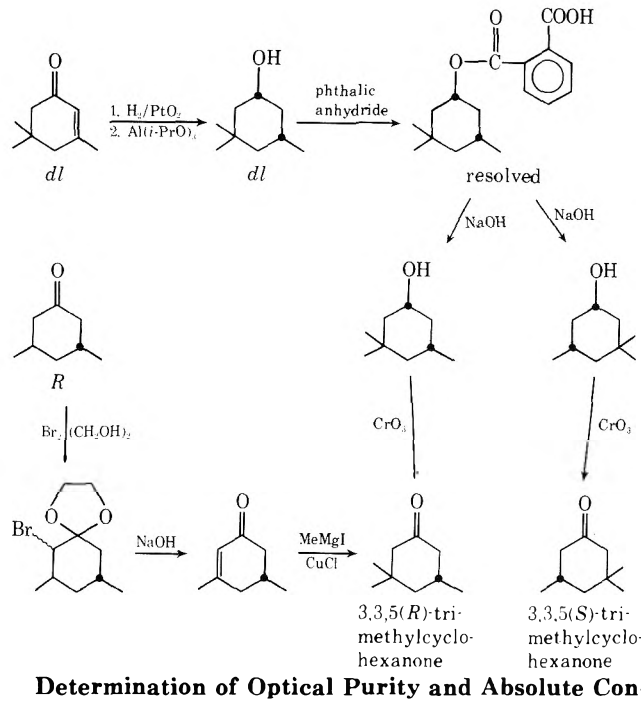
began with 5-methyl-1,3-cyclohexanedione.[26] The preparation of such cyclic enol ethers has been studied by others, and an improved procedure was reported by Frank and Hall.[27] Reduction of the cyclic enol ether by means of lithium aluminum hydride, followed by hydrolysis, gave the desired 5-methyl-2-cyclohexenone in 94% yield.

It is possible to resolve 3-methylcyclohexanone, and then to convert this to *trans*-3(*S*),5(*S*)-dimethylcyclohexanone through the corresponding α,β-unsaturated ketone. While this was a successful approach, a more convenient synthesis (which gave the other enantiomer) is to begin with pulegone. This was converted by retroaldolization into (+)-3(*R*)-methylcyclohexanone.[28] This compound was converted to 2-bromo-5-methylcyclohexanone by modification of published procedures.[28-30]

Dehydrobromination[31] of *trans*-2-bromo-5-methylcyclohexanone was accomplished in either of two ways: (a) via ethylene ketal formation followed by dehydrobromination with alkali and hydrolysis to the α,β-unsaturated ketone; or (b) direct dehydrobromination with semicarbazide, followed by hydrolysis to the ketone. Of the two procedures, a gave a higher overall yield (65%) but was time consuming, whereas b gave a reduced overall yield (55%) but was faster and involved fewer steps. The addition of methyl Grignard to the α,β-unsaturated ketone gave *trans*-3(*R*),5(*R*)-dimethylcyclohexanone, which was purified via this semicarbazone followed by vapor phase chromatography.

Synthesis and Resolution of 3,3,5-Trimethylcyclohexanone. The desired product was synthesized in two ways. Beginning with *trans*-3(*R*),5(*R*)-dimethylcyclohexanone obtained as previously described, bromination in ethylene glycol gave in 87% yield a mixture of the ethylene ketals of the diastereomeric 2-bromo derivatives. Dehydrobromination with alcoholic alkali gave 3,5-dimethyl-2-cyclohexenone. To this was added methylmagnesium iodide in the presence of cuprous chloride, which gave the desired 3,3,5(*R*)-trimethylcyclohexanone.

The enantiomer of the latter was also obtained beginning with isophorone. The latter was reduced to the corresponding dihydro ketone with hydrogen and platinum oxide. When this ketone was reduced with aluminum isopropoxide, according to the modified method of Wicker,[32] there was obtained a 68% yield of the stable cis alcohol. This was converted to the acid phthalate, which was resolved with brucine. The salt was hydrolyzed with acid to give back the phthalate, which upon saponification gave the optically active alcohol, which was oxidized with Jones reagent[33] to the 3,3,5(*S*)-trimethylcyclohexanone.



Determination of Optical Purity and Absolute Configuration. Stringent precautions were taken during the course of all reactions and purifications to eliminate contamination. There was no possibility of racemization throughout the reaction scheme. In the step where the Grignard reagent was added to 5-methyl-2-cyclohexenone, any addition from the wrong side of the ring leads not to the enantiomer, but to the diastereomeric meso compound. The latter is separable by vapor phase chromatography, and therefore the *trans*-3(*R*),5(*R*)-dimethylcyclohexanone obtained from pulegone was considered to be optically pure.

The 3,3,5-trimethylcyclohexanone obtained from pulegone must similarly be optically pure, and of the *R* configuration. The sample obtained by resolution of *dl-cis*-3,3,5-trimethylcyclohexanyl acid phthalate had a rotation only 75% that of the sample obtained from pulegone, and of the opposite sign. It was accordingly assigned the *S* configuration and an optical purity of 75%. The optical rotatory dispersion (ORD) and circular dichroism data (CD) are summarized in Table I.

Results and Discussion

The amplitude of the ORD curve for *trans*-3(*R*),5(*R*)-cyclohexanone is +37°, and the contribution of the equatorial methyl should be +26°, so this leaves a contribution of +11° for the axial methyl. The trimethyl ketone also has a positive contribution from the axial methyl. Since the second extremum could not be located, its magnitude cannot be ascertained.

The circular dichroism curve for 3,5-dimethylcyclohexanone is in reasonable agreement with the ORD curve, and when the curves were determined as functions of temperature, no qualitative change was observed. For the 3,3,5-trimethylcyclohexanone, the circular dichroism curve is very weakly positive at room temperature, and becomes more positive as the temperature is lowered. The ORD curve is qualitatively positive.

The octant rule indicates that a negative contribution is to be expected from the axial methyl in question, and the one-electron theory[6] gives the magnitude on the order of −50° for this group. Since the experimental values and absolute configurations seem secure, the result was quite surprising at the time, and required rationalization. There seemed to be three possible explanations: (1) anomalous

Table I
Optical Rotatory Dispersion and Circular Dichroism Data

ORD Cotton Effect Curve (MeOH), at 25°

Compd	Extrema				
	[α]	λ, nm	[α]	λ, nm	[A]
trans-3(*R*),5(*R*)-Dimethylcyclohexanone	+1191	308	−1708	268	+37
3,3,5(*R*)-Trimethylcyclohexanone	−17	330[a]	−10	310[a]	
3,3,5(*S*)-Trimethylcyclohexanone (75% resolved)	+24	330[a]	+18	310[a]	

CD Cotton Effect Curves

A. *trans*-3(*R*),5(*R*)-Dimethylcyclohexanone (EPA)

Temp, °K	$[\theta]_{max}$	λ, nm	[A]
298	+1904	298	+23
199	+1925	298	+24
81	+2745	298	+33

B. 3,3,5(*R*)-Trimethylcyclohexanone (EPA)

Temp, °K	$[\theta]_{max}$	λ, nm	[A]
298	+96	296	+1
244	+140	295	+2
199	+277	295	+3
81	+867	293	+11

[a] The extrema at 330 nm are not those directly pertaining to the Cotton effect, but are a result of the Cotton effect being superimposed on a plain curve of opposite sign. The first extrema of the Cotton effect curves are those at 310 nm. The second extrema were not detected down to 270 nm.

solvent effects are present; (2) boat forms contribute appreciably to the Cotton effect; (3) the octant rule is invalid. These possibilities will be examined.

(1) The possibility of an equilibrium involving differently solvated species may be considered. Such equilibria are known to occur, but generally involve α-substituted cyclohexanones or their analogs.[34] Although in the present case the possibility of solvational equilibria cannot be ruled out, it seems an unlikely interpretation of the facts.

(2) In principle, the possibility always exists that a small concentration of a conformation with a very large Cotton effect will override the modest Cotton effect of the major conformation present. In this case, the question is whether or not sufficient nonchair form could be present to account for the observed results. In each of the molecules studied there is present one axial methyl group at C-3 in the chair form. Because of the 3-alkyl ketone effect, the conformational enthalpy of a 3-axial methyl group is approximately 1.4 kcal/mol.[35] This repulsion could be relieved if the molecule were to adopt a suitable boat or twist conformation. The most thorough studies reported on the energies of nonchair forms of cyclohexanone give values for the twist boat (C_2) of 2.72 kcal/mol,[36] for the C_1 boat 3.77 kcal/mol, and for the C_s boat, 5.33 kcal/mol. If the unfavorable steric effects of the axial methyl could be completely relieved in the twist-boat conformation, the latter would still have an energy of 1.3 kcal/mol, relative to the chair form. Thus if the anomalous positive Cotton effect were a result of the minor concentration of boat forms, the Cotton effect would have to shift in the negative direction upon the reduction of the temperature. This is not what is observed, and it rules out the possibility that the anomaly is due to boat forms.

(3) The only remaining alternative is the failure of the octant rule in the case at hand. The octant rule in its original form was concerned only with perturbing groups placed in the environment of the carbonyl. To the extent that that simple picture is correct, the quantitative theory developed should probably also be correct, although it was a one-electron theory, and not free from the various shortcomings associated with such a theory. Thus while the quantitative value predicted by the theory might be questioned, it seems clear that the qualitative result predicted by the octant rule is simply not borne out by experiment.

When this work was completed in 1966, we were unable to proceed beyond this point. However, subsequent publications now make it clear what the situation actually is. First, there is the important paper by Pao and Santry,[10] which takes into account the entire valence shell of the molecule, and predicts anti-octant behavior of modest magnitude for the effect of the β-axial methyl. They did not speculate in any detail as to why anti-octant behavior was calculated for the methyl, but say it is a result of the *n* orbital being mixed into the σ part of the carbon framework.

Note that the theoretical work to date has not allowed for deformations of the cyclohexanones from ideal geometry, but for the cases at hand, such deformation will probably lead to only small numerical differences, not to qualitative differences. Finally, additional experimental examples have been found[8,9] where a β-axial methyl leads to a small or anti-octant behavior in other systems which are rigid, so deformation into boat structures is impossible.

The octant rule as originally proposed was a simple model, based on an isolated carbonyl group and a perturbing group. Whether the octant rule for predicting the sign of an ORD curve would work depended on the accuracy to which this model represented the real situation. As the work of Pao and Santry shows, the octant rule is simply

wrong in the case of a β-axial methyl group. The model predicts an effect opposite from that which is given by more complete calculations, and the latter are borne out by experiment. The important point to be made is that if the model used to develop the octant rule fails, then it fails, and the fact that it works in a great many cases is of limited consolation. It means that the rule will be successful and will work in cases which are essentially identical with those where it is already known to work, but when one faces structural situations which are novel, one cannot count on the octant rule. On the other hand, presumably the method of Pao and Santry, perhaps with further refinement if necessary, should be extendable to the general case. There has been some recent discussion about the "front octants", and their location, and the effect of putting substituents into those octants.[37] The important point made here is that because of extra nodal surfaces appearing in the orbital which is nominally considered to be the *n* orbital on oxygen, the original octant rule is quite invalid. The observed effects may well result from something quite different than the presence of a "front octant". Quantitative calculations on the experimentally studied systems are needed to settle the point.

Experimental Section

***dl*-5-Methyl-2-cyclohexenone.** 5-Methyl-1,3-cyclohexanedione was prepared from the ethoxide-promoted reaction of ethyl crotonate with acetoacetic ester.[26] The dione was converted to the enol ether (3-ethoxy-5-methyl-2-cyclohexenone) with *p*-toluenesulfonic acid in ethanol.[27] The enol ether was reduced with lithium aluminum hydride to give, after fractional distillation through a 1-ft Podbielniak column, a 94% yield of a colorless oil: bp 54° (5 mm); n^{25}D 1.4740 [reported[19] bp 60° (8 mm), $n^{25}D$ 1.4739]; $\nu_{C=O}$ 1691 cm^{-1} (neat). A sample of the ketone was purified through the semicarbazone. Recrystallization gave plates, mp 178–179° (reported[19] mp 177.5–179°).

The 2,4-dinitrophenylhydrazone, from ethyl acetate–ethanol, was obtained as orange-red needles, mp 152–152.3° (reported[19] mp 152–152.5°).

***dl-trans*-3,5-Dimethylcyclohexanone.** The dimethyl ketone was prepared according to the method used by Kharasch and Tawney[25] for the preparation of 3,3,5,5-tetramethylcyclohexanone. Magnesium turnings (2.7 g) were covered with 110 ml of dry ether under nitrogen, and 15.6 g of methyl iodide in 50 ml of ether was added with stirring at a rate so as to keep the ether refluxing. More ether (110 ml) was added at the end of 15 min and 1 hr (50 ml). As the magnesium was dissolved and the refluxing ceased, 100 mg of dry curpous chloride was added and the mixture was cooled to 5°. A solution of 11 g of ketone in 50 ml of ether was added in the course of 1 hr. The mixture was stirred and maintained at about 10° during the addition of the ketone, heated for an hour, and then allowed to stand overnight. Ice and glacial acetic acid were added to decompose the reaction complex, with cooling. The ether layer was separated and dried over sodium carbonate and the ether was evaporated. The residue was distilled through a 1-ft Podbielniak column, bp 36–37° (1.5 mm). The yield of colorless oil was 55–68%. The 2,4-dinitrophenylhydrazone was obtained as orange needles, mp 109.6–110.5° (reported[16] mp 109.6–110.3°). The mixture melting point with the cis isomer (mp 167–168°) was depressed but that with the authentic trans compound[16] was not. A sample of the ketone was purified further by means of vapor phase chromatography using a column of tricyanoethoxypropane (20%) of 60–80 mesh firebrick, and comparison with authentic samples[16] showed that the ketone contained 94–96% of the trans isomer and 4–6% of the cis isomer.

Synthesis of *trans*-(−)-3(*R*),5(*R*)-Dimethylcyclohexanone. (+)-3(*R*)-Methylcyclohexanone. Commercially available (+)-pulegone (Aldrich Chemical Co., 300 g) was converted to (+)-3-methylcyclohexanone, bp 47° (10 ml) (146 g, 66%), according to usual methods.[28] An equimolar amount of semicarbazide hydrochloride (147 g) was dissolved in 500 ml of water and 160 ml of pyridine and the ketone in 500 ml of methanol was added. The mixture was then warmed gently on the steam bath until the solution was clear and it was then seeded and cooled. The crude solid was recrystallized from 70% ethanol. Three crystallizations were necessary to obtain a constant melting point and specific rotation, and furnished 189.5 g of product in 86% yield, mp 180–181°, $[\alpha]^{25}$D −20.7° (*c* 1.45, absolute ethanol).

Anal. Calcd for $C_8H_{15}N_3O$: C, 56.78; H, 8.93. Found: C, 56.53; H, 8.71.

Hydrolysis of the semicarbazone with aqueous hydrochloric acid solution followed by distillation furnished 124 g of the pure ketone, bp 167–167.5° (745 mm), d^{25} 0.9109, $[\alpha]^{25}$D +12.56° (neat) [reported[28] $[\alpha]^{25}$D +12.01° (neat), bp 166.5–168° (735 mm)].

(−)-*trans*-2-Bromo-5-methylcyclohexanone. The bromination of (+)-3(*R*)-methylcyclohexanone was carried out by a modification of the procedure of Djerassi,[29] as follows. To the 35.75 g of ketone in 100 ml of water was added 50.94 g of bromine dropwise with vigorous stirring. The reaction flask was cooled to 15–20° and the rate of addition was adjusted so as to maintain a faint coloration of bromine at all times (*ca.* 8 hr). Sodium chloride was added to saturate the water layer, and the product was extracted with ether. The combined ether solutions were washed with water, sodium carbonate solution and water, the solution was dried over magnesium sulfate, and the solvent was evaporated, leaving 64 g of a pale yellow oil. The oil was twice distilled, and the fraction boiling at 72–77° (3 mm) was collected (54 g). The colorless oil was dissolved in a minimum amount of pentane and placed in a Dry Ice–acetone bath. After the collection of crystalline product, the mother liquor was condensed and the crystallization was repeated. After recrystallization of the crude product from ether–pentane, there was obtained a 32% yield of the pure bromo ketone, bp 58° (0.5 mm), mp 82.5–83°, $[\alpha]^{25}$D −64.8° (*c* 1.16, toluene) [reported[29] mp 83.5–84°, $[\alpha]$D −64.4° (*c* 1.06, toluene)]. This procedure gives a much better yield than that previously reported[28-30] (21%). The infrared spectrum was identical with that reported.

(−)-5-Methyl-2-cyclohexenone. A. From the Ethylene Ketal of (−)-*trans*-2-Bromo-5-methylcyclohexanone. (−)-*trans*-2-Bromo-5-cyclohexenone (12.5 g) was heated in 200 ml of benzene containing some ethylene glycol and 100 mg of *p*-toluenesulfonic acid for 6 hr, with continuous removal of the water formed. The mixture was washed with sodium carbonate solution and extracted with pentane, and the extracts were dried. Anhydrous sodium carbonate (20 g) was added to the pentane solution to take up excess glycol. Filtration of the solution, evaporation of the solvent, and distillation of the residue yielded 92% of the ketal, bp 77° (1 mm), d^{25} 1.3806, $[\alpha]^{25}$D −173.0° (neat).

Anal. Calcd for $C_9H_{15}O_2Br$: C, 45.98; H, 6.43. Found: C, 46.17; H, 6.36.

The dehydrobromination of 10 g of the bromo ketal was carried out by refluxing in 50 ml of methanol containing 12.5 g of sodium hydroxide for 72 hr. The solution was diluted with water, and the product was extracted with ether. The extracts were washed, and dried, and the solvent was evaporated. Distillation gave the unsaturated ketal (71%), bp 71° (10 mm), $[\alpha]^{25}$D −127.66° (*c* 1, chloroform).

The hydrolysis of the unsaturated ketal in dilute hydrochloric acid gave 96.3% of (−)-5-methyl-2-cyclohexenone, $[\alpha]^{25}$D −90.17° (*c* 0.767, chloroform), and the infrared spectrum was identical with those of the *dl* and (+) isomers. A sample of the ketone was converted to its semicarbazone derivative, mp 176.5–178°, $[\alpha]^{25}$D −206.01° (*c* 0.505, absolute ethanol) (reported[19] mp 177.5–179°).

B. By Direct Formation of the Semicarbazone of (−)-5-Methyl-2-cyclohexenone. (−)-2-Bromo-5-methylcyclohexanone (1.91 g) in 10 ml of glacial acetic acid in a flask under a nitrogen atmosphere was heated with stirring, 1.125 g of freshly prepared semicarbazide was added, and the solution was maintained at boiling for 5 min. After dilution of the solution with water, the product was collected and recrystallized from ethyl acetate–ethanol. A 65% yield of the semicarbazone was obtained, $[\alpha]^{25}$D −205.88 (*c* 0.601, EtOH), mp 175–177.5° (reported[19] mp 177.5–179°). There was no depression of the mixture melting point with the sample obtained from A described above. Hydrolysis of the semicarbazone gave the ketone (−)-5-methyl-2-cyclohexenone, identical with that prepared from procedure A. The 2,4-dinitrophenylhydrazone had $[\alpha]^{25}$D −221.9° (*c* 0.261, chloroform) [reported[29] mp 143–145°, $[\alpha]$D −219° (*c* 0.06, chloroform)].

***trans*-3(*R*),5(*R*)-Dimethylcyclohexanone.** From 9 g of (−)-5-methyl-2-cyclohexenone, 7.2 g (69.8%) of *trans*-3(*R*),5(*R*)-dimethylcyclohexanone was obtained according to the method described above for the preparation of the *dl* compound. The ketone was purified via the semicarbazone derivative, mp 180–181°, $[\alpha]^{25}$D −54.89° (*c* 1, absolute ethanol).

Anal. Calcd for $C_9H_{17}N_3O$: C, 58.98; H, 9.35. Found: C, 59.03; H, 9.43.

After hydrolysis of the semicarbazone, the ketone was further purified by vapor phase chromatography, $[\alpha]^{25}D$ −15.05° (neat), $[\alpha]^{25}D$ −12.28° (*c* 1.118, chloroform). The infrared and NMR spectra were identical with those of the *dl* compound.

Synthesis of 3,3,5(*R*)-Trimethylcyclohexanone. A. By Resolution of *dl*-3,3,5-Trimethylcyclohexanone. *dl-cis*- and *trans*-3,3,5-Trimethylcyclohexanol. Purified isophorone[37] was reduced with 1 mol of hydrogen and platinum oxide. Distillation gave 93% of 3,3,5-trimethylcyclohexanone, bp 67–69° (10 mm). This ketone was then reduced with aluminum isopropoxide according to Hardly and Wicker[32] as follows: 140.5 g of the ketone was mixed with aluminum isopropoxide solution (900 ml of 10% solution in isopropyl alcohol) and the resulting solution was refluxed for 24 hr and then very slowly distilled until acetone was no longer detectable in the distillate by dinitrophenylhydrazone formation (6 hr). Most of the isopropyl alcohol was then removed, the residue was poured into 2 l. of water, and hydrochloric acid was added until the solid had dissolved. The mixture was extracted with ether using a continuous extractor. The ether solution was washed with water and dilute carbonate solution, and the solvent was evaporated. The residue was distilled to give a 68% yield of *cis*-3,3,5-trimethylcyclohexanol, after fractional recrystallization from hexane as described above.

The cis alcohol (128 g) was dissolved in 400 ml of dry pyridine, the solution was cooled to 0°, and 185.6 g of purified *p*-nitrobenzoyl chloride was added in small portions. The solution was allowed to stand overnight with stirring. The mixture was poured into water, and the crude product was collected by filtration, dried, and extracted with petroleum ether through a Soxhlet tube to remove insoluble *p*-nitrobenzoic acid. The product was allowed to crystallize, and recrystallization from petroleum ether and methanol gave the ester (86%), mp 80.5–81°.

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27. Found: C, 65.79; H, 7.42.

The benzoate (65 g) was added to 400 ml of hot, stirred 2.5 *N* sodium hydroxide solution. The alcohol was removed as formed by azeotropic distillation with water. The distillate was extracted with ether, the combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated. The residue was distilled through a 1-ft Podbielniak column at reduced pressure, yield 87%, mp 36–36.4° (reported[38] mp 37°).

***dl-cis*-3,3,5-Trimethylcyclohexanyl Acid Phthalate.** A solution of *dl-cis*-3,3,5-trimethylcyclohexanol (72 g) with 74 g of phthalic anhydride in 300 ml of benzene was refluxed for 16 hr. After cooling, the reaction mixture was filtered and the solvent was distilled. The residue was dissolved in anhydrous ether and cooled in the refrigerator. After three recrystallizations there was obtained 132.9 g (91%) of pure acid phthalate, mp 129–129.5° (reported[39] mp 129°).

Cinchonine Salt of *dl-cis*-3,3,5-Trimethylcyclohexanyl Acid Phthalate. The *dl-cis*-3,3,5-trimethylcyclohexanyl acid phthalate (58 g) in 500 ml of dry acetone–chloroform (1:1) with 58 g of cinchonine was refluxed until the solution was clear. The solvent was removed, and the residual oil was dissolved in a minimum amount of warm chloroform. The solution was then cooled to room temperature and allowed to stand. After about seven crystallizations, the rotation remained constant, $[\alpha]^{24.5}D$ +93.83° (c 5, chloroform), mp 99–101°.

Anal. Calcd for $C_{36}H_{44}N_2O_5$: C, 73.93; H, 7.53. Found: C, 73.87; H, 7.44.

(−)-*cis*-3,3,5-Trimethylcyclohexanyl Acid Phthalate. The cinchonine salt (15 g) was added to hot 10% hydrochloric acid, and the solution was stirred for 30 min. The suspension was cooled and filtered. The solid collected was ground in a mortar with a small amount of water, refiltered, and washed with dilute hydrochloric acid and distilled water. After air drying, the solid was recrystallized from ether to constant rotation, yield 5.5 g, mp 129–129.5°, $[\alpha]^{24.5}D$ −3.19° (*c* 5, chloroform).

(−)-*cis*-3,3,5-Trimethylcyclohexanol. The acid phthalate (18 g) was dissolved in 100 ml of 0.5 *N* sodium hydroxide solution and the solution was refluxed for 1 hr, then cooled and extracted with ether. The extracts were dried over magnesium sulfate, and the solvent was evaporated. The residual oil was distilled through a 1-ft Podbielniak column and gave an almost quantitative yield of the alcohol, which boiled at 85° (10 mm). The alcohol was further purified by sublimation, mp 34–34.5°. The specific rotation of the alcohol was not changed by the sublimation, $[\alpha]^{24.5}D$ −2.99° (c 1, chloroform).

3,3,5(*R*)-Trimethylcyclohexanone. To the alcohol (4.3 g), in 20 ml of acetone was added Jones reagent (8 *N*),[33] over a period of 10 min with stirring. The addition was stopped as the solution turned to a slightly brown color. The stirring was continued for an additional 10 min, and the solution was poured into 200 ml of water. The resulting solution was extracted with ether, the extracts were dried over sodium sulfate, and the solvent was evaporated. The residual oil was distilled through a 1-ft Podbielniak column, yield 93%, bp 67° (ca. 10 mm). The rotation, $[\alpha]^{24.5}D$ −6.52° (c 5, chloroform), indicated that the ketone was only partially resolved.

B. From *trans*-3(*R*)-5(*R*)-Dimethylcyclohexanone. (−)-3,5-Dimethyl-2-cyclohexenone. To *trans*-3(*R*),5(*R*)-dimethylcyclohexanone (4.5 g) in 45 ml of ethylene glycol was added 5.73 g of bromine during 6 hr. The reaction mixture was worked up according to the procedure described for the preparation of the ethylene ketal of 2-bromo-5-methylcyclohexanone and gave 7.66 g (87.6%) of the bromo ketal, bp 73° (0.3 mm), $[\alpha]^{25}D$ −16.72° (*c* 1, chloroform). The bromo ketone was dehydrobrominated in 29% yield, applying the same procedure as was described for the preparation of the ketal of 5-methyl-2-cyclohexenone. Hydrolysis of the ketal with 10% hydrochloric acid gave 470 mg of (−)-3,5-dimethyl-2-cyclohexenone, which was purified further by vapor phase chromatography, bp 73° (ca. 10 mm), $n^{25}D$ 1.4820, $[\alpha]^{25}D$ −138.39° (c 0.8, chloroform) [reported[40] bp 84–85° (11 mm), $n^{20}D$ 1.4843].

3,3,5(*R*)-Trimethylcyclohexanone. The (−)-3,5-dimethyl-2-cyclohexenone purified by vapor phase chromatography (470 mg) in 5 ml of anhydrous ether was allowed to react with the Grignard reagent prepared from 96.6 mg of magnesium, 564 mg of methyl iodide, and 5 mg of cuprous chloride following the procedure described for the synthesis of *trans*-3,5-dimethylcyclohexanone. There was obtained, after further purification by vapor phase chromatography, 414 mg (78%) of the trimethyl ketone, $[\alpha]^{25}D$ −27.04° (*c* 0.9, chloroform). The infrared spectrum was identical with that of the *dl* isomer.

Synthesis of 3,3,5(*S*)-Trimethylcyclohexanone. Brucine Salt of *dl-cis*-3,3,5-Trimethylcyclohexyl Acid Phthalate. A solution of 58 g of *dl-cis*-3,3,5-trimethylcyclohexyl acid phthalate in 500 ml of reagent acetone with 79 g of powdered anhydrous brucine was warmed until the solution was clear. It was then placed in a refrigerator overnight and gave an almost quantitative yield of the salt. This mass was crushed to a powder and subjected to fractional extraction through a Soxhlet tube with dry acetone. The less soluble isomer which remained in the thimble after the extraction with about 2 l. of acetone was removed and recrystallized twice from acetone, three times from methanol, and five times from ethyl acetate until the specific rotation was constant, mp 130–132°, $[\alpha]^{24.5}D$ −15.2° (*c* 5, chloroform).

Anal. Calcd for $C_{40}H_{48}N_2O_8$: C, 69.53; H, 8.46; N, 3.47. Found: C, 69.61; H, 8.34; N, 3.59.

(+)-*cis*-3,3,5-Trimethylcyclohexanyl Acid Phthalate. The hydrolysis of the brucine salt was carried out by the same procedure as described for that of the cinchonine salt. The half-ester had mp 129.5°, $[\alpha]^{24.5}D$ +8.16° (*c* 5, chloroform).

(+)-*cis*-3,3,5-Trimethylcyclohexanol. The (+) acid phthalate (22 g) was saponified by the procedure used for the preparation of (−)-cis alcohol. A 94.6% yield of (+)-cis alcohol having $[\alpha]^{24.5}D$ +9.43° (c 1, chloroform), mp 37.5°, was obtained.

3,3,5(*S*)-Trimethylcyclohexanone. The Jones oxidation was carried out as described for the *R* isomer. The yield was 4.67 g (92%), bp 67° (ca. 10 mm), $[\alpha]^{24.5}D$ +20.29° (c 1, chloroform). The ultraviolet absorption spectrum showed a peak at 292 mμ (ε 19.7, 0.03914 g/100 ml of ethanol solution). A sample of the ketone was purified via the semicarbazone. Recrystallization gave plates, mp 194–195°, $[\alpha]^{25}D$ +201.2° (*c* 1, chloroform).

Anal. Calcd for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71. Found: C, 60.93; H, 9.88.

After hydrolysis of the semicarbazone, the ketone obtained was further purified by vapor phase chromatography; however, there was no change in the optical rotation, indicating that the material was only 75.0 ± 0.2% optically pure.

Registry No.—5-Methyl-1,3-cyclohexanedione, 4341-24-6; *dl*-5-methyl-2-cyclohexenone, 54352-35-1; *dl*-5-methyl-2-cyclohexenone semicarbazone, 54307-70-9; *dl*-5-methyl-2-cyclohexenone 2,4-dinitrophenylhydrazone, 54307-71-0; *dl-trans*-3,5-dimethylcyclohexanone, 54307-72-1; *trans*-(−)-3(*R*),5(*R*)-dimethylcyclohexanone, 54352-36-2; (+)-3(*R*)-methylcyclohexanone, 13368-65-5; (+)-3(*R*)-methylcyclohexanone semicarbazone, 54307-73-2; (−)-*trans*-2-bromo-5-methylcyclohexanone, 18951-83-2; (−)-5-methyl-2-cyclohexenone, 54307-74-3; (−)-*trans*-2-bromo-5-methylcyclohexanone ethylene ketal, 54307-75-4; ethylene glycol, 107-21-1; (−)-5-methyl-2-cyclohexenone ethylene ketal, 54307-76-5; (−)-5-

methyl-2-cyclohexenone semicarbazone, 54352-37-3; (−)-5-methyl-2-cyclohexenone 2,4-DNP, 54307-77-6; *trans*-3(*R*),5(*R*)-dimethylcyclohexanone semicarbazone, 54307-78-7; 3,3,5(*R*)-trimethylcyclohexanone, 33496-82-1; *dl-cis*-3,3,5-trimethylcyclohexanol, 54307-79-8; *p*-nitrobenzoic acid, 62-23-7; *dl-cis*-3,3,5-trimethylcyclohexanyl *p*-nitrobenzoate, 54307-80-1; *dl-cis*-3,3,5-trimethylcyclohexanyl acid phthalate, 54307-81-2; phthalic anhydride, 85-44-9; *dl-cis*-3,3,5-trimethylcyclohexanyl acid phthalate cinchonine salt, 54307-82-3; cinchonine, 24831-03-6; (−)-*cis*-3,3,5-trimethylcyclohexanyl acid phthalate, 54352-38-4; (−)-*cis*-3,3,5-trimethylcyclohexanol, 54352-39-5; (−)-3,5-dimethyl-2-cyclohexenone, 54307-83-4; 3,3,5(*S*)-trimethylcyclohexanone, 33496-83-2; brucine, 357-57-3; *dl-cis*-3,3,5-trimethylcyclohexanyl acid phthalate brucine salt, 54307-84-5; (+)-*cis*-3,3,5-trimethylcyclohexanyl acid phthalate, 54352-40-8; (+)-*cis*-3,3,5-trimethylcyclohexanol, 54352-41-9; 3,3,5(*S*)-trimethylcyclohexanone semicarbazone, 54307-85-6.

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Effect of Changes in Surfactant Structure on Micellarly Catalyzed Spontaneous Decarboxylations and Phosphate Ester Hydrolysis[1]

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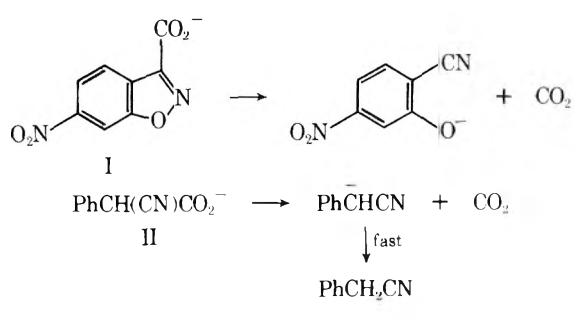
Micelles of the zwitterionic surfactant, *N,N*-dimethyl-*N*-dodecylglycine, catalyze the spontaneous decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion 170-fold and that of cyanophenyl acetate ion 690-fold, and they, and micelles of the corresponding alanine surfactant, are better catalysts than dodecyltrimethylammonium bromide by factors of almost 3-fold. The catalytic efficiency of cationic micelles of *N,N*-dimethyl-*N*-hydroxylethyl-2-hexadecylammonium bromide is also increased 2-fold by conversion of this surfactant into a zwitterion at high pH. Lecithin and lysolecithin are very poor catalysts, showing that the arrangement of charge in the zwitterionic head group is of key importance. Catalysis by micelles of *N,N*-dimethyl-*N*-dodecylglycine is subject to large salt effects which depend upon the anion, but differ from those typical of micellar catalysis. Salts having hydrophilic anions tend to increase catalysis and those having hydrophobic anions decrease it. Chemically inert solutes such as phenols and aliphatic amines change the catalytic effectiveness of micelles of cetyltrimethylammonium bromide, but these micelles in aqueous ethylene glycol, or the reverse micelles in hexanol–water, are poor catalysts both for decarboxylation and for the spontaneous hydrolysis of 2,4-dinitrophenyl phosphate dianion.

The spontaneous decarboxylations of 6-nitrobenzisoxazole-3-carboxylate ion (I)[3] and 2-phenylcyanoacetate ion (II)[4] are catalyzed strongly by cationic micelles[5,6] and by cyclodextrins.[7] The micellar catalysis is enhanced by some electrolytes, which is an unusual feature because micellar catalysis is generally decreased by added electrolytes.[8]

These decarboxylations are much faster in organic or aqueous organic solvents than in water,[3,4] and these observations together with the unusual electrolyte effect on micellar catalysis suggest that these reactions may provide a useful probe of the nature of the micellar surface.[5,6] The enhancement of the rate of decarboxylation of I in cationic micelles of cetyltrimethylammonium bromide (CTABr)



containing less than 1 equiv of sodium tosylate was explained in part in terms of an initial state electrostatic re-

pulsion between the carboxylate moiety of the substrate and tosylate ion occupying neighboring sites in the micelle, and it seemed probable that micelles of zwitterionic surfactants might be effective catalysts.[11,12] Micelles of synthetic zwitterionic surfactants and liposomes of phospholipids have been shown to be effective catalysts of the addition of cyanide ion to *N*-alkylpyridinium ions,[13] but our interest was in a micellarly catalyzed unimolecular reaction, where the factors affecting the catalysis are more easily analyzed.[5]

Reverse micelles have been found to be powerful catalysts for many bimolecular reactions,[14] and therefore we examined their effect upon the unimolecular decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion and also upon the spontaneous hydrolysis of the 2,4-dinitrophenyl phosphate dianion, because this reaction is similar to the spontaneous decarboxylations of I and II in its solvent[15] and micellar effects.[16] The spontaneous decomposition of 2,4-dinitrophenyl sulfate is catalyzed strongly by reverse micelles of alkylammonium carboxylates in benzene.[17]

The dependence of catalysis upon micellar charge is well understood, and for bimolecular reactions catalysis is decreased by screening the micelle with counterion or by going from ionic to zwitterionic head groups.[9-12] The aim of the present work was to examine the extent to which catalysis of unimolecular reactions could be controlled by changing the charge arrangement of the head group, or by incorporation of inert solutes into the Stern layer.

Experimental Section

Materials. The preparation and purification of the substrates and most of the surfactants have been described.[5,6,16,18]

The *N,N*-dimethyl glycine and alanines were prepared by reductive methylation,[19] and were purified by recrystallization from MeOH–Me_2CO or EtOH–Et_2O at 0°. Their melting points and optical rotation agreed well with literature values. These amines were quaternized with bromododecane, usually in 2-propanol, and the glycine derivative (III) and the alanine derivative (IV)[20] were crystallized from acetone. The rotation of the hydrobromide of *N*-dodecyl-*N,N*-dimethyl-L-alanine was $[\alpha]^{25}_D$ −9.58° (lit.[20a] $[\alpha]^{20}_D$ −9.50°).

Sodium salts were generally reagent grade or were prepared in solution by neutralization of the acids, although the sodium arenesulfonates were recrystallized from EtOH, as were the mandelic acids (Aldrich). The phenols and amines were redistilled, generally under reduced pressure.

Kinetics. The reactions were followed spectrophotometrically at 25.0° using Gilford or Cary spectrophotometers with water-jacketed cell compartments.[5,6,16] The first-order rate constants, k_ψ, are in reciprocal seconds. The concentration of 6-nitrobenzisoxazole-3-carboxylate ion was generally 7×10^{-5} *M*, but because of the relatively small absorbance change during reaction that of 2-cyano-2-phenylacetate ion had to be in the range $7–10 \times 10^{-4}$ *M*.[6]

The surfactants were dodecyl- and hexadecyltrimethylammonium bromide (DDTBr and CTABr), *N,N*-dimethyl-*N*-dodecylglycine and -alanine (III and IV), and *N,N*-dimethyl-*N*-2-hydroxyethyl hexadecyl ammonium bromide (V).

$$n\text{-}C_{12}H_{25}\overset{+}{N}Me_2CH_2CO_2^- \quad \text{III}$$

$$n\text{-}C_{12}H_{25}\overset{+}{N}Me_2CHMeCO_2^- \quad \text{IV}$$

$$n\text{-}C_{16}H_{33}\overset{+}{N}Me_2CH_2CH_2OH\ Br^- \quad \text{V}$$

In the figures and tables C_D is used to denote the concentration of surfactant (detergent).

Effect of Phospholipids. We examined the effect of α-lecithin upon the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion using sonicated α-lecithin (Schwarz Mann, egg white, sonicated at 0° for 5-min periods until clear). However although the solutions were initially clear, they gradually became cloudy during the reaction so that we could not get good rate data. From the initial rate of formation of the phenoxide ion product we estimated that 2×10^{-3} *M* sonicated α-lecithin in 2×10^{-3} *M* ammonia buffer at pH 9.2 increased the reaction rate by a factor of less than threefold. Cordes and his coworkers noted that it was difficult to get good rate data for the reaction of cyanide ion with *N*-alkylpyridinium ions using liposomes of sonicated phospholipids.[13]

Table I
Salt Effects on the Decarboxylation of 6-Nitrobenzisoxazole-3-Carboxylate Ion in the Presence of Lysolecithin[a]

Added salt, m*M*	$10^6 k_\psi$, sec^{-1}	Added salt, m*M*	$10^6 k_\psi$, sec^{-1}
	3.7	27 $MgCl_2$	3.9
5.1 NaCl	6.6	0.26 $CaCl_2$	4.4
6.0 NaBr	4.8	0.51 $CaCl_2$	4.5
30 NaBr	2.9	1.3 $CaCl_2$	5.5
13 $NaNO_3$	2.5	5.1 $CaCl_2$	8.3
13 $MgCl_2$	4.6	13 $CaCl_2$	8.7

[a] With 6.3×10^{-4} *M* lysolecithin at 25.0° at pH 9.5 in 5×10^{-3} *M* NH_4Cl buffer: in the absence of lysolecithin $10^6 k = 2.8$ sec^{-1}.

Because of these problems with sonicated α-lecithin we also used lysolecithin (Sigma) because it forms normal micelles rather than liposomes.[21] Solutions of lysolecithin became cloudy during reaction of I, but this cloudiness was removed by centrifugation. Our first-order rate constants were determined by following the formation of the nitrophenoxide ion for approximately 1 half-life of reaction, and determining the absorbance of nitrophenoxide ion at complete reaction after centrifugation. By this method we could obtain reasonable first-order rate constants for up to 50% reaction. These normal micelles of lysolecithin are also poor catalysts (Table I), and only a low concentration of lysolecithin was used because of turbidity at higher concentrations. We ascribe this low catalytic efficiency of both α-lecithin and lysolecithin to the nature of the zwitterionic head group with its terminal quaternary ammonium ion.

Some added salts increase the rate of decarboxylation in the presence of lysolecithin (Table I). Calcium chloride is the most effective salt which we examined, probably because interactions between the phosphate moiety and calcium ions tend to convert the zwitterionic micelle of lysolecithin into a normal cationic micelle, although these interactions should also change the micellar structure. Sodium salts having relatively large anions, bromide or nitrate, have little effect or slightly inhibit the reaction (Table I).

Results

Decarboxylation of 2-Cyano-2-phenylacetate Ion (II). This substrate was not used extensively because its decarboxylation was followed at 235 nm, where many solutes absorb, and the overall absorbance change during reaction is small.[6]

The cationic surfactant dodecyltrimethylammonium bromide (DDTBr) is not as effective a catalyst as is CTABr (Figure 1). For CTABr the rate enhancement is by a factor of 660-fold at 25.0°, whereas for DDTBr it is 280-fold. (The broken line in Figure 1 relates to CTABr.[6]) As is generally found, the amount of surfactant required for catalysis de-

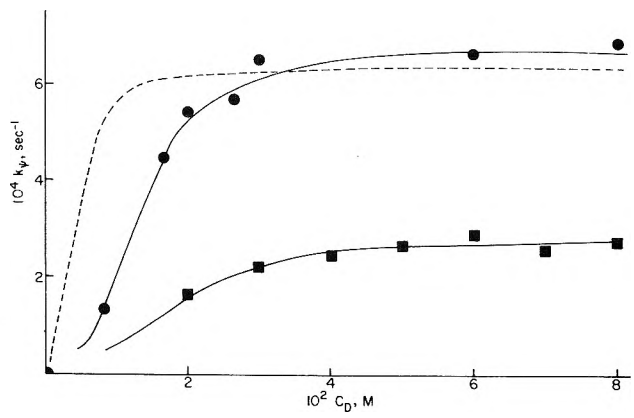


Figure 1. Decarboxylation of 2-phenylcyanoacetate ion at 25.0° in trisbuffer at pH 8: ■, DDTBr; ●, *N,N*-dimethyl-*N*-dodecylglycine. (The broken line is for CTABr, ref 6.)

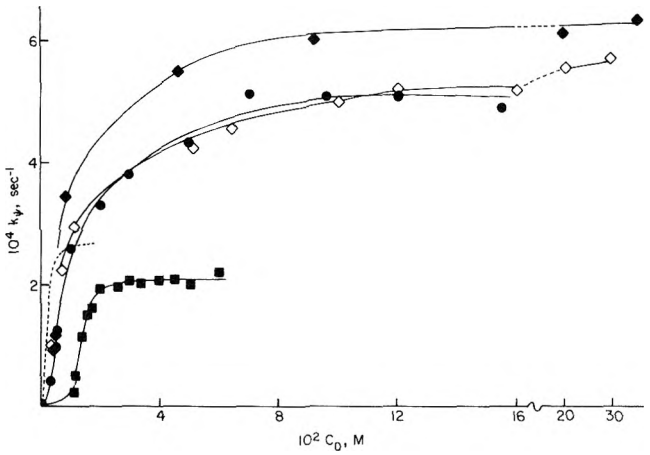


Figure 2. Decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion at 25.0° in ammonia buffer, pH 9.2: ■, DDTBr; ●, *N,N*-dimethyl-*N*-dodecylglycine; ◊ and ♦, L- and DL-*N,N*-dimethyl-*N*-dodecylalanine, respectively. (The broken line is for CTABr, ref 5.)

creases with increasing length of the *n*-alkyl group, e.g., the amount of surfactant required for 50% of the maximum rate is 1.8×10^{-2} *M* for DDTBr and ca. 0.5×10^{-2} *M* for CTABr. This difference comes in part from the lower cmc of CTABr as compared with the other surfactants,[20b] but probably the substrate is drawn more deeply into the Stern layer of the larger micelles formed by CTABr.

Micelles of the zwitterionic surfactant *N,N*-dimethyl-*N*-dodecylglycine (III) give greater rate enhancements for the reaction of II than does DDTBr, and despite the shorter chain length are slightly more effective than micelles of CTABr. In the absence of surfactant[6] $k_\psi = 9 \times 10^{-7}$ sec^{-1}.

Decarboxylation of 6-Nitrobenzisoxazole Carboxylate Ion in the Presence of Synthetic Surfactants. The overall pattern for micellar effects upon this reaction are qualitatively very similar to those described earlier for reaction of 2-cyano-2-phenylacetate ion (II). Micelles of the cationic dodecyl surfactant, DDTBr, are not as catalytically effective as those of CTABr; the respective rate enhancements are 70- and 95-fold; the surfactant concentrations for 50% rate enhancement are respectively 1.2×10^{-2} and 1.6×10^{-3} *M* (Figure 2).

Micelles of the zwitterionic dodecyl surfactants III, L-IV, and DL-IV derived from glycine and alanine are better catalysts than the cationic micelles, DDTBr and CTABr, even though their hydrophobic *n*-alkyl groups are shorter than that of the hexadecyl surfactant, CTABr.

Effect of Micelles of 1-Hydroxyethyl-2-hexadecyldimethylammonium Bromide. Micelles of the hydroxyethyl surfactant V are effective catalysts for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion (Table II).

The rate enhancement (90-fold) is very similar to that given by CTABr, but if the hydroxide ion concentration is increased so that V is converted into the zwitterion VI, the catalysis increases (Table II), as expected for a zwitterionic micelle. The pK_a of V estimated kinetically is 12.4,[18] which,

$$n\text{-}C_{16}H_{33}NMe_2CH_2CH_2OH + OH^- \rightleftharpoons n\text{-}C_{16}H_{33}\overset{+}{N}Me_2CH_2CH_2O^-$$

V VI

despite some dubious assumptions,[22] is in reasonable agreement with pK_a = 13.9[23] for choline, because micellization should increase acidity.

There is no evidence that the decarboxylation of I is affected by added strong bases of nucleophiles,[3] so the increasing catalysis by micelles of zwitterionic surfactant VI must be a medium effect due to the changing charge of the head group. [In high concentration (>1 *M*) sodium hydroxide increases the rate of decarboxylation catalyzed by dimethyldodecylglycine (III), and this increase is considered in the discussion of electrolyte effects, but this rate enhancement was observed only at hydroxide ion concentrations very much greater than those used with the hydroxyethyl surfactant.]

Table II
Effect of Hydroxide Ion on the Catalysis of the Decarboxylation of 6-Nitrobenzisoxazole Carboxylate Ion by Micelles of V[a]

	$10^2 C_D$, *M*						
C_{OH^-}, *M*	0.04	0.4	0.8	1.0	1.2	4.0	5.0
pH 9[b]							2.55
pH 10[b]						2.35	
0.002							2.72
0.005							2.71
0.008							2.89
0.01	2.41	3.24	3.26		3.01	3.40	
0.02							3.38
0.04							4.15
0.10				5.16			
0.12							4.94
0.18				5.47			
0.20				5.26		5.39	5.41
0.30				5.77			
0.50				6.14			5.75
0.90				6.35			6.40

[a] Values of $10^4 k_\psi$, sec^{-1}, at 25.0°. [b] 10^{-3} *M* ammonia buffer.

Effect of Added Solutes on Decarboxylation Catalyzed by Zwitterionic Micelles. The salt effect upon the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion catalyzed by micelles of CTABr was unusual in that salts having hydrophilic anions increased the reaction rate, and salts of some aromatic acids which increased reaction rate in low concentration decreased it at high. Salts having nonaromatic hydrophobic anions decreased the reaction rate at all concentrations, as did thiocyanate ion, which can interact strongly with a cationic micelle.[5] Salts generally decrease micellar catalysis,[9-11] and the behavior of the nonaromatic hydrophobic anions was typical, in that such ions generally retard reaction by competing with ionic reagents for the micelle. The effects of the hydrophilic anions were explained in terms of a reduction in the charge density of the micelle when relatively hydrophilic ions cluster around it. The unusual effects of aromatic anions were considered to be caused by changes in micellar structure by insertion of anions such as tosylate.[5]

The salt effects upon decarboxylation catalyzed by zwitterionic micelles are also unusual, and brook no simple explanation. For simplicity we consider salts of organic and inorganic acids separately.

The pattern for the effects of sodium salts of organic acids is straightforward (Figure 3). Sodium formate, acetate, and oxalate have relatively little effect, but the other more hydrophobic salts inhibit reaction, and the retardation parallels anion hydrophobicity, at least qualitatively. Because micelles of zwitterionic surfactants catalyze decarboxylation of the carboxylate ions I and II we assume that they also take up relatively hydrophobic carboxylate or sulfonate anions, and the micelle then goes from being formally uncharged to anionic, and should become ineffective as a catalyst. This explanation is consistent with the absence of

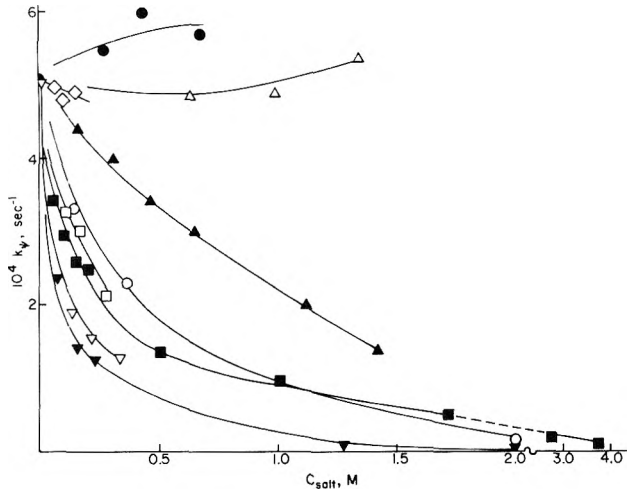


Figure 3. Effect of sodium salts of organic acids on the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion in micelles of *N,N*-dimethyl-*N*-dodecylglycine at 25.0° in ammonia buffer, pH 9.2: ●, AcO^-; ▲, $Me_3CCO_2^-$; ■, $CF_3CO_2^-$; ▼, $CCl_3CO_2^-$; ◊, $(CO_2^-)_2$; ○, n-$C_6H_{13}CO_2^-$; △, HCO_2^-; □, $PhCO_2^-$; ▽, p-$MeC_6H_4SO_3^-$.

the rate maxima in plots of k_ψ against salt concentration which we observed in CTABr-catalyzed decarboxylation in the presence of, for example, sodium tosylate.[5]

The pattern for the effect of inorganic salts (Figure 4) is also straightforward. The effects appear to depend upon the anion; for example, the chlorides of Li^+, Na^+, K^+, and NH_4^+ have little effect on the rate, or depress it slightly, and potassium nitrate retards the reaction. However, fluorides, sulfates, carbonates, and phosphate and sodium hydroxide increase the reaction rate, although relatively high concentrations (>2 *M*) are required for large rate increases. The anions which give these rate enhancements have high charge densities and they tend to organize water molecules about them, i.e., they are structure-making ions,[24] and we note that formate and acetate ions, which behave differently from the other organic anions (Figure 3), are also "structure makers".

In these solutions of high ionic strength, ions will be close to the micellar surface,[9-11] and may compete with the carboxylate groups of the micellized surfactant for water molecules, and therefore change micellar structure. Any effect which decreases the ability of water molecules at the micellar surface to hydrogen bond to carboxylate ions should assist reaction, first by decreasing the ability of water molecules to hydrate the substrate which is bound to the micelle, and second by reducing screening of the carboxylate head groups of the surfactant, and therefore increasing the initial-state charge repulsions which are responsible for the high catalytic effectiveness of the zwitterionic surfactants. It has been noted that ions can change the "dynamic basicity" of water,[25] although this conclusion was based on experiments involving proton loss from carbon acids, which does not proceed via a hydrogen-bonded species.

Some effects of uncharged solutes upon the decarboxylation of I catalyzed by zwitterionic micelles should be noted here. Ammonia has an appreciable effect on the reaction rate (Figure 4), and urea somewhat diminishes the micellar catalysis (by ca. 25% in 4 *M* urea). Urea disrupts water structure and modifies those of micelles and macromolecules, and its effects on reactions in micelles have been explained in these terms.[26] The effect of urea on decarboxylation of I in CTABr is similar to that found here.[5]

Decarboxylation in Zwitterionic Micelles of *N,N*-Dimethyl-*N*-dodecylalanine and the Effect of Sodium

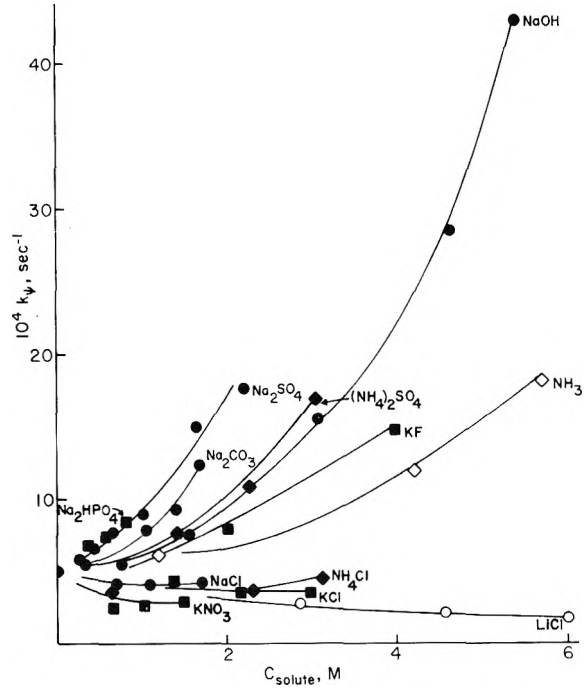


Figure 4. Effect of inorganic solutes on the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion in micelles of *N,N*-dimethyl-*N*-dodecylglycine.

Table III
Inhibition of Micellarly Catalyzed Decarboxylation by Mandelate Ions[a]

Na mandelate	Surfactant L-IV[b]	Surfactant DL-IV[c]
DL–	0.66	0.55
D(–)	0.63	0.64
L(+)	0.64	0.65

[a] Values of k_m^s/k_m^o for decarboxylation of I in micelles of 0.2 *M* L- and DL-IV at 25.0° in 2×10^{-3} *M* ammonia buffer, pH 9.2, and 7.7×10^{-5} *M* substrate. [b] Using 0.35 *M* salt; in the absence of added salt $10^4 k_\psi = 5.60$ sec^{-1}. [c] Using 0.32 *M* salt; in the absence of added salt $10^4 k_\psi = 6.12$ sec^{-1}.

Mandelate. The differences in the rates of reaction of 6-nitrobenzisoxazole-3-carboxylate ion in micelles of the zwitterionic L- and DL-dimethyldodecylalanines (Figure 2) suggest differences in the surface structures of the micelles of the optically active and racemic surfactants. The micellar catalysis is reduced by sodium mandelate, and the inhibition is similar to that found on the addition of relatively hydrophobic carboxylate ions to *N,N*-dimethyl-*N*-dodecylglycine (Figure 3). However, there are only small differences in the inhibitions shown by the various mandelates (Table III), and as expected D- and L-mandelates have the same effects on reaction rates catalyzed by the DL surfactant (DL-IV), but DL-mandelate ion behaves differently. However, the relative inhibitions by the various mandelate ions of decarboxylation catalyzed by micelles of the L surfactant are within experimental error, so that only the effects upon catalysis by the DL surfactant appear to be significant. Effects due to surfactant or inhibitor chirality which rely upon physical interactions seem to be small because micellization depends upon the sum of a large number of weak physical interactions. Moss and Sunshine have used micelles of optically active surfactants as catalysts for reactions of optically active substrates (generally carboxylic esters) and found essentially no stereoselectivity toward enantiomeric substrates.[27] However, appreciable stereo-

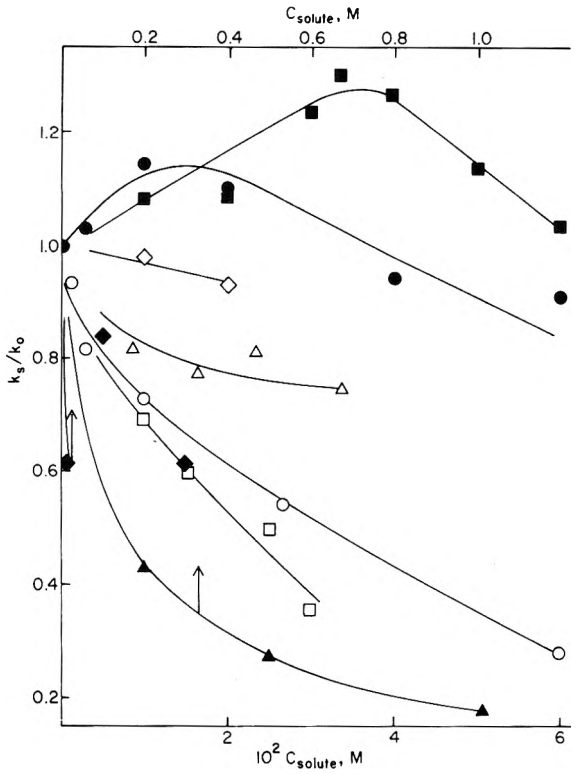


Figure 5. Effect of solutes on the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion in 2×10^{-2} *M* CTABr: ○ ●, phenol; □ ■, *p*-cresol; ◊, benzene; △, anisole; ▲, CF_3CO_2Na; ♦, *n*-$C_{10}H_{21}CO_2Na$. The open points represent runs at pH 7.5 and the solid points runs in 0.1 *M* NaOH except for ▲, which was at pH 9.2.

selectivity has been found using a functional micelle derived from L-histidine.[28]

Effect of Aromatic Solutes on Decarboxylation Catalyzed by CTABr. There is considerable spectral and other evidence that aromatic compounds interact strongly with both cationic micelles and unmicellized tetraalkylammonium ions,[5,29-33] and the enthalpies of transfer of a number of aromatic compounds from water to CTABr have been found to be much larger than for otherwise similar aliphatic compounds.[31] This favorable enthalpy change is indicative of a strong interaction between the cationic head groups and the aromatic residues. The unusual salt effects of arenesulfonate and similar anions upon the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion I in CTABr were explained in terms of an insertion of the phenyl group into the micelle and NMR and uv spectroscopic evidence,[5,32] and the effects of micelles on buffer equilibria of aromatic acids can be similarly explained.[30] Uncharged aromatic compounds having electron-releasing groups (OH or OMe) decrease the catalysis of the decarboxylation of I by CTABr (Figure 5), but in agreement with earlier work benzene has very little effect.[5] The aromatic solutes are in considerable excess over the substrate, whose concentration is $<10^{-4}$ *M*, and they can reduce the reaction rate both by inserting into the micelle and excluding substrate and by modifying the surface structure of the micelle. This insertion should be assisted by electron-releasing groups which should increase the interaction between the π-rich phenyl group and the quaternary ammonium head groups of the micelle. Paradoxically, the phenoxide ions increase the catalytic effectiveness of the cationic micelle, and behave similarly to arenesulfonate ions in this respect,[5] and this effect may be in part due to Coulombic initial state repulsions between the carboxylate ion of the substrate and the anionic oxygen of the phenoxide ion.[12]

For comparison purposes the inhibitions by sodium decanoate and trifluoroacetate are shown in Figure 5, and the uncharged benzenoid compounds are effective inhibitors by comparison with these relatively hydrophobic carboxylate ions. Decanoate is as expected a much better inhibitor than trifluoroacetate, and it probably interacts so strongly with CTABr that a catalytically ineffective anionic comicelle is formed. Examples of other inhibiting anions are given in ref 5 and trifluoroacetate ion is similar to trimethylacetate ion in its ability to reduce catalysis by CTABr.

Table IV
Effect of *n*-Alkylammonium Chlorides on Decarboxylation in CTABr[a]

Alkyl	10^4 k_ψ, sec^{-1}
	3.38[b]
n-Butyl	3.02
n-Octyl	2.84
n-Nonyl	2.77
n-Decyl	2.38
n-Dodecyl	1.34

[a] At 25.0° with 2×10^{-2} *M* alkylammonium chloride in 2×10^{-2} *M* CTABr and 0.022 Tris buffer, pH 7. [b] In the absence of added amine salt.

Table V
Effect of *n*-Alkylamine Decarboxylation in CTABr[a]

Alkyl	C_{RNH_2}, *M* 0.01	0.015	0.02
n-Butyl			3.55
n-Hexyl			3.05
n-Octyl	3.10		2.65
n-Nonyl	3.41	3.89	4.08
n-Decyl	3.80	4.43	5.26
n-Dodecyl	3.81	4.12	

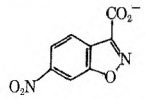
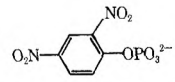
[a] Values of k_ψ, sec^{-1}, at 25.0°; in the absence of amine 10^4 k_ψ = 3.71 sec^{-1} in 2×10^{-2} CTABr and 0.1 *M* NaOH.

Effect of *n*-Alkylamines and Their Hydrochlorides on the Decarboxylation of I in CTABr. Decarboxylation is inhibited by solvents which strongly hydrogen bond to the carboxylate ion,[3] and we noted earlier that the substrate in a cationic micelle should be less strongly hydrogen bonded than in water. On this hypothesis incorporation of a primary alkylammonium ion into the cationic micelles should inhibit reaction, as is observed (Table IV), because a primary alkylammonium ion should be a good hydrogen-bonding donor. Increasing the length of the *n*-alkyl group should bind the ammonium ion more strongly to the micelle, and the inhibition is greatest with the most hydrophobic ammonium ion (Table IV).

Unprotonated *n*-alkylamines slightly change the micellar catalysis (Table V). The rate at first decreases as the length of the *n*-alkyl group increases, but then increases. Possibly the less hydrophilic amines merely interact with the micellar surface, whereas the more hydrophobic ones comicellize and increase reaction rate by decreasing charge density of the micelle, and we note that the nonionic surfactant Igepal increases the rate of decarboxylation of I by a similar mechanism.[5]

Micellar Effects in Aqueous Organic Solvents. With ionic surfactants in mixtures of relatively hydrophobic alcohols and water, normal ionic micelles form when the water content is high, but with decreasing water content the nature of the aggregate changes, and when the water content is low, reverse micelles form.[14,34] However, normal micelles form in ethylene glycol[35] and presumably also in its mixtures with water. The rates of some reactions are very sensitive to reverse micelles in nonpolar solvents, but

Table VI
Effect of Organic Solvents on the Decarboxylation of 6-Nitrobenzisoxazole and on Phosphate Ester Hydrolysis[a]

Solvent	Substrate 	
H_2O	3×10^{-6}	0.8×10^{-5}
95% *n*-HexOH (w/w)	1.24×10^{-4}	2.2×10^{-4}
77.5% $(CH_2OH)_2$ (w/w)	3.2×10^{-5}	

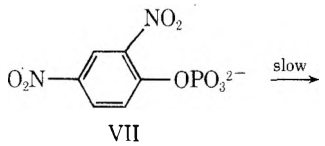
[a] Values of k_ψ, sec^{-1}, at 25.0°.

Table VII
Effect of CTABr in Organic Solvents on Decarboxylation of 6-Nitrobenzisoxazole Carboxylate Ion[a]

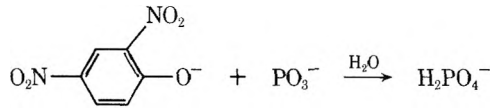
$10^3 c_D$[b]	$10^4 k_\psi$, sec^{-1}	$10^3 c_D$[b]	$10^4 k_\psi$, sec^{-1}
	1.24	11.2	2.63
0.06	1.34	21.0	3.76
0.52	1.59		0.32[c]
3.2	1.98	6.2	2.46[c]
7.0	2.14	11.0	2.83[c]
9.4	2.37	16.0	3.28[c]

[a] At 25.0° with 3×10^{-4} *M* KOH unless specified and 1-hexanol–water (95:5 w/w) unless specified. [b] As mole fraction. [c] In ethylene glycol–H_2O (77.5:22.5 w/w) and 3×10^{-3} *M* NaOH.

to date these have generally been bimolecular reactions involving acids or bases,[14,34] although the decomposition of 2,4-dinitrophenyl sulfate occurs readily in benzene containing *n*-alkylammonium carboxylates.[17] The rate of the SN1 bromodecarboxylation of 3-bromo-3-phenylpropionate ion to give mainly styrene was not especially sensitive to reverse micelles,[36] but it is also relatively insensitive to solvent effects,[37] and we also examined two reactions which are highly solvent sensitive. One was the decarboxylation of 6-nitrobenzisoxazole carboxylate ion (I),[3] and the other was the spontaneous hydrolysis of the 2,4-dinitrophenylphosphate dianion (VII).[15] Both these reactions are catalyzed by normal cationic micelles in water.[5,16]



VII



In agreement with earlier evidence the reaction rates in the absence of surfactant are increased by addition of organic solvents, and micellar effects on these reactions in both *n*-hexanol–water and ethylene glycol–water are small (Tables VI–VIII). In contrast to the small micellar catalysis of decarboxylation of I in these solvents by CTABr there is a 95-fold rate enhancement in water,[5] and for hydrolysis of the 2,4-dinitrophenylphosphate dianion in water the rate enhancement is 25-fold.[16] These results are understandable if we assume that decreased hydration of the substrate when it is incorporated into the micelle is important, because in going from initial- to transition-state electrons are transferred from the hydrophilic carboxylate or phosphate

Table VIII
Effect of Surfactants in 1-Hexanol–Water on Phosphate Ester Hydrolysis[a]

Surfactant	$10^3 c_D$[b]	$10^4 k_\psi$, sec^{-1}
		2.2
CTABr	7.2	1.05
CTABr	20	0.71
V[c]	1.3	1.87
V[c]	5.4	0.93
V[c]	8.8	0.84

[a] At 25.0° in 1-hexanol–water (95:5 w/w) and 5×10^{-3} *M* KOH. [b] Surfactant concentration as mole fraction. [c] *n*-$C_{16}H_{33}N^+Me_2$-$CH_2CH_2OHBr^-$.

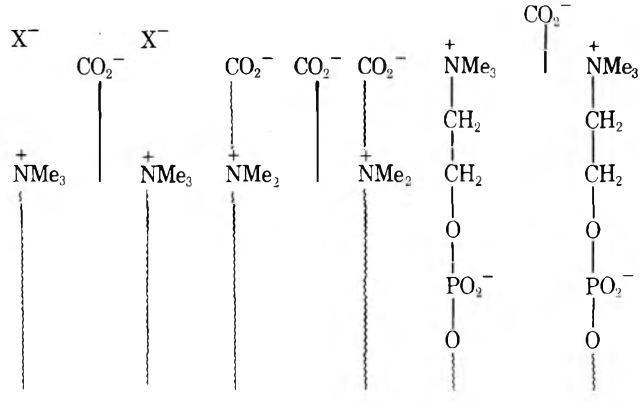
groups into the organic residue, where they are delocalized by resonance. Thus the role of a cationic micelle should be considerably reduced when initial-state hydration is decreased by addition of an organic solvent.

Discussion

Effects of Changes in Surfactant Structure. Decarboxylations of the anionic substrates I and II are strongly catalyzed by cationic micelles,[5,6] and replacing one methyl in the head group of CTABr by a 2-hydroxyethyl group does not affect the catalysis, but the rate of reaction in the micelle is approximately doubled when the pH is high enough to convert V into the zwitterion VI. Consistently, micelles of zwitterionic surfactants are better catalysts than the corresponding cationic micelles.

The charge distribution in zwitterionic micelles derived from an amino acid is similar to that of a cationic micelle surrounded by counterions (Scheme I). In both cases a sub-

Scheme I



strate having its organic residue located between the ammonium head groups will be subject to Coulombic repulsions between its carboxylate ion and the negative charges on or adjacent to the micelle, but in the transition state the negative charge moves out of the carboxylate group and into the heterocyclic moiety, giving the transition state considerable carbanionoid character, as shown below for decarboxylation of I. Thus the negative charge will move

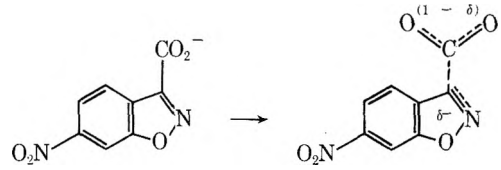
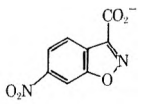


Table IX
Micellar Catalysis of Decarboxylation[a]

Surfactant	Substrate: $PhCH(CN)CO_2^-$	Substrate: 
n-$C_{12}H_{25}\overset{+}{N}Me_3Br^-$	280 (0.018)	70 (0.012)
n-$C_{16}H_{33}\overset{+}{N}Me_3Br^-$	660 (< 0.005)[b]	95 (0.0016)[c]
n-$C_{12}H_{25}\overset{+}{N}Me_2CH_2CO_2^-$	690 (0.013)	170 (0.01)
DL-n-$C_{12}H_{25}\overset{+}{N}Me_2CHMeCO_2^-$		210 (0.006)
L-n-$C_{12}H_{25}\overset{+}{N}Me_2CHMeCO_2^-$		185 (0.008)
n-$C_{16}H_{33}\overset{+}{N}Me_2CH_2CH_2OH$		~90
n-$C_{16}H_{33}\overset{+}{N}Me_2CH_2CH_2O^-$		~200[d]

[a] Values of rate constants relative to those in water (k_m/k_o) at 25.0°; the values in parentheses are the molarities of surfactant required for 50% catalysis. [b] Reference 6. [c] Reference 5. [d] pH ~ 14.

closer to the quaternary ammonium center, with which it will interact beneficially.

The situation will be completely different with a micelle or liposome of a phospholipid,[10b] where the cationic ammonium ion moiety is at the head of the surfactant. The unfavorable initial-state interactions will be absent, and as the charge moves into the organic residue in the transition state it will interact unfavorably with the anionic phosphate group.

The zwitterionic micelles of III and IV are between two- and threefold more catalytically effective than the corresponding cationic micelles even though the micellar surface should be highly aqueous, which should decrease Coulombic interactions. Jencks has noted that unfavorable initial-state interactions, e.g., the introduction of steric strain in a substrate which is relieved in the transition state, may be important factors in enzymic catalysis.[38] Coulombic repulsions should be much greater in a hydrophobic cavity than at the surface of a micelle in water, where the dielectric constant is relatively high,[39] so that unfavorable initial-state Coulombic interactions which we observe in our aqueous systems could be playing a much more important role in enzymic catalysis.

In our system the hydrophobic interactions between the substrate and the micelle overcame the local Coulombic repulsions between anionic groups. The concentration of surfactant required for 50% of the total rate enhancement is an indication of the strength of micelle–substrate binding,[10] and it is not particularly affected by the nature of the micellar head group (Table IX). Table IX also summarizes the micellar rate enhancements of decarboxylation. There are examples in which bimolecular reactions are catalyzed by zwitterionic micelles,[9-11] but generally a zwitterionic micelle is a much poorer catalyst than the corresponding cationic micelle, as expected from electrostatic considerations.

As noted in the Results section, the effects of phenols and alkylamines are obtained with solute concentrations similar to that of the surfactant, suggesting a close interaction between the micelle and these chemically inert solutes which affects the micellar catalysis without changing the effective micellar charge.

Registry No.—I, 42540-91-0; II, 34220-42-3; III, 683-10-3; L-IV, 54385-46-5; DL-IV, 52665-42-6; V, 20317-32-2; VII, 18962-96-4; DDTBr, 1119-94-4; CTABr, 57-09-0; DL-Na mandelate, 34166-39-7; D(−)-Na mandelate, 54385-47-6; L(+)-Na mandelate, 19944-52-6; n-$C_{16}H_{33}N^+Me_2CH_2CH_2O^-$, 54385-45-4.

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Possible Anchimeric Assistance in the Hydration–Decarboxylation of a Propiolic Acid. Synthesis of Methyl 3-(17β-Acetoxy-3-oxoandrosta-4,6-dien-17α-yl)propionate

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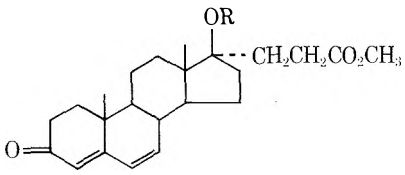
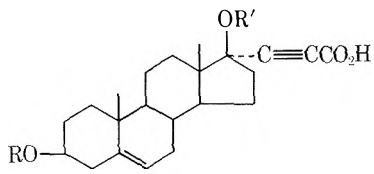
3-(3β,17β-Diacetoxyandrost-5-en-17α-yl)propiolic acid (**2b**) decomposes on prolonged standing or when treated with dilute acetic acid to afford 3β,17β-diacetoxy-17α-pregn-5-en-20-one (**9**). The facility with which this conversion is achieved suggests the participation of the neighboring acetoxy group in the transformation. Two processes were investigated for the synthesis of the title compound (**1a**). One involved acetylating **1b** with acetyl chloride and stannic chloride at low temperature. The other began with the diol propiolic acid **2a**. Successive methylation, acetylation, hydrogenation, selective hydrolysis, oxidation, and dehydrogenation converted **2a** into **1a**.

As part of an effort to determine the structural features which are essential for antimineralocorticoid activity, methyl 3-(17β-acetoxy-3-oxoandrosta-4,6-dien-17α-yl)propionate (**1a**) was prepared and tested. Two processes were investigated for the synthesis of this compound. The first made use of an observation that a 17β-hydroxy steroid with a 17α-alkynyl substituent is less likely to undergo elimination to generate a carbocation at C-17 than one in which the substituent at the 17α position is an alkyl group.[1]



1a, R = Ac
b, R = H

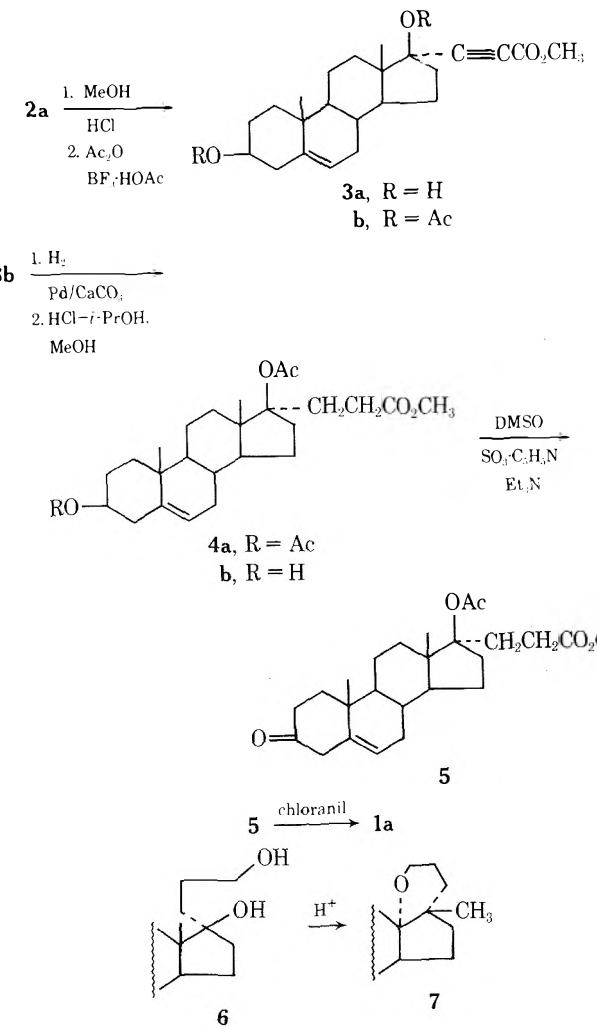


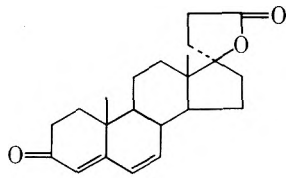
2a, R = R′ = H
b, R = R′ = Ac

The starting compound, the propiolic acid **2a**,[2] was converted into the methyl ester **3a** with methanol and hydrochloric acid. Acetylation of **3a** with acetic anhydride in the presence of boron trifluoride in acetic acid gave in good yield the diacetate **3b**.[3] Hydrogenation of the triple bond was accomplished over palladium on calcium carbonate. Although three ester groups are present in **4a**, selective hydrolysis of the C-3 acetoxy group was achieved with hydrogen chloride in methanol. Oxidation of the resultant product **4b** with dimethyl sulfoxide in the presence of sulfur trioxide–pyridine and triethylamine[4] gave predominantly the β,γ-unsaturated ketone **5**. The uv spectrum of the product indicated that the conjugated ketone was present, but in less than 10% amount. Earlier, Turner had shown that a β,γ-unsaturated ketone undergoes ready dehydrogenation with a high potential quinone to afford a linear dienone system.[5] When **5** was treated with chloranil, the desired product **1a** was, indeed, obtained. Chloranil was used instead of dichlorodicyanobenzoquinone in the present instance in order to minimize the possibility of further dehydrogenation at the 1,2 position.[5]

The alternate synthesis of **1a** involved finding conditions which would minimize dehydration and/or rearrangement. The diol **6** is known to undergo a Wagner–Meerwein rearrangement to afford, inter alia, the ether **7** in an acid medium.[6] Hence, several attempts were made to acetylate methyl 3-(17β-hydroxy-3-oxoandrosta-4,6-dien-17α-yl)propionate (**1b**) under basic conditions, but without success. The starting methyl ester **1b** was obtained from the spirolactone 8[2] by treatment with potassium hydroxide followed by alkylation of the resultant salt with methyl iodide in dimethylformamide.[7] Acetylation of **1b** with a mixture of acetic anhydride, triethylamine, and 4-dimethylaminopyridine[8] resulted mainly in the regeneration of the lactone **8**.

At the suggestion of Dr. Dryden, acetylation of **1b** with acetyl chloride and stannic chloride at low temperature was tried. When the reaction was allowed to proceed in dichloromethane at −40° for 20 min, the desired product **1a** was obtained in 47% yield. The principal by-product proved to be the spirolactone **8**.





8

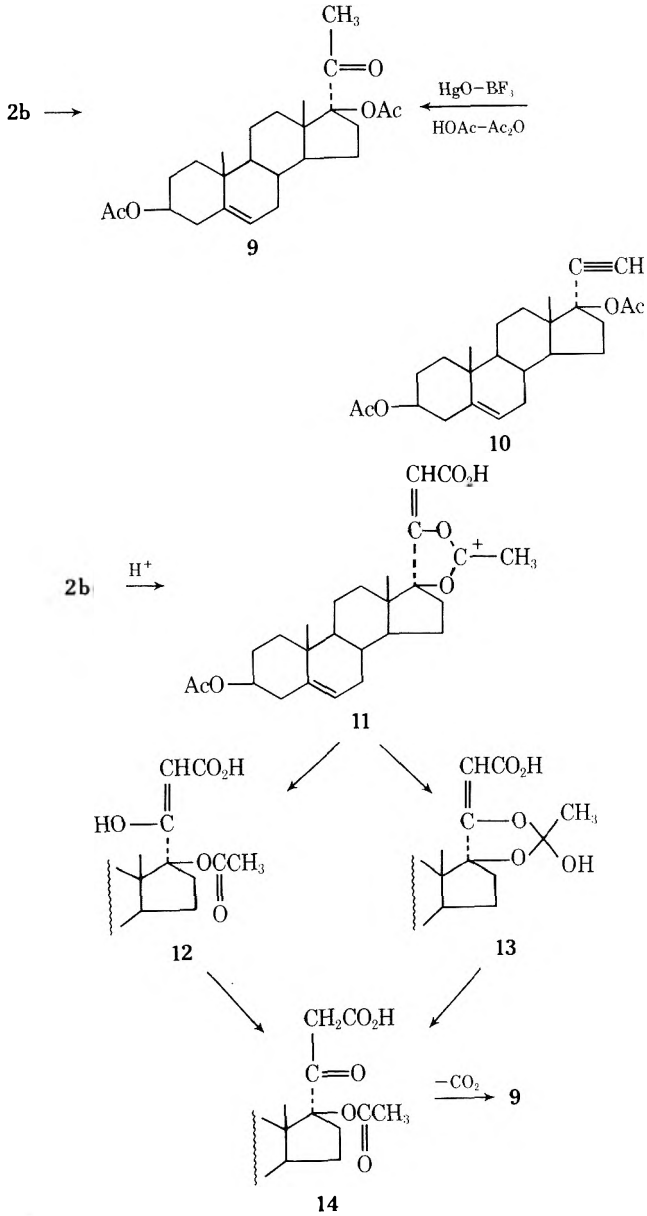
Of the two procedures which afforded **1a**, the one involving acetylation of 1b with acetyl chloride and stannic chloride furnished the purer product. The uv absorption maximum (282 nm) of **1a** prepared in this manner has a molecular extinction coefficient (ϵ) of 25,800. The corresponding value for **1a** prepared by the other procedure is 22,590. A contaminant in the latter appears to be the 3-keto Δ^4-steroid, judging from the extent of the uv absorption at 240 nm and the appearance of faint signals at 70.5 and 53.5 Hz in the NMR spectrum of **1a** derived from the chloranil dehydrogenation of the β,γ-unsaturated ketone **5**. When tested in the standard antimineralocorticoid test,[2] **1a** failed to block the mineralocorticoid effect of deoxycorticosterone acetate at the screening dose of 2.4 mg.

Interestingly, while the diol propiolic acid **2a** is a stable substance, the diacetate **2b** decomposed on prolonged standing. The product obtained after chromatography on silica gel proved to be 3β,17β-dihydroxy-17α-pregn-5-en-20-one 3,17-diacetate (**9**).[9a] The product was identical with a sample prepared by the mercuric oxide–boron trifluoride-catalyzed hydration[9b] of 3β,17β-dihydroxy-17α-pregn-5-en-20-yne 3,17-diacetate (**10**).

When **2b** was heated in dilute acetic acid, it was converted mainly into **9**. The presence of **9** in the reaction mixture was established not only by TLC and GLC, but also by isolation of the product and comparison with an authentic sample. The diol acid **2a** was recovered unchanged when similarly treated.

The conversion of **2b** to **9** appears to be facilitated by the presence of the acetoxy group at C-17. A priori the inductive effect of the acetoxy group is expected to retard hydration of the propiolic acid triple bond. However, in solvolytic studies it has been shown that a neighboring acetoxy group has a rate-enhancing effect. This has been attributed to anchimeric assistance involving the formation of a quasicyclic intermediate.[10a–c] Conceivably, this phenomenon occurs also in the protonation of the α-carbon atom of the propiolic acid, a step which has been shown to be rate determining in the acid-catalyzed hydration of certain substituted propiolic acids.[11] The participation of a neighboring acetoxy group in an electrophilic attack on a triple bond is not unprecedented, as such a process has been postulated in the addition of difluorocarbene to ethynyl carbinol acetates.[12]

In the transformation of **2b** to **9**, protonation of the α carbon is likely to be facilitated by the participation of the neighboring acetoxy group to furnish **11**. Solvolysis of **11** either at C-20 or at the carbocation affords, respectively, **12** and **13**. Both species can isomerize to the β-keto acid **14**. Decarboxylation of **14** will then yield **9**.



Experimental Section

Melting points were determined on a Fisher-Johns melting block and are uncorrected. NMR spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Unless specified otherwise, optical rotations were determined in chloroform.

3-(3β,17β-Diacetoxyandrost-5-en-17α-yl)propiolic Acid (2b). A mixture of 2.0 g (5.58 mmol) of 3-(3β,17β-dihydroxyandrost-5-en-17α-yl)propiolic acid (**2a**),[2] 60 ml of isopropenyl acetate, and 200 mg of *p*-toluenesulfonic acid monohydrate was subjected to slow distillation over a period of 1.5 hr. After 200 mg of NaOAc was added, the reaction mixture was concentrated by distillation under reduced pressure. The residue was diluted with a large volume of water, and the mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water, treated with Darco, dried over Na_2SO_4, and distilled to dryness under reduced pressure. The residual oil was treated with 100 ml of 5% $NaHCO_3$ and heated until complete solution was achieved. The solution was cooled in an ice bath, whereupon the sodium salt of **2b** began to crystallize. The salt was collected and dried: ir (KBr) 3470 (H_2O), 1745, 1617 cm^{-1}; NMR (CD_3OD) 325 (br, 1, 6-H), 283 (s, CD_3OH, H_2O), 120 (s, 6, OAc), 64 (s, 3, 19-CH_3), 55.5 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{26}H_{33}O_6Na \cdot 2H_2O$: C, 62.38; H, 7.45. Found: C, 62.69; H, 7.07.

The preparation was repeated starting with 20 g (55.8 mmol) of **2a** and a proportionately larger quantity of reagents. The salt, however, was not isolated. Instead, the mixture containing the salt was acidified with 6 *N* HCl. The resultant solid, **2b**, was collected, washed well with water, and dried: yield 23 g (93%); mp 104–108°; ir (KBr) 3200, 2217, 1740 cm^{-1}; NMR ($CDCl_3$) 325 (br, 1, 6-H), 124, 122.5 (s, s, 6, OAc), 62.5 (s, 3, 19-CH_3), 53 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.12; H, 7.73.

3β,17β-Diacetoxy-17α-pregn-5-en-20-one (9). A. After standing for ca. 1 year, a bottle of **2b** was found to have undergone considerable decomposition. A 2.0-g sample was chromatographed on 200 g of silica gel. Elution with 5% ethyl acetate in benzene gave 1.1 g of a solid which was crystallized from ethyl acetate–hexane to yield 0.9 g of **9**, mp 191–194°, $[\alpha]^{25}D$ −54° (*c* 1.0, dioxane) (lit.[9a] mp 194–195°, $[\alpha]D$ −54°). Admixture with an authentic sample of

9, prepared as described in the literature,[9a,b] resulted in no depression of the melting point. The ir spectra of the two samples were identical.

B. A 1.2-g (2.8 mmol) sample of freshly prepared **2b** was dissolved in 50 ml of glacial acetic acid and 50 ml of water. The reaction mixture was heated under reflux for 40 min. TLC showed the absence of starting material. The cooled mixture was distilled nearly to dryness under reduced pressure. The resultant mixture was extracted with chloroform. The chloroform extract was washed successively with 5% $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated to dryness to afford 0.95 g of a solid. TLC indicated that the major component of the residue had the same R_f value as **9**. GLC revealed that it had an identical retention time with that of **9** and that it comprised 76.5% of the residue. The solid was chromatographed on silica gel to afford 0.65 g (56%) of **9**: mp 191–193°; NMR ($CDCl_3$) 326 (br, 1, 6-H), 127.5, 124.5, 122 (s, s, s, 9, $-COCH_3$ and $-OAc$), 62.5 Hz (s, 6, 18-CH_3, 19-CH_3); ir ($CHCl_3$) 1740, 1375, 1260, 1045 cm^{-1}. The NMR and ir spectra were identical with those of an authentic sample of **9**.

Attempted Solvolysis of 3-(3β,17β-Dihydroxyandrost-5-en-17α-yl)propiolic Acid (2a). A 120-mg (0.34 mmol) sample of **2a** in 30 ml of glacial acetic acid and 20 ml of water was heated under reflux for 40 min. The cooled reaction mixture was poured into a large volume of water. The solid product was collected by filtration, washed with water, and dried, yield 109 mg (91%), mp 228–233° (lit.[2] mp 234–235° dec). The melting point was undepressed when the product was admixed with the starting acid **2a**. The ir spectra of the two samples were identical.

Methyl 3-(3β,17β-Dihydroxyandrost-5-en-17α-yl)propiolate (3a). A mixture of 20.0 g (55.8 mmol) of 3-(3β,17β-dihydroxyandrost-5-en-17α-yl)propiolic acid (**2a**), 150 ml of methanol, and 2 ml of aqueous 12 *N* HCl was heated under reflux in an atmosphere of N_2 for 3.5 hr, during which time a crystalline product formed. The reaction mixture was cooled to room temperature, and the crystalline ester **3a** was collected and dried: yield 18.8 g (90.5%); mp 236–240°; $[\alpha]^{25}D$ −133° (*c* 1.0, dioxane); ir (KBr) 3490, 3380, 2230, 1705 cm^{-1}; NMR ($CDCl_3$) 324 (br, 1, 6-H), 228 (s, 3, CO_2CH_3), 62.5 (s, 3, 19-CH_3), 54 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.06; H, 8.65.

Methyl 3-(3β,17β-Diacetoxyandrost-5-en-17α-yl)propiolate (3b). A mixture of 10.0 g (26.84 mmol) of **3a**, 200 ml of glacial acetic acid, 50 ml of acetic anhydride, and 3 ml of the $BF_3 \cdot 2HOAc$ complex was allowed to stand at room temperature for 20 hr. The reaction mixture was diluted with water and then extracted with ether. The ether extract was washed successively with 5% Na_2CO_3 and water, dried over $MgSO_4$, and distilled to dryness under reduced pressure. The residual oil was stirred with water for 2 hr, when a crystalline product formed. The solid was collected and dried. Crystallization from hexane afforded 10.8 g (88%) of **3b**: mp 118–120°; $[\alpha]^{25}D$ −113° (*c* 1.0); ir (KBr) 2230, 1752, 1737, 1715, 1678 cm^{-1}; NMR ($CDCl_3$) 324 (br, 1, 6-H), 275 (br, 1, 3-H), 226 (s, 3, CO_2CH_3), 123, 121 (s, s, 6, OAc), 62.5 (s, 3, 19-CH_3), 54 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{27}H_{36}O_6$: C, 71.02; H, 7.95. Found: C, 71.26; H, 8.02.

Methyl 3-(3β,17β-Diacetoxyandrost-5-en-17α-yl)-propionate (4a). A solution of 5.0 g (10.9 mmol) of **3b** in 300 ml of methanol was hydrogenated over 438 mg of 5% palladium on calcium carbonate at atmospheric pressure and room temperature. After the calculated amount of hydrogen was absorbed in 3 hr, the catalyst was removed by filtration. The filtrate was distilled to dryness under reduced pressure to afford an oily residue, which was chromatographed on 100 g of silica gel. Elution with 2% ethyl acetate in benzene afforded an oil. The oil was crystallized from hexane to yield 3.25 g (64.5%) of **4a**: mp 85–87°; $[\alpha]^{25}D$ −78° (*c* 0.98); ir (KBr) 1743 cm^{-1}; NMR ($CDCl_3$) 325 (br, 1, 6-H), 280 (br, 1, 3-H), 219 (s, 3, CO_2CH_3), 120.5, 118.5 (s, s, 6, OAc), 61.5 (s, 3, 19-CH_3), 50 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.34; H, 8.84.

Methyl 3-(17β-Acetoxy-3β-hydroxyandrost-5-en-17α-yl)-propionate (4b). A mixture of 2.0 g (4.34 mmol) of **4a**, 20 ml of methanol, and 2 ml of an isopropyl alcohol solution of HCl (0.273 g/ml) was stirred at room temperature for 3 hr. The reaction mixture was then cooled in an ice bath, whereupon **4b** crystallized from the solution. The product was collected: yield 1.2 g (66%); mp 142–146° $[\alpha]^{25}D$ −90° (*c* 0.4); ir (KBr) 3545, 1735 cm^{-1}; NMR ($CDCl_3$) 323 (br, 1, 6-H), 219.5 (s, 3, CO_2CH_3), 210 (br, 1, 3-H), 119.5 (s, 3, 17-OAc), 61 (s, 3, 19-CH_3), 50 Hz (s, 3, 18-CH_3) Hz.

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.45; H, 9.11.

Methyl 3-(17β-Acetoxy-3-oxoandrost-5-en-17α-yl)propionate (5). To a mixture of 10.0 g (23.89 mmol) of **4b** in 100 ml of dimethyl sulfoxide were added in succession 50 ml of triethylamine and a solution of 20 g of the sulfur trioxide–pyridine complex[4] in 100 ml of dimethyl sulfoxide. The reaction mixture was stirred under N_2 for 0.5 hr and then poured into a large volume of ice water. The resultant precipitate **5** was collected, washed with water, and dried: yield 9.1 g (91.5%); mp 127–131°; ir (KBr) 1749, 1735, 1722, 1680 cm^{-1}; NMR ($CDCl_3$) 320 (br, 1, 6-H), 219.5 (s, 3, CO_2CH_3), 120 (s, 3, 17-OAc), 71 (s, 3, 19-CH_3), 51.5 Hz (s, 3, 18-CH_3). The product showed slight uv absorption at 240 nm (ε 1460).

Methyl 3-(17β-Acetoxy-3-oxoandrosta-4,6-dien-17α-yl)propionate (1a). A. A mixture of 4.0 g (9.6 mmol) of **5**, 500 ml of *tert*-butyl alcohol, and 12.0 g (48 mmol) of chloranil was heated under reflux for 24 hr in a N_2 atmosphere. The reaction mixture was coooled to room temperature. The precipitate was removed by filtration, and the filtrate was distilled to dryness under reduced pressure. The residual oil was extracted with ethyl acetate. The ethyl acetate extract was washed successively with water, 5% KOH, and water again. It was then dried over $MgSO_4$ and distilled nearly to dryness under reduced pressure. The semisolid residue was crystallized first from ethyl acetate–ether and then from methanol to afford 2.2 g (55%) of **1a**: mp 184–187°; uv max (MeOH) 282 nm (ε 22,590); ϵ_{240} 4165; ir (KBr) 1745, 1735, 1673, 1623, 1591 cm^{-1}; NMR ($CDCl_3$) 368 (s, 6-H, 7-H), 341.5 (s, 1, 4-H), 221 (s, 3, CO_2CH_3), 121.5 (s, 3, 17-OAc), 68 (s, 3, 19-CH_3), 55.5 Hz (s, 3, 18-CH_3). The NMR spectrum also displayed weak signals at 70.5 and 53.5 Hz.

B. To a mixture of 7.7 ml of stannic chloride and 40 ml of dichloromethane, stirred at −13°, was added dropwise a solution of 17 ml (238 mmol) of acetyl chloride in 40 ml of dichloromethane. The resultant solution was then cooled to −44°, following which a solution of 24.9 g (67 mmol) of **1b** (vide infra) in 300 ml of dichloromethane was added over a period of 12 min. The reaction mixture was stirred at −40° for 8 min. A solution of 50 g of potassium sodium tartrate and 50 g of $KHCO_3$ in 500 ml of water was carefully added. The reaction mixture was stirred for 1 hr at −5 to 9°. The organic phase was separated, washed successively with 10% $KHCO_3$ and water, dried over Na_2SO_4, and distilled nearly to dryness under reduced pressure. The solid residue was triturated with 25 ml of hot methanol. The solid was collected by filtration and washed with a mixture of isopropyl ether and methanol. It was dissolved in 700 ml of hot methanol. The solution was concentrated until crystallization ensued. The crystalline ester **1a** was collected, washed with isopropyl ether–methanol, and dried: yield 13.1 g (47%); mp 193–194°; $[\alpha]^{25}D$ −27.6° (c 1.0); uv max (MeOH) 282 nm (ε 25,800); ϵ_{240} 3520. Except for the absence of the signals at 70.5 and 53.5 Hz, the NMR spectrum of **1a** thus prepared was identical with that of the sample of **1a** prepared by the preceding procedure.

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.45; H, 8.33.

The methanol trituration solution was concentrated. The residue was diluted with isopropyl ether to afford 3.4 g (15%) of 3-(17β-hydroxy-3-oxoandrosta-4,6-dien-17α-yl)propionic acid γ-lactone (**8**) whose NMR spectrum was identical with that of an authentic sample of **8**.[2]

Methyl 3-(17β-Hydroxy-3-oxoandrosta-4,6-dien-17α-yl)propionate (1b). A mixture of 1 kg (2.94 mol) of 3-(17β-hydroxy-3-oxoandrosta-4,6-dien-17α-yl)propionic acid γ-lactone (**8**),[2] 10 l. of methanol, and 0.7 l. of 4.0 *N* methanolic potassium hydroxide was heated under reflux for 50 min. The mixture was then filtered, and the filtrate was concentrated to 1 l. by distillation at atmospheric pressure. The residue was diluted with 6 l. of ethyl acetate. The resultant mixture was concentrated to 100 ml by distillation under reduced pressure. The residue was diluted with a fresh portion of ethyl acetate. The solid potassium salt was collected by filtration, washed with ethyl acetate, and dried.

A 198-g (0.5 mol) sample of the salt was combined with 142 g (1.0 mol) of methyl iodide in 1 l. of dimethylformamide.[7] The reaction mixture was allowed to stand at room temperature for 21 hr, after which it was poured into 5 l. of ice water. The resultant precipitate was collected by filtration and washed with water. The wet solid was dissolved in 1.3 l. of tetrahydrofuran. After 250 ml of hexane was added, the resultant solution was washed successively with 5% potassium bicarbonate and water. The solution was then dried over Na_2SO_4. Removal of the solvents by distillation under reduced pressure gave an oil which was thrice crystallized from isopropyl acetate to afford 112.6 g (61%) of **1b**: mp 144–145.5°; ir

($CHCl_3$) 1734, 1658 cm^{-1}; NMR ($CDCl_3$) 367 (s, 2, 6-H, 7-H), 340.5 (s, 1, 4-H), 221.5 (s, 3, CO_2CH_3), 68 (s, 3, 19-CH_3), 58.5 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.26; H, 8.82.

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Registry No.—**1a**, 54498-03-2; **1b**, 54498-04-3; **2a**, 3460-93-3; **2b**, 54516-82-4; **2b** sodium salt, 54498-05-4; **3a**, 54498-06-5; **3b**, 54498-07-6; **4a**, 54498-08-7; **4b**, 54498-09-8; **5**, 54498-10-1; **8**, 976-71-6; **9**, 1176-21-2.

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Photolysis of Some Carbohydrate Dithiobis(thioformates)[1a]

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The photolysis of several oxidatively coupled xanthates of model sugar compounds has been investigated. The photolysis of bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)dithiobis(thioformate) (**2**) gave the xanthate ester, bis(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) 6-*O*,6′-*S*-dithiocarbonate (**5**), in 78% yield. In concentrated solutions, bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) tetrathiobis(thioformate) (**3**) was produced along with **5**. The photolysis of bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) dithiobis(thioformate) (**14**) gave bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) 3-*O*,3′-*S*-dithiocarbonate (**15**), in which an oxygen atom on the sugar ring has been replaced with sulfur with retention of configuration. A cyclic mechanism in which either the excited thiocarbonyl sulfur or a sulfur of the disulfide linkage attacks the carbon giving a front-side displacement of oxygen has been proposed to account for the observed results.

The relatively high efficiency with which sulfur compounds absorb light, especially compounds which contain the thiocarbonyl group, has resulted in a large number of reports on the photochemistry of organic sulfur compounds.[2-4] The xanthate group [λ_{max} (H_2O) 305 nm (ε 12,000–17,000)] and derivatives thereof exhibit a very strong absorbance of uv light and, therefore, have the potential of photochemical transformations by direct irradiation. The photolyses of some xanthate esters have been reported. Okawara and coworkers subjected *O*-ethyl *S*-benzyl xanthate to uv irradiation and found benzyl mercaptan and carbonyl sulfide as major products, which were obtained in low yields.[5-7] When styrene or methyl methacrylate was added to the reaction mixture, polymerization occurred, indicating a free-radical mechanism for the photodecomposition of the xanthate ester. Photolysis of *O*-benzyl *S*-methyl xanthate in the presence of cyclohexene gave methyl mercaptan, carbonyl sulfide, 3-benzylcyclohexene, and 3-(2-cyclohexene-1-yl)cyclohexene (**1**). The xanthate ester, *O*-diphenylmethyl *S*-methyl xanthate, gave 1,1,2,2-tetraphenylethane and **1**. The results suggested the formation of a carbene intermediate. In ethanol no decomposition of *O*-benzyl *S*-methyl xanthate occurred. However, addition of triethylamine gave methyl benzyl thioether, *S*-benzyl ethyl thiocarbonate, dibenzyl thioether, and dibenzyl disulfide.[8]

Acyl xanthate esters have been photolyzed and produced acyl radicals and xanthate radicals.[9] The acyl radical then loses carbon monoxide, and a recombination reaction occurs between the new alkyl radical and the xanthate radical to give a xanthate ester which is stable to Pyrex-filtered light. Shah, Singh, and George[10,11] observed that the photolytic decomposition of a dixanthate gave a mixture of dimeric compounds which appeared to be formed from a carbene intermediate. Another similar xanthate ester was prepared by Schonberg and Sodtke[12] and was photolyzed to produce a coupled product.

Xanthates have been used as photoinitiators in polymerization reactions[5,7,13-16] and incorporated in polymers for grafting sites.[15,16]

We have previously reported on the ground-state chemistry of the oxidatively coupled xanthate, dithiobis(thioformate), which is also called xanthide.[17]

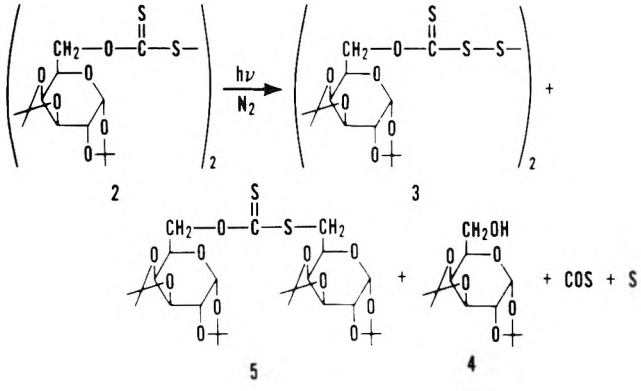
Because of the strong absorption of light by the xanthide group [λ_{max} (EtOH) 230–240 nm (ε 15,800–18,900), 280–290 (6600–8900)],[18] the photoreactivity of xanthate derivatives,

and the chemical reactivity of the xanthide group, a study of the photochemistry of some carbohydrate xanthides was undertaken.

Results

Photolysis of Bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) Dithiobis(thioformate) (2). Photolysis of **2** through quartz (λ > 200 nm) in methanol gave a white solid (**3**), which was filtered off. Column chromatography of the filtrate afforded unreacted **2**, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**), sulfur, and a component (**5**) of R_f intermediate to that of **2** and **4** (Scheme I).

Scheme I

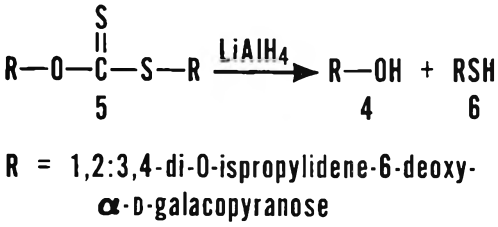


The uv spectrum of **5** showed absorption at 285 nm characteristic of a xanthate ester.[18]

From elemental analysis, **5** was formulated as bis(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) 6-*O*,6′-*S*-dithiocarbonate. Compound **5** was isolated in 35% yield. The NMR spectrum showed a two-proton absorption centered at τ 6.68, which is in the expected range for thiomethylene protons.[17]

Additional evidence for the structure of **5** was obtained by reductive cleavage with $LiAlH_4$[19] to give **4** and 1,2:3,4-di-*O*-isopropylidene-6-thio-α-D-galactopyranose (**6**) (Scheme II). The structure of **6** was confirmed by NMR

Scheme II



and elemental analysis. The NMR of this sample showed a one-proton doublet at τ 8.37, which slowly disappeared when kept with D_2O for 18 hr. The slow exchange and the position of the peak is indicative of a thiol group.[17] A two-proton multiplet centered at τ 7.31, assigned to the protons of the thiol-substituted methylene group, collapsed to a broad doublet when the deuterium exchange was complete.

The mass spectrum of **5** showed a high-mass peak at *m/e* 563 which corresponds to M − 15. Other mass peaks supporting the structure appeared at *m/e* 319, 303, and 275, which corresponds to M − CH_3 − $C_{12}H_{20}O_5$, M − $C_{12}H_{19}O_5S$, and the radical ion $C_{12}H_{19}O_5S$.

The white solid **3** showed a strong, continuous absorption from 350 to 220 nm with an ill-defined shoulder at approximately 315 nm (ε 7150) and a maximum at 240 nm (ε 21,000). From the NMR and elemental analysis, **3** was formulated as bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) tetrathiobis(thioformate). Although this compound had a fairly wide melting range, 160–164°, its physical properties were the same as those of an authentic sample prepared from the sodium xanthate salt of **4** and sulfur monochloride. Attempted recrystallization from hot methanol gave **2**, free sulfur, and a component of mp 149–151° identified as bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) trithiobis(thioformate) (**7**). This decomposition might be expected, since polysulfides are known to readily lose sulfur to form disulfides.[20]

Table I
Solvent Effect on Molar Yield of Products from Irradiation of 2[a]

Product	Irradiation time, hr: 13 Cyclohexane	23 Cyclohexane	19 Methanol	13 2-Propanol	5.5 Cyclohexane	
Sulfur	0.80	0.75	0.88	0.34	0.34	0.33
8[b]	0.11	0.2	0.09	0.2	0.16	0.23
5[a]	0.74	0.5	0.57	0.31	0.27	0.74
4[a]	0.15	0.21	0.55	0.80	1.07	0.25
COS	0.34		0.25		0.81	
CS_2	0.0		0.27		0.81	

[a] See Scheme II. [b] 6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose.

In addition to the products discussed above, COS was the major gas evolved, but after 3 hr CS_2 was also detected by the method of Brady.[21] This result suggests decomposition of the photoproduct.

Using cyclohexane solvent and similar reaction conditions, the same products were obtained in nearly the same yields when **2** was photolyzed in methanol. Longer irradiation in either solvent gave more complex mixtures, because **5** also undergoes photodecomposition under these reaction conditions and evolves CS_2. The yield of **3** was increased by photolyzing at 5° rather than at 25°. When Corex-filtered light (λ > 260 nm) was used, **5** did not react to any significant extent. Therefore, a cyclohexane solution (0.064 *M*) of **2** was irradiated for 22 hr with Corex-filtered light (λ > 260 nm) to yield **3** (37%), **5** (35%), **4** (13%), and COS, but no CS_2 could be detected. A more dilute solution (0.003 *M*) gave **5** in 74% yield and **3** could not be detected after 5.5 hr. However, when irradiation was stopped after 2 hr, an apparent mixture of polysulfides was obtained, based on mp 145–153° and elemental analysis.

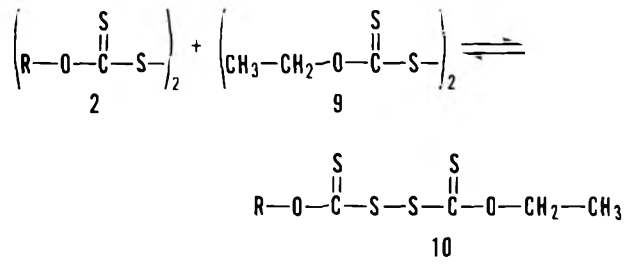
The photolysis of the tetrasulfide **3** in cyclohexane resulted in the formation of the xanthate ester **5**, but at a slower rate than from **2**. For example, under similar conditions, a 9.2% yield of **5** was obtained from **3** compared to 35% from **2**.

The effect of solvent on the reaction mixture is shown in Table I. The results show that the yield of **5** is highest in cyclohexane, and in the alcohol solvents more **4** is produced along with CS_2. In all cases, some 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactose (**8**) was obtained. However, the yield of **8** was not greatly increased when 2-propanol was used.

The photolysis of a solution of **2** and ethyl xanthide (**9**) in cyclohexane rapidly gave the mixed xanthide **10** (Scheme III). After 15–20 min, an apparent photostationary state of the three xanthides was established.

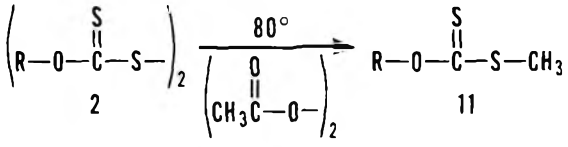
Compound **2** was found to react readily with methyl radicals generated by the thermal decomposition of acetyl peroxide. Using approximately 2 mol of acetyl peroxide per mole of **2**, 1.1 mol of *S*-methyl xanthate ester **11** was obtained (Scheme IV). The structure of **11** was confirmed by

Scheme III



R = 1,2:3,4-di-O-isopropylidene-6-deoxy-α-D-galactopyranose

Scheme IV

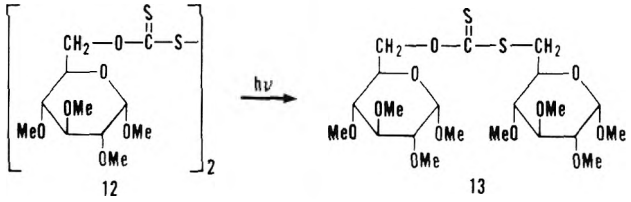


R = 1,2:3,4-di-O-isopropylidene-6-deoxy-α-D-galactopyranose

comparison of its properties to that of an authentic sample prepared from the sodium xanthate salt of 4 and methyl iodide.

Photolysis of Bis(methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside) 6,6′-Dithiobis(thioformate) (12). The photolysis of 12 (λ > 200 nm) in cyclohexane resulted in the formation of the corresponding xanthate ester (13) in 47% yield (Scheme V). No attempt was made to identify

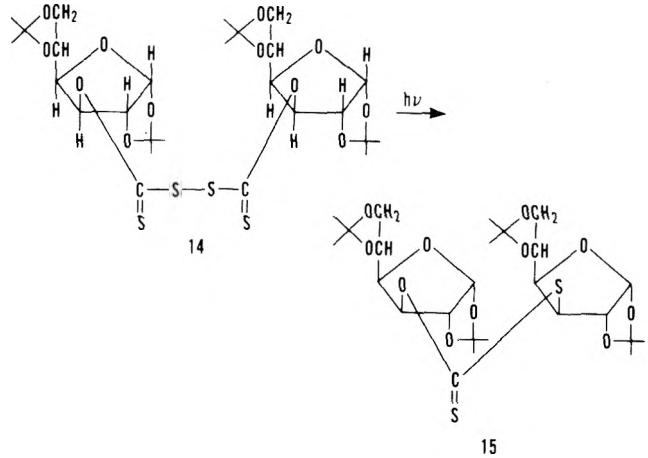
Scheme V



any polysulfides similar to 3, and products having disulfide bonds were destroyed by reaction with thiophenol or *p*-chlorothiophenol.[22]

Photolysis of Bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose) 3,3′-Dithiobis(thioformate) (14). The photolysis of 14 with Corex-filtered light gave the xanthate ester, bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) 3-*O*,3′-*S*-dithiocarbonate (15) (Scheme VI), as a

Scheme VI

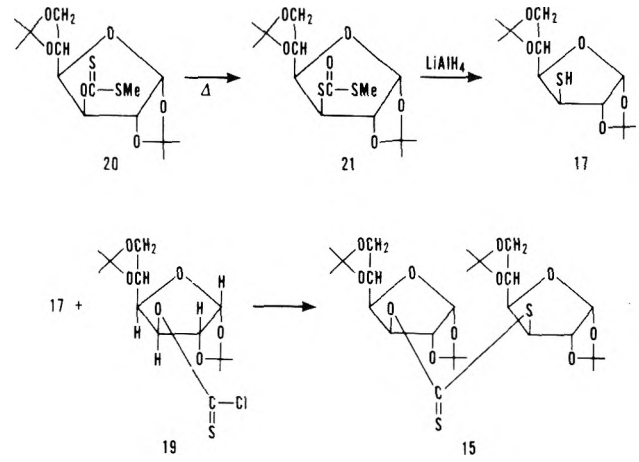


white, crystalline solid in 34% yield in which S has replaced O without inversion. Analysis of the original reaction mixture by measurement of the absorption of 283 nm showed that the total xanthate ester formed was 37%. Therefore, the xanthate ester formation occurred with at least 92% retention of configuration.

This xanthate ester **15** was reduced with $LiAlH_4$ to give 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**16**) and 1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose (**17**). The NMR spectrum of **17** was identical with that of the known **17** prepared by the method of Heap and Owen.[19] The thiol was also converted to the *S*-acetyl derivative (**18**) and exhibited properties identical with those previously reported for this compound.[19]

The xanthate ester **15** was independently synthesized by reaction of the 3-thiol **17**, prepared by the method of Heap and Owen,[19] with the 3-chlorothioformate **19** of **16** described by Shasha and Doane[23] (Scheme VII). The xan-

Scheme VII



thate ester prepared by this procedure had the same properties as the product obtained from the photolysis of **14**. A mixture of the two showed no depression of the melting point.

Examination of the minor components of the reaction mixture showed no components which could be identified as the xanthate ester in which the inversion had occurred.

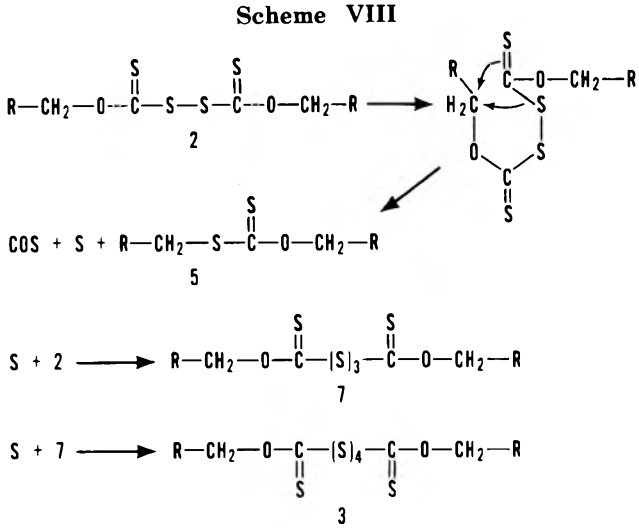
Discussion

The photochemical transformation of **2** to **3** and **5** is in contrast to the pyrolysis reaction reported by Trimnell et al.[17] in which **2** gave only bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) 6,6′-thionocarbonate. However, on pyrolysis bis(methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside) 6,6′-dithiobis(thioformate) (**12**) rearranged to the corresponding dithiocarbonate **13**.[17] They also reported that dithiocarbonates were not formed when xanthides attached to secondary positions were pyrolyzed. In the present work, photolyzing **14** gave the dithiocarbonate **15**.

The mechanism proposed to account for the observed products is shown in Scheme VIII. This mechanism involves the attack of an excited sulfur atom on the methylene carbon, which requires a seven-membered cyclic transition state if it involves the thiocarbonyl sulfur, or a five-membered transition state if it involves a sulfur of the disulfide linkage. The reaction then proceeds with the elimination of carbonyl sulfide and free sulfur. This molecular sulfur may insert into a disulfide bond or possibly abstract another atom of sulfur to form S_2, which could insert into a disulfide bond. Gunning et al.[24,25] have shown that condensed-phase photolysis of COS yields long-chain sulfur

biradicals and have proposed that either sulfur atoms or S_2 biradicals are the propagating species. These insertion reactions would account for the formation of the trisulfide and tetrasulfide products.

Scheme VIII



The proposed mechanism does not account for the apparent preference of tetrasulfide formation. However, Hoffmeister and Tarbell[26] found a similar preferential formation of a hexasulfide on pyrolysis of benzoyl cyclopentamethylene thiocarbamyl disulfide. The photolysis of benzoic pyrrolidine dithiocarbamic anhydride gave a hexasulfide, while photolysis of benzoic morpholine dithiocarbamic anhydride gave a tridecasulfide.[27] They suggested that the selective formation of the polysulfides is due to the lower solubilities of these polysulfides. This appears to be the most plausible explanation of the results presented here, for disulfide exchange would be expected to occur very rapidly to form many polysulfides based on the rapid exchange of ethyl xanthide and **2**.

The rapid exchange reaction of ethyl xanthide with **2** is assumed to proceed by a radical mechanism based on results of Siebert,[13] who has shown that photolysis of xanthide will catalyze the polymerization of butyl acrylate, and on results of Walling and Rabinowitz,[28] which showed that disulfides photolyze to thiyl radicals. The above results indicate the xanthate radical is relatively stable and does not readily abstract hydrogen atoms from cyclohexane, since **4** was obtained in low yield and carbon disulfide could not be detected in the reaction mixture when Corex-filtered light was used. However, methanol or 2-propanol appear to serve as a hydrogen source for the xanthate radical in dilute solution, since carbon disulfide and **4** are produced in larger quantities at the expense of **5** when photolysis is carried out in these solvents.

Although methyl radicals readily attacked the disulfide bond of the xanthide, which supports a free-radical mechanism, the stereoselectivity in the formation of **15**, the low yield of **5** from the tetrasulfide **3**, the high yield of **5** in dilute solution, and the low yield of the 6-deoxy derivative, **8**, in 2-propanol strongly favor the cyclic mechanism. If a free radical were formed on C_3 of the glucose, one would expect to obtain both the allo and the gluco configuration in the 3-thio sugar.

An initial isomerization similar to the thermal rearrangement of xanthate esters was considered unlikely, since, under the reaction conditions, no carbonyl-containing products could be detected by ir analysis of the reaction mixture.

The photolysis of either the mono- or the dixanthide of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside under similar reaction conditions did not give a xanthate ester. Likewise, the monoxanthide of *trans*-1,2-cyclohexanediol did not give a xanthate ester product.

Experimental Section

Melting points were determined with a Fisher-Johns[29] apparatus and are uncorrected. Optical rotations were determined in a 1-dm tube with a Rudolph polarimeter. Ir spectra were recorded with a Beckman IR-33 spectrophotometer. NMR spectra of $CDCl_3$ solutions were recorded on a Varian HA-100 spectrometer with tetramethylsilane as internal reference standard (τ 10.0). A Perkin-Elmer Model 202 spectrophotometer was used to record uv spectra. For TLC, silica gel G was used as the adsorbent and 19:1 (v/v) methanol–sulfuric acid as the spray reagent. Mallinckrodt silicic acid (100 mesh) was used for large-scale chromatography. All reagents were reagent grade and were used without further purification. The light source was a Hanovia high-pressure mercury arc lamp (450 W, No. 679A) in a quartz immersion well, with or without additional filters.

Preparation of Bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) Dithiobis(thiformate) (2). Compound **2** was prepared by the procedure of Shasha et al.[30] and exhibited properties as reported by Doane et al.[31]

Photolysis of 2. A. Quartz, Methanol (0.016 *M*). A solution of **2** (2.5 g) in methanol (230 ml) was sparged with nitrogen for 10 min. The light yellow solution was then irradiated for 3 hr, while the flow of nitrogen continued. The insoluble solid present in the reaction mixture was collected to yield **3** (0.247 g): mp 160–164°; $[\alpha]^{23}D$ 0.0° (*c* 1, $CHCl_3$); λ_{max} (ether) 315 nm (ϵ 7150) and 240 (21,000); λ_{max} (film) 1250 cm^{-1} [OC(S)SS]; NMR τ 4.49 (d, $J_{1,2}$ = 7 Hz, H-1), 5.20–5.44 (m), 5.60–5.84 (m), 8.43, 8.57, 8.68 (s, CMe_2).

Anal. Calcd for $C_{26}H_{38}O_{12}S_6$: C, 42.5; H, 5.3; S, 26.2; mol wt, 738. Found: C, 42.3; H, 5.5; S, 26.4; mol wt, 778 (vapor pressure osmometry, $CHCl_3$).

The methanol filtrate was concentrated and kept in an ice bath for 4 hr to yield a white precipitate. Recrystallization from methanol gave **2** (0.777 g), mp 130–134°.

Combining the methanol filtrates and evaporation of the solvent at 40° under reduced pressure gave a yellow syrup, which was chromatographed on silicic acid. The column was eluted with acetone–hexane (1:50). The first component eluted was free sulfur (0.005 g). Next eluted was a mixture of **2** and **5** (0.078 g) determined by TLC. Continued elution gave **5** (0.578 g, 27%) as a yellow syrup: $[\alpha]^{23}D$ −55° (*c* 1, $CHCl_3$); λ_{max} (MeOH) 283 nm (ϵ 8200); NMR τ 4.50 (two-proton, four-line m, H-1, H-1′), 5.1–5.5 (four-proton m), 5.6–6.1 (six-proton m), 6.68 (two-proton m), 8.51, 8.59, 8.66 (24 protons, s, CMe_2).

Anal. Calcd for $C_{25}H_{38}O_{11}S_2$: C, 51.9; H, 6.6; S, 11.1; mol wt, 578. Found: C, 51.6; H, 6.6; S, 11.4; mol wt, 586 (vapor pressure osmometry, $CHCl_3$).

Next eluted was **4** (0.227 g). Compound **5** was recrystallized from hexane at −20° on long standing to give a crystalline product of mp 107–110°.

B. Quartz, 2-Propanol (0.016 *M*). A solution of **2** (2.5 g) in 2-propanol (230 ml) was irradiated under N_2 for 3 hr using the quartz immersion well. The reaction mixture was filtered and the solvent was evaporated at 40° under reduced pressure. TLC of the resulting light yellow syrup showed three components: one of R_f equal to the R_f of **2**, one of R_f equal to the R_f of **5**, and the other of R_f equal to the R_f of **4**. The syrup was dissolved in methanol (50 ml) and kept for 1.5 hr. A white precipitate (0.39 g) formed of mp 149–151°, which was formulated from elemental analysis as bis-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) trithiobis-(thioformate) (**7**).

Anal. Calcd for $C_{26}H_{38}O_{12}S_5$: C, 44.6; H, 5.32; S, 22.8. Found: C, 44.3; H, 5.14; S, 22.2.

The filtrate was kept for 72 hr at −20° and a second precipitate (0.50 g) formed of mp 130–152°. This precipitate was assumed to be a mixture of **2** and **7**, since TLC showed only one component. The methanol was evaporated and the remaining syrup was chromatographed to give free sulfur (0.024 g), **2** (0.25 g), **5** (0.30 g), and **4** (0.60 g).

C. Quartz, Cyclohexane (0.016 *M*). A solution of **2** (2.5 g) in cyclohexane (230 ml) was irradiated for 3 hr under N_2 using the quartz immersion well. The reaction mixture was concentrated at 40° under reduced pressure. The resulting syrup was dissolved in methanol (50 ml) and kept at −20°. A white precipitate formed, which was collected, washed with methanol, and dried (0.9 g), mp 130–162°, assumed to be a mixture of **2**, **3**, and other polysulfides.

The methanol was evaporated and the resulting syrup was chromatographed to give **2** (0.2 g), **5** (0.75 g), **4** (0.41 g), and sulfur (0.035 g).

D. Corex, Cyclohexane (0.064 *M*). A solution of **2** (10.0 g) in cyclohexane (230 ml) was irradiated under a continuous flow of N_2 for 24 hr using Corex-filtered light. The reaction mixture was filtered to remove the insoluble **3** (0.448 g) which had formed. The volatile components were then removed at room temperature. The resulting yellow syrup was dissolved in methanol (500 ml) and the methanol was slowly evaporated. As the solvent evaporated, a white precipitate formed (2.8 g, mp 152–158°). Recrystallization from methanol (250 ml) gave **3** (mp 159–163°). The remaining original methanol solution was kept at 5° for 18 hr to give **2** (2.8 g) as a white precipitate. Filtration of the supernatant liquid and concentration of the solvent at 40° under reduced pressure gave a yellow syrup, which was chromatographed on silica gel to give **2** (0.27 g), **5** (3.2 g), and **4** (0.53 g).

E. Pyrex, Cyclohexane (0.003 *M*). A solution of **2** (0.5 g) in cyclohexane (230 ml) was irradiated under a continuous flow of N_2 for 14 hr using Pyrex-filtered light. The volatile components were evaporated at room temperature. The resulting light yellow syrup was chromatographed to give sulfur (0.019 g), **8** (0.040 g), **5** (0.320 g), and **4** (0.030 g). No CS_2 could be detected in the effluent gases, but COS (0.25 mmol) was determined by uv analysis as a diethylamine complex in an ethanol (1 l.)–diethylamine (4.0 ml) solution.

F. Pyrex, 2-Propanol (0.003 *M*). A solution of **2** (0.5 g) in 2-propanol (230 ml) was irradiated under a continuous flow of N_2 for 23 hr. The volatiles were evaporated at room temperature. The resulting syrup was chromatographed to yield sulfur (0.008 g), **5** (0.14 g), and **4** (0.15 g). Compound **8** was obtained as a mixture (0.040 g). A mixture of CS_2 (0.62 mmol) and COS (0.60 mmol) was detected in the effluent gases by uv analysis of an ethanol (1 l.)–diethylamine (4.0 ml) solution into which the gases had been sparged.

G. Pyrex, Methanol (0.003 *M*). A solution of **2** (0.5 g) in methanol (230 ml) was irradiated under a continuous flow of N_2 for 19 hr using Pyrex-filtered light. The cloudy reaction mixture was kept at room temperature and the volatiles were allowed to evaporate. The resulting syrup was chromatographed to yield sulfur (0.021 g), a mixture containing mostly **8** (0.016 g), **5** (0.25 g), and **4** (0.107 g). Analysis of the effluent gases showed a mixture of COS (0.185 mmol) and CS_2 (0.205 mmol), determined by uv analysis after reaction with diethylamine.

H. Corex, Cyclohexane (0.003 *M*). A solution of **2** (0.5 g) in cyclohexane (230 ml) was irradiated with Corex-filtered light under a continuous flow of N_2 for 5.5 hr. The volatiles were removed at room temperature and the resulting syrup was chromatographed to yield sulfur (0.008 g), **5** (0.32 g), and **4** (0.087 g). Only COS could be detected in the effluent gases by uv analysis after reaction with diethylamine in ethanol.

Irradiation of Bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) Tetrathiobis(thioformate) (3). A methanol (230 ml) suspension of **3** (2.4 g) was irradiated for 3 hr under N_2 using quartz-filtered light. The reaction mixture was filtered and unreacted **3** (1.3 g) was recovered. The solvent was removed from the filtrate and the resulting syrup was treated with pyridine (5 ml) and *p*-chlorothiophenol (1 g). After 30 min, the pyridine was evaporated and the sample was chromatographed to give **5** (0.197 g) and **4** (0.540 g).

Preparation of 1,2:3,4-Di-*O*-isopropylidene-6-thio-α-D-galactopyranose (6) from 5. Compound **5** (0.5 g) was dissolved in ether (20 ml), and $LiAlH_4$ (0.25 g) was added in portions over a 5-min period. The resulting black-gray mixture was then refluxed for 1 hr. TLC of the reaction mixture showed two components, one of R_f equal to that of **4** and the other of R_f greater than that of **5**. "Newcell" thiol spray reagent indicated that the component of higher R_f was a thiol. After the excess $LiAlH_4$ was destroyed by adding ethyl acetate, the reaction mixture was poured into 5% aqueous acetic acid (50 ml). The reaction flask was rinsed with acetic acid (2 ml) and the combined acetic acid solutions were extracted three times with ether (50-ml portions). The ether solution was kept over sodium bicarbonate until neutral, then washed with water and dried over sodium sulfate. Evaporation of the ether gave a colorless syrup, which was chromatographed on silica gel. Elution with hexane–$CHCl_3$ (4:1) gave **6** (0.165 g): NMR τ 4.51 (one-proton d, $J_{1,2}$ = 5 Hz, H-1), 5.40 (one-proton q, $J_{2,3}$ = 8, $J_{3,4}$ = 3 Hz, H-3), 5.70 (two-proton m, H-2,4), 6.25 (one-proton m, $J_{4,5}$ = 2, $J_{5,6}$ = 6 Hz, H-5), 7.31 (two-proton m, H-6), 8.37 (one-proton d, J = 9 Hz, H-thiol), 8.49, 8.60, 8.69, 8.76 (12 protons, s, CMe_2). The signal at τ 8.37 disappeared when kept with D_2O for 18 hr and the signal at τ 7.31 became a broad doublet.

Photolysis of 2 and Ethyl Xanthide. A solution of **2** (2.5 g) and ethyl xanthide (2.5 g) in cyclohexane (230 ml) was photolyzed under nitrogen (quartz). After 5 min, a new component was detected by TLC. This component had an R_f identical with that of an authentic sample of the mixed xanthide.[32] After 30 min, the mixed xanthide became a major component. Carbonyl sulfide was detected in the effluent gases by uv analysis of an ethanol solution containing piperidine.

Reaction of 2 with Acetyl Peroxide. Cyclohexane (50 ml) containing **2** (1.0 g) was warmed to 70°, and acetyl peroxide (0.2 ml) was added.[33] After 1 hr of gentle reflux, more acetyl peroxide (0.4 ml) was added. The reaction mixture was refluxed for 1 hr. After cooling, the solvent was removed by evaporation at 50° under reduced pressure to yield a light yellow syrup.

Chromatography gave a major component (0.58 g), which was identified as 1,2:3,4-di-*O*-isopropylidene-6-*O*-[methylthio(thiocarbonyl)]-α-D-galactopyranose (**11**). The uv, NMR, and mass spectra were identical with those of an authentic sample.

Anal. Calcd for $C_{14}H_{22}O_6S_2$: C, 48.0; H, 6.2; S, 18.3. Found: C, 47.9; H, 6.5; S, 17.8.

Preparation of 1,2:3,4-Di-*O*-isopropylidene-6-*O*-[methylthio(thiocarbonyl)]-α-D-galactopyranose (11). Dimethyl sulfoxide (DMSO, 5.0 ml), **4** (5.0 g), 5 *N* sodium hydroxide (5.0 ml), and carbon disulfide (7.5 ml) were stirred for 10 min. The reaction mixture was cooled to 5°, and methyl iodide (5.0 ml) was added. After 1 min, a precipitate formed; the mixture was kept for 15 min. Then water (100 ml) and $CHCl_3$ (50 ml) were added to the brown mixture, and the two phases were separated. The $CHCl_3$ solution was washed three times with H_2O (100 ml) and dried with Na_2SO_4 and the solvent was removed. The resulting dark brown syrup was dissolved in 1:1 hexane–chloroform and filtered through silica gel. Evaporation of the solvent gave a bright yellow syrup. This syrup was dissolved in methanol and treated with charcoal. The solvent was removed at 50° under reduced pressure to give a nearly colorless syrup.

Anal. Calcd for $C_{14}H_{22}O_6S_2$: C, 48.0; H, 6.3; S, 18.3. Found: C, 47.9; H, 6.2; S, 18.6.

Preparation of Bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) Tetrathiobis(thioformate) (3). A mixture of **4** (4.5 g), DMSO (5 ml), 5 *N* NaOH (5.0 ml), and carbon disulfide (5 ml) was stirred for 10 min. After addition of acetic acid (0.6 ml), sulfur monochloride (1.0 ml) was added. A precipitate formed, which was collected and washed with acetone (30 ml) and ether (150 ml). The sample was dried and suspended in acetone (50 ml). The mixture was filtered and the filtrate was evaporated to give an off-white solid, mp 158–162°. The NMR of this sample was identical with that of **3** from the photolysis of **2**.

Anal. Calcd for $C_{26}H_{38}O_{12}S_6$: C, 42.6; H, 5.2; S, 26.2. Found: C, 42.0; H, 5.2; S, 25.8.

Preparation of Bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) 3,3′-Dithiobis(thioformate) (14). This compound was prepared according to the method of Shasha et al.[30]

Photolysis of Bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) 3,3′-Dithiobis(thioformate) (14). A. Corex, Cyclohexane (0.064 *M*). A solution of **14** (10.0 g) in cyclohexane (230 ml) was irradiated under N_2 for 27 hr using Corex-filtered light. The solution was kept at room temperature and the volatile components were evaporated. Hexane was added to the syrup and the resulting solution was filtered. The hexane filtrate was seeded with crystalline **15** and kept at 5°. A crystalline precipitate (2.02 g) of **15** formed, which was collected and washed with cold hexane. TLC of the supernatant showed considerable **15** in solution along with unreacted **14** and **16**.

B. Corex, Cyclohexane (0.016 *M*). A solution of **14** (2.5 g) in cyclohexane (230 ml) was irradiated under N_2 for 20 hr using Corex-filtered light. The volatile components were evaporated at room temperature and the yellow syrup was chromatographed to give sulfur (0.10 g), **14** (0.25 g), **14** and **15** (0.36 g), **15** (0.92 g), and **16** (0.56 g).

Compound **15** was recrystallized from hexane and exhibited the following properties: mp 133–135°; $[\alpha]^{23}D$ − 56° (*c* 1, acetone); λ_{max} (EtOH) 282 nm (ε 9600).

Anal. Calcd for $C_{25}H_{38}O_{11}S_2$: C, 52.0; H, 6.5; S, 11.1; mol wt, 578. Found: C, 51.6; H, 6.7; S, 11.6; mol wt, 550 (vapor pressure osmometry in $CHCl_3$).

NMR spectrum shows the following: τ 4.15 (three-proton m, H-1, H-1′, H-3′), 5.31 (two-proton d, H-2, H-2′), 5.6–6.1 (nine-proton m), 8.48, 8.60, 8.70 (24 protons, s, CMe_2).

C. Pyrex, Cyclohexane (0.003 *M*). A solution of **14** (0.5 g) in cyclohexane (230 ml) was irradiated under N_2 for 13.5 hr using Pyrex-filtered light. The volatile components of the reaction mixture were evaporated at room temperature and the remaining syrup was chromatographed to give sulfur (0.013 g), 1,2:5,6-di-*O*-isopropylidene-3-*O*-[cyclohexylthio(thiocarbonyl)]-α-D-glucofuranose (0.044 g), **14** (0.080 g), **15** (0.250 g), and **16** (0.066 g).

Reduction of 15 with $LiAlH_4$. Compound **15** (0.5 g) was dissolved in ether (20 ml) and $LiAlH_4$ (0.25 g) was added in small portions over a 5-min period. The resulting gray-black mixture was then refluxed for 1 hr. After the excess $LiAlH_4$ was destroyed with ethyl acetate, the reaction mixture was poured into 5% acetic acid (50 ml). The mixture was transferred to a separatory funnel, and the flask was rinsed with acetic aicd (2.0 ml). The ether layer was separated and the water layer was washed twice with ether (50 ml). The ether extracts were combined and washed with $NaHCO_3$ solution and with water. The ether layer was dried with Na_2SO_4. Evaporation of the ether and addition of hexane to the colorless syrup gave a crystalline precipitate, identified as **16** (0.291 g) by comparison with an authentic sample. The hexane solution was concentrated to a colorless syrup, which was purified by chromatography on silica gel. Elution with $CHCl_3$ gave a colorless syrup (0.188 g) which was identified as 1,2:5,6-di-*O*-isopropylidene-3-thiol-α-D-glucofuranose (**17**). The NMR spectrum of this sample was identical with that of an authentic sample prepared by the method of Heap and Owen.[19]

Anal. Calcd for $C_{12}H_{20}O_5S$: C, 52.2; H, 7.3; S, 11.6; mol wt, 276. Found: C, 52.1; H, 7.4; S, 11.5; mol wt, 312 (vapor pressure osmometry in $CHCl_3$).

Preparation of Bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) 3-*O*,3′-*S*-Dithiocarbonate (15) from 17 and 19. To a solution of **17** (1.0 g) in ether (10 ml) was added **19** (1.2 g).[23] Triethylamine (0.5 ml) was added dropwise to produce immediately a white precipitate. TLC indicated that nearly all **17** and **19** had reacted and gave a product of R_f equal to that of **15**. The white precipitate was removed by filtration. After evaporation of the ether, the syrup was dissolved in chloroform, washed with water, and dried with sodium sulfate, and the solvent was evaporated. After 10 days, the sample was chromatographed to give **15**, which crystallized from hexane, mp 133–134°. A portion of the product was mixed with **15** obtained from the photolysis of **14** and gave mp 132–134°; NMR, uv, and ir of both products were identical.

Preparation of 3-*S*-Acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (18) from 17. An ether solution (10 ml) containing **17** (0.125 g) was treated with acetic anhydride (2.5 ml) and pyridine (3.0 ml). The solution was kept for 3 days. The excess reagents were evaporated at room temperature (72 hr). The resulting syrup was dissolved in ether (20 ml) and the solution was extracted twice with water (10 ml). The ether solution was dried with sodium sulfate and the solvent was evaporated to give a colorless syrup (0.075 g), $[\alpha]^{23}D$ −47° (c 1, $CHCl_3$) (lit. $[\alpha]^{23}D$ − 46°).

Anal. Calcd for $C_{14}H_{22}O_6S$: C, 52.7; H, 6.95; S, 10.0. Found: C, 52.9; H, 7.19; S, 9.9.

Photolysis of Bis(methyl 2,3,4-tri-O-methyl-α-D-glucopyranoside) 6,6′-Dithiobis(thioformate) (12). A solution of **12** (2.5 g) in methanol (230 ml) was irradiated under N_2 for 3 hr using a quartz immersion well. The solution was concentrated at 50° under reduced pressure to yield a yellow syrup. This syrup was treated with *p*-chlorothiophenol and pyridine to destroy unreacted **12** and polysulfides. The pyridine was evaporated and the remaining syrup was chromatographed to give **13** (0.970 g, 46%) and methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside.

Registry No.—**2**, 4239-75-2; **3**, 54497-83-5; **4**, 4064-06-6; **5**, 54497-84-6; **6**, 16714-07-1; **7**, 54497-85-7; **8**, 4026-27-1; **9**, 502-55-6; **10**, 54497-86-8; **11**, 53867-05-3; **12**, 35905-03-4; **13**, 35905-04-5; **14**, 2946-03-4; **15**, 54497-87-9; **16**, 582-52-5; **17**, 54497-88-0; **18**, 28251-80-1; **19**, 31818-50-5; acetyl peroxide, 79-21-0.

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Reactions of Sulfonates with Sodium Ethylxanthate

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Various 6-*O*-tosyl- and 6-*O*-mesyl-α-D-glucopyranosides reacted with sodium ethylxanthate in either water or organic solvents to give 6-ethoxythiocarbonyl-6-thio derivatives. Methyl 6-ethoxythiocarbonyl-6-thio-α-D-glucopyranoside on treatment with sodium hydroxide yielded the 6-thiol, which on oxidation gave the 6,6′-disulfide. Cyclohexyl tosylates reacted with sodium ethylxanthate to give *S*-cyclohexyl-*O*-ethyl dithiocarbonates. Although the reaction of 1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose with sodium ethylxanthate was negligible in solvents, in the dry state at 150° mainly bis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranose) 6,6′-sulfide resulted.

Displacements of sulfonyloxy groups by thiocyanate,[3] thiolacetate,[4] thiolbenzoate,[5] and thiosulfate[6] are well known, and the products resulting may be converted to thiols by saponification or reduction. Thiol groups have also been introduced into sugars and polysaccharides by transformations of various thiocarbonate esters.[7-11]

We displaced tosyloxy and mesyloxy groups of various blocked sugars and cycloaliphatic compounds with xanthate ion to produce dithiocarbonate esters from which we obtained thiols by treatment with such bases as sodium hydroxide or ammonia. Previously, such dithiocarbonates were formed by displacement of halides from 6-iodo sugars[12] and glycosyl bromides or chlorides.[13,14] Maki and Tejima[14] reported that sodium ethylxanthate displaced the bromide of 2-deoxy-3,4-di-*O*-acetyl-6-*O*-tosyl-α-D-glucopyranosyl bromide, but they did not report any displacement of the sulfonyloxy group by the xanthate.

The displacement of the sulfonyloxy groups with xanthate, followed by saponification, gives a facile procedure for achieving thiolation at primary positions in carbohydrates. The displacement takes place in aqueous media

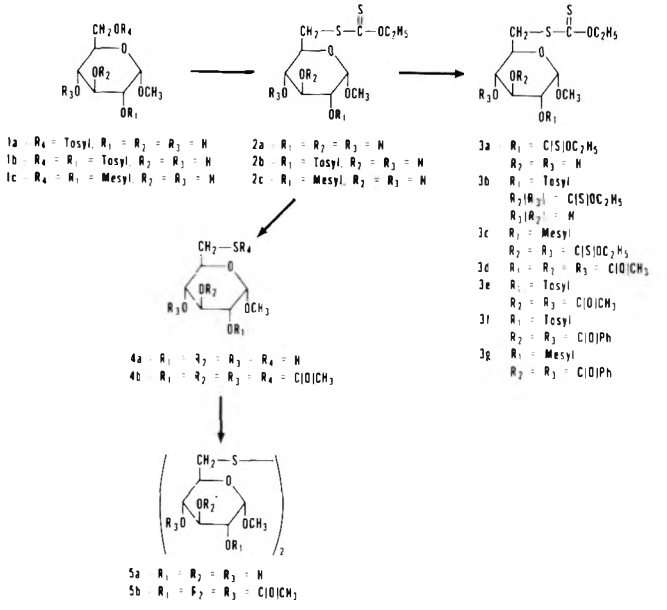
$$RCH_2OSO_2R' + C_2H_5OCS_2Na \longrightarrow RCH_2S_2COC_2H_5 + R'SO_2ONa \quad (1)$$

$$RCH_2S_2COC_2H_5 + H_2O \xrightarrow{NaOH} RCH_2SH + COS + C_2H_5OH \quad (2)$$

even where the starting compound is insoluble, as in reactions involving methyl 2,6-di-*O*-tosyl-α-D-glucopyranoside and tosylated starches. The displacements occur also in organic solvents, such as acetone, dimethyl sulfoxide, or *N,N*-dimethylformamide, either overnight at room temperature (25°) or within several hours at elevated temperatures (50–85°).

The 6-*O*-tosyl (**1a**),[15] 2,6-di-*O*-tosyl (**1b**),[16] and 2,6-di-*O*-mesyl (**1c**)[17] derivatives of methyl α-D-glucopyranoside have been treated with sodium ethylxanthate to give the corresponding 6-dithiocarbonates (**2a–c**) by selective displacement of sulfonyloxy groups at the 6 position. Minor products of the reaction were identified as ethoxythionocarbonate derivatives, such as **3b**, and thiols, similar to **4a** (Scheme I). The inactivity of the 2 position toward displacement in **1b** and **1c** was consistent with the inactivity of methyl 2-*O*-tosyl-α-D-glucopyranoside[18] toward sodium ethylxanthate under these conditions. The 6-dithiocarbonates, **2a–c**, were further characterized as acetates **3d,e** and benzoates **3f,g**. When **1a** was treated in water with stoichiometric amounts of sodium ethylxanthate at 65° for 3.5 hr, **2a** crystallized in 74% yield from the cooled reaction

Scheme I



mixture. Similarly, **1b** was transformed to **2b** (23%) and **1c** to **2c** (60%). Structures of these products and related derivatives were determined by elemental analyses and by uv, ir, and NMR spectra.

When **2a** was treated with sodium hydroxide, methyl 6-thio-α-D-glucopyranoside (**4a**) was obtained crystalline, and converted to the known peracetate **4b**.[19]

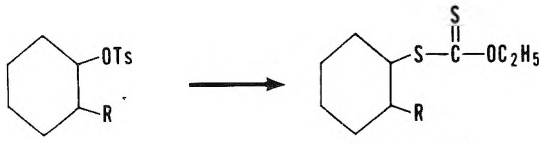
Compound **4a** was oxidized to disulfide **5a** by using diethyl dithiobis(thioformate) in pyridine.[20] Amorphous **5a** was converted to the fully acetylated derivative (**5b**).

Cyclohexyl tosylates **6a**[21] and **6b** underwent reaction with sodium ethylxanthate in acetone to give *S*-cyclohexyl-*O*-ethyl dithiocarbonates **7a** and **7b** and demonstrated that displacement was possible with certain secondary sulfonate positions in ring systems. NMR spectra did not clearly indicate stereochemical changes in going from **6b** to **7b** (Scheme II).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose (**8**)[22] did not readily react with sodium ethylxanthate in organic solvents. When the reactants were mixed in the dry state and kept under vacuum at 150° for 1 hr, **8** was transformed to a mixture of persubstituted sugars. The major component was identified as the crystalline monosulfide **9**. None of the expected dithiocarbonate was obtained in this reaction (Scheme III).

1,2:5,6-Di-*O*-isopropylidene-3-*O*-tosyl-α-D-glucofuran-

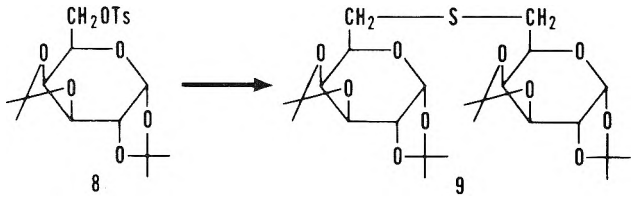
Scheme II



6a · R = H
6b · R = OH

7a · R = H
7b · R = OH

Scheme III



8 9

ose (**10**)[23] likewise did not react with sodium ethylxanthate in acetone at 25–65°, but in *N,N*-dimethylformamide at 130° compound **10** was converted to the known 3,4 olefin **11**.[23] Similarly, **11** was the only product identified on vacuum pyrolysis of **10** with sodium ethylxanthate under conditions used to convert **8** to **9**.

Experimental Section

The sulfonate esters were prepared by known methods. Melting points were determined in a Büchi apparatus and are uncorrected. Optical rotations were read with a Rudolph polarimeter. Ir and uv spectra were recorded with Perkin-Elmer 137 and 202 spectrometers, respectively. NMR spectra were determined with a Varian HA-100 spectrometer in pyridine d_5, chloroform-*d*, and/or carbon tetrachloride using tetramethylsilane (τ 10.00) as internal reference standard and a Model 200 AB Hewlett-Packard audiofrequency oscillator for decoupling experiments. Silica gel G was used for TLC, and sulfuric acid (5%) in methanol was the spraying agent. Silicic acid (Mallinckrodt, 100 mesh) was selected for larger scale separations.

Acetylations of **2a, 2b, 4a,** and **5a** were carried out in acetic anhydride and pyridine for 3 hr at 25°. Reaction mixtures were precipitated in water, and the resulting products were crystallized from alcohol or hexane. Products difficult to crystallize were precipitated from ether–hexane mixtures at 5°.

Benzoylations of **2b** and **2c** were conducted with benzoyl chloride and pyridine overnight at 25°. Reaction mixtures were diluted with chloroform and the solutions were washed with 5% HCl, 5% $NaHCO_3$, and water. After the solutions were dried and the solvent was evaporated, the benzoate esters were extracted from the residues with hexane or were precipitated from ether solution by hexane at 5°.

Reaction of Methyl 6-*O*-Tosyl-α-D-glucopyranoside (1a) with Sodium Ethylxanthate. A solution of **1a** (3.5 g, 10 mmol) and sodium ethylxanthate (1.5 g, 10 mmol) in water (10 ml) was kept at 65° for 3.5 hr. When the solution was diluted to 20 ml and cooled to room temperature, crystals formed. After 3 hr the mixture was filtered, and the crystals were washed with water and hexane. A second crop of crystals was obtained upon concentrating the filtrate and cooling: total yield 2.20 g (74%). The product, identified as methyl 6-*S*-ethoxythiocarbonyl-6-thio-α-D-glucopyranoside (**2a**), was recrystallized twice from water and vacuum dried at 55° for 1 hr: mp 110–112°; $[\alpha]^{21}D$ +158° (*c* 0.87, ethanol); ir (KBr) 8.05, 9.60 μ (OCS_2); uv max (ethanol) 358–362 nm (ε 57), 280–282 (11,520); NMR (C_5D_5N) τ 5.00 (d, H-1), 6.1–6.6 (m, 2 H, H-6, H-6′), 6.59 (s, 3 H, OCH_3), 5.42 (q, 2 H, OCH_2CH_3), 8.77 (t, 3 H, OCH_2CH_3).

Anal. Calcd for $C_{10}H_{18}O_6S_2$: C, 40.3; H, 6.08; S, 21.5. Found: C, 40.1; H, 5.91; S, 21.5.

When **1a** was treated with sodium ethylxanthate in organic solvents (acetone, dimethyl sulfoxide), yields of **2a** were similar. In addition several minor less polar by-products were separated by chromatography. Ir and uv of the major by-product suggested that both dithiocarbonate and thionocarbonate groups (7.7–8.2 μ, 230 and 280 nm) were present. NMR (C_5D_5N) indicated methyl 2-*O*-ethoxythiocarbonyl-6-*S*-ethoxythiocarbonyl-6-thio-α-D-glucopyranoside (**3a**): τ 4.70 (d, H-1), 4.38 (dd, H-2), 6.1–6.6 (m, 2 H, H-6, H-6′), 6.73 (s, 3 H, OCH_3), 5.43 (q, 2 H, OCH_2CH_3), 5.70 (q, 2 H, OCH_2CH_3), 8.81 (t, 3 H, OCH_2CH_3), 8.95 (t, 3 H, OCH_2CH_3).

Methyl 2,3,4-Tri-*O*-acetyl-6-*S*-ethoxythiocarbonyl-6-thio-α-D-glucopyranoside (3d). Acetylation of **2a** (0.160 g, 0.54 mmol) gave the known **3d** (0.228 g, 89%), which was recrystallized from ethanol or hexane: mp 57–60°; $[\alpha]^{23}D$ +116.8° (c 0.43, methanol) [reported mp 61–62°, $[\alpha]^{27}D$ +117.7° (methanol)].[12] We found NMR (C_5D_5N) τ 4.94 (d, H-1), 4.83 (dd, H-2), 4.18 (t, H-3), 4.74 (t, H-4), 5.86 (m, H-5), 6.24 (dd, H-6), 6.68 (dd, H-6′), 6.72 (s, 3 H, OCH_3), 5.46 (q, 2 H, OCH_2CH_3), 8.80 (t, 3 H, OCH_2CH_3), 7.92, 8.03, 8.09 (3 s, 9 H, OAc).

Reaction of Methyl 2,6-Di-*O*-tosyl-α-D-glucopyranoside (1b) with Sodium Ethylxanthate. A suspension of **1b** (5.0 g, 10.0 mmol) was agitated in water (5 ml) with sodium ethylxanthate (2.0 g, 14.0 mmol) and kept at 75–85° for 4 hr. The mixture was cooled and extracted with chloroform (70 ml). The extract was washed with water and dried. After filtration the chloroform solution was mixed with an equal volume of hexane and adsorbed onto silicic acid (200 g). Elution with ethyl acetate–hexane (1:7) desorbed a multicomponent minor fraction (0.21 g) from which was separated chromatographically methyl 3(4)-*O*-ethoxythiocarbonyl-6-*S*-ethoxythiocarbonyl-2-*O*-tosyl-α-D-glucopyranoside (**3b**).

Anal. Calcd for $C_{20}H_{28}O_9S_4$: C, 44.4; H, 5.22; S, 23.7. Found: C, 44.6; H, 5.17; S, 23.5.

Subsequent elution with ethyl acetate–hexane (1:3) desorbed a fraction (1.41 g) containing methyl 6-*S*-ethoxythiocarbonyl-6-thio-2-*O*-tosyl-α-D-glucopyranoside (**2b**), a syrup, which was purified by further chromatography: 1.01 g (23%); $[\alpha]^{24}D$ +129° (c 0.75, ethanol); uv max (ethanol) 280–282 nm (ε 10,210), 225–226 (15,950); ir (film) 8.4, 8.5 (OTs), 8.25 μ (OCS_2); NMR (C_5D_5N) τ 5.02 (d, H-1), 5.22 (dd, H-2), 6.1–6.7 (m, 2 H, H-6, H-6′), 6.79 (s, OCH_3), 7.85 (d, CH_3 of tosyl), 5.47 (q, OCH_2CH_3), 8.82 (t, OCH_2CH_3).

Anal. Calcd for $C_{17}H_{24}O_8S_3$: C, 45.1; H, 5.35; S, 21.3. Found: C, 45.2; H, 5.55; S, 20.8.

The yield of **2b** was slightly better if acetone was used as the solvent with a large excess of sodium ethylxanthate. A solution of **1b** (1.5 g, 3.0 mmol) and sodium ethylxanthate (5.0 g, 34.6 mmol) in acetone (30 ml) was kept at 25° for 28 hr and poured into ice water (500 ml). The mixture was acidified (1 *N* HCl) and extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ solution, then with water, and dried. Evaporation of solvent left a yellow syrup from which **2b** was obtained pure by desorption chromatography on silicic acid with ethyl acetate–hexane, 0.39 g (29%).

Methyl 3,4-Di-*O*-acetyl-6-*S*-ethoxythiocarbonyl-6-thio-2-*O*-tosyl-α-D-glucopyranoside (3e). Acetylation of **2b** (0.92 g, 2.0 mmol) gave **3e** as a syrup (0.65 g, 60%). After vacuum drying at 70° for 2 hr: $[\alpha]^{22}D$ +92.3° (*c* 0.81, ethanol); uv (ethanol) 280 nm (ε 10, 730), 227 (18,158); ir (film) 5.7 (C=O), 8.4 (OTs), 8.2, 9.6 μ (ester); NMR (C_5D_5N) τ 4.98 (d, H-1), 4.23 (t, H-3), 4.78 (t, H-4), 5.02 (dd, H-2), 5.88 (m, H-5), 6.30 (m, H-6), 6.70 (m, H-6′), 6.78 (s, 3 H, OCH_3), 7.81 (s, 3 H, OTs), 7.93, 8.21 (2 s, 6 H, OAc), 8.82 (t, 3 H, OCH_2CH_3), 5.46 (q, 2 H, OCH_2CH_3).

Anal. Calcd for $C_{21}H_{28}O_{10}S_3$: C, 47.0; H, 5.26; S, 17.9. Found: C, 47.4; H, 5.23; S, 17.3.

Methyl 3,4-Di-*O*-benzoyl-6-*S*-ethoxythiocarbonyl-6-thio-2-*O*-tosyl-α-D-glucopyranoside (3f). Benzoylation of **2b** (0.12 g, 0.27 mmol) gave **3f:** 0.11 g (64%); mp 167–168° (ethanol); ir (film) 5.78 (C=O), 7.92 (ester), 8.4, 8.5 (OTs), 8.2, 9.6 μ (OCS_2).

Anal. Calcd for $C_{31}H_{32}O_{10}S_3$: C, 56.4; H, 4.88; S, 14.6. Found: C, 56.6; H, 4.95; S, 14.9.

Reaction of Methyl 2,6-Di-*O*-mesyl-α-D-glucopyranoside (1c) with Sodium Ethylxanthate. A solution of **1c** (3.5 g, 10.0 mmol) in water (20 ml) containing sodium ethylxanthate (2.0 g, 14.0 mmol) was kept at 75–85° for 2.5 hr. The clear solution was cooled and extracted with chloroform (100 ml). The chloroform extract was dried, the solvent was evaporated, the residue was taken up in ether (15 ml), and the ether solution was added dropwise to hexane (300 ml) cooled to 5°. A solid precipitated which was filtered after 1 hr and identified as methyl 6-*S*-ethoxythiocarbonyl-2-*O*-mesyl-6-thio-α-D-glucopyranoside (**2c**): 2.25 g (60%); mp 71–73° (crystallized from ether–hexane); $[\alpha]^{24}D$ +135° (c 1.04, ethanol); uv max (ethanol) 280 nm (ε 10,480), 224 (5430); ir (film) 2.8 (OH), 7.4, 8.5 (OMs), 8.2, 9.6 μ (OCS_2); NMR (C_5D_5N) τ 4.83 (d, H-1), 5.15 (dd, H-2), 6.1–6.6 (m, 2 H, H-6, H-6′), 6.63, 6.70 (2 s, 6 H, OCH_3, OMs).

Anal. Calcd for $C_{11}H_{20}O_8S_3$: C, 35.1; H, 5.36; S, 25.6. Found: C, 35.2; H, 5.47; S, 25.9.

The filtrate from the initial precipitation of **2c** contained a per-substituted compound (0.015 g) tentatively identified as methyl

3,4-di-*O*-ethoxythiocarbonyl-6-*S*-ethoxythiocarbonyl-2-*O*-mesyl-6-thio-α-D-glucopyranoside (**3c**): ir (film) 7.3, 8.5 (OMs), 7.7 (OCSO), 8.1, 9.6 μ (OCS_2); NMR (CCl_4) τ 5.10 (d, H-1), 4.02 (t, H-3), 4.41 (t, H-4), 6.52 (s, 3 H, OCH_3), 7.10 (s, 3 H, OMs), 8.4–8.8 (m, OCH_2CH_3), 5.3–5.6 (m, OCH_2CH_3).

Methyl 3,4-Di-*O*-benzoyl-6-*S*-ethoxythiocarbonyl-2-*O*-mesyl-6-thio-α-D-glucopyranoside (3g). Benzoylation of **2c** (0.43 g, 1.14 mmol) gave **3g:** 0.20 g (30%); mp 60–70° (amorphous); ir (film) 5.77 (C=O), 7.4, 8.5 (OMs), 7.9 (ester), 8.2 μ (OCS_2).

Anal. Calcd for $C_{25}H_{28}O_{10}S_3$: C, 51.4; H, 4.84; S, 16.5. Found: C, 51.4; H, 5.05; S, 16.3.

Methyl 6-Thio-α-D-glucopyranoside (4a). A mixture of **2a** (0.298 g, 1.0 mmol) and 1 *N* sodium hydroxide (10 ml) was stirred at 50° for 10 min. The resulting clear solution was cooled, neutralized with 1 *N* hydrochloric acid (10 ml), and flushed with nitrogen for 2 min. The solvent was evaporated and the residue was extracted with four 25-ml portions of chloroform. The extracts were combined and dried. Evaporation of chloroform left a syrup which was kept under vacuum at 60° for 1 hr. Compound **4a** crystallized upon evacuation at room temperature: 0.168 g (80%); mp 100–102°; $[\alpha]^{24}D$ +145° (*c* 0.4, ethanol); ir (film) 3.88 μ (SH); NMR ($CDCl_3$) τ 8.33 (t, SH), 5.28 (d, H-1), 7.0–7.4 (m, 2 H, H-6, H-6′), 6.58 (s, 3 H, OCH_3).

Anal. Calcd for $C_7H_{14}O_5S$: C, 40.0; H, 6.7; S, 15.2. Found: C, 39.5; H, 6.6; S, 14.9.

This compound has been reported[19] as a syrup, $[\alpha]^{20}D$ +181° (c 0.5, ethanol), ir 2550 cm^{-1} (3.92 μ) for SH. We found that ion exchange resins used in desalting the reaction mixture caused some oxidation to the disulfide, which may account for the higher rotation reported (see preparation of **5a**).

Methyl 2,3,4-Tri-*O*-acetyl-6-*S*-acetyl-6-thio-α-D-glucopyranoside (4b). Acetylation of **4a** (0.159 g, 0.76 mmol) gave **4b** as a syrup: 0.279 g (97%); $[\alpha]^{26}D$ +119° (*c* 1.67, chloroform); $n^{20}D$ 1.4794; NMR (CCl_4) τ 7.72 (s, 3 H, SAc), 8.00, 8.03, 8.09 (3 s, 9 H, OAc).

Anal. Calcd for $C_{15}H_{22}O_9S$: S, 8.47. Found: S. 8.55. Reported[19] for this compound: $[\alpha]^{20}D$ +118° (c 1, chloroform), $n^{20}D$ 1.4792.

Bis(methyl 6-thio-α-D-glucopyranoside) 6,6′-Disulfide (5a). A solution of **4a** (0.189 g, 0.90 mmol) in pyridine (5 ml) was treated with diethyl dithiobis(thioformate) (0.109 g, 0.45 mmol). After 5 min the pyridine was evaporated and the residue was dissolved in ethanol (10 ml). Evaporation of the ethanol left a syrup which was vacuum dried at 70° for several hours: 0.189 g (quantitative); $[\alpha]^{23}D$ +347°; NMR (C_5D_5N) τ 4.96 (d, 2 H, H-1), 6.25 (dd, 2 H, H-6), 6.77 (dd, 2 H, H-6′), 6.58 (s, 6 H, OCH_2).

Anal. Calcd for $C_{14}H_{26}O_{10}S_2$: C, 40.2; H, 6.26; S, 15.3. Found: C, 39.9; H, 6.27; S, 15.3.

Bis(methyl 2,3,4-tri-*O*-acetyl-6-thio-α-D-glucopyranoside) 6,6′-Disulfide (5b). Acetylation of **5a** (0.084 g, 0.02 mmol) gave **5b:** 0.112 g (83%); mp 156° (ethanol); $[\alpha]^{26}D$ +259° (*c* 0.37, chloroform); NMR (C_5D_5N) τ 4.81 (d, 2 H, H-1), 4.74 (dd, 2 H, H-2), 4.13 (t, 2 H, H-3), 4.70 (t, 2 H, H-4), 5.78 (m, 2 H, H-5), 6.75 (dd, 2 H, H-6), 6.95 (dd, 2 H, H-6′), 6.59 (s, 6 H, OCH_3), 7.95, 8.02, 8.08 (3 s, 9 H, OAc).

Anal. Calcd for $C_{26}H_{38}O_{16}S_2$: C, 46.6; H, 5.71; S, 9.56. Found: C, 46.2; H, 5.49; S, 9.51.

***S*-Cyclohexyl-*O*-ethyl Dithiocarbonate (7a).** Cyclohexyl tosylate (**6a**, 1.0 g, 3.9 mmol) and sodium ethylxanthate (2.0 g, 14 mmol) in acetone (10 ml) were kept at 25° for 24 hr. Sodium tosylate (0.74 g) was removed by filtration and acetone by evaporation of the filtrate. The residue was extracted with hexane and the hexane was evaporated. The resulting colorless syrup was chromatographed with hexane as the eluent: 0.31 g (39%); uv (ethanol) 283 nm; NMR ($CHCl_3$) τ 5.47 (q, 2 H, OCH_2), 6.37 (m, CHS), 7.8–8.8 (13 H).

Anal. Calcd for $C_9H_{16}OS_2$: C, 52.9; H, 7.84; S, 31.3. Found: C, 53.1; H, 7.98; S, 30.8.

***trans*-Cyclohexyl-2-ol Tosylate (6b).** To a solution of *trans*-1,2-cyclohexanediol (12 g) in chloroform (200 ml) and pyridine (50 ml) was added a solution of *p*-toluenesulfonyl chloride (19 g) in benzene (130 ml) over a period of 45 min. The solution was stirred overnight and then warmed to 50° for 1 hr. The reaction mixture was extracted with H_2O (100 ml), hydrochloric acid (100 ml, 1 *N*), 5% sodium bicarbonate (50 ml), and H_2O (50 ml). The organic layer was dried and the solvent was evaporated. The resulting syrup was dissolved in $CHCl_3$ and hexane was added. The mixture was kept overnight at 5° to give a crystalline precipitate, 4.0 g, mp 85–95°. Recrystallization gave **6b:** mp 89–90°; NMR ($CDCl_3$) τ 2.2 (d, 2 H), 2.7 (m, 2 H), 5.74 (m, 1 H, CHOTs), 6.48 (m, 1 H, CHOH), 7.60 (s, 3 H, CH_3), 7.66–8.8 (8 H).

Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.8; H, 6.67; S, 11.8. Found: C, 57.5; H, 6.90; S, 11.5.

***S*-(Cyclohexyl-2-ol) *O*-Ethyl Dithiocarbonate (7b).** A solution of **6b** (1.0 g) in acetone (15 ml) was treated with sodium ethylxanthate (1.0 g). After the solution was heated for 4 hr at 50°, TLC (hexane–acetone, 4:1) showed that almost all the **6b** had reacted. The major product was isolated by chromatography and identified as *S*-(cyclohexyl-2-ol) *O*-ethyl dithiocarbonate (**7b**): ir (film) 2.8 μ (OH); uv (methanol) 283 nm; NMR ($CDCl_3$) τ 5.39 (q, 2 *H*, OCH_2CH_3), 5.92, 6.43 (m, 2 *H*, >*CHOH*, >*CHS*), 7.5–8.8 (m, 9 H).

Anal. Calcd for $C_9H_{16}O_2S_2$: C, 49.1; H, 7.27; S, 29.1. Found: C, 49.2; H, 7.33; S, 29.9.

Reaction of 1,2:3,4-Di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose (8) with Sodium Ethylxanthate. A solution of **8** (4.15 g, 10 mmol) was mixed with sodium ethylxanthate in a beaker and kept in a heated desiccator at 150° for 2.5 hr under vacuum. After this mixture was cooled, the residue was extracted with chloroform (150 ml) and filtered. The chloroform solution was washed with water and dried. TLC (ethyl acetate–carbon disulfide 1:9) showed a multicomponent mixture of at least six components, R_f 0.14–0.46, the major one of which was R_f 0.14 (starting material, R_f 0.20 in this system). The chloroform was evaporated to a syrup (3.4 g), and the higher R_f components were removed by desorption from silicic acid (200 g) with 5–15% ethyl acetate in hexane. Subsequent elutions with 20–25% ethyl acetate in hexane yielded mixtures containing R_f 0.14 component and the pure R_f 0.14 component, identified as bis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranose) 6,6′-sulfide (**9**): 0.40 g (15%); mp 114–115° (hexane); NMR (C_5D_5N) τ 4.35 (d, 2 H, H-1), 5.4–5.6 (m, 4 H, H-2, H-4), 5.26 (dd, 2 H, H-3), 5.80 (t, 2 H, H-5), 6.7–7.1 (m, 4 H, H-6, H-6′), 8.4–8.8 (m, 24 H, isopropylidene).

Anal. Calcd for $C_{24}H_{38}O_{10}S$: C, 55.6; H, 7.39; S, 6.18. Found: C, 55.2; H, 7.56; S, 6.33.

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Registry No.—**1a,** 6619-09-6; **1b,** 54497-89-1; **1c,** 14257-63-7; **2a,** 54497-90-4; **2b,** 54497-91-5; **2c,** 54497-92-6; **3a,** 54497-93-7; **3b,** 54498-02-1; **3c,** 54497-94-8; **3d,** 24274-52-0; **3e,** 54497-95-9; **3f,** 54497-96-0; **3g,** 54497-97-1; **4a,** 40652-97-9; **4b,** 54497-98-2; **5a,** 54497-99-3; **5b,** 54498-00-9; **6a,** 953-91-3; **6b,** 15051-90-8; **7a,** 54497-82-4; **7b,** 54498-01-0; **8,** 4478-43-7; **9,** 54532-14-8; sodium ethylxanthate, 140-90-9; diethyl dithiobis(thioformate), 502-55-6; *trans*-1,2-cyclohexanediol, 1460-57-7; *p*-toluenesulfonyl chloride, 98-59-9.

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(2) Work conducted as a research project in an undergraduate organic chemistry course.
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Reaction of Diphenylcyclopropenone with Dimethyloxosulfonium Methylide

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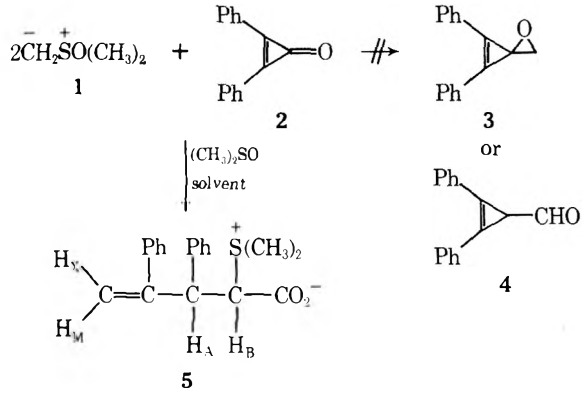
Diphenylcyclopropenone reacts with 2 mol of dimethyloxosulfonium methylide to give the betaine **5**. Structure proof of the betaine is presented and its formation is interpreted in terms of a complex mechanism initiated by conjugate addition of the nucleophilic ylide to the ketone. On heating (135°), **5** gave the isomeric betaine **11** and 2,3-diphenylcyclopent-2-en-1-one (**12**).

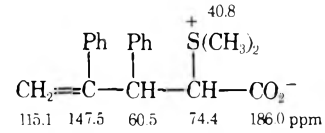
Dimethyloxosulfonium methylide (**1**) is particularly useful for the preparation of aldehydes via the isomeric epoxides.[2,3] Reaction of this ylide with diphenylcyclopropenone (**2**) using dimethyl sulfoxide solvent provided neither the epoxide **3** nor the previously known[4] aldehyde **4**, but the ring-opened betaine **5**, 2-dimethylsulfonio-3,4-diphenylpent-4-enoate.



The structure of **5** is based on the following data. Elemental and mass spectral analysis, including relative abundances of isotope peaks, confirmed the molecular formula $C_{19}H_{20}O_2S$. A styryl group was indicated by the ultraviolet spectrum, which had λ_{max} 210 nm (ϵ 25,450) and 255 (18,850). The infrared spectrum had intense bands at 1540 and 1360 cm^{-1}, characteristic of carboxylate, and the pattern of the 5–6-μ region as well as the long-wavelength diagnostic bands established the presence of one or more phenyl groups. The nuclear magnetic resonance spectrum ($CDCl_3$) exhibited a ten-proton multiplet centered at 7.3 ppm (two phenyl groups), a six-proton singlet at 3.2 ppm [$(CH_3)_2S^+$], and an array of four slightly broadened signals at 4.42 (H_B), 4.73 (H_A), 5.12 (H_M), and 5.58 ppm (H_X). Expansion of the four-proton array and double-resonance technique revealed an uncoupled signal (H_B) and a weakly coupled AMX pattern: J_{AM} = 1.2, J_{AX} = 0.4, and J_{MX} = 1.0 Hz. Chemical shift assignments were established by comparisons with α-methylstyrene, 3,4-diphenylpent-4-enoic acid,[5] and model sulfonium salts.[6] The slight broadening of the H_B signal 4.42 ppm we attribute to a nuclear Overhauser interaction between this proton and the dimethyl protons. This conclusion is based on two observations. (1) Irradiation of the dimethyl signal caused a significant enhancement of the H_B signal. (2) When the NMR spectrum was recorded using dimethyl sulfoxide-d_6 solvent, this signal was similarly enhanced and shifted downfield to 4.95 ppm. In the same solvent the dimethyl signal was shifted to 3.4 ppm. Other signals were not significantly altered by solvent change. Apparently dimethyl sulfoxide solvates the sulfonio group, removing the nuclear Overhauser effect.[7]

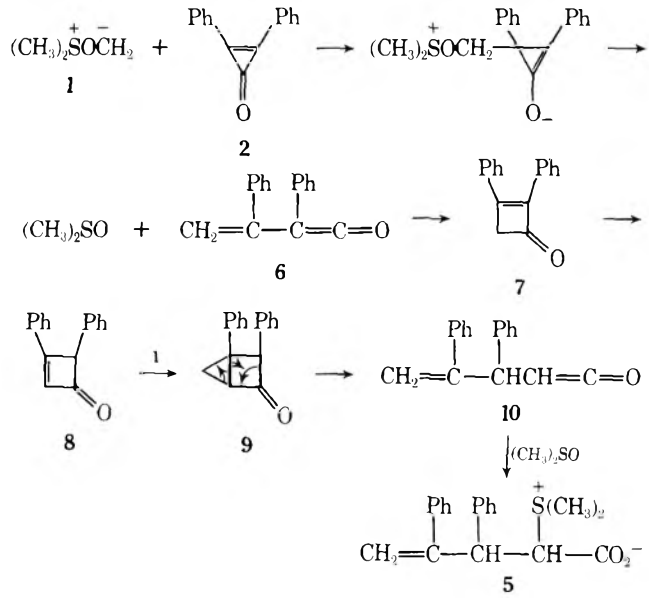
Given the presence of a styryl group, there are six positional isomers of the betaine **5**. Three of the betaines, including **5**, have the dimethyl sulfonio group α to the carboxylate group and the remaining four have a β arrangement. An α arrangement was established by measuring the pK_a of the protonated betaine. The observed pK_a, 2.59, is consistent with an α arrangement.

The structure of the betaine, aside from configuration, was established with finality by its ^{13}C NMR spectrum. Chemical shift assignments, summarized in the following formula, were established by comparison with suitable model compounds.[8] Aromatic carbons had the expected



chemical shifts and all carbons had the expected multiplicities.

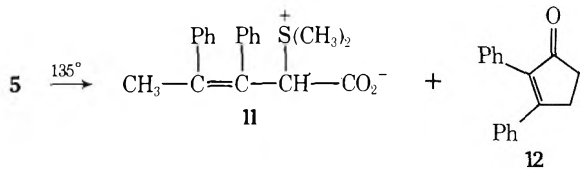
Mechanism of Formation of 5. Ring-opened products are almost always obtained in the reactions of cyclopropenones with nucleophiles and, depending on the nature of the attacking nucleophile, the apparent mechanisms of these reactions are of varying degrees of complexity.[9] The mechanism summarized in the following scheme provides a chemically plausible rationale for the formation of the betaine.



Although obviously complex, the above mechanism is buttressed by substantial chemical precedent. Thus, the reaction of dimethyloxosulfonium methylide with α,β-unsaturated ketones usually proceeds via attack at the β car-

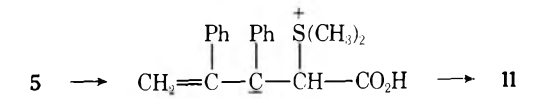
bon and yields a cyclopropyl ketone.[3] In the present case ring strain would undoubtedly facilitate opening to the vinyl ketene **6**. Jenny and Roberts[10] have shown that vinyl ketenes close rapidly to cyclobutenones, so that conversion of **6** to **7** is predictable. It is clear from the composition of the betaine that it is the product of a diphenylcyclopropenone molecule, two CH_2 units, and a unit of dimethyl sulfoxide. Further, it is necessary at some stage to shift a hydrogen atom. The ylide **1** is probably sufficiently basic to effect isomerization of **7** to **8**, especially in dimethyl sulfoxide. This step accomplishes the required hydrogen shift. Formation of the "housone" **9** is straightforward, and its isomerization to the allyl ketene **10** is analogous to reactions implicated recently in the photochemistry of some cyclopentenones[5] and the thermal–photochemical reactions of some functionalized cyclopropenes.[11] Addition of dimethyl sulfoxide to ketenes appears not to have been reported but the result here, in the addition to the ketene **10**, is similar to the addition reaction of dimethyl sulfoxide with dimethyl acetylenedicarboxylate, in which the oxygen on sulfur is transferred to carbon to yield a dimethylsulfonio enolate betaine.[12]

Thermal Reactions of the Betaine. Attempts to transform the betaine to known compounds by treatment with a variety of bases, acids, and reducing agents were singularly unfruitful. However, in refluxing chlorobenzene (135°) the betaine gave the isomeric betaine **11**, 2-dimethylsulfonio-3,4-diphenylpent-3-enoate (stereochemistry of the double bond not established), and 2,3-diphenylcyclopent-2-en-1-one (**12**).

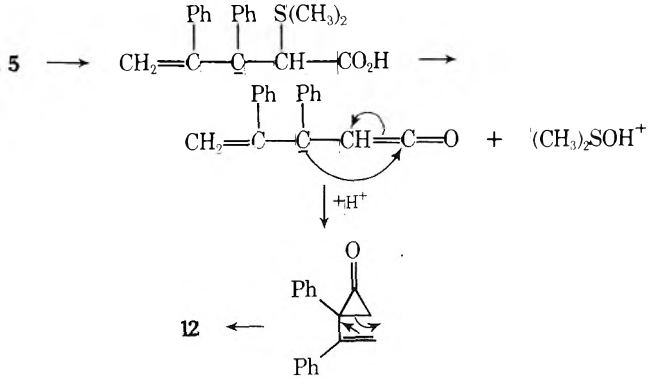


The structure of the isomeric betaine was established by means of analytical and spectroscopic data. The cyclopentenone has been known for some time,[13] although its structure was in question for many years until it was established with the aid of ultraviolet spectroscopy.[14] Our analysis of its NMR spectrum confirms the structure.

The origin of the isomeric betaine is mechanistically straightforward.



The origin of the cyclopentenone is more complex. The following tentative mechanism is suggested.



Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Uv spectra were recorded with a Beckman DB-GT spectrophotometer using methanol solvent; ir spectra were recorded on a Wilks Hilger-Watts Infragraph; proton NMR spectra were recorded at 60 MHz on a Varian T60-A spectrometer and at 30 MHz on a Varian EM-300 spectrometer; chemical shifts are relative to internal tetramethylsilane at δ 0. ^{13}C NMR spectra were recorded on a Jeol FX-60 instrument using dimethyl sulfoxide-d_6 solvent; chemical shifts are relative to tetramethylsilane at δ 0. Mass spectra were obtained from Morgan-Schaffer, Montreal, Canada. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y.

2-Dimethylsulfonio-3,4-diphenylpent-4-enoate (5). A stirred solution of trimethyloxosulfonium iodide[2] (1.76 g, 8 mmol) in 10 ml of dry dimethyl sulfoxide (DMSO) at 10° under nitrogen was treated with 5 ml of 1.6 *M* *n*-butyllithium in hexane (Foote Mineral Co.). After 10 min 2,3-diphenylcyclopropenone[15] (1.03 g, 5 mmol) in 10 ml of dry DMSO was added in one portion. The mixture was stirred for 3 hr at 50–55°, then cooled and diluted with water (50 ml), and the mixture was shaken with 1:1 benzene–hexane (50 ml). The organic layer was separated, washed five times with water, dried ($MgSO_4$), and filtered. Evaporation of the filtrate gave a glassy solid (1.01 g) which was recrystallized from benzene–hexane to give **5** (0.44 g), colorless microcrystals: mp 129–131°; mass spectrum *m/e* (rel intensity, ion) 312 (0.7, M^+), 234 [16, $M^+ - (CH_3)_2SO$], 119 (100). The $M^+ + 1$ and $M^+ + 2$ peaks had, respectively, intensities of 25.6 and 8.7 relative to M^+ at 100; calculated intensities for $C_{19}H_{20}O_2S$ are $M^+ + 1$, 21.7 and $M^+ + 2$, 6.9. Additional spectroscopic data are discussed in the text. The pK_a of the protonated betaine in 20% H_2O–80% EtOH, determined by standard technique,[16] was 2.59.

Anal. Calcd for $C_{19}H_{20}O_2S$: C, 73.04; H, 6.45; S, 10.27. Found: C, 72.92; H, 6.34; S, 10.46

Thermal Isomerization of 5 to 11 and Fragmentation to 12. A solution of **5** (43 mg) in chlorobenzene (10 ml) was refluxed for 24 hr under nitrogen. Evaporation of the solvent gave a yellow, glassy solid which was triturated with warm ether. An insoluble crystalline fraction (A) was filtered from the soluble fraction (B).

Fraction A. The Isomeric Betaine 11. The filtered solid (10 mg), mp 155–159°, was recrystallized twice from ethyl acetate to give **11** as colorless crystals: mp 158–160°; uv 210 nm (ϵ 18,400), 260 (18,400); ir (KBr) 1530, 1390, 1205, 1140, 1035, 900, 800, 770, 750, 715, 705, and 690 cm^{-1}; NMR ($CDCl_3$, 30 MHz) δ 7.05 (m, 10, 2 phenyls), 4.45 (s, 1, methine H), 3.33 [s, 6, $(CH_3)_2S^+$], and 2.30 (s, 3, vinyl CH_3).

Anal. Calcd for $C_{19}H_{20}O_2S$: C, 73.04; H, 6.45; S, 10.27. Found: C, 73.25; H, 5.6.39; S, 10.54.

Fraction B. 2,3-Diphenylcyclopent-2-en-1-one (12). The soluble fraction was evaporated to dryness and the residue (26 mg) was crystallized from ligroin containing a small amount of ether to give **12** as colorless crystals: mp 93–94° (lit.[13] mp 92°); NMR ($CDCl_3$, 30 MHz) δ 7.2 (s, 10, 2 phenyls), 2.3–2.4 (m, A_2B_2 symmetry, 4, $-CH_2CH_2-$); uv identical with that reported by Allen and Van Allan.[14] The 2,4-dinitrophenylhydrazone had mp 227–228° (lit.[13] mp 228°).

Acknowledgments. We thank Mr. Joseph Lewandowski for pK_a measurements, Ms. Barb Erwine of Varian Associates for excellent NMR spectra, and Mr. Kokichi Ishibitsu of Jeol for invaluable ^{13}C NMR spectra. We are grateful to Mr. Joseph R. De Filippis for many stimulating discussions.

Registry No.—**1**, 5367-24-8; **2**, 886-38-4; **5**, 54446-68-3; **11**, 54446-69-4; **12**, 4258-40-6.

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Preparation and Reactions of α-Lithiobutanesultams

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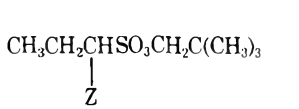
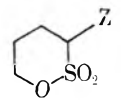
Received December 16, 1974

Metalations of *N*-methyl- and *N*-phenylbutanesultam were conveniently effected by means of *n*-butyllithium in THF–hexane at 25° to give α-lithio salts which were condensed with representative electrophiles to afford α-substituted derivatives in good to excellent yields. The electrophiles studied included benzyl chloride, various aldehydes and ketones, methyl benzoate, and benzonitrile. Several reactions with lithio-*N*-methylbutanesultam did not proceed in a predictable manner. Thus, this salt with benzonitrile and chalcone surprisingly afforded a primary enamine and an aminosultone, respectively, rather than the expected ketosultams. Also, this salt and aldehydes gave analytically pure β-hydroxysultams with melting point ranges of up to 30°. Metalation of *N*-methylbutanesultam was also effected by sodium amide in liquid ammonia.

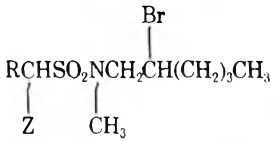
It has long been known that hydrogen atoms α to sulfonyl-containing functional groups are sufficiently acidic that they can be ionized by basic reagents to afford the corresponding carbanionic derivatives. For example, sulfonate esters like **1** have been converted to anions like **1'** by alkali metal amides in ammonia.[2] Similarly, sultones like **2** have been metalated by *n*-butyllithium in THF–hexane at −78° to give α-lithio salts like **2'**.[3] Various sulfonamides have likewise been metalated. Thus, bromosulfonamides **3** give sultams **4** via **3'** upon treatment with *n*-butyllithium in THF–hexane at −70°.[4] Sulfonamide **5** has even been *gem*-dimetalated by this same base at 25° to give **5''**.[5]



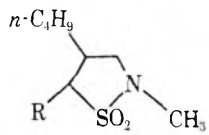
1, Z = H
1', Z = K



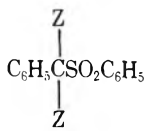
2, Z = H
2', Z = Li



3, Z = H; R = H or CH_3
3', Z = Li; R = H or CH_3



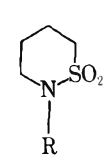
4
(R = H or CH_3)



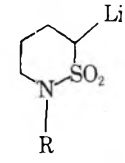
5, Z = H
5'', Z = Li

In contrast, there appear to be no reports of metalation of α hydrogens of sultams. This is somewhat surprising not only because of the above work on open-chain sulfonamides but also because sultams are more resistant to ring opening then are sultones. In light of the latter, in fact, sultams should be capable of being metalated at temperatures more convenient than those necessary for metalation of sultones. Moreover, once formed, α-lithiosultams should be more stable than α-lithiosultones. That such is the case is illustrated in this paper, which describes successful metalations of *N*-methyl- and *N*-phenylbutanesultam and subsequent reactions of the resulting carbanions with electrophiles.

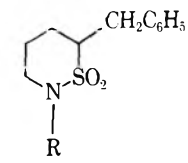
First, *N*-methylbutanesultam (**6**) was converted to its α-lithio salt (**6'**) at 25° by *n*-butyllithium in THF–hexane in only 10 min as evidenced by deuteration with deuterium oxide to give **6**-α-*d*, in a yield of 95–100%. Anion **6'** was also alkylated by benzyl chloride to afford the corresponding alkyl derivative **8** in a yield of 65%. Likewise, anion **7'** was prepared from *N*-phenylbutanesultam (**7**) and *n*-butyllithium. Alkylation of **7'** by benzyl chloride gave **9** in a yield of 70%.



6, R = CH_3
7, R = C_6H_5

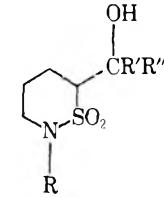


6', R = CH_3
7', R = C_6H_5



8, R = CH_3
9, R = C_6H_5

Next, anions **6'** and **7'** were condensed with various aldehydes and ketones to afford β-hydroxysultams. Thus, treatment of **6'** with benzophenone, benzaldehyde, and anisaldehyde gave **10**, **11**, and **12** in yields of 91, 80, and 86%, respectively. Similar condensations of **7'** with these same compounds afforded **13**, **14**, and **15** in yields of 86, 63, and 78%, respectively.

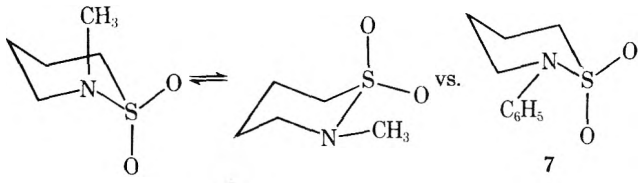


10, R = CH_3; R' = R'' = C_6H_5
11, R = CH_3; R' = C_6H_5; R'' = H
12, R = CH_3; R' = *p*-$CH_3OC_6H_4$; R'' = H
13, R = R' = R'' = C_6H_5
14, R = R' = C_6H_5; R'' = H
15, R = C_6H_5; R' = *p*-$CH_3OC_6H_4$; R'' = H

Incidentally, an attempt was made to prepare anions **6'** and **7'** by the interaction of the sultams and sodium amide in liquid ammonia. In the case of **6**, anion **6'** (M = Na) was

indeed formed, since addition of benzophenone gave adduct **10** in a yield of 66%. On the other hand, either **7** was not converted to **7′** (M = Na) or the latter salt was insoluble in the liquid ammonia, since addition of the ketone gave no **13**; instead, only starting materials were recovered.

The above alcohols derived from the parent sultams and benzaldehyde and anisaldehyde were particularly interesting because although those from **6** (**11** and **12**) were analytically pure, they had melting ranges of 15 and 30°, respectively. In contrast, those from **7** (**14** and **15**) exhibited sharp melting points. Moreover, the NMR spectra of these compounds indicated that the hydroxyl protons of **11** and **12** resided in at least four different environments while those of the *N*-phenyl derivatives (**14** and **15**) resided in only two different environments. The above data lead one to suggest that internal hydrogen bonding must be of major importance in this series of compounds. To visualize this, the possible conformations of **6** and **7** were examined using space-filling models. Thus, the *N*-methyl group of sultam **6** can reside in either an axial or an equatorial position (eq 1). In contrast, the more bulky *N*-phenyl group of sultam **7** can reside only in an equatorial position.



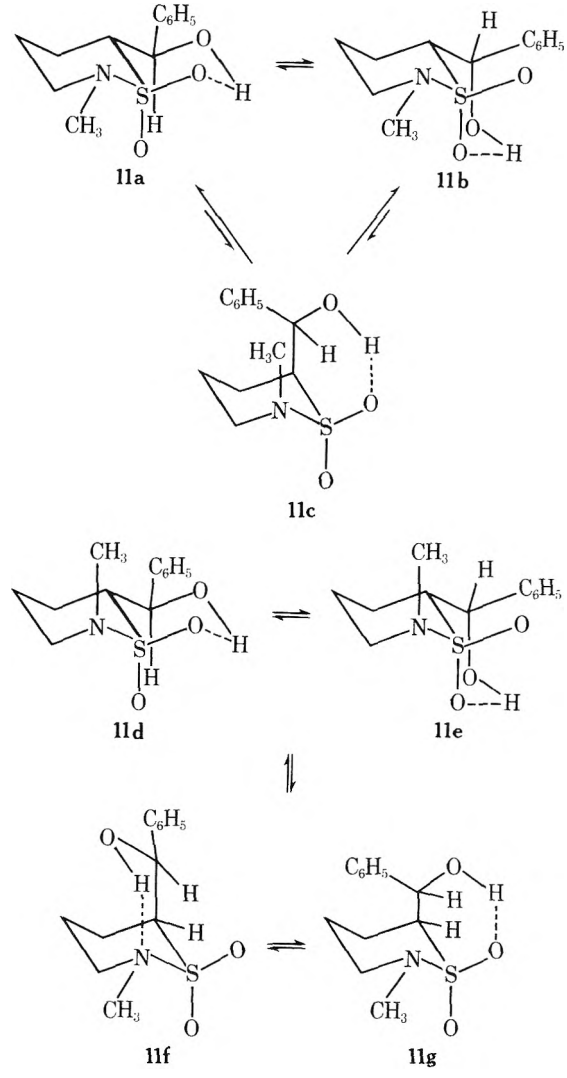
6 **7** (1)

Now, the addition of an aldehyde α to the sulfonyl group gives an alcoholic proton which can form six-membered rings through internal hydrogen bonding with either of the sulfonyl oxygens or with the sulfonamide nitrogen. Using compound **11** as an example, the possible hydrogen-bonded forms are illustrated as **11a–g** along with the possibilities for equilibrium which exist among these different forms (Scheme I). In addition, the carbinol carbon and the α carbon of the ring are chiral, thus affording 14 possible hydrogen bonded conformations for **11**. Therefore, it is not surprising that the analytically pure sample had a wide melting point range and a rather complex NMR spectrum. Compound **12**, derived from **6′** and anisaldehyde, should be similar.

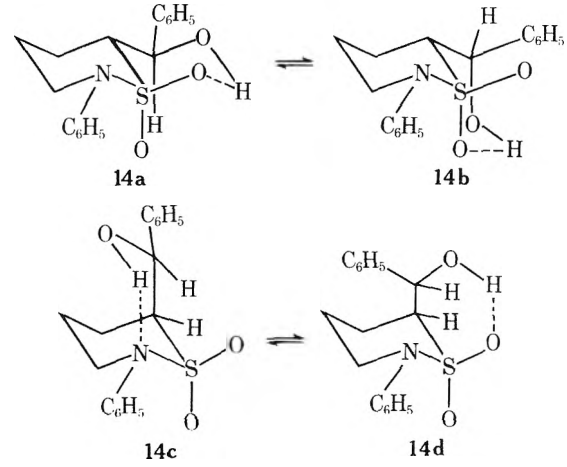
Likewise, the hydrogen-bonded isomers of **14**, derived from **7′** and benzaldehyde, are illustrated as **14a–d** (Scheme II). When the chiral carbinol carbon and the α carbon of the ring are included, there are eight internally hydrogen bonded isomers that could be present. However, since **14** has a sharp melting point, either this reaction occurs stereospecifically or the above isomers are physically nearly identical. Hydroxysultam **15**, derived from **7′** and anisaldehyde, is similar.

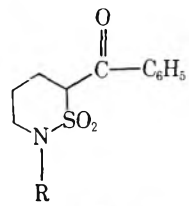
Next, **6′** and **7′** were condensed with methyl benzoate to give ketones **16** and **17** in yields of 84 and 69%, respectively. As is usual in the reaction of carbanions with esters,[6] a 2:1 ratio of lithiosultams to methyl benzoate was employed to maximize the yields of ketones. Lithio salts **6′** and **7′** were also condensed with benzonitrile to give enamine **18** and ketone **17** in yields of 79 and 64%, respectively. The condensations of **6′** and **7′** with benzonitrile are interesting for two reasons. First, under the same hydrolysis conditions, the intermediate nitrogen-containing compound from **7′** and the nitrile, either **19** or **21**, is converted to ketone while, in contrast, **18** is stable to such treatment. Second, **18** constitutes a rare example of a primary enamine.[7] Examination of space-filling models suggests why the above is realized. In essence, the primary enamine **18** is stable because of more favorable hydrogen bonding of the amino hydrogen atoms with the sulfonyl oxygen atoms through a six-membered ring than can be realized in the imine **20**. On the other hand, models of **19** indicate that in order to have hydrogen bonding as in **18**, sufficient steric interaction is present that rotation of the *N*-phenyl group is restricted. Thus, such hydrogen bonding is presumably absent and **19** or **21** are hydrolyzed to ketone **17**.

Scheme I

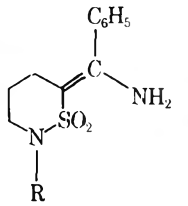


Scheme II

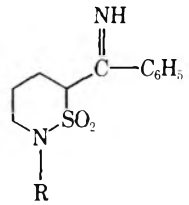




16, R = CH_3
17, R = C_6H_5

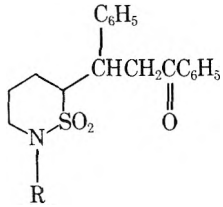


18, R = CH_3
19, R = C_6H_5

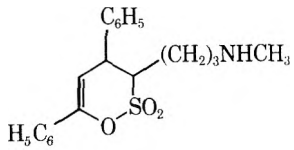


20, R = CH_3
21, R = C_6H_5

Finally, 6′ and 7′ were treated with α,β-unsaturated ketones to give products arising from 1,4-conjugate additions. However, drastically different results were obtained depending upon the N substituent of the sultam and the structure of the carbonyl compound. Thus, 7′ was condensed with chalcone to give the expected ketosultam **22** in a yield of 88%. Surprisingly, similar reaction of 6′ with this ketone gave the aminosultone **23** in a yield of 36%. Presum-



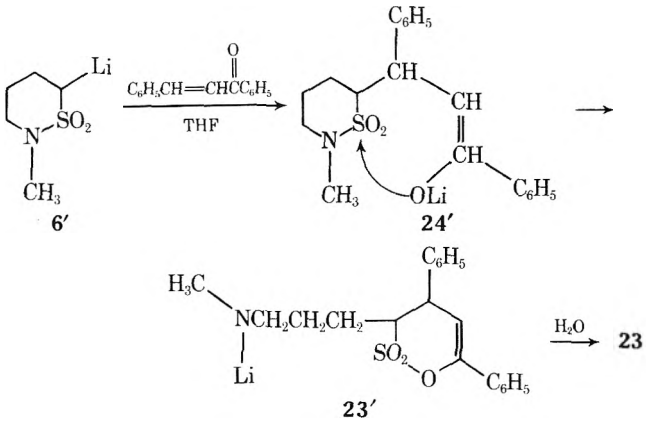
22, R = C_6H_5
25, R = CH_3



23

ably, the latter condensation proceeded via the intermediacy of 1,4-adduct **24**, which underwent ring opening and reclosure as indicated in Scheme III. Formation of **23** instead

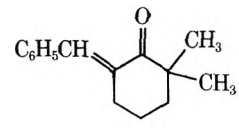
Scheme III



of the expected **25** is surprising in light of the fact that the proposed nucleophilic attack by the alkoxide ion of **24** leads to the more strongly basic nitrogen anion of **23′** (Scheme III). Previous workers investigating the interaction of certain sulfonamides with various alkoxides to give sulfonate esters and substituted amines reported that much more vigorous conditions were required to effect their transformations than were used in the current study.[8]

In an attempt to find another example of the above rearrangement, 6′ was condensed with 2,2-dimethyl-6-benzylidenecyclohexanone (**26**). The product obtained, though, was the ketosultam **27** in a yield of 70%, not the anticipated aminosultone **28**. Presumably, potential steric constraint in **28** was sufficient to preclude its formation.

All of the sultam derivatives reported above are new. Their structures were supported by elemental analyses and by ir and NMR spectroscopy. The above condensations should be capable of being extended to other sultams as well as other electrophiles. Of particular interest would be



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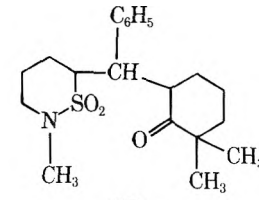

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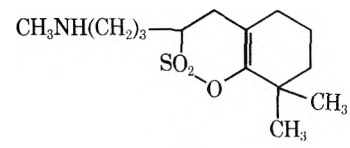

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a systematic study of other α,β-unsaturated carbonyl compounds to ascertain if the scope of the rearrangement of alkoxysultams to aminosultones could be broadened.

Experimental Section

Infrared spectra were measured on a Perkin-Elmer Model 237 grating infrared spectrometer. NMR spectra were obtained on a Varian Associates A-60 spectrometer using tetramethylsilane as internal standard. *n*-Butyllithium in hexane was purchased from Apache Chemical Co., Rockford, Ill. Tetrahydrofuran was dried by distillation from calcium hydride and stored over sodium wire under an atmosphere of helium. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preparation of Starting Materials. 4-Chlorobutanesulfonyl chloride was prepared by the method of Williams.[9] *N*-Methyl-4-chlorobutanesulfonamide was prepared using an adaptation of the method of Bliss and coworkers.[10] *N*-Methylbutanesultam (**6**) was prepared by cyclization of *N*-methyl-4-chlorobutanesulfonamide using potassium hydroxide according to the method of Bliss and coworkers.[10] *N*-Phenylbutanesultam was prepared from 4-chlorobutanesulfonyl chloride, aniline, and sodium carbonate as previously described.[11] 2,2-Dimethyl-6-benzylidenecyclohexanone (**26**) was prepared as described by Johnson.[12]

Preparation of the Lithium Salts of *N*-Methyl- and *N*-Phenylbutanesultams. To a 100-ml three-necked flask equipped with a septum, a magnetic stirrer, and a reflux condenser under a helium atmosphere were added 2.85 g (0.02 mol) of *N*-methylbutanesultam (**6**) and 25 ml of anhydrous THF followed by 12.8 ml (0.02 mol) of 15% *n*-butyllithium in hexane. The resulting pale yellow solution was stirred for 10 min, then treated with an appropriate electrophile as outlined in Table I. Lithio-*N*-phenylbutanesultam was similarly prepared using 3.15 g (0.015 mol) of sultam **7** in 50 ml of anhydrous THF and 9.6 ml (0.015 mol) of 15% *n*-butyllithium in hexane. The resulting white suspension was stirred for 10 min, then treated with an appropriate electrophile as outlined in Table I. The condensations were performed at 25°.

Condensations of Lithio Salts 6′ and 7′ with Electrophiles. Since the results of the condensations of 6′ and 7′ with electrophiles are summarized in Table I, and since conditions are standard for each class of electrophile, only one specific example will be presented below for alkyl halides, aldehydes and ketones, esters, benzonitrile, and α,β-unsaturated ketones, respectively.

A. Preparation of 2*H*-2-Phenyl-6-benzyltetrahydro-1,2-thiazine 1,1-Dioxide (9). Alkylation. To a suspension of 0.015 mol of lithio-*N*-phenylbutanesultam (7′) was added dropwise 1.90 g (0.015 mol) of benzyl chloride in 20 ml of THF. The mixture was stirred for 1 hr, neutralized by the addition of wet THF, and filtered, and the solvent was removed under vacuum to give a yellow tar. This tar was allowed to stand overnight in 25 ml of ethyl ether and the crystals that formed were filtered and recrystallized from benzene to give 3.15 g (70%) of **9**, mp 97–99°.

B. Preparation of 2*H*-2-Methyl-6-(diphenylhydroxymethyl)tetrahydro-1,2-thiazine 1,1-Dioxide (10). Condensation with Benzophenone. To a solution of 0.025 mol of lithio-*N*-methylbutanesultam (6′) was added dropwise a solution of 4.56 g (0.025 mol) of benzophenone in 20 ml of THF. The resulting suspension was stirred for 30 min, neutralized with wet THF, filtered, and concentrated under vacuum to afford a yellow solid. Recrystallization of the solid from toluene gave 7.54 g (91%) of **10**, mp 182–185°.

C. Preparation of 6-(2*H*-2-Phenyltetrahydro-1,2-thiazine 1,1-Dioxide) Phenyl Ketone (17). Acylation. To 0.03 mol of 7′ in 50 ml of THF was added dropwise 2.04 g (0.015 mol) of methyl

Table I
Products Derived from Condensation of Lithiosultams with Electrophiles[a]

Sultam	Coreagent	Product	Yield, %	Mp, °C	Recrystn solvent	Nmr, δ[b]
6	Benzyl chloride	8	65	61–63[c]		1.55 (m, 4, CH_2), 2.62 (s, 3, CH_3), 2.80 (m, 5, CH, CH_2), 7.04 (s, 5, ArH)
	Benzophenone	10	91	182–185	Toluene	1.67 (m, 2, CH_2), 2.00 (m, 2, CH_2), 2.83 (s, 3, CH_3), 3.30 (m, 2, CH_2), 4.11 (m, 1, CH), 4.64 (s, 1, OH), 7.50 (m, 10, ArH)
	Benzaldehyde	11	80	91–108	1:2 petroleum ether–benzene	1.80 (m, 4, CH_2), 2.95 (s, 3, CH_3), 3.30 (m, 3, CH, CH_2), 3.46 (d, 1, OH), 5.82 (s, 1, CH), 7.48 (s, 5, ArH)
	Anisaldehyde	12	86	115–145	Benzene	1.40 (m, 4, CH_2), 2.68 (s, 3, CH_3), 3.10 (m, 3, CH, CH_2), 3.40 (d, 1, CH), 3.75 (s, 3, OCH_3), 5.30 (m, 1, OH), 6.95 (q, 4, ArH)
	Methyl benzoate	16	84	135–137	Ethanol	1.83 (m, 2, CH_2), 2.36 (m, 2, CH_2), 2.97 (s, 3, CH_3), 3.44 (m, 2, CH_2), 5.00 (q, 1, CH), 7.80 (m, 5, ArH)
	Benzonitrile	18	79	140–142	Ethanol	1.60 (m, 2, CH_2), 2.68 (t, 2, CH_2), 3.05 (s, 3, CH_3), 3.65 (t, 2, CH_2), 5.45 (s, 2, NH), 7.66 (s, 5, ArH)
	Chalcone	23	36	186–188	2:1 Ethanol–benzene	1.95[d] (m, 2, CH_2), 2.41 (m, 3, CH, CH_2), 3.01 (s, 3, CH_3), 3.45 (m, 3, CH, CH_2), 4.64 (m, 2, NH_2^+), 6.90 (s, 1, vinyl CH), 7.20 (m, 10, ArH)
	26	27	70	164–167	Ethanol	0.90 (s, 3, CH_3), 1.00 (s, 3, CH_3), 1.60 (m, 10, CH_2), 2.55 (s, 3, NCH_3), 3.15 (m, 4, CH, CH_2), 3.80 (m, 1, CH), 7.20 (m, 5, ArH)
7	Benzyl chloride	9	70	97–99	Benzene	2.11 (m, 4, CH_2), 3.02 (m, 1, CH), 3.68 (m, 4, CH_2), 7.50 (s, 5, ArH), 7.58 (s, 5, ArH)
	Benzophenone	13	86	170–172	Benzene	1.91 (m, 2, CH_2), 2.10 (m, 2, CH_2), 4.00 (m, 3, CH, CH_2), 4.91 (s, 1,OH), 7.32 (m, 15, ArH)
	Benzaldehyde	14	63	145–147	Ethanol	2.10 (m, 4, CH_2), 3.58 (m, 1, OH), 3.82 (m, 3, CH, CH_2), 5.90 (s, 1, CH), 7.62 (d, 10, ArH)
	Anisaldehyde	15	78	135–137	Ethanol	1.97 (d, 4, CH_2), 3.70 (m, 4, CH, OH, CH_2), 4.02 (s, 3, CH_3), 5.40 (d, 1, CH), 7.35 (q, 4, ArH), 7.58 (s, 5, ArH)
	Methyl benzoate	17	69	151–153	Ethanol	2.10 (m, 4, CH_2), 3.77 (m, 2, CH_2), 5.11 (q, 1, CH), 7.35 (m, 8, ArH), 8.00 (m, 2, ArH)
	Benzonitrile	17	64	151–153	Ethanol	
	Chalcone	22	88	164–166	Ethanol	1.78 (m, 2, CH_2), 2.21 (m, 2, CH_2), 3.40 (m, 2, CH_2), 4.00 (m, 4, CH, CH_2), 7.30 (m, 13, ArH), 8.00 (m, 2, ArH)

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all the sultam derivatives. [b] The solvent was deuteriochloroform unless noted otherwise. [c] The compound was first distilled at 151–154° (2 mm) and solidified upon scratching. [d] The solvent was trifluoroacetic acid.

benzoate in 20 ml of THF. After 30 min, the mixture was neutralized and worked up as in A and B to give a yellow oil which crystallized upon standing in ether for 30 min. The product was recrystallized from ethanol to give 3.25 g (69%) of **17**, mp 151–153°.

D. Preparation of 2*H*-2-Methyl-6-(1-amino-1-phenylmethylidene)tetrahydro-1,2-thiazine 1,1-Dioxide (18). Condensation with Benzonitrile. To 0.025 mol of **6'** in 25 ml of THF was added 2.56 g (0.025 mol) of benzonitrile in 15 ml of THF. After 30 min, the mixture was worked up as above to give a tan solid that was recrystallized from ethanol to give 4.99 g (79%) of **18**, mp 140–142°.

E. Preparation of 2*H*-2-Phenyl-6-(1,3-diphenyl-3-oxo-1-propyl)tetrahydro-1,2-thiazine 1,1-Dioxide (22). Condensation with Chalcone. To 0.015 mol of **7'** in 50 ml of THF was added 3.12 g (0.015 mol) of chalcone in 20 ml of THF. After stirring for 0.5 hr, the orange mixture was worked up in the usual fashion to afford a yellow tar that was allowed to stand overnight in 25 ml of ether. The solid that formed was collected and recrystallized from ethanol to give 5.50 g (88%) of **22**, mp 164–166°.

Ionization of *N*-Methylbutanesultam by Sodium Amide in Ammonia. Condensation with Benzophenone. To a gray suspension of 0.03 mol of sodium amide in 250 ml of anhydrous liquid ammonia[13] was added 4.48 g (0.03 mol) of sultam **6** in 25 ml of THF. The mixture was stirred for 20 min, then treated dropwise with a solution of 5.46 g (0.03 mol) of benzophenone in 30 ml of THF. After 5 min, the mixture was poured into a beaker containing 1.61 g (0.03 mol) of ammonium chloride, and the ammonia and the THF were allowed to evaporate. The residual solid was dissolved in 40 ml of water and the product was extracted by benzene. Evaporation of the benzene gave a solid that was recrystallized from toluene to give 6.52 g of **10**, mp and mmp 183–195°.

A similar series of reactions involving *N*-phenylbutanesultam afforded only recovered starting materials.

Registry No.—**6**, 54531-78-1; **6′**, 54531-79-2; **7**, 54531-80-5; **7′**, 54531-81-6; **8**, 54531-82-7; **9**, 54531-83-8; **10**, 54531-84-9; **11**, 54531-85-0; **12**, 54531-86-1; **13**, 54531-87-2; **14**, 54531-88-3; **15**, 54531-89-4; **16**, 54531-90-7; **17**, 54531-91-8; **18**, 54531-92-9; **22**, 54531-93-0; **23**, 54531-94-1; **26**, 17622-50-3; **27**, 54531-95-2; benzyl chloride, 100-44-7; benzophenone, 119-61-9; benzaldehyde, 100-52-7; anisaldehyde, 123-11-5; methyl benzoate, 93-58-3; benzonitrile, 100-47-0; chalcone, 94-41-7.

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Notes

One-Step, High Yield Conversion of Penicillin Sulfoxides to Deacetoxycephalosporins

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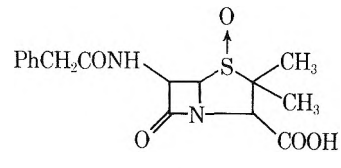
Morin and coworkers demonstrated the chemical relationship between the penicillin and cephalosporin skeleton by an unprecedented acid-catalyzed rearrangement.[1] Because of the therapeutic utility of cephalexin[2] (**2a**), a deacetoxycephalosporin, a high yield conversion of a penicillin sulfoxide to a deacetoxycephalosporanic acid would be very attractive. The known methods, of which some give yields of >80%,[3] have the disadvantage of being limited to the conversion of esters of a penicillin sulfoxide to the corresponding esters of the deacetoxycephalosporin, which requires two more reaction steps, viz., the esterification of the starting penicillin compound as well as the de-esterification of the deacetoxycephalosporin. Rearrangement of the acids gives either decarboxylated products[1] or 3-hydroxy-3-methylcepham compounds.[4] In some cases deacetoxycephalosporanic acids are also formed but the yields are low.[5]

The present paper describes a convenient and efficient method to convert penicillin sulfoxides to deacetoxycephalosporanic acids by using silyl protection.

The use of the silyl group for protection of a carboxyl group has advantages such as easy introduction and removability over the use of other protecting groups. The conversion of a penicillin sulfoxide to a deacetoxycephalosporin implies the liberation of a molecule of water. Accordingly, the known rearrangement procedures[3] fail when applied to silylated penicillin sulfoxides,[6] since silyl esters[7] are very susceptible to cleavage by water. The use of an excess of silyl compound, e.g., trimethylchlorosilane, seemed to offer the best chance of success for three reasons: the carboxyl group is protected against decarboxylation, the HCl that is formed catalyzes the ring enlargement reaction, and attack on the silylated carboxyl group is prevented because the excess silyl compound traps the water[8] formed during the reaction. However, when an attempt was made to rearrange benzylpenicillin sulfoxide (**1**) with a sufficiently large excess of trimethylchlorosilane to fulfil the conditions mentioned above, formation of deacetoxycephalosporanic acid could not be detected. Better results were obtained when a large excess of a rather weak base was added to the reaction mixture. In this way benzylpenicillin sulfoxide was converted in a yield of 75% to a mixture of ring-enlarged products, consisting of Δ^2- and Δ^3-benzyldeacetoxycephalosporanic acid and the decarboxylated cephalosporin (method A), from which the Δ^3 compound could be isolated in yields of up to 50%. Interesting is a side reaction, viz., the formation of the oxazolonethiazolidine compound (**3**), better known as "dehydrobenzylpenicillin".[9] The control of this product ratio was insufficient which is obviously related to the triple role played by the silyl compound and especially to the fact that the amount of HCl present during the reaction is



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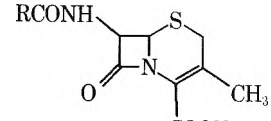
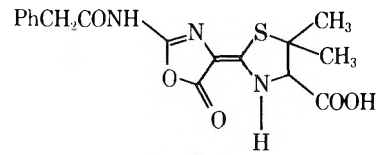


2a, R = PhCH(NH$_2$)

b, R = PhCH$_2$



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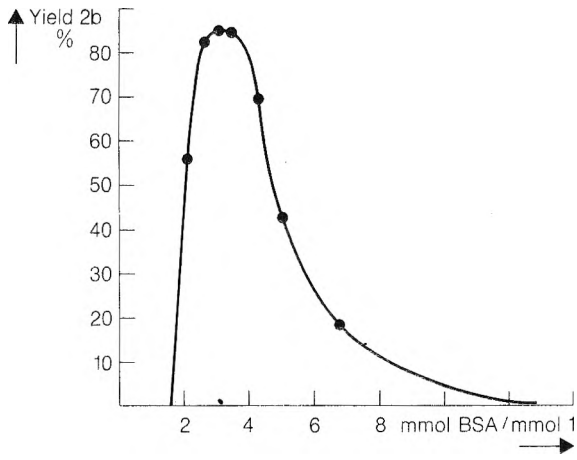

Figure 1. Correlation between the yield of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid (**2b**) and the amount of BSA.

not constant. The problem was solved by the use of silylating agents which could not give rise to the formation of acids during the reaction and which are more reactive than the silylated β-lactams toward reactive intermediates. Such a compound is *N,O*-bis(trimethylsilyl)acetamide (BSA), which has a strong silylating capacity.

An acid sufficiently strong to prevent its own silylation by BSA was now required as catalyst. After extensive experimentation it became apparent that HBr gave higher yields than other strong acids. Also, the amount of base could be reduced drastically which had the advantage of preventing the formation of the Δ^2 isomer. When the amount of BSA was varied, the yield of deacetoxycephalosporanic acid showed a peak at a ratio of BSA: 1 of ~3:1 (Figure 1), which suggests that only one of the two silyl groups of the BSA molecule is reactive enough to ensure both sufficient protection of the carboxyl group and the trapping of the water formed during the ring enlargement. The use of still larger amounts of BSA causes considerable silylation of HBr and consequently a strong decrease in the yield. Under the right conditions yields of >80% of Δ^3-deacetoxycephalosporanic acid were obtained[10] (method B).

Experimental Section[11]

Preparation of Benzylpenicillin Sulfoxide (1). A mixture of 75 g (0.19 mol) of the potassium salt of benzylpenicillin, 1 l. of water, and 45.5 g (0.20 mol) of sodium metaperiodate was stirred for 2 hr at 25°. After cooling to 0°, the reaction mixture was extracted with chloroform at pH 1. The chloroform layer was concentrated to a volume of ~150 ml and 400 ml of diethyl ether was added. The precipitated benzylpenicillin sulfoxide was filtered off, washed with diethyl ether, and dried under reduced pressure to yield 64 g (90% **1**): mp 142.5–143.5° dec; NMR ($CDCl_3$) δ 1.23 (s, 3), 1.66 (s, 3), 3.55 (s, 2) 4.52 (s, 1), 4.98 (d, 1, J = 4.5 Hz), 5.81 and 5.98 (dd, 1, J = 4.5 and 10 Hz), 7.23 (s, 5), 7.37 (d, 1, J = 10 Hz).

Conversion of Benzylpenicillin Sulfoxide to Δ^3-7-Phenylacetamidodeacetoxycephalosporanic Acid (2b). Method A. A mixture of 90 g (0.257 mol) of benzylpenicillin sulfoxide, 210 ml (1.66 mol) of trimethylchlorosilane, 900 ml (9 mol) of α-picoline, and 900 ml of chloroform was heated for 20 hr at 83°. The reaction mixture was cooled and stirred with water, after which the pH was adjusted to 7.5 with a 4 N potassium hydroxide solution. The aqueous layer contained 52 g (55% yield) of the potassium salt of **2b** as estimated by a direct microbiological assay using *Escherichia coli* as the test microorganism. The aqueous layer was separated, adjusted to pH 1.5 with 4 N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate was then replaced by 1-propanol (925 ml) and the propanolic solution cooled to ~0°. Addition of 3.5 ml of water and 100 ml of a 1.25 M solution of the potassium salt of 2-ethylcaproic acid in butyl acetate gave a precipitate which was filtered off and dried. The solid material (57 g) contained 45 g of the potassium salt of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid (yield 47%) and 7 g of the Δ^2 isomer.

Method B. To 10.5 g (30 mmol) of benzylpenicillin sulfoxide were added successively 195 ml of dioxane, 25 ml (102 mmol) of *N,O*-bis(trimethylsilyl)acetamide, 6 ml (61 mmol) of α-picoline, and 5.2 ml of a 5.8 M solution of α-picoline hydrobromide in dichloromethane. After refluxing for 6 hr at 102°, the reaction mixture was cooled to 20° and poured into 1500 ml of ice–water. Then 650 ml of ethyl acetate and 50 ml of butyl acetate were added and with stirring the pH was adjusted to 7 with 4 N potassium hydroxide solution. The mixture was allowed to separate and the organic layer was set aside. The aqueous layer was washed with 300 ml of ethyl acetate and 50 ml of butyl acetate. The resulting organic layer was combined with the one obtained before and the combination re-extracted with 200 ml of a 0.75 M potassium phosphate aqueous solution buffered to pH 7. The extract was added to the main aqueous solution. This combined aqueous mixture contained 9.2 g of the potassium salt of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid as determined by a direct microbiological assay using *Escherichia coli* as the test microorganism. After addition of 500 ml of butyl acetate to the aqueous solution, the mixture was stirred and the pH was adjusted to 2 with 4 N sulfuric acid. The mixture was allowed to stand and the organic extract was separated. The aqueous layer was re-extracted with 250 ml of butyl acetate. The combined butyl acetate extracts were filtered through a water repellent filter. To the butyl acetate solution was then added with rapid strring 2.65 g of anhydrous, finely powdered potassium acetate. After the mixture stirred for 3 hr at room temperature, the precipitate was isolated by filtration, washed with a little butyl acetate, and dried in vacuo at 30°, giving 10.2 g of the potassium salt of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid, with a purity of 85% as estimated by microbiological assay (yield 78%). The NMR spectrum (D_2O) showed signals at δ 1.94 (s, 3), 2.99 (d, 1, J = 18 Hz), 3.44 (d, 1, J = 18 Hz), 3.62 (s, 2), 4.97 (d, 1, J = 4.5 Hz), 5.58 (d, 1, J = 4.5 Hz), and 7.27 (s, 5), which corresponded exactly, as did the ir and uv spectra, with those of an authentic sample prepared according to Stedman et al.[12]

Correlation between the Yield of Δ^3-7-Phenylacetamidodeacetoxycephalosporanic Acid and the Amount of BSA. A mixture of 1.05 g (3 mmol) of benzylpenicillin sulfoxide, 0.9 ml (9 mmol) of α-picoline, and a solution of 3.0 mmol of hydrogen bromide in dioxane was refluxed for 4.5 hr with different amounts of BSA (the total volume was always 2.4 ml). The yield of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid was estimated by microbiological assay and plotted against the amount of BSA (Figure 1).

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Registry No.—**1**, 4052-54-4; **2b**, 27255-72-7; **2b** potassium salt, 34708-38-8; benzylpenicillin potassium salt, 113-98-4; trimethylchlorosilane, 75-77-4; BSA, 10416-59-8.

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Carbon Disulfide as a 2-π Component in Its Cycloaddition with 1-Azirines

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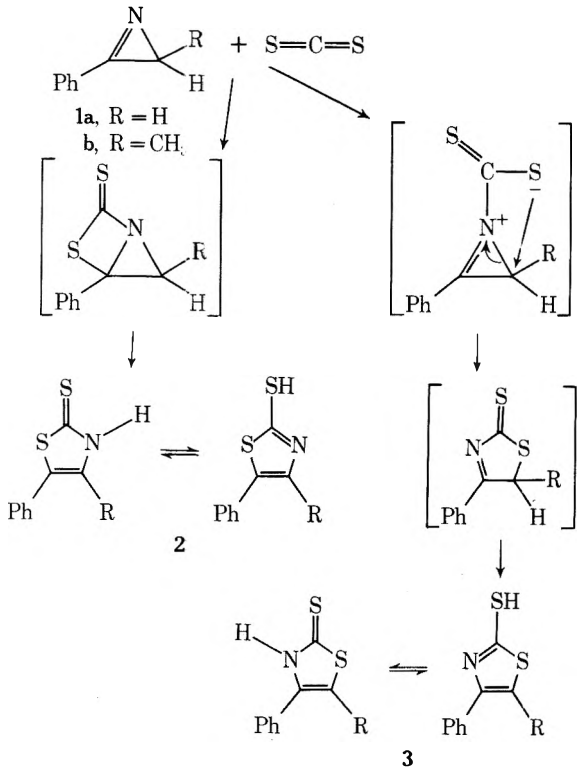
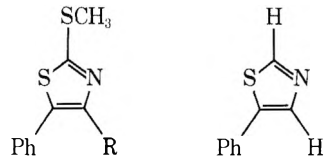
Thermally induced [2 + 2] cycloadditions are rarely encountered. Orbital symmetry analysis reveals that additions of this type that involve relatively low activation energies require special inherent geometric and/or electronic properties of the component(s).[1] The dienophilic and dipolarophilic character of 1-azirines in their thermal cycloadditions has already been established.[2-7] Most reactions of carbon disulfide proceed from an initial nucleophilic attack on carbon.[8-11] The few cycloadditions known are 1,3 dipolar in nature with carbon disulfide as the dipolarophile.[12,13]

We wish to report on the reaction of carbon disulfide with 1-azirines and discuss its mechanistic implications.

When 2-phenyl-1-azirine was dissolved in an excess of carbon disulfide and heated at 100° for 3 hr in a Carius tube, pale yellow needles were obtained, mp 208–209°. Mass spectral data (M^+ at *m/e* 193) and elemental analysis were consistent with the molecular formula $C_9H_7NS_2$, and therefore a 1:1 adduct. The infrared spectrum showed absorptions at 3110 (NH), 1610 (C=C), 1500 (C=S), 1060, 1040 cm^{-1} (C–S–C). Resonances in its ^1H NMR spectrum (in DMSO-d_6) were centered at δ 7.43 (5 H), 7.79 (1 H), and 13.27 (1 H). The broad absorption peak at δ 13.27 underwent rapid exchange with D_2O. Its pulse Fourier transform ^{13}C NMR spectrum (in DMSO-d_6) showed singlets in the phenyl carbon region and a singlet at δ 187.34 which we attribute to a C=S carbon.[14] Collectively, the data are consistent with a thiazole ring system. The adduct could be methylated with methyl iodide in the presence of 1 *M* NaOH. Two plausible structures are **2** and **3**. Compound **2** could conceivably be the eventual result of a [2 + 2] cycloaddition and hydrogen shift(s). Compound **3** (thioenol form) might result from initial nucleophilic attack by the lone pair of the azirine nitrogen on the reactive electrophilic carbon of carbon disulfide followed by 1,3-bond scission, cyclization, and 1,5 sigmatropic rearrangement.



Spectroscopic data did not provide an unambiguous assignment. Structural differentiation came from treatment of the adduct with nitric acid,[15] which gave the known 5-phenylthiazole (**5**), mp 45°.[16] Compound **5** must arise from



4 **5**

2 by a desulfurization reaction. Our spectroscopic data suggest that **2** exists predominantly in the thioketo form.

The formation of the adduct **2** appears therefore to proceed via a regioselective cycloaddition of carbon disulfide to the π bond of the 1-azirine. To our knowledge this is the first example of such an addition of carbon disulfide to a C=N bond. Whether this combination involves a concerted [$_\pi2_s + {}_\pi2_a$] pathway or a stepwise mechanism involving a dipolar transition state is not known.

These studies were extended to another representative azirine, 3-methyl-2-phenyl-1-azirine (**1b**). Similar results were observed.

Experimental Section

Reaction of 2-Phenyl-1-azirine (1a) with Carbon Disulfide. A mixture of 0.468 g (4 mmol) of 2-phenyl-1-azirine and 1.00 g (13.2 mmol) of carbon disulfide in a Carius tube was heated at 100° for 3 hr. Excess CS_2 was removed and the resultant solid material crystallized from dichloromethane–ether to give 0.182 g (24%) of **2a** as pale yellow needles: mp 208–209°; ir ν_{max} (Nujol) 3110, 1610, 1500, 1270, 1060, 1040, 750 cm^{-1}; ^1H NMR δ_{Me_4Si} (DMSO-d_6) 7.43 (s, br, 5 H), 7.79 (s, 1 H), 13.27 (s, br, 1 H, exchanges with D_2O); ^{13}C NMR δ_{Me_4Si} (DMSO-d_6) 125.09, 128.06, 129.08, 129.41, 129.89, 187.34; mass spectrum (70 eV) *m/e* 193 (M^+), 161 (M^+ − S), 134 [Ph-(c-C_2S)-H; c-C_2S-azirine ring], 121 (PhCS), 102 (PhC≡CH), 91, 77.

Anal. Calcd for $C_9H_7NS_2$: C, 55.93; H, 3.65; N, 7.25. Found: C, 55.90; H, 4.03; N, 7.34.

Methylation of Thiazole (2a). To a suspension of 0.120 g (0.62 mmol) of **2a** in 6 ml of 1 *M* NaOH was added 0.110 g (0.78 mmol) of methyl iodide in 4 ml of 1 *M* NaOH, and the reaction mixture was stirred at room temperature for 3 hr. The reaction mixture was then brought to pH 7 with dilute acetic acid and then extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and the solvent was then removed in vacuo. The residual material was purified by preparative layer chromatography using silica gel PF_{254} plates with 50% ether–pentane as the developing solvent. The thiazole thioether (**4a**) was obtained as a pale yellow oil (0.089 g, 70%); ^1H NMR δ_{Me_4Si} ($CDCl_3$) 2.68 (s, 3 H), 7.21–7.48 (m, 5 H), 7.77 (s, 1 H); mass spectrum (70 eV) *m/e* 207.

Anal. Calcd for $C_{10}H_9NS_2$: C, 57.94; H, 4.38; N, 6.76. Found: C, 57.60; H, 4.07; N, 6.67.

Desulfurization of Thiazole (2a). A suspension of 0.150 g (0.78 mmol) of **2a** in 10 ml of water and 4 ml of concentrated nitric acid was stirred at room temperature for 4 hr. The reaction mixture was neutralized with 10 *M* NaOH and extracted with chloroform. The combined extracts were washed with water and dried (Na_2SO_4). Removal of solvent and purification of the product by preparative layer chromatography on aluminum oxide PF_{254} plates with 50% ether–pentane as the developing solvent gave 0.064 (51%) of 5-phenylthiazole (**5**) as white prisms: mp 45° (lit.[16] mp 45–46°); ^1H NMR δ_{Me_4Si} ($CDCl_3$) 7.23–7.58 (m, 5 H), 8.06 (s, 1 H), 8.75 (s, 1 H); mass spectrum (70 eV) *m/e* 161 (M^+), 134 [Ph-(c-C_2S)-H], 102 (PhC≡CH).

Anal. Calcd for C_9H_7NS: C, 67.05; H, 4.38; N, 8.69. Found: C, 66.72; H, 4.15; N, 8.53.

Reaction of 3-Methyl-2-phenyl-1-azirine (1b) with Carbon Disulfide. The azirine **1b** (0.524 g, 4 mmol) was dissolved in car-

bon disulfide (1.00 g, 13.2 mmol) and heated at 100° as described above for **1a**. The thiazole **2b** crystallized from dichloromethane–ether as pale yellow needles (0.324 g, 39%): mp 223–224°; ir ν_{max} (Nujol) 3120, 1605, 1505, 1090, 1075, 710 cm^{-1}; ^1H NMR δ_{Me_4Si} (DMSO-d_6) 2.23 (s, 3 H), 7.36 (s, br, 5 H), 13.09 (s, br, 1 H, exchanges with D_2O); ^{13}C NMR δ_{Me_4Si} (DMSO-d_6) 12.46, 122.50, 127.95, 128.60, 128.97, 134.10, 186.21; mass spectrum (70 eV) *m/e* 207 (M^+), 175 ($M^+ - S$), 148 [Ph-(c-C_2S)-CH_3], 121 (PhCS), 116 (PhC≡CCH_3), 91, 77.

Anal. Calcd for $C_{10}H_9NS_2$: C, 57.94; H, 4.38; N, 6.75. Found: C, 58.00; H, 4.81; N, 6.64.

Methylation of Thiazole 2b. The thiazole **2b** (0.238 g, 1.2 mmol) was methylated with methyl iodide (0.200 g, 1.4 mmol) in 15 ml of 1 *M* NaOH as described above for **2a**. The thiazole thioether **4b** was obtained as a pale yellow oil (0.220 g, 87%); ^1H NMR δ_{Me_4Si} ($CDCl_3$) 2.42 (s, 3 H), 2.64 (s, 3 H), 7.31 (s, br, 5 H); mass spectrum (70 eV) *m/e* 221 (M^+).

Anal. Calcd for $C_{11}H_{11}NS_2$: C, 59.69; H, 5.01; N, 6.33. Found: C, 59.33; H, 4.95; N, 6.16.

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Registry No.—**1a**, 7654-06-0; **1b**, 16205-14-4; **2a**, 25445-02-7; **2b**, 7725-94-2; **4a**, 25445-03-8; **4b**, 54410-38-7; **5**, 1826-13-7; carbon disulfide, 75-15-0.

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Pyrolysis of 2-Alkoxy-1-azetines

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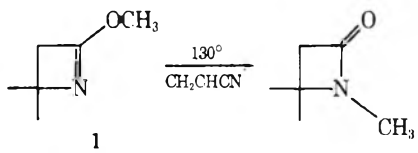
In studies of addition reactions of imino ethers,[1] we were concerned about the conditions necessary for thermal ring opening of 2-alkoxy-1-azetines.[2] We find that complete rearrangement occurs within 8 hr at 200° for 2-methoxy-1-azetines. For azetine **1**, vacuum pyrolysis at 200° for 8 hr results in complete conversion to the unsaturated imino ether **3**. Azetine **4** at 200° for 8 hr gives complete conversion to the analogous unsaturated imino ether **6**. These products can be rationalized by 1,5-hydrogen shifts of the expected intermediates **2** and **5**. Vacuum pyrolysis of azetine **8** under identical conditions gives a 40:60 mixture of isomers **10** and **11** separated by VPC. The compound with the greater retention time was assigned structure **10** by comparison with **3** and **6**. Compound **11** is the product of the alternative 1,5-hydrogen transfer process from **9**. Although **8** readily gives **11**, the analogous product **7** is not formed from azetine **4**. Apparently the *E* isomer of **5**, which would be required for a 1,5-hydrogen shift to produce **7**, is not formed from **4** because of methyl group repulsions.[3] This observation is in good accord with a mechanism involving ring opening of 1-azetines to vinyl imines like **5**, and it eliminates the possibility of a 1,4-diradical intermediate,[2] which would not be expected to specifically give **6** and no **7**.

Paquette and coworkers[2] have reported that ring opening of both (*Z*)- and (*E*)-3,4-diethyl-2-methoxy-1-azetines **12** at 600° give the same mixture of unsaturated imino ethers **14** and **15**. (*Z*)-**12** should open to the *E*, anti vinyl imine **13**, but it should not be capable of 1,5-hydrogen shifts by analogy with our results on pyrolysis of **4**. The

rearrangement of (*Z*)-**12** to the same mixture of 1,5-hydrogen shift products as from (*Z*)-**12** can be explained by assuming that **14** and **15** interconvert by equilibration of each with (*Z*)-**12**. These products could be formed from (*E*)-**12** via *Z*, *anti*-**13**, which could rearrange to the *Z*, syn vinyl imine **13** by inversion at the imine nitrogen. A 1,5-hydrogen shift would then provide **15** [in equilibrium via (*Z*)-**12** with **14**]. Inversion at nitrogen would be expected to occur readily at these temperatures.[4] Furthermore, in the pyrolysis of 1-azirines, Wendling and Bergman have shown such an azetine to vinyl imine reaction to be reversible at 500° as required for equilibration of **14** and **15**,[5] and we have observed that **10** and **11** slowly equilibrate at 200° to give mainly **10** (with less than 5% **11**).

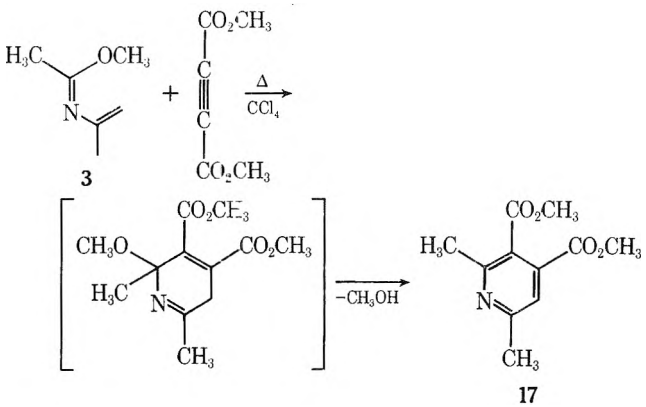
Rates of thermal ring opening of azetines **1**, **4**, and **8** were determined approximately by pyrolysis in the gas phase at 160°. Under these conditions, the dimethylazetine **1** opened to **3** with a rate constant of 0.75×10^{-5} sec^{-1}, while the opening of **4** to **6** was somewhat faster ($k \simeq 2.2 \times 10^{-5}$ sec^{-1}). Relief of the cis-methyl repulsion on opening from **4** to **5** can account for the increased rate for the trimethylazetine **4**. The tetramethylazetine **8** shows the slowest rate at 160° ($k = 0.27 \times 10^{-5}$ sec^{-1}), presumably because of the strong methyl group repulsions on opening to **9**.[3] The rates of these reactions are nearly the same as the rates of ring opening of analogous cyclobutenes to butadienes.[6] This is in contrast to the effect of oxygen and nitrogen on the rates of rearrangement of 2-oxetenes[7] and other heterocycles,[8,9] which rearrange more rapidly than analogous hydrocarbons. The rates of ring opening of 2-azetines appear to be variable. Some 2-azetines[10-13] have been reported to be stable up to 140°, while another rearranges at 25°.[12]

In contrast to the thermal ring opening of 2-alkoxy-1-azetines in the vapor phase, 2-alkoxy-1-azetines rearrange to a Chapman product at high concentration in the liquid phase. Thus, heating a concentrated solution of **1** in acrylonitrile to 130° for 4 days results in an intermolecular[14] Chapman rearrangement to the *N*-methyl-β-lactam **16** and no acrylonitrile addition to **1**.[15]



1 16

To investigate the competition between reaction of the imino ether function with dimethyl acetylenedicarboxylate (DMAD)[1] and a possible Diels–Alder reaction, the addition of DMAD to the unsaturated imino ether **3** was investigated. The reaction gives the substituted pyridine **17** (46%) derived from elimination of methanol from the expected Diels–Alder adduct.



3 17

Experimental Section

General Procedure for Pyrolyses of Azetines. Approximately 40 mg (0.35 mmol) of azetine was freeze degassed and vacuum transferred into a 200-ml reaction vessel. The vessel was sealed and placed in an oven set at either 162.6 ± 0.2 or 198.2 ± 0.2° for 8 hr with a sample pressure of ca. 50 mm. The end of the sample tube was cooled to −196° and opened. The NMR spectrum (in CCl_4) was integrated or the sample was analyzed by VPC to give the percentage composition of the reaction mixture. Approximate first-order rate constants were obtained from two kinetic points within the first 2 half-lives. The pyrolyses gave no nonvolatile material or side products.

Pyrolysis of 2-Methoxy-4,4-dimethylazetine (1). A. When 46 mg of **1**[1a] was heated to 200° for 8 hr according to the general procedure above, it gave compound **3** cleanly by bulb-to-bulb distillation: ir (CCl_4) 3080, 2960, 1680, 1625, 1440, 1370 cm^{-1}; NMR (CCl_4) δ 1.75 (m, 3 H), 1.87 (s, 3 H), 3.60 (s, 3 H), 3.90 (m, 1 H); 4.17 (m, 1 H); mass spectrum (70 eV) *m/e* 113.0839 (calcd for $C_6H_{11}NO$, 113.0841); *m/e* (rel intensity) 113 (M^+, 38), 98 (10), 83 (13), 82 (8), 81 (5), 72 (7), 71 (5), 70 (5), 58 (10), 57 (8), 56 (10), 43 (24), 42 (100), 41 (32), 40 (8), 39 (18), 29 (5, 28 (18), 27 (8), 15 (12).

B. When **1** was heated to 162.6° according to the general procedure above, it gave a first-order rate constant of $0.75 \pm 0.1 \times 10^{-5}$ sec^{-1} based on NMR analysis of the products. When compound **3** was heated to 160° for 24 hr, no **1** was observed by NMR.

Pyrolysis of 2-Methoxy-3,4,4-trimethylazetine (4). A. When 40 mg of **4**[1a] was heated to 200° for 8 hr according to the general procedure above, it gave compound **6** cleanly by bulb-to-bulb distillation: ir (CCl_4) 3090, 2975, 2940, 1680, 1625, 1465, 1440, 1330, 1270, 1230 cm^{-1}; NMR (CCl_4) δ 1.08 (t, J = 7.7 Hz, 3 H), 1.73 (m, 3 H), 2.26 (q, J = 7.7 Hz, 2 H), 3.58 (s, 3 H), 3.88 (m, 1 H), 4.14 (m, 1 H); mass spectrum (70 eV) *m/e* 127.0993 (calcd for $C_7H_{13}NO$, 127.0997); *m/e* (rel intensity) 127 (M^+, 41) 112 (31), 97 (13), 84 (19), 71 (11), 70 (9), 58 (38), 57 (19), 56 (100), 55 (16), 42 (20), 41 (31), 39 (21), 28 (31), 27 (17), 15 (16).

B. When **4** was heated to 162.6° according to the general procedure above, it gave a first-order rate constant of $2.2 \pm 0.3 \times 10^{-5}$ sec^{-1}.

Pyrolysis of 2-Methoxy-3,3,4,4-tetramethylazetine (8). A. When **8**[1a] was heated to 200° for 20 hr according to the general procedure above, it gave a mixture composed of 40% compound **10** and 60% compound **11** cleanly by bulb-to-bulb distillation. The compounds were separated on a 0.25 in. × 10 ft column of 10% SE-30 on 60/80 Chromosorb W, giving pure **10** and pure **11**. Pure **10**: retention time (79°) 9.7 min; ir (CCl_4) 3090, 2970, 2935, 1675, 1630, 1470, 1290, 1260, 1100 cm^{-1}; NMR (CCl_4) δ 1.07 (d, J = 6.9 Hz, 6 H), 1.73 (m, 3 H), 2.94 (heptet, J = 6.9 Hz, 1 H), 3.58 (s, 3 H), 3.87 (m, 1 H), 4.12 (m, 1 H); mass spectrum (70 eV) *m/e* 141.1154 (calcd for $C_8H_{15}NO$, 141.1154); *m/e* (rel intensity) 141 (M^+, 11), 126 (10), 98 (2.5), 96 (2.5), 84 (8), 70 (10), 69 (12), 68 (6), 58 (14), 56 (25), 55 (3), 43 (13), 42 (8), 41 (17), 39 (8), 32 (4), 29 (3), 28 (29), 27 (6), 18 (100), 17 (19), 15 (5). Pure **11**: retention time (79°) 8.2 min; ir (CCl_4) 3080, 2960, 1675, 1640, 1295, 1205, 1160 cm^{-1}; NMR (CCl_4) δ 1.01 (d, J = 6.2 Hz, 3 H), 1.82 (m, 3 H), 3.54 (s, 3 H), 3.54 (heptet, J = 6.2 Hz, 1 H), 4.80 (m, 1 H), 5.05 (m, 1 H); mass spectrum (70 eV) *m/e* 141.1155 (calcd for $C_8H_{15}NO$, 141.1154); *m/e* (rel intensity) 141 (M^+, 32) 140 (15), 126 (56), 98 (10), 85 (10), 70 (12), 69 (34), 68 (59), 59 (17), 58 (24), 56 (32), 55 (12), 43 (24), 42 (22), 41 (85), 40 (10), 39 (34), 28 (44), 27 (20), 18 (100), 17 (20), 15 (22). Uv spectra of **10** and **11** showed only end absorption with a shoulder at 240 nm (ε ~800).

B. When **8** was heated according to the general procedure above, it gave a first-order rate constant of $0.21 \pm 0.03 \times 10^{-5}$ sec^{-1} at 162.8° and 9×10^{-5} sec^{-1} at 198.2°. Using a log A of 14.0, these rate constants are consistent with $E_a \cong 39.0$ kcal/mol. Heating **8** at 198.2° for 100 hr gave a mixture containing 90% of **10** and 10% of **11** by VPC analysis. Heating **10** at 198.2° for 100 hr gave less than 5% of **11**. Thus **10** and **11** equilibrate at 198.2° to give mainly **10**.

Liquid-Phase Thermolysis of 2-Methoxy-4,4-dimethylazetine (1). A mixture of 176 mg of **1** and 183 mg of acrylonitrile was freeze degassed and vacuum sealed in an NMR tube. The tube was placed in an oil bath at 130° with the solution level at the oil level. The solution was heated in this manner for 3 days. Following the course of the reaction by NMR showed the buildup of 1,4,4-trimethyl-1-azacyclobutan-2-one (**16**) at the expense of azetine **1**. The tube was heated for 3 days longer to ensure complete conversion to the β-lactam **16**. The tube was opened and the β-lactam **16** was isolated by bulb-to-bulb distillation: ir (CCl_4) 1750 cm^{-1};

NMR (CCl_4) δ 1.37 (s, 6 H) and 2.65 (s, 5 H) [lit. NMR ($CDCl_3$) δ 1.35 (s, 6 H) and 2.65 (s, 5 H)].[16]

Reaction of 3 with DMAD. A mixture of 40 mg (0.354 mmol) of **3** and 47 mg (0.331 mmol) of DMAD in 4 ml of carbon tetrachloride was refluxed for 2 days and the solvent was removed in vacuo. Vacuum distillation gave 34 mg (46% yield) of dimethyl 2,6-dimethylpyridine-3,4-dicarboxylate (**17**): bp ca. 100° (10^{-3} mm); ir (CCl_4) 3000, 1745, 1600, 1580, 1445, 1380, 1325, 1270, 1220, 1160, 1085 cm^{-1}; NMR (CCl_4) δ 2.53 (s, 3 H), 2.57 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 7.33 (s, 1 H); mass spectrum (70 eV) *m/e* 223.0848 (calcd for $C_{11}H_{13}NO_4$; 223.0844); *m/e* (rel intensity) 223 (M^+, 2), 192 (10), 191(12), 159 (6), 133 (6), 128 (8), 101 (3), 100 (7), 85 (2), 68 (9), 59 (4), 58 (4), 44 (5), 43 (21), 42 (4), 41 (5), 40 (2), 39 (3), 32 (5), 31 (5), 29 (5), 28 (21), 27 (2), 18 (100), 17 (18), 15 (15).

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Registry No.—**1**, 23974-38-1; **3**, 54384-93-9; **4**, 52856-04-9; **6**, 54384-94-0; **8**, 49680-46-8; **10**, 54384-95-1; **11**, 54384-96-2; **16**, 23974-51-8; **17**, 54384-97-3; DMAD, 762-42-5.

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Photolysis of Azido-1,3,5-triazine. Photocycloaddition of Singlet Nitrene to Nitriles

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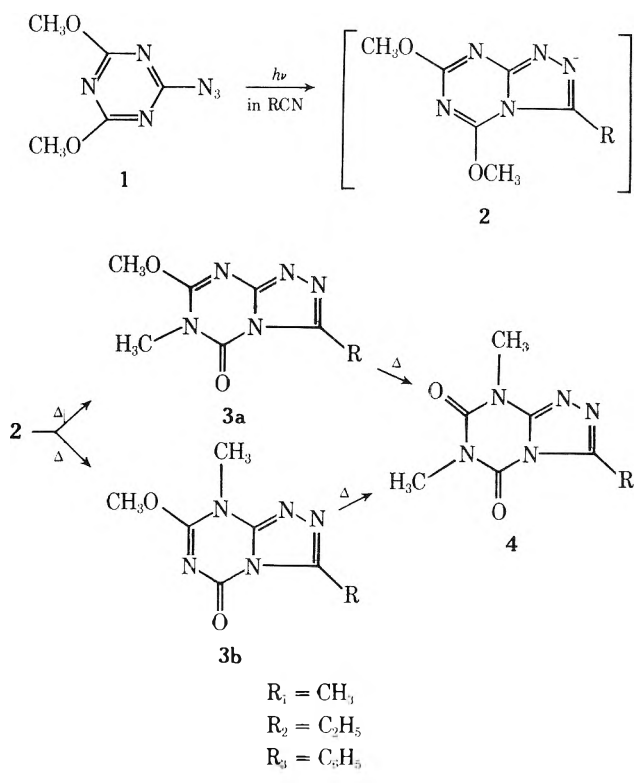
There has been considerable interest recently in the field of nitrene chemistry, and many nitrene reactions (addition to olefins, insertion into the C–H bond, ylide formation with Lewis bases, and other reactions) have been reported.[1] As for the reaction of nitrenes with nitriles, carbethoxynitrene[2,3] and acetylnitrene[4] add to the nitrile group to yield 1,3,4-oxadiazoles. However, little mechanistic work has been reported and photolysis of azido-1,3,5-triazine has not been studied. The reactivity of the triazinyl nitrene is unknown. Triazine derivatives give rise photochemically to interesting reactions: the photo-Smiles rearrangement,[5] the photo-Fries rearrangement,[6] and the phototriazinylation.[7] During the course of our studies on triazine photochemistry, we have carried out the photolysis of azidotriazine in nitriles, and observed the photocycloaddition of singlet triazinyl nitrene to the CN group.

The photolysis of 2-azido-2,4-dimethoxy-1,3,5-triazine (**1**) in degassed and aerated nitriles at 254 nm is shown in Scheme I. The photoproducts which could be isolated are listed in Table I.

Scheme I



The uv spectral change of **1**, for example, in acetonitrile (R_1CN) showed a great decrease in the λ_{max} (238 nm) of the starting material[8] and a slight increase in the 260–310-nm range during the photolysis. This change indicates that both **3a**R_1 (7-methoxy-3,6-dimethyl-*s*-triazolo[4,3-*a*]-1,3,5-triazin-5-one) and **3b**R_1 (7-methoxy-3,8-dimethyl-*s*-triazolo[4,3-*a*]-1,3,5-triazin-5-one) were not primary photoproducts, but were formed thermally from **2**R_1 (5,7-dimethoxy-3-methyl-*s*-triazolo[4,3-*a*]-1,3,5-triazine), because the absorption maxima of **2a**R_1 and **3b**R_1 are at 240 and at 255 nm, respectively. This result was confirmed by a change in the NMR spectra of the photolyzed solution[9] that occurred after standing at room temperature, and the appearance of only weak ir absorption at the characteristic 1735-cm^{-1} absorption of **3a** and **3b** immediately after irradiation.

Similarly, the photoadducts **3a**R_2 and **3b**R_2 (trace) were detected in the photolyzed solution of **1** in propionitrile (R_2CN). In the case of benzonitrile (R_3CN), the final product **4**R_3 (6,8-dimethyl-3-phenyl-*s*-triazolo[4,3-*a*]-1,3,5-triazine-5(6*H*),7(8*H*)-dione) was the only one isolated:[10] the analytical and spectral data agreed with those reported by Kobe et al.[11] The O → N shifts of methyl groups[12] in the photoproducts **2** took place easily even at room temperature. The lack of aromaticity in the compounds **2** and **3** may facilitate the O → N shifts of methyl groups, as has been suggested by Reynolds et al.[13] The O → N shift of

Table I
Properties of Starting Material and Photoadducts[d]

Substance	Chemical yield, %	Mp, °C	MS, m/e	NMR[c]
1		85–85.5[a]		4.05 (2,4-OCH_3)
$3aR_1$	7	153–154	195	2.47 (3-CH_3), 3.60 (6-CH_3) 4.22 (7-OCH_3)
$3bR_1$	15	155–156.5	195	2.80 (3-CH_3), 4.05 (7-OCH_3) 3.80 (8-CH_3)
$3aR_2$	17	153–154	209	1.37 (3 H), 2.88 (2 H), in 3-C_2H_5 3.60 (6-CH_3), 4.22 (7-OCH_3)
$4R_3$	2	213–214 (222–225)[b]	257	8.10 (2 H), 7.52 (3 H), in 3-C_6H_5 3.34 (6-CH_3), 3.58 (8-CH_3)

[a] See ref 17. [b] From Kobe et al., see ref 11. [c] In $CDCl_3$; for the NMR data of **2**, see ref 9. [d] Satisfactory analysis (±0.3% for C, H and N) were reported for $3aR_1$ and $3bR_1$; for $3aR_2$, calcd N, 33.48; found, 32.87; for **4**, calcd C, 56.02, found, 55.58. Ed.

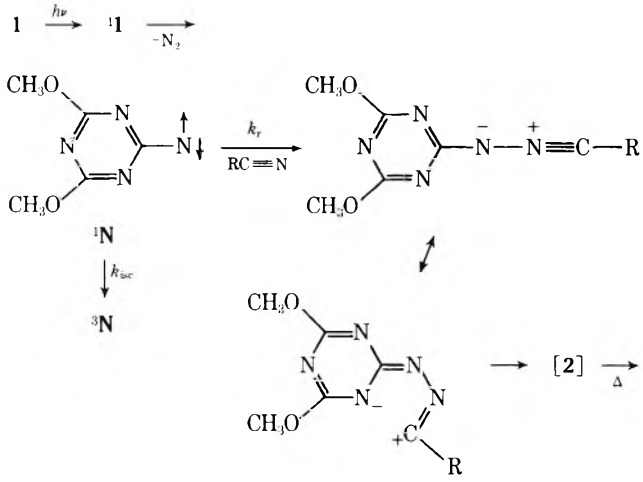
methyl group at the 5 position should occur more readily than that at the 7 position, since the anion generated by the heterolytic fission of OCH_3[12] at the 5 position is expected to be more stable than that at the 7 position.

The absorption spectrum (λ_{max} 313 nm, see Figure 1) of triplet triazinyl nitrene (^{3}**N**) was observed during the photolysis of **1** in a rigid EPA matrix at 77 K and at 254 nm: the ^{3}**N** should be formed via fast intersystem crossing in the singlet nitrene ^{1}**N**.[14] The lowest transition energy in ^{3}**N** (3.96 eV) was larger than that in triplet phenylnitrene (~3.35 eV) reported by Reiser et al.[14] The photosensitization of **1** in degassed R_1CN by triplet benzophenone has been carried out.[15] The sensitized photodecomposition of **1** took place to a large extent. However, the cycloaddition products shown in Table I could not be detected.[16] The quantum yields for the $2R_1$ formation both in aerated and degassed R_1CN were close to unity (0.90 ± 0.10).

From these results, we conclude that the singlet triazinyl nitrene (^{1}**N**) attacks the cyano group in the nitriles. It is well known that singlet nitrenes are electrophilic,[1a] and this tendency in ^{1}**N** may be strengthened by the electron-withdrawing power of the triazinyl nucleus. The reaction rate k_r[RCN] may be faster than the k_{isc} of the intersystem crossing ^{1}**N** → ^{3}**N**.

Finally, the primary photochemical reactions can be accounted for by Scheme II, where ^{1}**1** denotes the excited singlet state of **1**.

Scheme II



Experimental Section

Materials. The starting material 2-azido-4,6-dimethoxy-1,3,5-triazine (**1**) was prepared by treating 2-chloro-4,6-dimethoxy-1,3,5-triazine with NaN_3 and purified by repeated recrystallizations from benzene–ligroin.[17] The solvents were G. R-grade products of Tokyo Kasei Co. Ltd., and they were used without further purification. The solution of **1** was degassed by the freeze–pump–thaw method.

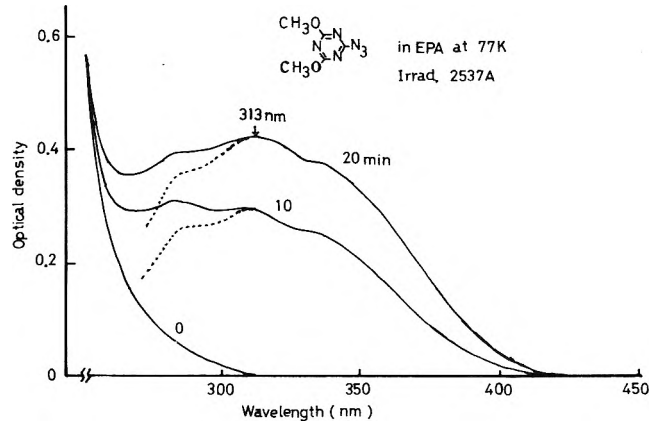


Figure 1. Spectral change of rigid EPA matrix of **1** at 77 K with lapse of time at 2537 Å. Numbers refer to time in minutes. Dotted lines denote the corrected absorption spectra of ^{3}**N**.

Light Sources and Actinometry. A 30-W low-pressure Hg lamp was used as the 254-nm radiation source. In the benzophenone photosensitization, a 100-W high-pressure Hg lamp was used with a glass cutoff filter (>310 nm). The actinometry was carried out using a ferric oxalate solution (0.006 *M*).[18] The amount of product $2R_1$ was determined by means of NMR at the characteristic peak (δ 2.80) due to the methyl group on the 3 position in $2R_1$, calibrated against 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (δ 3.10).

Registry No.—**1**, 30805-07-3; $2R_1$, 54410-40-1; $3aR_1$, 54410-41-2; $3aR_2$, 54410-42-3; $3bR_1$, 54410-43-4; $4R_3$, 28750-32-5; 2-chloro-4,6-dimethoxy-1,3,5-triazine, 3140-73-6; NaN_3, 26628-22-8.

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(6) H. Shizuka, T. Kanai, T. Morita, Y. Ohto, and K. Matsui, *Tetrahedron*, **27**, 4021 (1971); Y. Ohto, H. Shizuka, S. Sekiguchi, and K. Matsui, *Bull. Chem. Soc. Jpn.*, **47**, 1209 (1974).
(7) H. Yamada, H. Shizuka, S. Sekiguchi, and K. Matsui, *Bull. Chem. Soc. Jpn.*, **47**, 238 (1974).
(8) ε 1.36 × 10^4 at 238 nm in acetonitrile.
(9) The NMR spectra of $2R_1$ and $2R_2$ in $CDCl_3$ follow: $2R_1$, δ 2.80 (3-CH_3), 4.35 (5-CH_3O), 4.10 (7-CH_3O); $2R_2$, δ 1.25 (3 H) and 3.10 (2 H) in 3-ethyl, 4.30 (5-CH_3O), 4.10 (7-CH_3O).
(10) The incident light at 254 nm was absorbed by the solvent (R_3CN) com-

pletely, and the decomposition of **1** sensitized by the singlet excited state of R_3CN would undergo the photocycloaddition to R_3CN.

(11) J. Kobe, B. Stanovnik, and M. Tisler, *Tetrahedron*, **26**, 3357 (1970). They synthesized the compound $4R_3$ thermally.

(12) Similar phenomena in trimethylcyanurate have been reported by Paoloni et al., and they have shown that the rearrangements proceed via the heterolytic fission of the O–CH_3 bond. See L. Paoloni, M. L. Tosato, and M. Cignitti, *J. Heterocycl. Chem.*, **5**, 533 (1968); L. Paoloni and M. L. Tosato, *Ann. Chim. (Rome)*, **54**, 897 (1964).

(13) G. F. Reynolds, P. A. Larson, and J. A. C. Allison, *Mich. Acad.*, **4**, 345 (1972).

(14) The ESR measurements of the ground-state triplet nitrenes have been carried out by the Bell Telephone Laboratories group. They demonstrate that the ground state of nitrene is triplet. See R. W. Murray, A. M. Trozzolo, E. Wasserman, and W. A. Yager, *J. Am. Chem. Soc.*, **84**, 3213 (1962); G. Smolinsky, E. Wasserman, and W. A. Yager, ibid., **84**, 3220 (1962); G. Smolinsky, L. C. Snyder, and E. Wasserman, *Rev. Mod. Phys.*, **35**, 576 (1963); E. Wasserman, R. W. Murray, W. A. Yager, A. M. Trozzolo, and G. Smolinsky, *J. Am. Chem. Soc.*, **89**, 5076 (1967). As for uv, spectra of aromatic nitrenes have been reported by Reiser et al. and by Kashiwagi et al. See A. Reiser, G. Bowes, and R. J. Horne, *Trans. Faraday Soc.*, **62**, 3162 ([966(: H. Kashiwagi, S. Iwata, T. Yamaoka, and S. Nagakura, *Bull. Chem. Soc. Jpn.*, **46**, 417 (1973).

(15) Benzophenone concentration in R_3CN was 0.1 *M*. There was no uv absorption band of **1** in wavelengths longer than 310 nm.

(16) Unfortunately, the decomposition products of **1** could not be identified.

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N-Dealkylation of Pyrazoles Using Pyridine Hydrochloride

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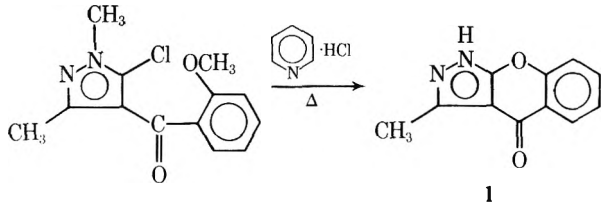
We wish to report that *N*-alkylpyrazoles can be conveniently N-dealkylated by heating in anhydrous pyridine hydrochloride at reflux temperature. We fortuitously observed this N-dealkylation when 5-chloro-1,3-dimethylpyrazol-4-yl-*o*-methoxyphenyl ketone[1] was heated for 16 hr at 215° with this reagent and the product was shown to be 3-methyl[1]benzopyrano[2,3-*c*]pyrazol-4(1*H*)-one (**1**) (Scheme I).

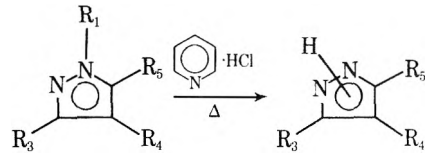
Scheme I



1

There are only a few reports on the removal of N substituents from pyrazoles[2–6] and most of these N substituents are of such low stability as to preclude their use for protective purposes. Thus base and heat have been shown to remove the *N*-hydroxymethyl,[2] N-substituted aminomethyl,[2] and *N*-2,4-dinitrophenyl[3] groups. Also oxidative reagents remove particularly sensitive N-substituents.[4,5] The most synthetically useful N-protecting group in pyrazole chemistry is the *N*-benzyl group[6] (readily removed by sodium and liquid ammonia reduction, but suffering the usual disadvantages associated with this method of removal). Therefore, we decided to test the generality of this N-dealkylation (Scheme II). *N*-Alkylcarboxylic acid amides, anilides,[7] and *N*-methyl- and *N*-ethylphenothiazine[8] have been dealkylated by this reagent. The generality of this reaction has been questioned, since *N*-alkylcarbazoles are unaffected by this reagent.[9]

Scheme II



Results

Both simple and complex *N*-methylpyrazoles as well as *N*-ethylpyrazoles (see compounds **5** and **8**, Table I) and one example of an *N*-methylindazole (see compound **3**) were successfully N-dealkylated. The reaction was successful with a wide variety of substituents on the carbon atoms of the pyrazole ring, including both electron-attracting and -releasing substituents. Wide differences in the rate of N-dealkylations were observed [see time of heating, Table I, and comparison of synthesis of **6** from 1,3-dimethylpyrazol-5-yl phenyl ketone[10] or the isomeric 1,5-dimethylpyrazol-3-yl phenyl ketone (**9**) in Experimental Section]. This is a rapid, simple method and gives reasonably good yields of N-unsubstituted pyrazoles. The examples include a number of compounds that would be difficult or impossible to prepare by other methods. While the examples have included only *N*-methyl and *N*-ethyl substituents, in analogy with the known N,N′-dealkylations of *N,N′*-pyrazolium and *N,N′*-indazolium quaternary salts[11,12] other alkyl groups should be removed with equal facility.

Mechanistic Considerations. The reaction most likely proceeds by protonation of the pyrazole ring and the formation of the alkyl halide by the attack of chloride ion and expulsion of the neutral N-dealkylated pyrazole. The high temperature drives out the low-boiling alkyl halide, helping to drive the reaction to completion. This is consistent with the mechanism in the N,N′-dealkylations of *N,N′*-dialkylpyrazolium halides.[11] Examination of the crude product in the synthesis of **6** demonstrated the presence of an *N*-methyl shift as reported in N,N′-dealkylations of *N*-methyl-*N′*-alkylpyrazolium salts.[11]

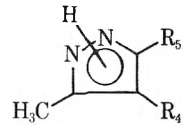
Experimental Section[13]

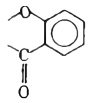
Reagents and Starting Materials. The pyridine was purchased from J. T. Baker Chemical Co. The following compounds were synthesized as described in the references given: 5-chloro-1,3-dialkylpyrazol-4-yl aryl ketones;[1] 1,3-dimethylpyrazol-5-yl phenyl ketone;[10] 1-ethyl-3-methyl-4-nitropyrazol-5-yl phenyl ketone;[14] 1,3,5-trimethylpyrazole;[15] 5-amino-1,3-dimethylpyrazole;[16] 1,5-dimethyl-3-pyrazolecarboxamide;[17] 1,3-dimethyl-1*H*-indazole.[18]

General Procedure. Anhydrous pyridine hydrochloride was freshly prepared by the method of Curphey et al.[19] (dried by distillation up to 210° and cooled under a stream of N_2). The pyrazole was added to a three- to tenfold molar excess of the reagent and the mixture was stirred at 180–218° for 1–40 hr. Products less basic than pyridine could be isolated by dilution of the cooled reaction mixture with water followed by filtration or extraction with diethyl ether or chloroform. The extracts were dried ($MgSO_4$) and concentrated and the products were recrystallized. If the product was a stronger base than pyridine, it was isolated by addition of an excess of 29% ammonia and extraction. Many of the keto pyrazoles were best separated from unreacted starting material by extraction into 1 *N* sodium hydroxide solution followed by neutralization with an equivalent amount of hydrochloric acid.

3-Methylpyrazol-5-yl Phenyl Ketone (6). 1,3-Dimethylpyrazol-5-yl phenyl ketone[10] was treated with the reagent for 1 hr at 218°. A VPC on the crude reaction mixture showed a three-component mixture: starting material (5%), **6** (80%), and an unknown, **9** (15%). Two recrystallizations from toluene yielded **6** (52%) (see Table I for physical data). The unknown **9** was shown to be the

Table I
N-Delakylated Products[a]



Compd	R_4	R_5	Temp, °C	Heating period, hr[b]	Yield, %[c]	Mp, °C	Recrystn solvent[d]	Empirical formula	Ir, cm^{-1} (N–H; C=O)
1			215	16	61	298–300	A	$C_{11}H_8N_2O_2$	3205; 1650
2	H	CH_3	180	16	70	106–107[e]			
3			210	40	72	112–113[f]			
4	H	HNC(=O)Ph	218	0.75	60[g] (40)[h]	210–212	B	$C_{11}H_{11}N_3O$	3300; 1648
5	NO_2	O=CPh	210	3	56[i]	138–140	C	$C_{11}H_9N_3O_3$	3260; 1658
6	H	O=CPh	218	1	52[j]	110–112	D	$C_{11}H_{10}N_2O$	3225, 3160; 1630
7	CPh (=O)	Cl	200	3	63	169–171	E	$C_{11}H_9ClN_2O$	3235; 1630
8	C-*o*-ClPh (=O)	Cl	200	3	62 (69)[k]	135–137	F	$C_{11}H_8Cl_2N_2O$	3195; 1660

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed. Mass spectra were also taken and indicated the correct molecular weights, as well as the absence of the higher molecular weight and more volatile *N*-alkyl starting materials. Dealkylations of starting materials with *N*-ethyls are indicated in footnotes *i* and *k*. [b] Too extensive a heating time appeared to be important only when the products were susceptible to further reactions, i.e., compounds 7 and 8. [c] The yields are those isolated and purified. Yields were not maximized and changes in the temperature, heating time, and isolation procedures would improve them. [d] A, Soxhleted from insolubles using THF; B, CH_3OH–Et_2O; C, Et_2O; D, toluene; E, toluene–petroleum ether; F, toluene–cyclohexane. [e] Lit. mp 106–107°; L. Knorr and G. D. Rosengarten, *Justus Liebigs Ann. Chem.*, **279**, 237 (1894). [f] Lit. mp 113°; E. Fischer and J. Tafel, ibid., **227**, 303 (1885). [g] From starting material **12** with only one *N*-methyl to be removed. [h] From starting material **11** with two *N*-methyls to be removed. [i] An example of *N*-ethyl removal. [j] Crude yield by VPC 80% + 15% *N*-methyl shift. [k] First yield from *N*-methyl removal, second yield from *N*-ethyl removal.

Table II
Chemical Shifts for Compounds in Table I[a]

Compd	N–H	3-CH_3	R_4	R_5
1	10–11 (very broad)	2.63	7.2–8.3 (4 H)	
4	12.1 (broad singlet	2.24	6.42 (1 H)	7.2–8.2 (5 H) 10.66 (1 H)
5	11–12 (very broad)	2.48		7.2–8.2 (5 H)
6	13–14 (very broad)	2.21	6.63 (1 H)	8.0–8.4 (2 H) 7.3–7.8 (3 H)
7	13–14 (very broad)	2.22	7.2–7.9 (5 H)	
8	13–14 (very broad)	2.28	7.4–7.7 (4 H)	

[a] δ (TMS) (Me_4Si) in DMSO-d_6.

product of *N*-methyl transfer, i.e., 1,5-dimethylpyrazol-3-yl phenyl ketone (**9**). This was proven by comparison of VPC retention time, NMR spectrum location of the *N*-methyl and 4-H, and mixture melting point (after isolation by column chromatography) with a sample synthesized in the following manner. 1,5-Dimethyl-3-pyrazolecarboxamide[17] was dehydrated using phosphorus oxychloride to yield 1,5-dimethyl-3-pyrazolecarbonitrile (**10**, 80%), mp 68–69° (from EtOH). Anal. Calcd for $C_6H_7N_3$: C, 59.50; H, 5.82; N, 34.70. Found: C, 59.11; H, 5.95; N, 34.16. **10** was treated with an excess of phenyl Grignard reagent and after acid hydrolysis yielded **9** (73%), mp 55–57°. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.96; H, 6.07; N, 13.99. Found: C, 72.30; H, 6.11; N, 13.99.

Rate of the Dealkylation Reaction of 1,5-Dimethylpyrazol-3-yl Phenyl Ketone (9). When **9** was treated with the reagent for 3 hr at 218° [three times the time period used to produce 95% dealkylation of 1,3-dimethylpyrazol-5-yl phenyl ketone[10]], VPC analysis showed only a 50% conversion to **6** along with 50% **9**. The rate difference may be due to a slower rate of protonation due to differences in the basicities of the 1,5 vs. the 1,3 ketone in the reagent or a lower susceptibility of attack on the *N*-alkyl bond due to the different relationship with the electron-withdrawing carbonyl group.

***N*-(1,3-Dimethylpyrazol-5-yl)-*N*-methylbenzamide (11).** 5-Amino-1,3-dimethylpyrazole[16] was treated in chloroform with 1 equiv of benzoyl chloride in the presence of an excess of calcium hydroxide to yield *N*-(1,3-dimethylpyrazol-5-yl)benzamide (**12**, 89%), mp 133–135° from toluene. Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.19; N, 19.52. Found: C, 66.85; H, 6.13; N, 19.37. **12** was treated with iodomethane and sodium methoxide in THF to yield **11** (82%), mp 98–100° from ethyl acetate–petroleum ether. Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.32. Found: C, 68.02; H, 6.71; N, 18.45.

Registry No.—**1**, 54384-65-5; **2**, 67-51-6; **3**, 3176-62-3; **4**, 52566-42-4; **5**, 54384-66-6; **6**, 54384-67-7; **7**, 54384-68-8; **8**, 54384-69-9; **9**, 54384-70-2; **10**, 54384-71-3; **11**, 54384-72-4; **12**, 54384-73-5; pyridine hydrochloride, 628-13-7; 5-chloro-1,3-dimethylpyrazol-4-yl-o-methoxyphenyl ketone, 29938-78-1; 1,3,5-trimethylpyrazole, 1072-91-9; 1,3-dimethyl-1*H*-indazole, 34879-84-0; 1-ethyl-3-methyl-4-nitropyrazol-5-yl phenyl ketone 26308-47-4; 1,3-dimethylpyrazol-5-yl phenyl ketone, 32500-76-8; 1,3-dimethyl-5-chloropyrazol-4-yl phenyl ketone, 29938-70-3; 5-chloro-1,3-dimethylpyrazol-4-yl o-chlorophenyl ketone, 29938-74-7; 5-chloro-1-ethyl-3-methylpyrazol-4-yl o-chlorophenyl ketone, 29938-93-0; 1,5-dimethyl-3-pyrazolecarboxamide, 54384-74-6; 5-amino-1,3-dimethylpyrazole, 3524-32-1.

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Addition of Benzyne to *cis*- and *trans*-1,3-Pentadiene

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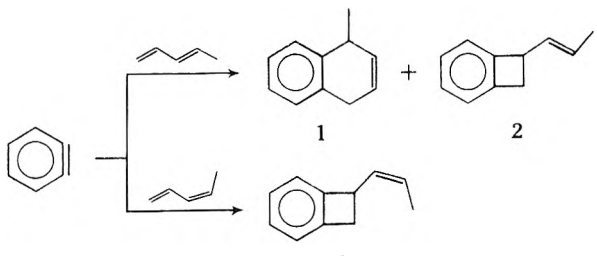
The addition of benzyne to alkyl-substituted dienes can conceivably give [2 + 2], [2 + 4], and "ene" reaction products.[1] When the diene can achieve the s-cis conformation, [2 + 4] addition predominates over [2 + 2] addition.[2] When an ene reaction is possible, it predominates over the [2 + 2] reaction path in most olefins.[3,4] We wish to report the addition of benzyne to *cis*- and *trans*-1,3-pentadiene, which surprisingly shows no ene product.

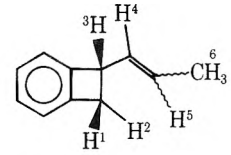
Benzyne, generated from benzenediazonium 2-carboxylate,[7] adds to *trans*-1,3-pentadiene giving two isomeric adducts, **1** (46%) and **2** (16%). Compound **1** had an NMR spectrum consistent with 1-methyl-1,4-dihydronaphthalene. In addition, oxidation of **1** with dichlorodicyanoquinone resulted in 1-methylnaphthalene, which was identical with an authentic sample. The NMR data for **2** are in Table I.



1 **2** **3**

When *cis*-1,3-pentadiene was used as the benzyne trap, 2-*cis*-propenylbenzocyclobutene (**3**) was formed in 24% yield. The NMR spectrum of **3** is very similar to that of **2** (see Table I). Oxidation of **3** with $KMnO_4$–$NaIO_4$ resulted in acetic acid and benzocyclobutene-2-carboxylic acid, which was identical with authentically prepared material.[8] No **3** was observed by NMR when the trans diene was used and no **2** was found when the cis diene was used. If benzyne was produced by the reaction of *o*-bromofluorobenzene with magnesium,[2a] cis–trans isomerization of the diene occurred (GLC analysis). Thus, **1** was observed when *cis*-1,3-pentadiene was used as the benzyne trap. When benzenediazonium 2-carboxylate was used as the benzyne precursor, no cis–trans diene isomerization was observed.

Table I
Nmr Spectra of *cis*- and *trans*-2-Propenylbenzocyclobutene



	Aromatic	H_1	H_2	H_3	H_4 and H_5	H_6
2	7.13[a]	3.45	2.84	4.05	5.68	1.68
3	7.1	3.52	2.86	4.38	5.6	1.76

	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{5,6}$
2	13.8	2.6	5.2	4.5
3	14.0	2.7	5.3	5.2

[a] In CCl_4/Me_4Si. Chemical shifts reported in parts per million (δ). Coupling constants reported in hertz.

The [2 + 4]/[2 + 2] ratio observed when benzyne adds to *trans*-1,3-pentadiene (3.9:1) is essentially the same as the ratio found when it adds to 1,3-butadiene (4:1[2e]). It is not surprising that the methyl group little affects the addition of benzyne to this diene. This report also shows that benzyne is unable to give a [2 + 4] addition product with *cis*-1,3-pentadiene owing to this diene's inability to achieve the required s-cis conformation.[9] In fact, maleic anhydride is the only dienophile reported to give a [2 + 4] product with the cis diene.[10,11] Since benzyne has an alternate reaction pathway ([2 + 2] addition), it is not required to partake in an inherently undesirable [2 + 4] addition to the cis diene.[12]

In dienes which have no conformational peculiarities, ene addition predominates over [2 + 2] addition. It is therefore noteworthy that no ene product is observed when benzyne adds to 1,3-pentadiene. Owing to rotation of the methyl group, a suitable conformation must be available for what is apparently a concerted ene reaction.[1b] The answer here might lie in an especially facile [2 + 2] addition of benzyne to 1,3-pentadiene. The determining factor could be a sterically less restricted approach to the terminal double bond in the pentadienes which is not possible in the other dienes that have been studied. Indeed, there could be a great inherent tendency for benzyne to undergo a [2 + 2] addition than an ene reaction with *any diene*.[14] This tendency may be masked by steric effects in most dienes.[15,16]

Experimental Section

General. The NMR spectra were obtained on a Varian Associates A-60 spectrometer. A Beckman IR-10 was used for the ir spectra. Mass spectra were determined on a Hitachi Model RMU-6E spectrometer at an ionizing voltage of 70 eV. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Gas–liquid phase chromatography was conducted on a Varian A-90P instrument. Tetrahydrofuran was distilled from lithium aluminum hydride before use. *cis*- and *trans*-1,3-pentadiene (PCR, Inc., greater than 99% geometric purity) were distilled before use.

Generation of Benzyne in the Presence of *cis*-1,3-Pentadiene. To 0.025 mol of benzenediazonium 2-carboxylate[7] was added 30 ml of chloroform and 2.04 g of *cis*-1,3-pentadiene (0.030 mol). The mixture was heated at 40–45° for 4.5 hr. After cooling, GLC analysis showed no *trans*-1,3-pentadiene. The solvent was removed under vacuum. The product, **3**, was isolated using column chromatography (alumina, *n*-pentane) and weighed 0.724 g (24%

yield). An analytical sample was isolated by preparative GLC (see Table I for NMR data): ir (neat) 3080 (w), 3020 (m), 2970 (m), 2930 (s), 1455 (m), 740 (s), 718 (m), and 700 cm^{-1} (m); mass spectrum *m/e* 144 (molecular ion). Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.47; H, 8.43.

Generation of Benzyne in the Presence of *trans*-1,3-Pentadiene. When the above procedure was applied using the trans diene, a mixture of **1** and **2** was isolated (62% yield combined). The ratio 1:2 was 3.9:1 (GLC). The isomers were separated by preparative GLC.

1: NMR ($CDCl_3$) 1.31 (d, J = 6.8 Hz, 3 H, methyl), 3.38 (broad s, 3 H, benzylic), 5.88 (m, 2 H, olefinic), and 7.16 ppm (m, 4 H, aromatic); ir (neat) 3035 (w), 3026 (m), 2970 (m), 2930 (m), 2880 (m), 1581 (w), 1492 (m), 1450 (m), 747 cm^{-1} (s); mass spectrum *m/e* 144 (molecular ion). Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.46; H, 8.43.

2: NMR, see Table I; ir 3080 (w), 3030 (m), 2970 (m), 2930 (w), 1460 (m), 965 (s), 745 cm^{-1} (s); mass spectrum *m/e* 144 (molecular ion). Anal. Calcd for $C_{11}H_{12}$: c, 91.61; H, 8.39. Found: C, 91.61; H, 8.33.

Oxidation of 3.[17] To 29 ml of a $NaIO_4$–$KMnO_4$ solution (0.38 M $NaIO_4$ and 0.0064 M $KMnO_4$) was added 20 ml of *t*-BuOH and enough K_2CO_3 to achieve a pH of 8. To this was added 20 mg of **3**. The solution was stirred at room temperature for 5 hr. After acidification with 2 M HCl, the solution was extracted five times with a 1:1 mixture of ether and pentane. The combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was removed by distillation. The acetic acid in this residue was removed by vapor transfer and identified by comparing its NMR spectrum with that of authentic material. The mass spectrum of the residue showed a molecular ion (*m/e* 148) consistent with $C_9H_8O_2$. The NMR spectrum was identical with that of independently prepared benzocyclobutene-1-carboxylic acid.

Oxidation of 1. A mixture of 40 mg of **1**, 63.5 mg of dichlorodicyanoquinone, and 1 ml of benzene was brought to reflux for 15 min. After cooling, 50 ml of pentane was added and the mixture was filtered. The filtrate was then passed through a short column of alumina using pentane as the eluent. The solvent was removed under vacuum. The NMR spectrum was identical with that of commercial 1-methylnaphthalene.

Acknowledgments. We would like to acknowledge the support of the Faculty Research Fund of Georgia College. We are grateful to Dr. W. M. Jones and the Department of Chemistry of the University of Florida, where the final ir, NMR, and mass spectra were obtained.

Registry No.—**1**, 21564-70-5; **2**, 54384-63-3; **3**, 54384-64-4; benzyne, 462-80-6; *cis*-1,3-pentadiene, 1574-41-0; *trans*-1,3-pentadiene, 2004-70-8; benzenediazonium 2-carboxylate, 1608-42-0; benzocyclobutene-1-carboxylic acid, 14381-41-0; dichlorodicyanoquinone, 84-58-2; 1-methylnaphthalene, 90-12-0.

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(7) (a) Crews' modification[1b] of Friedman's procedure[7b] was used. (b) F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Synth.*, **48**, 12 (1969).

(8) A similar oxidation of **2** was not possible owing to insufficient material. From their NMR spectra, it is apparent that **2** and **3** are geometric isomers. Furthermore, **2** has a strong band at 965 cm^{-1} in its ir spectrum, indicating the trans propenyl group. This band was absent in **3**.

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(10) D. Craig, *J. Am. Chem. Soc.*, **72**, 1678 (1950); D. Craig, J. J. Shipman, and R. B. Fowler, ibid., **83**, 2885 (1961).

(11) The necessary presence of *picric* acid in the *maleic* anhydride [2 + 4] addition to *cis*-1,3-pentadiene[10] obfuscates this comparison. The acid reportedly retards polymerization of the diene, but may also exert some catalytic effect.

(12) Stewart[13] has placed a relative rate limit on the addition of tetracyanoethylene to the cis and trans dienes. The ratio $k_{cis}/k_{trans} = 10^{-5}$ was based on the rate of color fading of the complex formed between the cis diene and TCNE. No adduct was isolated.

(13) C. A. Stewart, Jr., *J. Org. Chem.*, **28**, 3320 (1963).

(14) This is not the case for monoolefins. Stepwise [2 + 2] addition[2b] to simple olefins does not result in an allylic intermediate, which is the case when a diene is the benzyne acceptor.

(15) A reviewer commented on the observed [2 + 2] addition of benzyne to disubstituted double bonds in 2,3-dimethyl-1,3-butadiene[2a] and *trans*,*trans*-2,3-hexadiene.[2c] Although [2 + 2] addition was found in these systems, ene addition still predominated (although slightly with the 2,4-hexadiene). It is obviously a delicate balance of steric and electronic factors that determines the ene/[2 + 2] ratio. We thank the reviewer for his comments.

(16) In a recent publication, M. Jones, Jr., and coworkers report the thermolysis of **2** and **3**, which were prepared by the addition of benzyne (generated from the photolysis of phthaloyl peroxide) to *trans*- and *cis*-1,3-pentadiene: M. R. DeCamp, R. H. Levin, and M. Jones, Jr., *Tetrahedron Lett.*, 3575 (1974).

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Efficacious Cleavage of the Benzyl Ether Protecting Group by Electrochemical Oxidation

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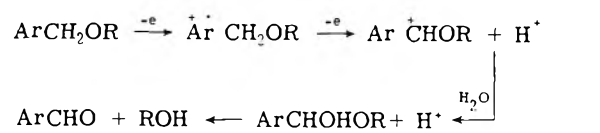
An effective way to protect an alcohol is via its benzyl ether.[2] However, the common ways used to remove this blocking group (i.e., catalytic hydrogenation or alkali metal reduction) involve conditions which may not be applied to molecules where other easily reduced functional groups are present. We wish to report a straightforward procedure whereby a benzyl group can be cleanly removed electrochemically under mild, *oxidative* conditions.[3] This provides a complementary alternative to the presently used reductive methods.

Early work by Lund[4] revealed that the oxidation potential for the benzyloxy group was low enough to allow electrochemical oxidation. This work was followed by other studies[5–7] which indicated that the oxidation of benzylic ethers, esters, or alcohols will proceed to form benzaldehyde. The probable mechanism of this reaction is as shown in Scheme I. Even though previous workers have focused

Scheme I



attention on the formation of the aromatic aldehyde, concomitant formation of the alcohol in the above sequence has been confirmed by Miller,[5] who, in fact, suggested the possible usefulness of this reaction as a method of cleaving benzyl protecting groups. However, the generality and utility of this reaction apparently have not been tested, possibly because of Miller's observation that constant "pulsing" of the electrode potential was necessary in order to obtain reasonable yields. Without this pulsing, Miller reports that under his conditions (anhydrous acetonitrile with added

Table I
Isolated Yields of Alcohols from Electrolyses of Their *p*-Anisyl Ethers at 1.65 V (SCE)

Alcohol	Yield, %	Alcohol	Yield, %
1-Octanol	98		74[a]
2-Octanol	90		
l-Borneol	93	$PhCH_2OH$	75
Cholesterol	89	2,6-Dichlorobenzyl alcohol	88
$PhOCH_2CH_2OH$	74	Cyclododecanol	89

[a] The dianisyl ether was used.

sodium carbonate) the anode becomes fouled, causing a significant drop in the current.

Viewing the above reaction in terms of its potential usefulness in the synthesis of complex molecules, we have sought to test the generality of the reaction on a variety of compounds, and to develop a simple methodology whereby consistently high yields would be possible.

Consideration of the mechanism in Scheme I would lead one to expect that an electron-supplying substituent on the aromatic ring would make the initial oxidation step easier. This is in fact observed;[4] so we have concentrated our efforts on the study of *p*-methoxy substituted benzyl ethers, thus enabling us to work at a potential lower than is necessary for the oxidation of most other substituted benzyl ethers, or simpled unsubstituted benzyl ethers. Although acids have been protected as their *p*-anisyl esters,[8,9] *p*-anisyl ethers have not been widely used previously, probably because no particular advantage over benzyl ethers was envisaged. We anticipate no problems in using them, however, and they are easily prepared.

Utilizing controlled-potential electrolysis, we have obtained good yields in a variety of functionalized systems when the electrolysis is performed in 60–85% aqueous acetonitrile[10] with lithium perchlorate (0.1 *M*) as the supporting electrolyte. The presence of water (as an available nucleophile capable of attacking the intermediate benzyloxy carbonium ion) produces a much cleaner reactions and obviates the need for electrode "pulsing", thus simplifying the experimental technique.[5] The electrolyses were performed at +1.65 V relative to SCE. Table I summarizes the results.

Since convenience in the isolation of the free alcohol is an important criterion, it should be pointed out that the other product of this reaction, anisaldehyde, is readily removed from the reaction mixture by extraction with saturated aqueous sodium bisulfite solution. In each case the product was appropriately purified (usually by distillation) to give the isolated yields listed in Table I. In some of the compounds studied it is not possible to remove the protecting group using standard reductive techniques without concomitant reduction of other functionality.

Although we have concentrated mainly on anisyl ethers owing to their low oxidation potential, benzyl ethers (or other types of substituted benzyl ethers) may also be removed in this manner by raising the oxidation potential to 2.0 V. The results of the oxidation of the benzyl ether of *l*-borneol is an illustrative example (68% yield). Since the oxidation potentials of *p*-anisyl and benzyl are substantially different, it should be possible[11] to have two different alcohol groups in the same molecule protected, one perhaps as the *p*-anisyl ether and the other as the benzyl ether, and to selectively remove first the anisyl protecting group by electrolysis at +1.65 V, and at a later time to remove the benzyl by electrolysis at +2.0 V. This high degree of selectivity is illustrated by the electrolyses of the *p*-anisyl ethers of benzyl alcohol and 2,6-dichlorobenzyl alcohol, which electrolyzed to produce benzyl alcohol and 2,6-dichlorobenzyl alcohol, respectively, uncontaminated with any anisyl alcohol.

Experimental Section

p-Anisyl chloride was prepared by treating anisyl alcohol with thionyl chloride in ether containing a catalytic amount of pyridine. Distillation gave the chloride in 86% yield, bp 85–90° (2 mm) [lit.[12] bp 101–103° (8–10 mm)].

Preparation of Anisyl Ethers. The ethers were prepared via a Williamson synthesis. The general procedure involved stirring the required alcohol with sodium hydride in anhydrous DMF until gas evolution had ceased. The resulting solution was treated with an equimolar amount of anisyl chloride. After 1 hr an additional amount of anisyl chloride was added so that it was present in a 20% excess. After stirring overnight, the solution was poured over ice and the resulting suspension was extracted with chloroform. The organic phase was washed with sodium hydroxide solution and with water, dried with magnesium sulfate, and concentrated to give the desired ether. Before electrolysis the crude ethers were distilled, recrystallized, or chromatographed.

Electrochemical Apparatus. A simple electrochemical cell was constructed from a beaker and a glass tube of about 75-ml capacity which was sealed at one end with a sintered glass frit of medium porosity. The frit was covered with a gel[13] of 0.1 *M* lithium perchlorate in DMF and methyl cellulose. This isolates the cathode and anode, while maintaining electrical conductivity between the two. The tube was suspended in the beaker and the inside of the tube was utilized as the anodic chamber. A platinum wire cathode and a platinum mesh anode were used. The power source was a Wenking 70HVI potentiostat (Brinkmann Instruments).

Electrochemical Oxidation. General Procedure. A solution of 60–85% aqueous acetonitrile was made 0.1 *M* in lithium perchlorate.[10] This solution was placed in the electrochemical cell. To the anode chamber was added 4 mmol of the compound to be electrolyzed, and the solution was electrolyzed at +1.65 V (SCE) until the initial current of ca. 200 mA had dropped to less than 3 mA. The anolyte was concentrated in vacuo with minimal heating until the acetonitrile was removed. (The solution may be neutralized before concentration to minimize any reaction under the acidic conditions of the concentrated solution, but for the compounds listed in Table I we observed no undesirable reactions when this neutralization was omitted. *Caution: Under no circumstances should the solution be evaporated to dryness.*) The resulting aqueous suspension was saturated with sodium chloride and extracted with ether. The combined ether extract was washed with saturated sodium bisulfite solution, dried, and concentrated to yield products which were essentially pure by NMR analysis. The residue was then appropriately purified. The yields of the purified materials are listed in Table I.

Acknowledgment. The authors wish to thank the Fordham Research Council, the Research Corporation, the National Institutes of Health (Grants No. CA12568 and AI12200), and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this work.

Registry No.—*p*-Anisyl chloride, 824-94-2; *p*-anisyl alcohol, 105-13-5; thionyl chloride, 7719-09-7; 1-octanol, 111-87-5; 2-octanol, 123-96-6; *l*-borneol, 464-45-9; cholesterol, 57-88-5; 2-phenoxyethanol, 122-99-6; 2,5-dimethyl-3-hexyne-2,5-diol, 142-30-3; benzyl alcohol, 100-51-6; 2,6-dichlorobenzyl alcohol, 15258-73-8; cyclododecanol, 1724-39-6; 1-octanol *p*-anisyl ether, 54384-75-7; 2-octanol *p*-anisyl ether, 54384-76-8; *l*-borneol *p*-anisyl ether, 54384-77-9; cholesterol *p*-anisyl ether, 33999-75-6; 2-phenoxyethanol *p*-anisyl ether, 54384-78-0; 2,5-dimethyl-3-hexyne-2,5-diol di-*p*-anisyl ether, 54384-79-1; benzyl alcohol *p*-anisyl ether, 3613-53-4; 2,6-dichlorobenzyl alcohol *p*-anisyl ether, 54384-80-4; cyclododecanol *p*-anisyl ether, 54384-81-5.

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Reactions of Molecular Bromine Chloride and Amine–Bromine Chloride Complexes with Cyclopentadiene

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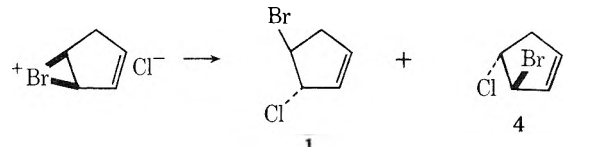
A survey of the literature reveals that there has been one study of the addition of bromine chloride to an allene,[1] and many investigations of the addition of this electrophile to olefins,[2a–e] but that no studies on the addition of bromine chloride to conjugated dienes have been undertaken. Earlier studies[2b–e] established that molecular bromine chloride adds to olefins via a bromonium ion–chloride ion ion pair, in which the rate-determining step involves formation of this ion pair. In the most recent investigation,[2a] Bellucci et al. compared the addition of bromine chloride with that of pyridine–bromine chloride complex, and concluded that the second, product-determining step is rate determining in the case of the complex.[3]

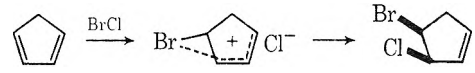
It seemed to us that it would be of interest to investigate the reaction of these halogenating agents with the conjugated diene cyclopentadiene. We chose cyclopentadiene because it offered the possibility of both cis and trans 1,2 and 1,4 addition, and because we had recently studied the additions of chlorine[4] and bromine[5] to this diene. In the present study we were particularly interested in comparing the addition of bromine chloride with amine–bromine chloride complexes, since if these reagents do involve different rate-determining steps they would likely produce a different mixture of stereoisomeric bromochlorocyclopentenes.

The possibility of anti-Markovnikov addition was also considered, since chloride ion could add to either of the carbons (bonded to bromine) as illustrated in the following reaction.



1 Markovnikov 4 anti-Markovnikov

Delocalization of the charge (resulting in unsymmetrical bridging, i.e., weaker bonding between carbon 3 and bromine) is probable here since a secondary carbonium ion would result.[6] Extensive delocalization should favor cis attack of chloride ion (as in the case of the chlorination of cyclopentadiene[4]) to give cis 1,2 addition as shown below.



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Results and Discussion

The addition of bromine chloride and amine–bromine chloride complexes to cyclopentadiene resulted in the formation of only three isomeric bromochlorocyclopentenes: *trans*-4-bromo-3-chlorocyclopentene (**1**), *trans*-3-bromo-5-chlorocyclopentene (**2**), and *cis*-3-bromo-5-chlorocyclopentene (**3**). The ratios and yields of these isomers formed under various conditions are shown in Table I.

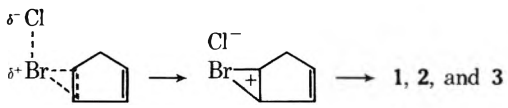
2 3

The data in Table I show that all of the amine–bromine chloride complexes react with cyclopentadiene to give very similar mixtures of bromochlorocyclopentenes, and that the product composition from the complexes is considerably different from that of bromine chloride. In particular, bromine chloride gives significantly more cis 1,4 addition

Table I
Addition of Bromine Chloride and Amine–Bromine Chloride Complexes to Cyclopentadiene

Halogenating agent	Solvent	Temp, °C	Bromochlorocyclopentenes 1	2	3	Yield, %
BrCl	C_5H_{12}	−15	34	18	48	78
BrCl	CH_2Cl_2	−15	22	15	63	68
BrCl	CCl_4	−15	25	12	63	76
			27	15	58	
Pyridine–BrCl	C_5H_{12}	−15	53	21	26	81
Pyridine–BrCl	CH_2Cl_2	−15	90	4	6	78
Pyridine–BrCl	CCl_4	−15	51	22	27	86
BrCl	CH_2Cl_2	25	25	15	60	64
Pyridine–BrCl	CH_2Cl_2	25	79	10	11	72
Quinoline–BrCl	CH_2Cl_2	25	63	16	21	83
3,5-Lutidine–BrCl	CH_2Cl_2	25	83	9	8	74
2,6-Lutidine–BrCl	CH_2Cl_2	25	73	13	14	108

(3), and the complexes give more trans 1,2 addition (1). In the case of bromine chloride the transition state (rate-determining step) leading to the ion pair can be described as follows.

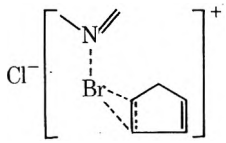


In proceeding from the transition state to the ion pair the chloride ion has been generated above the bromine atom. Collapse to product (apparently a rapid reaction) can occur with least reorientation of the ion pair by cis attack of the chloride ion on the 1 carbon atom to give 3 (cis 1,4 addition), since all that is required is that the chloride ion move over to the adjacent π lobe. Trans 1,4 addition (to give 2) would require the most extensive reorientation. The product ratios seem to reflect the energy requirements for reorientation of the ion pair.

In the case of the amine–bromine chloride complexes the structure of the electrophile is uncertain,[7] but we suspect that it is the $C_5H_5N^+Br$ ion (in the case of pyridine) whose formation is shown in the following reaction.

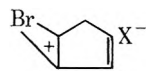
$$C_5H_5\overset{\delta+}{N}-Br\cdots\overset{\delta-}{Cl} \rightleftharpoons C_5H_5N^+-Br\ Cl^-$$

On the basis of the studies by Bellucci et al.[2a,8] and related studies of our own,[9] we suspect that the electrophile and cyclopentadiene react to form an ion pair in which bonding is maintained between the nitrogen and the halogen atom, as shown below.



In this ion pair the chloride ion will certainly not be formed above the plane of the cyclopentadiene ring (as occurred with BrCl) because of steric interaction with the ring of the amine and the adjacent π bond, but will be situated along the charged "side" of the cation (location of the anion will depend on the charge distribution). The unusually rapid attack at carbon 3 may occur because the chloride is situated close to this carbon in the ion pair and attack at this position requires least reorientation of the ion pair. On the other hand, the product-determining step may be rate determining (as suggested by Bellucci et al. for the cyclohexenes), and attack occurs at carbon 3 because the activation energy is lower for attack at this carbon than at carbons 4 or 1 (cis or trans). Our data simply do not allow us to choose between these alternatives.

It is also of interest to compare the additions of bromine chloride and bromine[5] to cyclopentadiene, since both of these additions involve identical bromonium ions in the intermediate ion pairs, as shown below



where X^- is Cl^- from bromine chloride, and Br^- (undoubtedly Br_3^- also, depending on conditions) in bromination. A summary of the previous study on bromination (averaging the percentages in the three solvents) is: *trans*-3,4-dibromocyclopentene (38%); *trans*-3,5-dibromocyclopentene (25%); and *cis*-3,5-dibromocyclopentene (37%). In comparison with bromine chloride addition (an average of the results), bromination gives approximately 20% less cis 1,4 addition, and 10% more trans 1,2 and 10% more trans 1,4 addition. We interpret these differences in the following manner. The large bromide ion (or larger tribromide ion) experiences steric hindrance (interaction with the nonbonded electrons of the bromine in the bromonium ion) as it approaches the 3 carbon atom, leading to cis 1,4 addition.[10] This type of interference is not experienced during attack at the 1 carbon (trans) or at the 3 carbon (trans). On the other hand, the chloride ion, being considerably smaller, experiences no steric hindrance during attack at any of the three positions.

The principal difference that surfaces in a comparison of the additions of bromine chloride and chlorine to cyclopentadiene relates to the fact that chlorination gives (averaging the results from the three solvents) extensive cis 1,2 addition (55%). Absence of cis attack[11] by the chloride ion (from bromine chloride) at the 3 carbon to give 5 can result from either steric hindrance between the bromine atom (in the bromonium ion) and the incoming chloride ion, or from sufficiently high electron density between the bromine and the 3 carbon atom to discourage attack at this position. From our experience with the bromination of the 2,4-hexadienes[5,12] we would anticipate extensive delocalization of charge in the bromonium ion of cyclopentadiene. Therefore we conclude that steric hindrance between the bromine atom and chloride ion is probably the primary factor involved in the failure of the chloride ion to undergo cis 1,2 attack.

No anti-Markovnikov product was observed.[11] Absence of this product implies that attack at the allylic carbon and the vinyl carbon is much faster than at the secondary 4 carbon, both in the cases of bromine chloride and the amine–bromine chloride complexes. This result is somewhat surprising inasmuch as carbons 3 and 4 are both secondary.[13]

Experimental Section

Materials. All solvents and reagents were obtained commercially in high purity, and were used without further purification unless indicated. Cyclopentadiene was prepared from its dimer. The amine–bromine chloride complexes were prepared according to the procedure of Williams.[14] Bromine chloride was prepared by adding an equimolar amount of bromine to a chlorine–carbon tetrachloride solution (0.5–1.0 *M*).

Reaction Conditions. The electrophiles were added to cyclopentadiene (mole fraction of 0.02 in diene) in the appropriate solvent (well stirred) and at the indicated temperature. The total reaction volumes varied from 10 to 25 ml. Sufficient halogen was added to consume 10–20% of the diene, and yields were based on the amount of halogen used. Each reaction was run at least twice and results were within ±2%.

The amine–bromine chlorides were insoluble in carbon tetrachloride or pentane and reacted slowly (approximately 1 hr to react at −15°). Reactions of the amine–bromine chlorides in dichloromethane and bromine chloride in all solvents occurred instantly.

Isolation of the Isomers. *trans*-4-Bromo-3-chlorocyclopentene (1) was isolated by fractional distillation, bp 50–55° (4 mm), from a large-scale addition of pyridine–bromine chloride[15] to cyclopentadiene. It was further purified by recrystallization from low-boiling petroleum ether at −70°.

cis-3-Bromo-5-chlorocyclopentene (3) was obtained by successive recrystallizations (−70°, low-boiling petroleum ether) of the product from the addition of pyridine–bromine chloride to cyclopentadiene in carbon tetrachloride. Separation of the cis isomer from the other isomers is possible, since the cis isomer has a higher melting point.

All attempts to isolate pure *trans*-3-bromo-5-chlorocyclopentene (2) failed.

Establishment of the Structures of the Isomers. Gas chromatographic analyses of the products from the addition of bromine chloride and the amine–bromine chlorides to cyclopentadiene showed only three peaks (other than dichlorides and dibromides)

under all analysis conditions (various column packings and temperatures). The three peaks had retention times of 4.4, 5.4, and 8.1 min under the following conditions: 6 ft × 0.25 in. column packed with 2.5% SE-30 on 60–80 mesh Chromosorb W (AW-DMCS) at 50° at a flow rate of 55 ml/min (N_2).

The compounds responsible for peaks 1 and 3 were assigned the structures of **1** and **3** primarily on the basis of NMR analyses of the pure isomers. The spectra assigned to **1** and **3** closely resembled those of the corresponding cyclopentadiene dibromides[5] and dichlorides.[4] Thus, the compound assigned structure **1** exhibited two absorptions assignable to methine hydrogens, a doublet (5.5 Hz) at 4.48 ppm (adjacent to methylene) and a broad singlet at 5.06 ppm (adjacent to vinyl). Absorptions for the methylene hydrogens also occur separately, a doublet at 2.76 ppm and a doublet of doublets at 3.35 ppm. The absorptions centered at 2.76 and 3.35 ppm each exhibit the geminal coupling at 18 Hz with the additional splitting of 5.5 Hz occurring in the 3.35-ppm absorption. The compound assigned structure **3** was identified particularly by absorptions of its methylene hydrogens. A pair of well-separated double triplets (2.57 and 3.14 ppm) was observed. The double triplet at 2.57 showed a small coupling (2.5 Hz) and that at 3.14 a larger coupling (6.6 Hz) consistent with their trans and cis vicinal relationship to the methine hydrogens, respectively (both double triplets show the geminal coupling of 16 Hz). The methine hydrogens have nearly the same chemical shift in **3** and appear as an unresolved multiplet. The 60-MHz spectral data (CCl_4) for **1** and **3** are summarized as follows: **1**, δ 2.76 [br d, 1, *cis*-C(Br)C(**H**)H, $J_{5,5'}$ = 18 Hz], 3.35 (dd, 1, *trans*-C(Br)C(**H**)H, $J_{5,5'}$ = 18, $J_{4,5}$ = 5.5 Hz], 4.48 [d, 1, $CH_2C(\mathbf{H})Br$, $J_{4,5}$ = 5.5 Hz], 5.06 [br s, 1, CH=CHC(H)Cl], 5.99 [br s, 2, CH=CH); **3**, δ 2.57 [dt, 1, *cis*-C(Cl,Br)C(**H**)H, $J_{4',4}$ = 16, $J_{4',3(5)}$ = 2.5 Hz], 3.14 [dt, 1, *trans*-C(Cl,Br)C(**H**)H, $J_{4,4'}$ = 16, $J_{4,3(5)}$ = 6.6 Hz], 4.92 (m, 2, CHBr and CHCl), 6.06 (m, 2, CH=CH)

The compound responsible for peak 2 was assigned the structure *trans*-3-bromo-5-chlorocyclopentene (**2**) on the basis of the following information. NMR analysis: Although a pure sample of **2** was not obtained, an NMR spectrum was prepared of a mixture of **2** (30%) and **1**, which indicated absorptions at 2.8, 5.0, and 6.0 ppm. These absorptions are consistent with the spectrum expected for **2** on the basis of that observed for the corresponding dibromide[5] and dichloride.[4] In particular, the spectrum in the methylene region showed absorptions clustered near 2.8 ppm which would be consistent with the near chemical shift equivalency expected for the methylene hydrogens. Unambiguous synthesis: We have shown previously[4] that *cis*-3,5-dichlorocyclopentene and *trans*-3,5-dichlorocyclopentene can be prepared from the corresponding dibromides by treatment with lithium chloride in DMSO. Therefore, when *trans*-3,5-dibromocyclopentene was treated with a *limited* (equimolar) amount of lithium chloride, VPC analysis showed that **3** was the only isomeric bromochlorocyclopentene that was formed. (*cis*-3,5-Dichlorocyclopentene and unreacted dibromide were also present.) Correspondingly, treatment of *cis*-3,5-dibromocyclopentene with limited lithium chloride gave a compound which had an identical retention time with that of **2**. (The expected dichloride and dibromide mixture was also formed.) By analogy to the reaction of the trans dibromide, we conclude that *trans*-3-bromo-5-chlorocyclopentene (**2**) is formed in the reaction of the cis dibromide. Formation upon rearrangement of **1** and **3**: When authentic **1** and **3** were refluxed in ether, containing a catalytic amount of zinc bromide, the compound assigned structure **2** was formed in largest amounts (percentages): **1** (15), **2** (46), and **3** (38). Previous experience with the equilibration of the dibromides from cyclopentadiene and 1,3-cyclohexadiene suggests that **2** should be the thermodynamically stable isomer, since in our previous studies the trans 1,4-dibromides were more stable.

Stability of the Products to Reaction and Analysis Conditions. When the amine–bromine chlorides react with cyclopentadiene, pyridine is formed. It seemed possible that pyridine might react with the bromochlorocyclopentenes and thus distort the composition of the product. We established that this did not occur by stirring a mixture of **1**, **2**, and **3** (of known composition) with pyridine under reaction conditions and observing that no change in composition or material balance occurred.

We made this assumption that rearrangement of the isomers did not occur during VPC analysis of the bromochlorocyclopentenes, since we previously confirmed that rearrangement did not occur under identical conditions with many similar systems (dibromides and dichlorides of butadiene, isoprene, piperylene, isomer 2,4-hexadienes, and cyclopentadiene).

Acknowledgment. Support for this work was provided by the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Atlantic Richfield Foundation.

Registry No.—**1**, 54384-85-9; **2**, 54384-86-0; **3**, 54384-87-1; BrCl, 13863-41-7; pyridine–BrCl, 21300-57-2; quinoline–BrCl, 54384-82-6; 3,5-lutidine–BrCl, 24068-43-7; 2,6-lutidine–BrCl, 24068-41-5; cyclopentadiene, 542-92-7.

References and Notes

(1) H. G. Peer, *Recl. Trav. Chim. Pays-Bas*, **81**, 113 (1962).
(2) (a) G. Bellucci, G. Ingrosso, F. Marioni, E. Mastrorilli, and I. Morelli, *J. Org. Chem.*, **39**, 2562 (1974); (b) H. J. Hageman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 1141 (1966); (c) R. E. Buckles, J. L. Forrester, R. L. Burham, and T. W. McGee, *J. Org. Chem.*, **25**, 24 (1960); (d) P. B. D. De La Mare and S. Galandauer, *J. Chem. Soc.*, **36** (1958); (e) E. P. White and P. W. Robertson, ibid., 1509 (1939).
(3) Bellucci and coworkers have suggested that the rate-determining step for other amine–halogen complexes (e.g., $C_5H_5NBr_2$) is also the product-forming step. See P. Barili, G. Bellucci, F. Marioni, I. Morelli, and V. Scartoni, *J. Org. Chem.*, **37**, 4354 (1972).
(4) V. L. Heasley, G. E. Heasley, P. D. Davis, D. M. Ingle, and K. D. Rold, *J. Org. Chem.*, **39**, 736 (1974).
(5) G. E. Heasley, V. L. Heasley, S. L. Manatt, H. A. Day, R. V. Hodges, P. A. Kroon, R. A. Redfield, T. L. Rold, and D. E. Williamson, *J. Org. Chem.*, **38**, 4109 (1973).
(6) We found that there was sufficient delocalization of charge in the intermediate bromonium ions in the case of the 2,4-hexadienes to give a nonstereospecific addition, but not with piperylene, since delocalization in the former involves formation of a secondary carbonium ion, whereas the latter would involve a primary carbonium ion.
(7) X-Ray defraction studies on pyridine–iodine chloride show that the N–I–Cl bonding system is linear with the N–I bond being nearly a typical covalent bond and the N–Cl bond being much longer than anticipated for a covalent bond, suggesting that charges have developed as shown below.

$$C_5H_5N\overset{\delta+}{\text{—}}I\cdots\overset{\delta-}{Cl}$$

For a detailed discussion of the bonding in these charge-transfer complexes see O. Hassel and C. Romming, *Q. Rev., Chem. Soc.*, **16**, 1 (1962). The following ionization of pyridine (py) bromine chloride in polar solvents has been confirmed: $2pyBrCl \rightleftharpoons py_2Br^+ BrCl_2^-$. See S. G. W. Ginn, I. Haque, and J. L. Wood, *Spectrochim. Acta, Part A*, **24**, 1531 (1968). Conceivably the electrophile is the py_2Br^+ ion. Also the undissociated charge-transfer complex may be sufficiently electrophilic to attack the π bond.
(8) This type of bonding in the ion pair is suggested by Bellucci and coworkers[2a] in the case of the substituted cyclohexenes. We see no reason to expect different behavior on the part of the electrophile with cyclopentadiene.
(9) In a recent study of ours on the reaction of olefins with Br_2, NBS, and NBA in a mixture of CH_3OH and DMSO, we found that the greater nucleophilicity (toward opening of the bromonium ion) of DMSO became apparent with the N–Br systems. We interpreted these results as meaning that with NBS and NBA there is bonding between nitrogen and bromine in the bromonium ions, and that the stronger nucleophile DMSO is more effective in this energy-demanding (rate-determining) step than is CH_3OH. See V. L. Heasley, G. T. Heasley, R. A. Skidgel, and D. Strickland, *J. Org. Chem.*, 39, 3953 (1974).
(10) We have already suggested that steric hindrance between the bromide ion and the bromine atom of the bromonium ion accounts for the fact that there is less cis 1,4 addition with cyclopentadiene than 1,3-cyclohexadiene.[5]
(11) Neither products **4** or **5** were detected in the VPC or NMR analyses. It is possible that one or both of these compounds were present in small amounts and not detected. Unambiguous syntheses would provide the only method of unequivocally confirming their absence.
(12) In the case of the isomeric 2,4-hexadienes, the 1,2 addition was nonstereospecific.[5] On the basis of this observation we concluded that the bond between bromine and the adjacent allylic carbon (in the bromium ion) was sufficiently weak (resulting from delocalization of charge) to permit rotation around this C–C bond. Since delocalization can occur in cyclopentadiene to give a secondary carbonium ion, as with the 2,4-hexadienes, we conclude that there is unsymmetrical bridging in the bromonium ion of cyclopentadiene.
(13) Dalton and Davis observed only the Markovnikov product in the addition of BrOH (NBS in DMSO and H_2O) to the 2,4-hexadienes. Also they did not observe any 1,4 addition and concluded that the charge was localized on the allylic carbon, with weak bonding to bromine. See D. R. Dalton and R. M. Davis, *Tetrahedron Lett.*, 1057 (1972). Since all our solvents are far less polar we would anticipate much greater delocalization of charge with our system and, hence, greater equalization of reactivities at the two secondary carbons, 3 and 4.
(14) D. M. Williams, *J. Chem. Soc.*, 2783 (1931).
(15) **1** was isolated from the addition of pyridine–bromine chloride rather than from bromine chloride because the product from the former was not contaminated with dibromides.

Sodium Borohydride Reduction of 5α,6β-Dibromocholestan-3-one. A Simple Method for the Preparation of *epi*-Cholesterol

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Usually, the sodium borohydride reduction of 3-keto steroids produces mainly the 3β-hydroxy isomer,[1] since hydride transfer to the carbonyl group proceeds preferentially from the less hindered side of the molecule, i.e., from the α side. Thus, reduction of cholestan-3-one in ethanol yields 89% cholestan-3β-ol and 5% cholestan-3α-ol,[2] and reduction of cholest-5-en-3-one in 2-propanol yields 83% cholesterol and 17% *epi*-cholesterol.[3] However, the presence of a substituent in the 5α position of the cholestane skeleton changes the stereochemical course of the reduction. For example, reduction of 5α-hydroxycholestan-3-one in methanol gives 67% 3α,5α-dihydroxycholestane and 33% 3β,5α-dihydroxycholestane.[4] Reduction of 5α,6α-dichlorocholestan-3-one in ether yields 56% of the corresponding 3α-hydroxy isomer and 44% of the 3β isomer.[5] It seems, therefore, that introduction of a large substituent in the 5α position of cholesterol could have been used as a tool for its isomerization to *epi*-cholesterol by, first, oxidation to the corresponding ketone, then sodium borohydride reduction, and finally removal of the 5α substituent.

For this purpose, 5α,6β-dibromocholestan-3β-ol seemed to be the most suitable substrate, since it is easily and quantitatively obtained from cholesterol,[6] it is oxidized smoothly to the ketone,[6] and the two bromine atoms can be easily removed by various methods. In addition, the steric effect of the 6β-bromo group on the reduction should be much smaller than that of the 5α-bromo group, since the latter is closer to the reaction center.

Reduction of 5α,6β-dibromocholestan-3-one (1) was studied both in ethanol and in 1,2-dimethoxyethane, and the results are given in Table I. In the two solvents treatment with a large excess of sodium borohydride affects both reduction of the carbonyl group and reductive elimination of the two bromine substituents, so that the two major products of the reaction are *epi*-cholesterol and cholesterol. Reaction pathways through which *epi*-cholesterol and cholesterol can be formed in the reduction of 1 are presented in the scheme. As the results in ethanol differ from those in 1,2-dimethoxyethane, we shall separate the discussion for each solvent. In ethanol, the relative amounts of

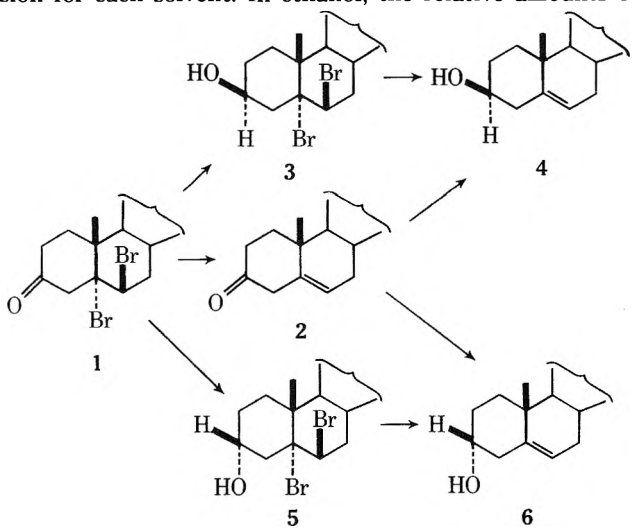
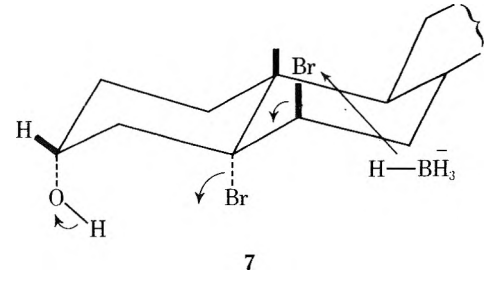


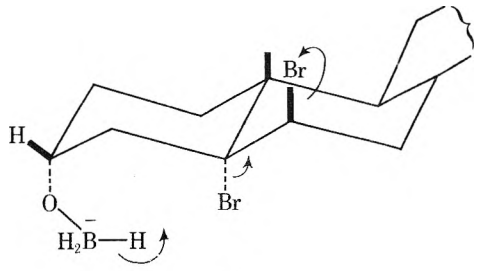
Table I
Reduction of 5α,6β-Dibromocholestan-3-one with a Large Excess of Sodium Borohydride

Solvent	Yield of *epi*-cholesterol, %	Yield of cholesterol, %
Ethanol	57	25
1,2-Dimethoxyethane	22	66

cholesterol (4) and *epi*-cholesterol (6) do not reflect the stereochemistry of the reduction of the carbonyl group in 1, since reductive elimination of the 5α,6β-dibromo grouping may proceed[7] parallel to the reduction of the carbonyl group. Indeed, the formation of cholesterol does not proceed via route 1 → 3 → 4, since 5α,6β-dibromocholestan-3β-ol (3) itself does not react with sodium borohydride under the same conditions in which ketone 1 is smoothly reduced to cholesterol and *epi*-cholesterol. Moreover, 3 could not be detected in the reaction mixture. Therefore, cholesterol is probably formed via route 1 → 2 → 4 in which reductive elimination takes place first to give cholest-5-en-3-one (2), which then undergoes further carbonyl reduction to cholesterol. In a careful examination of the reaction of 1 with 1 equiv of sodium borohydride, we could not detect any of 2. In this compound, the carbonyl group is less hindered and it is probably reduced much faster than any of the other compounds present in the reaction mixture. We observed also that with small amounts of sodium borohydride, because the overall reduction rate is low, several side reactions of 1 take place, such as hydrogen bromide elimination and substitution. No attempt was made to investigate these reactions in more detail.

In ethanol the yield of cholesterol is smaller than that of *epi*-cholesterol. This indicates that in 1 reductive elimination is slower than reduction of the carbonyl group. Moreover, route 1 → 2 → 6 cannot account for the formation of *epi*-cholesterol, since 2 is reduced mainly to the 3β-hydroxy isomer.[3] Therefore, *epi*-cholesterol is probably formed via route 1 → 5 → 6 in which the carbonyl group of 1 is first reduced to give 5α,6β-dibromocholestan-3α-ol (5), which then undergoes reductive elimination to give 6. When 1 was treated with 1 equiv of sodium borohydride, we were able to detect by TLC one major intermediate which was converted to *epi*-cholesterol on further addition of sodium borohydride. Several attempts to isolate this intermediate failed since it decomposed during work-up. It is interesting to note that the same intermediate is detected by TLC in the bromination of *epi*-cholesterol, but here again no dibromide could be isolated. Therefore, although there is no direct evidence for the formation of 5, we believe that this must be the intermediate through which *epi*-cholesterol is formed in the reduction of 1. These results suggest that 5 is capable of undergoing a faster reductive elimination than 3. The reason for this behavior is not yet clear. It is, however, possible that the 3α-hydroxy group of 5 catalyzes the reaction by neighboring group participation either by hydrogen bonding with the 5α bromine as in 7, or by complex formation with reducing agent as in 8. Another





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possibility is that steric interaction of the 3α,5α groups in **5** raises the energy of its ground state and is therefore responsible for the faster reductive elimination.

The reduction of 1 in ethanol is undoubtedly a very useful method for the preparation of *epi*-cholesterol. Several other more complicated procedures have been described in the literature[8] but none which gives a higher yield of *epi*-cholesterol. The method could also be used for the isomerization of other compounds having similar structure. For example, we propose the transformation of 3β,17β-dihydroxyandrost-5-ene into 3α,17β-dihydroxyandrost-5-ene.

In 1,2-dimethoxyethane the yield of cholesterol is much higher than that of *epi*-cholesterol. The effect of the solvent on the stereochemistry of the sodium borohydride reduction of 3-keto steroids is small.[2] Indeed, we find that reduction of 5α,6β-dichlorocholestan-3-one in ethanol yields the two isomers of 3-hydroxy-5α,6β-dichlorocholestane in the same ratio that is obtained in 1,2-dimethoxyethane.[9]

Therefore, we believe that in 1,2-dimethoxyethane, reductive elimination in 1 is faster than the reduction of the carbonyl group and this is the reason why a larger amount of cholesterol is formed. This suggestion is supported by the observation that 5α,6β-dibromocholestan-3β-ol itself undergoes smooth reductive elimination in 1,2-dimethoxyethane.

Experimental Section

All melting points were determined with a Fisher-Johns apparatus. Optical rotations were taken for solutions in chloroform with a Perkin-Elmer Model 141 polarimeter. Both qualitative and preparative TLC was carried out on silica gel G plates eluted with light petroleum (bp 60–80°) containing 10% acetone. 5α,6β-Dibromocholestan-3β-ol and 5α,6β-dibromocholestan-3-one were prepared according to the method of Fieser et al.[6] The dibromo ketone was dried in vacuo over sodium hydroxide. Absolute ethanol (Riedel-DeHaen) was used. 1,2-Dimethoxyethane (B. D. H.) was eluted through a column of alumina and then distilled from sodium.

Sodium Borohydride Reduction of 5α,6β-Dibromocholestan-3-one. In Ethanol. A suspension of the dibromo ketone (1.00 g) in absolute ethanol (100 ml) was treated with a large excess of sodium borohydride (0.50 g), and the mixture was stirred at room temperature for 3 hr. During this period hydrogen was evolved and all the material dissolved. Acetic acid was added to destroy the excess of sodium borohydride and after dilution with water the product was extracted with ether. The solution was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was separated by TLC to give pure *epi*-cholesterol (410 mg, 57%), mp 141–142° (from ethanol), $[\alpha]_D$ −41° (*c* 0.25) (lit.[8] mp 142–143°, $[\alpha]_D$ −42°). The material is identical with authentic *epi*-cholesterol by mixture melting point, ir, and TLC. Also isolated was pure cholesterol (180 mg, 25%), mp 148–149° (from ethanol), $[\alpha]_D$ −39° (*c* 0.50), identical with an authentic sample by mixture melting point, ir, and TLC.

In 1,2-Dimethoxyethane. The dibromo ketone (1.00 g) in 1,2-dimethoxyethane (100 ml) was treated with sodium borohydride (0.50 g), and the solution was stirred at room temperature for 6 hr. During this period hydrogen was evolved and a precipitate of sodium bromide was separated. Acetic acid was added to destroy the excess of sodium borohydride. The solution was evaporated under reduced pressure to a volume of 20 ml, then diluted with water and work-up was continued as above. Separation by TLC gave pure *epi*-cholesterol (158 mg, 22%) and pure cholesterol (475 mg, 66%). Both products were shown to be identical with authentic samples by mixture melting point, ir, and TLC.

Treatment of 5α,6β-Dibromocholestan-3β-ol with Sodium Borohydride. In Ethanol. The dibromide (1.00 g, mp 115–116° from methanol–ethyl acetate) in ethanol (100 ml) and ether (20 ml) was treated with sodium borohydride (0.50 g) and the solution was stirred at room temperature for 3 hr. TLC indicated no change. Work-up as above and recrystallization from methanol–ethyl acetate gave 890 mg of the starting material, mp 116–117°, and no depression on mixture melting point. When the reaction was carried out under the same conditions for 24 hr, a small amount of cholesterol could be detected by TLC, together with small amounts of other unidentified products.

In 1,2-Dimethoxyethane. The dibromide (0.50 g) in 1,2-dimethoxyethane (50 ml) was treated with sodium borohydride (0.25 g) and the solution was stirred at room temperature for 6 hr. During this period hydrogen was evolved and a precipitate of sodium bromide was separated. TLC indicated a clean reaction, with one product having the same R_f as cholesterol. Work-up as above and recrystallization from ethanol afforded pure cholesterol (300 mg, 83%), mp 149°, $[\alpha]_D$ −39°, ir identical with that of authentic sample.

Registry No.—**1**, 2515-09-5; **3**, 1857-80-3; **4**, 57-88-5; **6**, 474-77-1; sodium borohydride, 16940-66-2.

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Reduction of Organomercurials by Sodium Dithionite[1]

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The reduction of alkyl and aryl mercurials by various reducing agents such as magnesium,[2] sodium stannite,[3] metal hydrides,[4] and hydrazine[5] is well known. The types of reduction products are illustrated by the following equation.

$$\text{R-Hg-X} \xrightarrow{(H)} \underset{\mathbf{1}}{\text{R-H}} \text{ or } \underset{\mathbf{2}}{\text{R-Hg-R}} \text{ and Hg(0)}$$

The "symmetrization" product, **2**, is produced most often upon reduction with magnesium, sodium stannite, or hydrazine while product **1** is produced by reaction with metal hydrides.

Dithionites are powerful reducing agents as indicated by the couples below.

$$HS_2O_4^- + 2H_2O \longrightarrow 2H_2SO_3 + H^+ + 2e \quad E^\circ_{298} = 0.23 \text{ V}$$

$$S_2O_4^{2-} + 4OH^- \longrightarrow 2SO_3 + 2H_2O + 2e \quad E^\circ_{298} = 1.4 \text{ V}$$

Oxidants such as silver ion, iodine, iodate, permanganate, cupric ion, hydrogen peroxide, nitrous acid, molecular oxygen, and organic dyes are all reduced.[6]

We have studied the reaction products and stoichiometry in the reduction of *p*-chloromercuribenzoic acid (PMB) by sodium dithionite in aqueous ethanol. The stereochemical course of the reaction was investigated in the reduction of *exo-cis*-3-hydroxy-2-norbornylmercuric chloride according to the method of Traylor and Baker.[7]

Experimental Section

Reduction of *p*-Chloromercuribenzoic Acid. Sodium dithionite (0.3 g, 1.7×10^{-3} mol) was added to a suspension of *p*-chloromercuribenzoic acid[8] (0.43 g, 1.2×10^{-3} mol) in absolute ethanol under a nitrogen atmosphere, after which the mixture was vigorously stirred for 2 hr and then refluxed gently for 1 hr. The mixture was filtered to remove elemental mercury, the pH was adjusted to pH 7, and the filtrate was concentrated to one-third of the original volume. The filtrate was acidified to pH 4 with dilute HCl. The white precipitate which formed was identified as bis(*p*-carboxyphenyl)mercury, 0.27 g (99.5%), mp >300°. The product was identified by determination of its equivalent weight through titration with standard sodium hydroxide solution as 222 ± 8 (expected value 220), and through identity of its infrared spectrum with that of bis(*p*-carboxyphenyl)mercury prepared[9] by symmetrization of *p*-chloromercuribenzoic acid with sodium stannite. The pK_a values as determined from the titration curve were 3.0 ± 0.2 for pK_1 and 6.4 ± 0.1 for pK_2. Yield of the elemental mercury in several experiments was 46–48% of the mercury contained in the starting material.

Attempts to reduce bis(*p*-carboxyphenyl)mercury with sodium dithionite under the conditions described for the reduction of *p*-chloromercuribenzoic acid were unsuccessful and resulted in recovery of 98% of the starting material. When the reduction of *p*-chloromercuribenzoic acid was carried out in the presence of styrene, no polymerization of the styrene was observed, which indicated an absence of free-radical intermediates.

Reduction of *exo-cis*-3-Hydroxy-2-norbornylmercuric Chloride. To 2.4647 g (0.007 mol) of exo-cis-3-hydroxy-2-norbornylmercuric chloride (prepared according to Traylor and Baker[7]) dissolved in 50 ml of absolute ethanol was added 2.44 g (0.014 mol) of sodium dithionite. The reaction was allowed to proceed at ambient temperature in a covered beaker equipped with a magnetic stirrer. The solution gradually turned from clear to gray. The mixture was stirred for 24 hr and then it was refluxed gently for 30 min to decompose the excess dithionite. The metallic mercury which formed was filtered out along with inorganic salts not soluble in ethanol. Evaporation of the filtrate yielded 1.49 g (100%) of a white powder, di-*cis*-*exo*-3-hydroxy-2-norbornylmercury, mp 150–153° dec (lit.[7] mp 152–152.5°). Recrystallization from ether raised the melting point to 152–153°. The infrared spectrum of a CCl_4 solution of the product showed a sharp peak at 3601 cm^{-1} indicative of a cis-exo geometry.[7] The product was quantitatively cleaved back to the pure starting material by the action of $HgCl_2$, a procedure known[7] not to alter the stereochemistry, thus confirming the cis-exo geometry.

Results

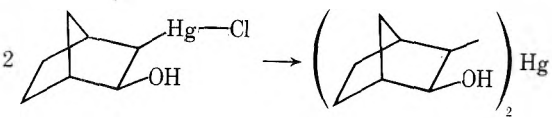
It was found that sodium dithionite is capable of effecting the quantitative reduction of both alkyl and aryl organomercurials, with the notable exception of bis(*p*-carboxyphenyl)mercury. The product of reduction is the symmetrization product of the ligand which is bonded through carbon to mercury.

The stoichiometry of the reduction process was found to be

$$2\text{R-Hg-X} + \text{Na}_2\text{S}_2\text{O}_4 \longrightarrow \text{R-Hg-R} + \text{Hg(0)} + 2\text{NaCl} + 2\text{SO}_2$$

as determined by quantitative determinations of the amount of R–Hg–R and metallic mercury produced, the observation that the dithionite sulfur is converted to sulfur dioxide (or sulfite), and the ability to obtain quantitative conversion of starting material to product with less than a 1:1 ratio of dithionite to oxidant (when O_2 is eliminated from the system). NaCl formation is observed even in nonaqueous systems not treated with HCl; therefore, it is formed as a product of the reaction. Its stoichiometry and that of SO_2 are assigned to fit the observed stoichiometry of the other reagents and were not directly determined.

The reduction is found to conserve the geometry about the carbon bonded to mercury as determined by the results of the reduction of the 3-hydroxy-2-norbornylmercuric chloride system



which was found to proceed with 100% retention of configuration at both carbons as determined by the method of Traylor and Baker.[7]

When the reduction by dithionite was carried out in the presence of styrene, the styrene remained unchanged, indicative of a nonradical mechanism. Further, the reaction proceeded in the presence of molecular oxygen (although a considerable amount of the reductant was lost by reaction with oxygen, accounting for the observed decrease in the amount of dithionite needed to effect reduction in the absence of oxygen).

Discussion

The reduction of organomercurials by sodium dithionite can best be interpreted as proceeding via a two-electron reduction scheme. Two known cases believed to involve two-electron reductions of organomercurials are symmetrization by magnesium metal and symmetrization by the action of hydrazine. In both cases the following mechanism has been proposed.[10]

$$\text{RHgX} + 2e \longrightarrow \text{RHg}^- + \text{X}^- \quad (1)$$

$$\text{RHg}^- + \text{RHgX} \longrightarrow \text{RHgHgR} + \text{X}^- \quad (2)$$

$$\text{RHgHgR} \longrightarrow \text{R—Hg}^-\text{—R} \longrightarrow \text{RHgR} + \text{Hg(0)} \quad (3)$$

$$\text{Hg}^+$$

The ease of reduction of R–Hg–X when X is halogen and the absence of reaction when X is *p*-carboxyphenyl suggest that the transition state of the rate-determining step of the reaction involves breaking the Hg–X bond. Apparently the reduction proceeds readily only when X can produce a stable anion.

The stereochemical result is consistent with the two-electron mechanism, since reduction by dithionite is found to proceed with 100% retention of configuration. This result does not completely rule out a radical mechanism, however, since the reduction of the same stereoisomer used herein with sodium borohydride has been shown to proceed with greater than 95% retention[11] even though the mechanism is believed to proceed via free radicals.[12]

Registry No.—PMB, 59-85-8; BCM, 2013-22-1; $Na_2S_2O_4$, 7775-14-6.

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Hydrogenation and Carbonylation of Organomercury Compounds Catalyzed by Group 8 Metal Complexes

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Replacement of mercury by hydrogen in organomercurials has traditionally been accomplished by cleavage with mineral acids[2] or by reduction with a chemical reducing agent[3]. Cleavage of the carbon–mercury bond by molecular hydrogen has not been described with the single exception of diphenylmercury, which gave benzene and mercury at 750 psig and 175–200°; catalysis by noble metals had no impact on the resistance of organomercurials to hydrogenation.[4]

The selective functionalization of hydrocarbons via their organomercury salts has been explored in these laboratories. As part of this program the reaction of arylmercurials with hydrogen was studied to determine if such a reduction could be induced. Control experiments with phenylmercury acetate in methanol failed to occur at room temperature at hydrogen pressures up to 50 psig for reaction periods up to 3 days.[5] The addition of Pt/C and Pd/C as catalysts did not promote hydrogenation, and the formation of benzene and mercury was not observed.[7]

The inability of supported catalysts to hydrogenate phenylmercury acetate was attributed to improper substrate–catalyst interactions and/or catalyst poisoning by mercury released by reduction of a fraction of the mercurial. Homogeneous hydrogenation catalysts afforded the prospect of resolving this dilemma, for both of these complications would be avoided. Hydrogenation of phenylmercury acetate proceeded smoothly over tris(triphenylphosphine)rhodium(I) chloride[8] to give an 85% yield of benzene and an 82% yield of mercury (eq 1). The triphenylphos-

$$C_6H_5HgOAc + H_2 \xrightarrow[30\text{–}50\ psig,\ 25^\circ]{[(C_6H_5)_3P]_3RhCl} C_6H_6 + Hg + HOAc \quad (1)$$

mole ratio Hg/Rh = 178:1

phine complexes of ruthenium,[9] platinum,[10] and palladium[10] also catalyzed this reaction, although the yields (15–25%) were depressed relative to rhodium. Hydrogenation over the rhodium catalyst was relatively insensitive to the mercury anion and the solvent; limited data indicate that ring substituents will exert some influence, but this feature has not been broadly explored. Table I summarizes some typical results. Optimum yields were provided by acetate and trifluoroacetate, a fact which complements the facile mercuration of aromatics by these mercury(II) salts.[11] The reduction of di(acetoxymercuri)benzene illustrated that this reaction was applicable to polymercurated substrates. The mercuration–hydromercuration sequence may permit the use of mercury as a blocking agent in organic synthesis, since the carbon–mercury bond can be cleaved under mild conditions with reagents that do not normally alter other functional groups.

Table I
Hydrogenation of Arylmercury Salts

$$YC_6H_4HgX \xrightarrow[solvent]{H_2,\ Rh\ catalyst} YC_6H_5 + Hg + HX$$

Registry no.	X	Y	Solvent	Yield of YC_6H_5[a]
62-38-4	OAc	H	CH_3OH	85
100-56-1	Cl	H	CH_3OH	73
332-11-6	$OOCCF_3$	H	CH_3OH	98
55-68-5	NO_3	H	CH_3COOH	40
	OAc	H	CH_2Cl_2	70
54446-55-8	Br	CH_3	$C_2H_5OOCCH_3$	80
34012-18-5	OAc	HgOAc	CH_3OH	61 (Y = H)
54446-56-9	OAc	COOH	CH_3OH	20

[a] Based on arylmercury salt.

The mechanism of this reduction has not been studied, but oxidative addition of the mercury salt to the rhodium complex followed by hydrogen insertion into the carbon–rhodium bond appears reasonable (eq 2).[12] Oxidative addi-

$$L_2RhCl + C_6H_5HgOAc \longrightarrow \underset{\mathbf{I}}{\text{L, Cl, Rh, L, } C_6H_5\text{, HgOAc}} \xrightarrow{H_2} L_2RhCl + C_6H_6 + Hg + HOAc \quad (2)$$

L = $(C_6H_5)_3P$

tion analogous to eq 2 to yield a bimetallic complex comparable to I has been briefly described.[13] In this work a stable compound has been isolated from the reaction of phenylmercury acetate and tris(triphenylphosphine)rhodium(I) chloride; elemental analysis and spectral properties were consistent with formula I. Reaction of I with hydrogen gave benzene and mercury.

The rhodium–mercury bimetallic complex (I) was tested for carbonylation activity. The hydroformylation of 1-hexene gave a 98% yield of C_7 aldehydes in which the normal/branched ratio was 70:30. The isomer distribution was nearly identical with that produced by bis(triphenylphosphine)rhodium(I) carbonyl chloride,[14] indicating the formation of this rhodium complex from I under reaction conditions. Complex I was inactive for the carbonylation of methanol to acetic acid.[15] Analysis of the recovered methanol by gas chromatography revealed the trace presence of a material with retention time different from that of methanol or acetic acid. Stripping the methanol provided no isolable product, but the flask possessed an odor characteristic of methyl benzoate, suggesting that carbonylation of the rhodium–carbon bond present in the bimetallic catalyst (I) had occurred to yield a tiny quantity of this ester. Carbonylation of phenylmercury acetate in methanol catalyzed by tris(triphenylphosphine)rhodium(I) chloride (mole ratio Hg/Rh 500:1) proceeded smoothly to give an 88% yield of methyl benzoate (38%) and benzoic acid (50%) (eq 3). A comparable yield of mercury was recovered as a shiny pool.

$$C_6H_5HgOAc + CO + CH_3OH \xrightarrow[100\ psig,\ 85^\circ]{catalyst} C_6H_5COOCH_3 + C_6H_5COOH + Hg + HOAc \quad (3)$$

Subsequent study of this reaction has shown that the carbonylation of organomercurials catalyzed by group 8 metal complexes represents a new, general synthesis of carboxylic acids–esters from hydrocarbons. The details of this chemistry and its synthetic utility will be fully presented in a future publication.

Experimental Section

All reagents were obtained from commercial sources and used as received. Arylmercury salts were prepared by published procedures.[1a] Group 8 metal complexes were purchased from commercial suppliers or synthesized by published techniques.[8–10] Infrared spectra were recorded on a Beckman IR-5A spectrophotometer; NMR spectra were measured on a Varian Associates A-60 spec-

trometer using tetramethylsilane as an internal standard. Vapor phase chromatography was performed on a Perkin-Elmer Model 226 capillary gas chromatograph equipped with 300 ft × 0.01 in. DC-550 silicone columns.

Hydrogenation of Phenylmercury Acetate. In a typical experiment a Parr low-pressure reactor[16] was charged with 6 g (17.8 mmol) of phenylmercury acetate, 90 mg (0.1 mmol) of tris(triphenylphosphine)rhodium(I) chloride, and 100 ml of methanol. The clear, yellow solution was pressurized with hydrogen to 36 psig at room temperature, and the reaction mixture was shaken overnight. The reactor pressure declined to ~19 psig, corresponding to the consumption of ~20 mmol of hydrogen. From the reaction was recovered 2.9 g of mercury (82%). The methanol was poured into water and was extracted with pentane. The extract was dried over magnesium sulfate and analyzed for benzene by VPC using *p*-xylene as an internal standard. The benzene yield was 1.2 g (85%).

Under similar conditions the following catalysts gave the benzene yields shown: tris(triphenylphosphine)ruthenium(II) chloride, 13%; hydridotris(triphenylphosphine)ruthenium(II) chloride, 17%; tetrakis(triphenylphosphine)palladium(0), 24%; tetrakis(triphenylphosphine)platinum(0), 16%; bis(triphenylphosphine)platinum(II) chloride, 14%.

Preparation of Bimetallic Complex (I). A solution of 264 mg (0.78 mmol) of phenylmercury acetate in 5 ml of chloroform was added to a solution of 691 mg (0.75 mmol) of tris(triphenylphosphine)rhodium(I) chloride in 5 ml of chloroform. The solution was stirred at room temperature for 15 min and the chloroform was removed by evaporation. The residue was recrystallized from 25 ml of methanol to yield 474 mg (63%) of yellow crystals, mp 184–186°.

Anal. Calcd for $C_{44}H_{38}ClO_2P_2HgRh$: C, 52.86; H, 3.83; Cl, 3.55; P, 6.20; Rh, Hg, 30.36. Found: C, 52.99; H, 3.93; Cl, 3.92; P, 6.79; Rh, Hg, 28.6.

The NMR spectrum ($CDCl_3$) showed a methyl singlet at 48 Hz and a broad multiplet of aromatic protons at 445 Hz. The observed proton areas were 6 (CH_3) and 94% (CH); the calculated values were 7.8 and 92.2%, respectively. The NMR and infrared spectra of the starting materials and product were totally different.

A 500 mg (0.5 mmol) sample of complex I was dissolved in methanol (50 ml) and hydrogenated at room temperature for 5 hr. Analysis of the methanol solution gave 30 mg (77%) of benzene. Filtration of the reaction mixture gave 70 mg of mercury (70%).

Hydroformylation of 1-Hexene. To an Autoclave Engineers 300-ml stainless steel autoclave were charged 30 ml of 1-hexene (20 g, 0.24 mol), 20 ml of benzene, and 0.3 g of complex I. The reaction was pressurized to 1500 psig with synthesis gas (H_2/CO 1:1) and stirred at 100° for 5 hr. Work-up of the benzene solution gave 26.8 g (98%) of C_7 aldehydes. The ratio of linear to branched isomers was 2.31.[17]

Carbonylation of Phenylmercury Acetate. To a 1-l. Parr 4500 Series autoclave was added 16.8 g (50 mmol) of phenylmercury acetate, 150 ml of methanol, and 0.1 g (0.10 mmol) of tris(triphenylphosphine)rhodium(I) chloride. The reactor was evacuated by a water aspirator, and carbon monoxide was pressured into the reactor to 110 psig. The reaction mixture was stirred at 85° for 25 min. Filtration of the reaction mixture gave 8.5 g (85%) of metallic mercury. From the methanol solution were recovered 2.5 g (38%) of methyl benzoate and 3.1 g (50%) of benzoic acid. The products were identified by comparison with authentic samples.

Registry No.—I, 54446-57-0; tris(triphenylphosphine)ruthenium(II) chloride, 15529-49-4; hydridotris(triphenylphosphine)ruthenium(II) chloride, 19631-00-6; tetrakis(triphenylphosphine)palladium(0), 14221-01-3: tetrakis(triphenylphosphine)platinum(0), 14221-02-4; bis(triphenylphosphine)platinum(II) chloride, 10199-34-5.

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Palladium-Promoted Cyclization of Diphenyl Ether, Diphenylamine, and Related Compounds

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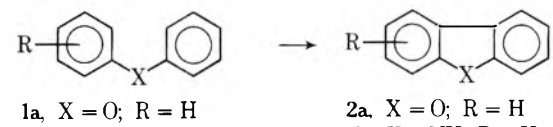
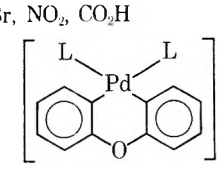
Aromatic compounds may be oxidatively coupled to biaryls and polyaryls by reaction with palladium acetate.[1-4] If diphenyl ether is used, a small amount of dibenzofuran, the product of intramolecular cyclization, is formed in addition to products from intermolecular coupling.[5] In fact, we have earlier shown that dibenzofuran is the only product if the reaction conditions are slightly modified.[6]

We now wish to present results which show that intramolecular cyclization is of general synthetic interest. When heated in acetic acid solution, which contained palladium acetate, diphenyl ether (**1a**), diphenylamine (**1b**), benzophenone (**1c**), and benzanilide (**1d**) gave high yields of cyclized products of the general structure **2** (Table I). An exception was diphenyl sulfide, which failed to yield a defined cyclization product.



1a, X = O; R = H	**2a**, X = O; R = H
b, X = NH; R = H	**b**, X = NH; R = H
c, X = CO; R = H	**c**, X = CO; R = H
d, X = CONH; R = H	**d**, X = CONH; R = H
e, X = NCH_3; R = H	**e**, X = NCH_3; R = H
f-m, X = NH; R = CH_3, CH_3O, Cl, Br, NO_2, CO_2H	**f-m**, X = NH; R = CH_3, CH_3O, Cl, Br, NO_2, CO_2H



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The investigation of a series of substituted diphenylamines showed that a large number of ring substituents were tolerated in the cyclization, e.g., methoxyl, methyl, carboxyl, and nitro groups (Table I). Therefore, the cyclization

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Table I
Results of the Cyclization

Compd, mmol	Palladium acetate, mmol	Solvent	Reaction time, hr	Product	Mp, °C	Yield, %
Diphenyl ether (**1a**), 2	4	Acetic acid	24	Dibenzofuran (**2a**)	85–86 (87)[8]	90
Diphenyl ether	2	Acetic acid	24	Dibenzofuran		45[a]
Diphenyl ether	2	Trifluoroacetic acid	1	Dibenzofuran		87[a]
Diphenyl ether	2	Acetic acid–methanesulfonic acid (15:1)	5 min	Dibenzofuran		40[a,b]
Diphenyl ether	2	Acetic acid–boron trifluoride (15:1)	1	Dibenzofuran		33[a,b]
Diphenylamine (**1b**), 1	1	Acetic acid	0.5	Carbazole (**2b**)	243.5–246 (246)[8]	70 (90[a])
Benzophenone (**1c**), 1	2	Acetic acid	48	9-Fluorenone (**2c**)	81–82 (83)[8]	65
Benzanilide (**1d**), 1	2	Acetic acid	48	6-Phenanthridone (**2d**)	294–296 (292–293)[9]	60
N-Methyldiphenylamine (**1e**), 1		Acetic acid	0.5	*N*-Methylcarbazole (**2e**)	138–139 (141)[10]	75 (90[a])
4-Methyldiphenylamine (**1f**), 1	1	Acetic acid	0.5	3-Methylcarbazole (**2f**)	206–208 (203)[11]	80 (90[a])
4-Methoxydiphenylamine (**1g**), 1	1	Acetic acid	0.5	3-Methoxycarbazole (**2g**)	149–151 (138–139)[12]	75 (90[a])
4-Chlorodiphenylamine (**1h**), 1	1	Acetic acid	0.5	3-Chlorocarbazole (**2h**)	198–200 (201.5)[13]	70 (90[a])
4-Bromodiphenylamine (**1i**), 1	1	Acetic acid	0.5	3-Bromocarbazole (**2i**)	193–195 (199)[14]	75 (90[a])
2-Chlorodiphenylamine (**1k**), 1	1	Acetic acid	1	1-Chlorocarbazole (**2k**)	113–114 (109–110)[15]	75 (90[a])
4-Nitrodiphenylamine (**1l**), 1	2	Acetic acid	2	3-Nitrocarbazole (**2l**)	214–216 (210)[16]	70 (90[a])
N-Phenylanthranilic acid (**1m**), 1	2	Acetic acid	2	Carbazole-1-carboxylic acid (**2m**)	273–274 (271–272)[17]	60

[a] Determined by GLC. [b] Longer reaction time gave no increase.

may be of interest as a general synthesis of condensed aromatic systems, e.g., alkaloids.

The rate of cyclization and the required relative amount of palladium acetate depend on the electron supply in the aromatic rings. Diphenylamine, where the connecting group is electron releasing, is rapidly cyclized in refluxing acetic acid. Only 1 equiv of palladium acetate is required to effect cyclization. This is also true for diphenylamines containing electron-releasing or moderately electron-attracting substituents, the time required for complete reaction being 0.5–1 hr. For diphenylamines containing strongly electron-attracting groups, 2 equiv of palladium acetate and a reaction time of 2 hr are necessary. Cyclization of diphenyl ether (**1b**) requires 2 equiv of palladium acetate and a reaction time of 24 hr, while the reactions of benzophenone (**1c**) and benzanilide (**1d**) are not quite completed after heating for 48 hr in the presence of 2 equiv of palladium acetate (Table I).

The cyclization is catalyzed by acids. When the reaction medium is changed from refluxing acetic acid to trifluoroacetic acid, the cyclization of diphenyl ether is complete within 1 hr and requires only 1 equiv of palladium acetate. Cyclization in acetic acid–methanesulfonic acid (15:1) is even more rapid, being essentially complete within 5 min at reflux (Table I). However, both hydrochloric and sulfuric acid inhibit cyclization. The influence of substituents and of the observed acid catalysis indicate that electrophilic attack by some palladium species on the aromatic rings is involved in the rate-determining step. A reactive intermediate of the type **3** has earlier been suggested[5-6] and is indicated indirectly by the fact that the reaction between a palladium chloride–phosphine complex and 2,2′-dilithiodiphenyl ether gave a high yield of dibenzofuran (**2a**) (X = O) while none of the anticipated palladium species **3**[7] could be observed. The mechanistic aspects and the synthetic scope of the cyclization are being studied.

Experimental Section

Materials. The starting materials **1a–m** and the expected products **2a–m** were either commercial samples or synthesized by standard methods.

Cyclization Procedure. A solution of the diaryl compound and palladium acetate in the appropriate solvent was heated at reflux until the starting material was consumed. The reaction was monitored by GLC and TLC. After evaporation of the solvent, the products were isolated by sublimation or column chromatography. The two procedures gave approximately the same yield. In most cases the yields were also determined by GLC of the reaction solution after addition of a known amount of biphenyl as an internal standard. The products were identified by comparison with authentic samples (ir, melting point, GLC, TLC).

Acknowledgment. We thank the Swedish Natural Science Research Council for financial support.

Registry No.—**1a**, 101-84-8; **1b**, 122-39-4; **1c**, 119-61-9; **1d**, 93-98-1; **1e**, 552-82-9; **1f**, 620-84-8; **1g**, 1208-86-2; **1h**, 1205-71-6; **1i**, 54446-36-5; **1k**, 1205-40-9; **1l**, 836-30-6; **1m**, 91-40-7; **2a**, 132-64-9; **2b**, 86-74-8; **2c**, 486-25-9; **2d**, 1015-89-0; **2e**, 1484-12-4; **2f**, 4630-20-0; **2g**, 18992-85-3; **2h**, 2732-25-4; **2i**, 1592-95-6; **2k**, 5599-70-2; **2l**, 3077-85-8; **2m**, 6311-19-9; palladium acetate, 3375-31-3.

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11-Methoxyakuammicine from *Alstonia muelleriana*

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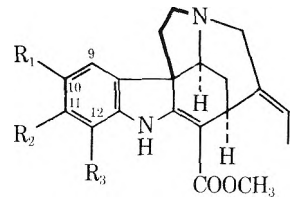
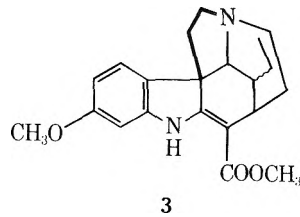
Received October 25, 1974

In our recent investigation of the alkaloids of *Alstonia muelleriana*[1] the isolation of a methoxyakuammicine alkaloid was reported. From spectral data, but without a direct comparison with authentic material, this alkaloid was judged to be identical with vinervinine (**1**), which had been isolated from *Vinca erecta* and assigned structure **1**, 11-methoxyakuammicine, by Yunusov and his coworkers.[2,3]





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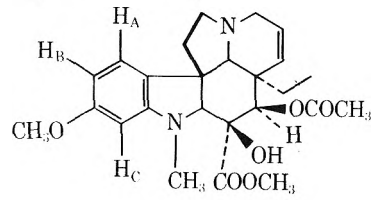
1. $R_1 = R_3 = H$; $R_2 = OCH_3$
2. $R_1 = R_2 = H$; $R_3 = OCH_3$
4. $R_1 = OH$; $R_2 = R_3 = H$;
   9-H = H_A; $R_2 = H_B$; $R_3 = H_C$



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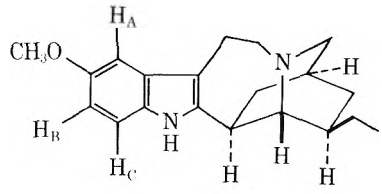

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Very recently,[4] the proposed structure **1** for vinervinine has been revised by Yunusov and coworkers to 12-methoxyakuammicine (**2**). We wish now to distinguish our alkaloid from vinervinine, and to support our original assignment of structure **1** to the compound from *A. muelleriana*.

The uv spectrum of our compound shows λ_{max} (MeOH) 232, 252 (sh), 298, 325 nm (ϵ 11,500, 9300, 7000, 6700), λ_{min} 272, 312 nm (ϵ 5600, 6400), which differs slightly from that which we reported previously.[1] These data are in better accord with those for 11-methoxy-14,19-dihydrocondylocarpine (**3**)[5] [λ_{max} (EtOH) 255, 286, 327 nm (ϵ 14,800, 10,900, 11,200), λ_{min} 275, 310 nm (ϵ 9500, 10,200)] than those for vinervinine [λ_{max} 237, 292, 334 nm (ϵ 13,000, 6600, 26,500)].[3] However, the definitive evidence for position assignment among phenolic functions of these alkaloids is from the NMR spectra of the aromatic region, as we have shown for sewarine (**4**, 10-hydroxyakuammicine),[6] the structure of which has also been confirmed crystallographically.[7]

Table I shows a comparison between the NMR spectra in the aromatic region for several indole alkaloids. It is clear that the spectrum of our alkaloid is very similar to those of vindoline (**5**) and 11-methoxy-14,19-dihydrocondylocarpine (**3**), but different from those for sewarine (**4**) and ibogaine (**6**). In particular, the spectrum in acetone-d_6 is especially revealing, and unequivocally indicates the identity of substitution pattern between our alkaloid and vindoline.[8] The spectra of 2,16-dihydrovinervinine and *N*-acetyldihydrovinervinine published in pictorial form by Yunusov et al.[4] are very different from any of these.

Table I
NMR Spectra (Aromatic Region) of Hydroxy- and Methoxyindole Alkaloids

Alkaloid	H_A, τ	J_{AB}, Hz	H_B	J_{BC}	H_C	Solvent	Ref
Vindoline (**5**)	3.09	8	3.70	2	3.92	$CDCl_3$	6
Ibogaine (**6**)	3.05	2	3.25	9	2.92	$CDCl_3$	6
Sewarine (**4**) HCl	3.02	2	3.30	7	3.17	CD_3OD	6
11-Methoxy-14,19-dihydrocondylocarpine (**3**)	3.02	9	3.5–3.8, 2 H multiplet			Probably $CDCl_3$	5
11-Methoxyakuammicine (**1**)[8]	3.0	8	~3.3, 2 H multiplet			$CDCl_3$	Present work and ref **1**
	2.65	8	3.5	2	3.3	CD_3COCD_3	

Acknowledgment. We thank Professor James P. Kutney for discussions.

Registry No.—**1**, 54484-54-7.

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(8) In $CDCl_3$, H_A appeared as a doublet (J = 8 Hz) at τ 3.0, while H_B and H_C gave superimposed signals at ca. τ 3.3. However, when the spectrum was repeated in acetone-d_6 the 1,2,4 pattern reminiscent of vindoline was quite clear (H_A, doublet, J = 8 Hz; H_B, doublet of doublets, J_{AB} = 8 Hz, J_{BC} = 2 Hz; H_C, doublet, J = 2 Hz).

Reactions of Dichlorocarbene with Methylenecyclohexan-4-one Ethylene Thioacetals

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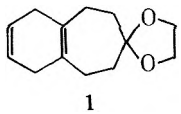
"Synergistic" carbenic cyclopropanation is dramatically illustrated by the Simmons–Smith reaction, in which a zinc carbenoid is intercepted by an hydroxyl, alkoxyl, or oxo substrate functionality, and the methylene fragment is subsequently transferred to a nearby π bond. Augmented addition rates and stereochemical control are observed in such reactions.[2,3] Substrate-assisted cyclopropanation is rarely observed with other carbenic species, however, and our attention was drawn to the suggestion that CCl_2 could be delivered to the central π bond of **1** by prior coordination to an oxygen atom, resulting in a threefold reactivity advantage of the central over the peripheral π bond.[4]



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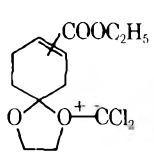

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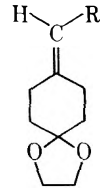


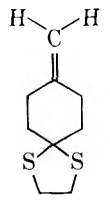
3a, R = H
b, R = $COOC_2H_5$

Unfortunately, no synergism could be detected in CCl_2 additions to various oxygen-functionalized cyclohexene derivatives,[5-7] including those in which the olefinic carbons were activated toward possible Michael addition of an anionic fragment representing a "trapped" CCl_2; cf. **2**.[7]

Addition–displacement cyclopropanations passing through **2**, or analogs, would require front-side displacement of the CCl_2 moiety from the oxygen carrier to complete the cyclopropanation.[8] The forbidden character of such displacements[9] could explain the observed lack of synergism. Moving the acceptor π bond from an endocyclic to an exocyclic position would obviate this problem, but CCl_2 additions to methylenecyclohexan-4-one ethylene acetals, **3**, were also found to occur without synergistic involvement of the acetal function.[10] Either oxygen atoms competed poorly with π bonds as sites for attack by the highly selective CCl_2,[11] or O-ylides which did form followed alternative, lower energy pathways in preference to addition–displacement.

On the other hand, S atoms do compete intramolecularly with π bonds for CCl_2. Whereas reaction of CCl_2 with allyl ethyl ether gave no evidence for O-ylide derived products,[12] S-ylide derived products were formed in reactions of CCl_2 with allylic sulfides.[13,14] Indeed, S-ylides formed by carbene capture have achieved substantial importance in sigmatropic rearrangement[15] and β-elimination reactions.[16]

The obvious superiority of sulfur over oxygen as a site for carbene attack prompted us to prepare methylenecyclohexan-4-one ethylene thioacetals **4** and **5**, and to examine their reactions with CCl_2, in search of S-ylide mediated cyclopropanations.



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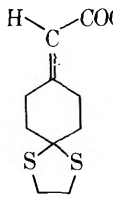

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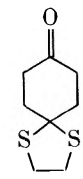

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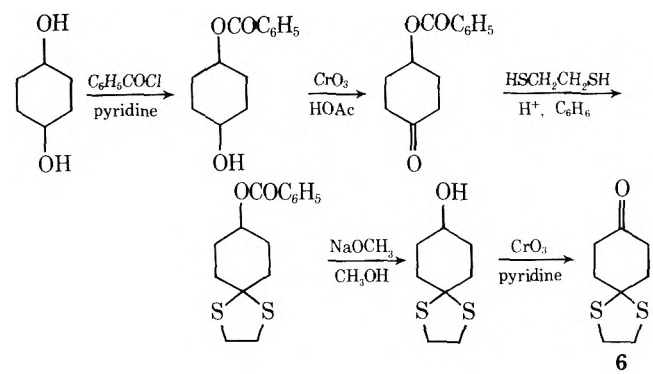
Olefinic thioacetals **4** and **5** were prepared by appropriate Wittig reactions on 1,4-cyclohexanedione monoethylene thioacetal (**6**), which was itself obtained from 1,4-cyclohexanediol by the procedure of Scheme I.

Scheme I



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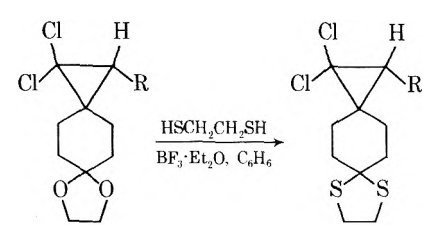
The CCl_2 adducts of **4** and **5** (**7** and **8**, respectively) were most readily prepared by acetal–thioacetal exchange reactions on oxygen analogs **7-Ox** and **8-Ox**, which were available in quantity from a previous study; cf. eq 1.[17]



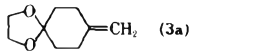
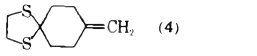
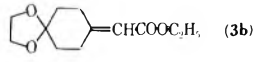
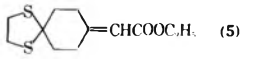
(1)

7-Ox, R = H
8-Ox, R = $COOC_2H_5$

7, R = H
8, R = $COOC_2H_5$

Mercurial-based CCl_2 precursors[12] did not convert **4** to **7**. However, **4** with sodium trichloroacetate in refluxing monoglyme[18] afforded **7** and a yet unidentified isomer in low yield. Similar attempts to add CCl_2 to **5** were fruitless. Cyclopropane **8** could not be obtained; rather, substrate **5** was *destroyed*, leaving behind a black, high-boiling tar. Control experiments showed that authentic **8** was stable to the reaction conditions, and could be readily detected by GC in the control product mixtures.

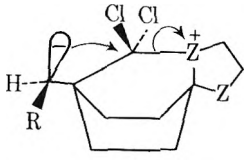
Table I
Relative Reactivities toward CCl_2 (80–85°)

Substrate	Reactivity
 (3a)	0.65
 (4)	0.79
	1.00
 (3b)	0.045
 (5)	*a*

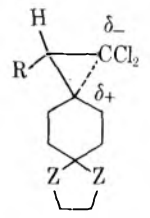
[a] The expected addition product, 8, could not be obtained; see text.

Relative to *cyclohexene*, the reactivity of **4** toward CCl_2 addition was found to be $3.60 \pm 0.18_2$ by the competition technique.[3] Previous data[10] allows us to write the relative reactivity sequence (80–85°) **3a**:**4**:methylenecyclohexane, 0.65:0.79:1.00. On this scale, the relative reactivity toward CCl_2 of **3b** is 0.045,[10] whereas that of **5** cannot be determined. For convenience, the reactivity data are gathered in Table I.

The quantitative data establish the absence of any kinetic advantage resulting from ylide-mediated addition–displacement cyclopropanation, with olefins **4**, **5**, **3a**, and **3b**, which could occur via intermediates such as **9** (Z = S or O; R = H or $COOC_2H_5$). The data suggest, instead, a normal cyclopropanation passing through transition state **10T**, in which partial positive charge resides mainly on the tertiary carbon of the methylenecyclohexane.[3,7,10] The inductively



9



10T

withdrawing heteroatoms of the remote acetal functions destabilize **10T**, and the reactivity order **3a** < **4** < methylenecyclohexane is quite reasonable. $\sigma_I(SCH_3)$ is smaller than $\sigma_I(OCH_3)$;[19] **10T** should be less destabilized when Z = S than when Z = O; hence thioacetal **4** is less deactivated toward CCl_2 addition than is acetal **3a**.

Although ylide-mediated cyclopropanation does not seem to occur, the thioacetal function must capture CCl_2 competitively with CCl_2 addition to π bonds. This is clearly seen on comparison of olefinic ester acetals **3b** and **5**. The former has a low reactivity toward CCl_2 addition because of the combined deactivating effects of its carboethoxy and ethylene acetal groups. However, the reactivity of the π bond in **5** is even lower, despite the fa[illegible] that the ethylene thioacetal group (of **5**) should be *less* deactivating than the ethylene acetal function (of **3b**); see **3a** vs. **4**, above.

This is understandable if S atoms capture CCl_2 at rates similar to those of the π bonds of disubstituted alkenes, and then nonproductively dispose of CCl_2. Because the substitution of a carboethoxy group on the exo methylene position of methylenecyclohexane decreases π-bond reactivity toward CCl_2 by ~17-fold,[10] the additionally deactivated double bond of **5** will not be able to compete for CCl_2 with the S atoms of the thioacetal group.

Further evidence on this point was obtained from experiments in which **5** and 4-methylcyclohexanone ethylene thioacetal (**11**) were shown to *inhibit* CCl_2 addition to cyclohexene; cf. Table II.

Table II
Inhibition of Dichloronorcarane Formation from Cyclohexene by Thioacetals[a]

Run	Thioacetal	Mg	Mmol (× 10)	7,7-Dichloronorcarane formed, mg	Residual thioacetal, mg
1	None	0	0.0	14.4	
2	5	20	0.78	6.8	0.0
3	5	39	1.5	4.9	0.0
4	5	58	2.2	3.4	0.0
5	5	82	3.2	1.8	0.0
6	11	21	1.1	6.7	0.03
7	11	42	2.2	2.9	5.2
8	11	60	3.2	1.9	15

[a] Conditions: 50 mg (0.61 mmol) of cyclohexene and 110 mg (0.60 mmol) of $NaOOCCCl_3$ were heated in monoglyme at 85° for 30 min. Product and residual thioacetals were analyzed by GC, relative to an internal *n*-dodecane standard.

When [thioacetal]/[cyclohexene] ~ 0.5, **5** inhibits CCl_2 addition to cyclohexene by 88% (run 5 vs. run 1), and **11** inhibits by 86% (run 8 vs. run 1). These results parallel those of Parham and Groen, who showed that *n*-butyl phenyl sulfide inhibited the addition of CCl_2 to cyclohexene.[13]

Table II also shows that, although **5** and **11** are similarly effective as inhibitors, **11** was only partially destroyed (75%) by 2 equiv of CCl_2 precursor, whereas **5** was totally destroyed (runs 8 and 5). This suggests that there *is* a synergistic relation between the conjugated ester and thioacetal functions of **5** (toward CCl_2), but that it leads to accelerated substrate destruction rather than to accelerated cyclopropanation.[13a]

By analogy,[13–16] the initial product formed from CCl_2 and an ethylene thioacetal should be a sulfonium ylide. Attempts to "trap" the CCl_2 moiety of such an ylide by generating CCl_2 in the presence of **11** and either pentanal or methyl acrylate have led only to unidentified products derived solely from thioacetal **11**.[20]

Finally, why are allylic sulfides good substrates for *S*-ylide mediated CCl_2 reactions, whereas "remote" olefinic substrates such as **4** and **5** are "poor"? The activation energy for the [2,3] sigmatropic rearrangement of an ylide formed by addition of CCl_2 to an allylic sulfide must be very low; such ylides are rapidly consumed by the rearrangement process.[21] On the other hand, substrate-assisted cyclopropanation of **5** would require passage through **9** (R = $COOC_2H_5$; Z = S), the formation of which involves a Michael addition to a tetrasubstituted alkene. The activation energy for this process appears to be high enough to permit alternative, intermolecular reactions (polymerization) to occur in preference to self-cyclopropanation.

Experimental Section[22]

4-Benzoyloxycyclohexanone. 1,4-Cyclohexanediol (250 g, 2.15 mol), benzoyl chloride (295 g, 2.10 mol), and pyridine (600 ml) in 1400 ml of chloroform gave 275 g (58%) of 4-benzoyloxycyclohexanol, bp 175–178° (0.2 Torr) [lit.[23] bp 175–178° (0.2 Torr)], according to the procedure of Jones and Sondheimer.[23] The product (260 g, 1.18 mol) was oxidized with 115 g (1.15 mol) of CrO_3 in 700 ml of acetic acid and 67 ml of water.[23] There was isolated 140 g (54%) of 4-benzoyloxycyclohexanone: mp 58–60° (lit.[23] mp 63°); NMR δ 8.20–7.93 and 7.63–7.23 (m's, 2 H + 3 H, aryl), 5.60–5.27 (m, 1 H, carbinyl), and 2.73–1.97 (m, 8 H, cyclohexyl).

4-Benzoyloxycyclohexanone Ethylene Thioacetal. The above keto ester (70 g, 0.32 mol), 30 g (0.32 mol) of ethane-1,2-dithiol, 200 mg of *p*-toluenesulfonic acid, and 600 ml of benzene were heated to reflux for 20 hr, during which time ~5.7 ml of water collected in a Dean-Stark trap. Removal of the benzene gave a white

solid which was used without further purification. A small sample was recrystallized from benzene–petroleum ether (bp 30–60°): mp 73–76°; NMR δ 8.23–7.90 and 7.67–7.20 (m's, 2 H + 3 H, aryl), 5.30–4.87 (m, 1 H, carbinyl), 3.27 (s, 4 H, thioacetal), and 2.43–1.73 (m, 8 H, cyclohexyl).

Anal. Calcd for $C_{15}H_{18}O_2S_2$: C, 61.2; H, 6.12. Found: C, 61.2; H, 6.15.

4-Hydroxycyclohexanone Ethylene Thioacetal. The crude ester thioacetal (90 g, 0.31 mol), 2 g of sodium methoxide, and 300 ml of methanol were refluxed for 15 hr. Methanol was distilled away; the solid residue was shaken twice with 2 × 500 ml of acetone. Each acetone extract was filtered, acetone was stripped from the combined filtrate, and the residue was distilled. Methyl benzoate was removed at ~31° (0.25 Torr). The pot residue was cooled and recrystallized from benzene–petroleum ether to give three crops (total yield ~50 g, 85%) of the desired product: mp 83.5–85°; NMR ($CDCl_3$) δ 3.93–3.53 (m, 1 H, carbinyl), 3.27 (s, 4 H, thioacetal), and 2.40–1.47, including a superimposed singlet (OH) at 1.57 (m, 9 H, cyclohexyl and OH).

Anal. Calcd for $C_8H_{14}OS_2$, C, 50.5; H, 7.36. Found: C, 50.7; H, 7.50.

1,4-Cyclohexanedione Monoethylene Thioacetal (6). CrO_3 (28.0 g, 280 mmol) was cautiously added to 300 ml of pyridine, followed by a solution of 21 g (110 mmol) of the above alcohol thioacetal in 100 ml of pyridine.[24] After the reaction mixture was stirred for 3 days at 25°, it was diluted with 500 ml of ether and filtered. The ethereal filtrate was washed with 3 × 150 ml of water and 3 × 150 ml of 2 *N* H_2SO_4, dried (Na_2SO_4), and stripped of solvent. The residue was maintained at 0.2 Torr for 12 hr, and then distilled to give 7 g (33%) of **6**: bp 102° (0.13 Torr); ir (film) 5.83 μ (s, C=O); NMR δ 3.33 (s, 4 H, thioacetal) and 2.40 ("s", 8 H, cyclohexyl[25]).

Anal. Calcd for $C_8H_{12}OS_2$: C, 51.0; H, 6.39. Found: C, 51.3; H, 6.46.

Methylenecyclohexan-4-one Ethylene Thioacetal (4).[26] Dimsyl sodium was prepared in a 100-ml, three-neck flask. NaH, 0.90 g of a 61% dispersion in mineral oil (22.9 mmol), was washed with petroleum ether, dried of solvent under vacuum, covered with N_2, and treated with 20 ml of DMSO (dried over 3A molecular sieves, and then distilled) at 65–70°, with stirring for ~30 min. After H_2 evolution ceased, the reaction mixture was cooled to 25°, and a solution of methyltriphenylphosphonium bromide (8.5 g, 23.8 mmol) in 30 ml of DMSO was added via syringe. After 10 min, 4.3 g (22.8 mmol) of ketone **6** was added. The orange ylide turned brown. The solution was heated to 70° for 3 hr, cooled, and diluted with 30 ml of petroleum ether and 60 ml of water. The aqueous layer was extracted with 3 × 20 ml of petroleum ether, and the combined organic extracts were washed with 30 ml of water, dried over Na_2SO_4, and stripped. Distillation of the residue gave 2.1 g (52%) of pure **4**: bp 55° (0.03 Torr); ir (CCl_4) 6.05 μ (m, C=C); NMR δ 4.60 ("s", 2 H, vinyl), 3.23 (s, 4 H, thioacetal), and 2.47–1.90 (m, 8 H, cyclohexyl).

Anal. Calcd for $C_9H_{14}S_2$: C, 58.1; H, 7.53; S, 34.4. Found: C, 58.1; H, 7.75; S, 34.1.

Carboethoxymethylenecyclohexan-4-one Ethylene Thioacetal (5).[27] NaH, 0.628 g of a 61% dispersion in mineral oil (15.9 mmol), was placed in a dry, 25-ml, three-neck flask equipped with a thermometer, N_2 inlet, addition funnel, and stirring bar. Dry benzene (10 ml) was added and stirring commenced. This was followed slowly by the addition of 3.58 g (15.9 mmol) of triethyl phosphonoacetate via the addition funnel. The temperature was kept at <35° during the addition. After an additional 1 hr of stirring, 3.0 g (15.9 mmol) of ketone **6** was added over 20 min. During the addition, the reaction mixture became very viscous, and was then warmed to 60°. Heating was continued for 30 min after the addition of **6** was completed. The reaction mixture was then cooled, benzene was decanted, and the residue was leached with 4 × 10 ml of hot benzene. All benzene fractions were combined and stripped; the residue was distilled to give 0.8 g of a mixture of **5** and **6** (95:5), bp 140–143° (0.3 Torr), followed by 1.85 g of GC-pure **5**, bp 143–146° (0.3 Torr). The overall yield was 63%: ir (film) 5.85 (s, C=O) and 6.16 μ (s, C=C); NMR δ 5.58 ("s", 1 H, vinyl), 4.10 (q, *J* = 7 Hz, 2 H, OCH_2), 3.28 (s, 4 H, thioacetal), 3.05 ("t", *J* = 7 Hz, 2 H, allylic CH_2 cis to carboethoxy), 2.58–1.98 (m, 6 H, other cyclohexyl), and 1.25 (t, *J* = 7 Hz, 3 H, methyl).

Exact mass. Calcd for $C_{12}H_{18}S_2O_2$: 258.074. Found: 258.072.[22]

1,1-Dichlorospiro[2.5]octan-6-one Ethylene Thioacetal (7) and 1,1-Dichloro-2-carboethoxyspiro[2.5]octan-6-one Ethylene Thioacetal (8). These compounds were prepared from their (oxy) acetal analogs, **7-Ox** and **8-Ox**, respectively.[17] The preparation of **7** is illustrative. In a test tube was placed 120 mg (0.51 mmol) of **7-Ox**, 0.2 ml of 1,2-ethanedithiol, and 0.2 ml of $BF_3 \cdot (C_2H_5)_2O$. The mixture was shaken, 2 ml of ether was added, and the solution was placed on a small alumina column (3 g). Elution with 10 ml of ether, followed by stripping of the eluate, gave an oil which was purified by GC,[28] retention time 13.5 min (the retention time of **8** was 22 min) on a 5 ft × 0.25 in., 15% SE-30 on 45/60 GCR column at 210°, He flow rate 70 ml/min. Both **7** and **8** were white solids. For **7**: NMR δ 3.23 (s, 4 H, thioacetal), 2.28–1.67 (m, 8 H, cyclohexyl), 1.20 (s, 2 H, cyclopropyl).

Exact mass. Calcd for $C_{10}H_{14}Cl_2S_2$: 267.991. Found: 267.989.[22]

For **8**: ir (CCl_4) 5.75 μ (C=O); NMR δ 4.13 (q, *J* = 7 Hz, 2 H, OCH_2), 3.23 (s, 4 H, thioacetal), 2.3–1.73 [m, with superimposed s at 1.98, 9 H, cyclohexyl and cyclopropyl (s)], and 1.27 (t, *J* = 7 Hz, 3 H, methyl).

Exact mass. Calcd for $C_{13}H_{18}Cl_2S_2O_2$: 340.012. Found: 340.012.[22]

4-Methylcyclohexanone Ethylene Thioacetal (11) was prepared from 10.0 g (89.5 mmol) of 4-methylcyclohexanone, 8.0 g (85 mmol) of 1,2-ethanedithiol, and 300 mg of *p*-toluenesulfonic acid in 50 ml of refluxing benzene, with azeotropic removal of water. Removal of solvent, followed by distillation afforded 13 g (81%) of the product, bp 81° (0.4 Torr). The thioacetal was GC pure and showed no carbonyl band in its ir spectrum: NMR δ 3.23 (s, 4 H, thioacetal) and 2.33–0.80 (m, with methyl signal superimposed at ~0.97, 12 H, cyclohexyl and methyl).

Exact mass. Calcd for $C_9H_{16}S_2$: 188.069. Found: 188.074.[22]

Relative Reactivity Experiments. Weighed samples of olefin A and olefin B were diluted with 3 ml of monoglyme (distilled from Na) and injected into a nitrogen-blanketed flask containing ~0.1 equiv of sodium trichloroacetate and *n*-hexadecane (~80 mg) as an internal standard. The reaction mixture was stirred magnetically and heated with an oil bath to 80–85° for 1 hr. The reaction mixture was then cooled and filtered; the filtrate was analyzed on either an 8 ft × 0.25 in. 10% or a 5 ft × 0.25 in. 15% SE-30 on 45/60 GCR column programmed between 100 and 200°. The relative reactivity toward CCl_2, k_A/k_B, was calculated in the normal manner from $(P_A/P_B)(O_B/O_A)$ where the *P* factor represents the product ratio and the *O* factor represents the initial olefin ratio.[3] Olefins were present in tenfold excess over carbene precursor. Data appear in Table III.

Table III
Relative Reactivity Experiments

Olefin A/olefin B	$(O_A/O_B)^a$	$(P_A/P_B)^b$	$k_A/k_B{}^c$	$k_A/k_B{}^d$
4/cyclohexene	0.266	1.01	3.80	3.46
4/cyclohexene	0.522	2.15	4.12	3.75
4/methylene-cyclohexane	0.972	0.735	0.756[e]	

[a] Mole ratio. [b] From integration of GC product peaks. [c] Uncorrected for relative thermal conductivity detector responses. [d] The detector response, C_K = (moles of 7/moles of dichloronorcarane)/(GC response of 7/GC response of dichloronorcarane), was 0.91. Crude k_A/k_B was multiplied by 0.91 to obtain the corrected k_A/k_B. The average corrected value is 3.60 ± 0.18. [e] From $(k_4/k_{cyclohexene})(k_{cyclohexene}/k_{methylenecyclohexane}) = 3.60 \times 1/4.57$,[10] we calculate $k_4/k_{methylenecyclohexane} = 0.788$, in good agreement with the observed cross-check value.

Inhibition of CCl_2 Additions. Conditions and results of these experiments are described in Table II and its note.

Control Experiments. To establish the stability of **8**, a solution of ~15 mg (0.044 mmol) of **8**, 10 μl of *n*-hexadecane, 80 mg (0.95 mmol) of cyclohexene, and 15 mg (0.081 mmol) of sodium trichloroacetate in 2 ml of glyme was heated for 1 hr at 85°. GC analysis gave the ratios, **8**/*n*-hexadecane, as 0.465 (before reaction) and 0.460 (after reaction). Dichloronorcarane *was* formed in this experiment.

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Registry No.—**3a**, 51656-90-7; **3b**, 51656-91-8; **4**, 54531-72-5; **5**, 54531-73-6; **6**, 54531-74-7; **7**, 54531-75-8; **7-Ox**, 51656-93-0; **8**, 54531-76-9; **8-Ox**, 51656-92-9; **11**, 41158-95-6; dichlorocarbene, 1605-72-7; 4-benzoyloxycyclohexanone, 23510-95-4; 1,4-cyclohex-

anediol, 556-48-9; benzoyl chloride, 98-88-1; 4-benzoyloxycyclohexanol, 6308-92-5; 4-benzoyloxycyclohexanone ethylene thioacetal, 54531-77-0; ethane-1,2-dithiol, 540-63-6; 4-hydroxycyclohexanone ethylene thioacetal, 22428-86-0; 4-methylcyclohexanone, 589-92-4.

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Communications

Heteroatom Directed Photoarylation. Photochemistry of Aryloxyenones

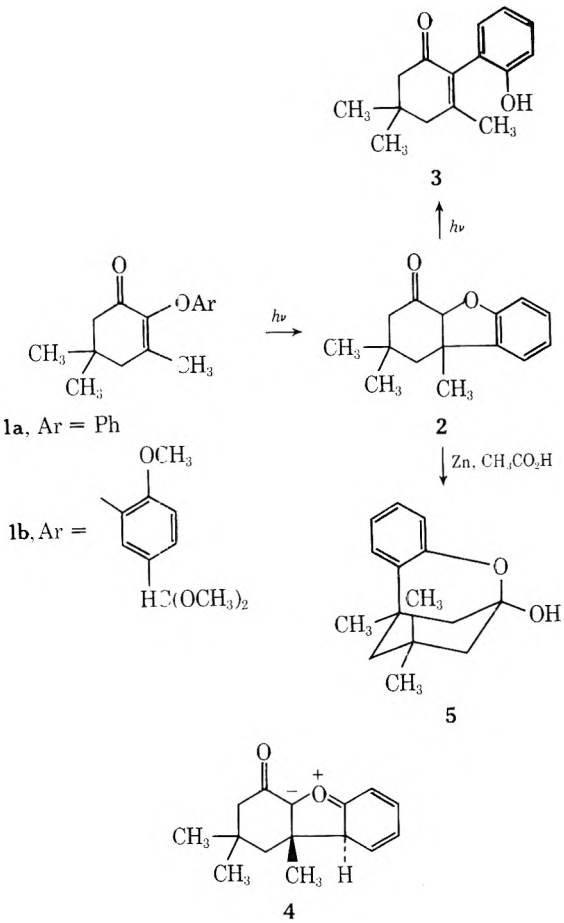
Summary: Aryloxyenones **1a** and **1b** undergo photocyclization–rearrangement to give dihydrofurans **2** and **7**, respectively.

Sir: Reported photoreactions of aryl ethers have been limited to (1) cleavage of the ether bond(s) followed by hydrogen abstraction from solvent to give phenols and (2) photorearrangement to give ortho- and para-substituted hydroxybiphenyls.[1] Photocyclization of unsubstituted diaryl ethers or aryl vinyl ethers to annelated dihydrofurans apparently has not been observed;[2,3] however, photocyclization–elimination of o-methoxyphenyl phenyl ethers[2] and o-chlorophenyl 1-naphthyl ether[3] to annelated furans in low to moderate yield has been reported. Herein, we communicate the photochemistry of 2-phenoxy-3,5,5-trimethylcyclohexen-2-one (**1a**), which represents the first report of nearly exclusive photochemical carbon–carbon bond formation from an unsaturated ether, to give an annelated dihydrofuran.

Aryloxyenone **1a** was prepared by the potassium hydride (0.1 equiv) assisted reaction of isophorone oxide[4] with 1.1 equiv of phenol in refluxing tetrahydrofuran solution containing 0.75 equiv of hexamethylphosphoramide (91% isolated yield, mp 104–105°). Pyrex-filtered photolysis of **1a** (20 g) was performed in benzene–methanol–acetic acid solution (2000 ml, equal portions of each solvent component) while purged with argon. After 23 hr irradiation with a 450-W high-pressure mercury arc lamp, <2% **1a** remained in the nearly colorless reaction mixture; formation of dihydrofuran **2** (95%), rearranged phenol **3** (~2%), and trace amounts of phenol and isophorone was observed (vpc analysis). Evaporation of solvent and partition of the reaction components between ether and 1 *N* sodium hydroxide solution gave nearly pure dihydrofuran **2** (88% yield) in the organic layer. Two crystallizations from ether–petroleum ether produced analytically pure **2** (80% yield, mp 85–87°, *m/e* 230).

Acidification of the sodium hydroxide layer gave, after ether extraction and crystallization from ether–petroleum ether, pure **3** (2% yield, mp 172–175°, *m/e* 230). The nmr spectrum of **3** in $CDCl_3$ above 5 ppm is nearly identical with that of **1** and displays singlets at 1.11 (6 protons, *gem*-dimethyl), 1.83 (3 protons, vinyl methyl), and 2.42 ppm (4 protons, two methylene groups). The phenolic proton in **3** appears as a broadened singlet at 5.8 ppm and exchanges with deuterium oxide, while the four aromatic protons appear as a complex multiplet at 6.8 to 7.4 ppm. Para aromat-

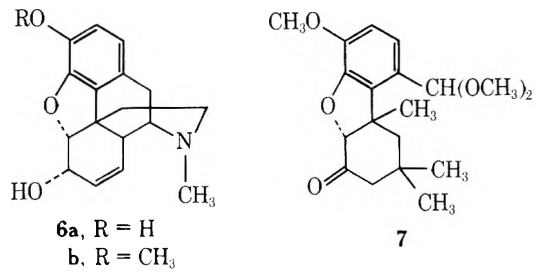
ic substitution in **3** is ruled out on the basis of NMR data. Good evidence for ortho substitution is obtained from the ir spectrum of **3** (Nujol) between 12 and 15 μ; i.e., a single strong absorption appears at 13.3 μ (C–H out-of-plane deformation).



The process **1a** → **2** presumably occurs by conrotatory photocyclization[8] of **1a**, leading to intermediate carbonyl ylide **4**, which undergoes rearrangement to give dihydrofuran **2**. Stereochemistry of the ring junction in **2** is considered to be cis, because this would be the stable configuration for a fused five–six-membered ring system capable of epimerization; on treatment with methanolic sodium hydroxide at room temperature, **2** was recovered unchanged.

Extended irradiation of solutions of **1a** resulted in increased amounts of rearranged phenol **3** at the expense of **2**. Independent photolysis of **2** gave a complex mixture of products, the major component of which was **3**. Thus, **3** is not formed directly from **1a**, but rather arises from a secondary photoreaction involving **2**. The detailed mechanism for this process as well as o-hydroxybiphenyl formation from diaryl ethers[1] currently is being investigated.

Photocyclization of aryloxyenones to dihydrofurans may have considerable synthetic importance. For example, approaches toward the synthesis of morphine alkaloids, here represented by morphine (**6a**) and codeine (**6b**), have been long and hence suffer from low overall yields.[9] Our approach toward the synthesis of morphine confronts the difficult task of forming the only carbon–carbon bond possessing a quaternary carbon atom by the technique of heteroatom-directed photoarylation.[6] In this regard, irradiation of model system **1b** resulted in nearly exclusive formation of dihydrofuran **7**.[10]



It should be noted that **2** undergoes quantitative conversion to an ortho-substituted phenol, isolated in hemiketal form **5** (mp 97–98°, *m/e* 232), on treatment with zinc dust in refluxing acetic acid solution. The method described here for the two step conversion **1** → **5** complements our recently reported method for preparation of complex meta-substituted phenols.[6]

Acknowledgment. This work was supported by an E. I. du Pont de Nemours and Co., Incorporated Young Faculty Grant, by a Fredrick Gardner Cottrell grant from the Research Corporation, by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Institutes of Health (Grant No. GM 21159-01).

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(5) Attempts to prepare **1** from phenol and isophorone oxide by the procedure of Tobias et al. failed; see M. A. Tobias, J. G. Strong, and R. P. Napier, *J. Org. Chem.*, **35**, 1709 (1970).
(6) Assignment of structure for **2** is based on spectral evidence and comparison to products characterized in a related study; see A. G. Schultz, *J. Org. Chem.*, **39**, 3185 (1974).
(7) Compounds **1**, **2**, **3**, and **5** gave correct elemental analysis.
(8) A. G. Schultz and M. B. DeTar, *J. Am. Chem. Soc.*, **96**, 296 (1974).
(9) G. Stork in "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1960, p 235.
(10) Aryloxyenone **1b** was prepared from isovanillin dimethyl acetal by the method described for the synthesis of **1a**. Both **1b** and photoproduct **7** gave NMR, ir, and mass spectra completely in accord with assigned structures.

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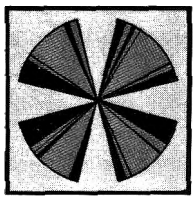
Polyethers



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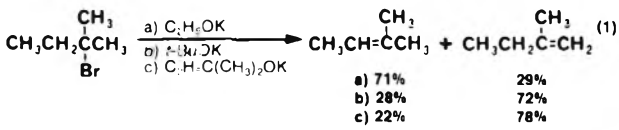
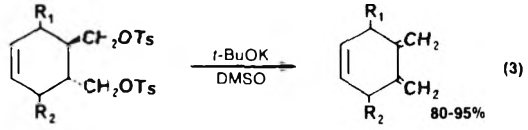


(1)

Carbene Generation

(2)

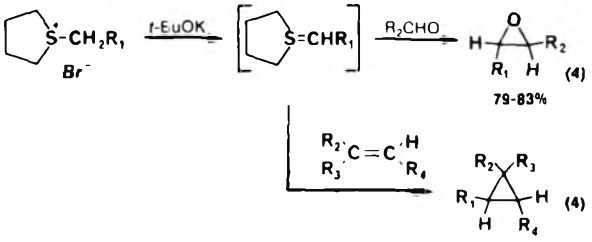
Reaction with Sulfonates



(3)

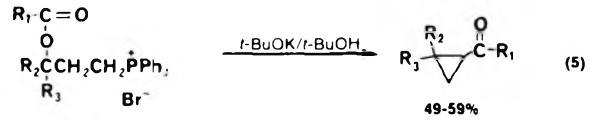
(1)

Preparation of Ylids



(4)

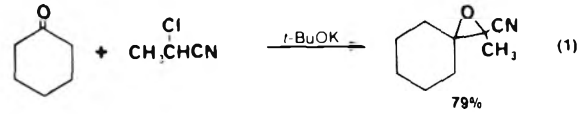
(4)



(5)

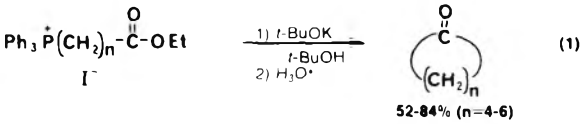
Condensations

(a) Darzens



(1)

(b) Dieckmann



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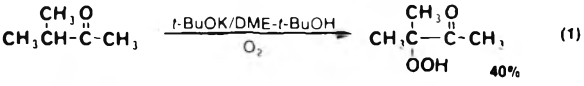
Oxidation



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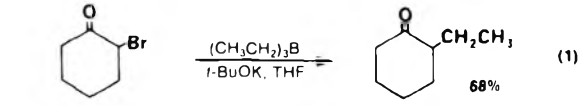
Alkylation



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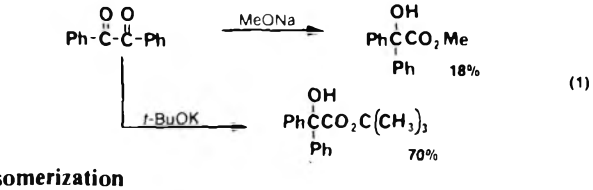
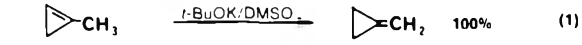
Benzilic Acid Rearrangement



(1)

Isomerization



(1)

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